SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF THE CHEMISTRY OF α-SUBSTITUTED DIAZENES.

SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF THE CHEMISTRY OF α-SUBSTITUTED DIAZENES.

By

J. Douglas McCallion

A Thesis

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TO MY PARENTS

AND

TO MY WIFE, MARY ANNE

Master of Science (1986) McMaster University

Hamilton, Ontario

TITLE: SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF THE CHEMISTRY OF α-SUBSTITUTED DIAZENES.

AUTHOR; J. Douglas McCallion, B.Sc. McMaster University

B.Ed. (University of Toronto)

SUPERVISOR: Professor John Warkentin

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ABSTRACT

It had been proposed that α-hydroperoxydiazenes decompose by the radical chain abstraction of the hydroxy group. This suggested that these compounds could be used as hydroxyalkylating agents for unsaturated systems.

Compounds 15 and 23 were prepared by the autoxidation of the corresponding hydrazone. α-Hydroperoxydiazenes 15 and 23 were used to hydroxyalkylate ethyl vinyl ether and 2-methoxypropene in yields of 62-65%. Mechanisms of the addition reaction are discussed.

In an attempt to alkylate a hetero atom system, compound 15 was thermolyzed with compound 25. The alkylation product was not obtained.

Compound 15 was converted to α-hydroxydiazene 34 by the action of Φ_3P. α-Hydroxydiazenes have been used synthetically in the hydroalkylation of alkenes. The rate constant of hydrogen abstraction was determined to be in the range of 1.5×10^5 $M^{-1}s^{-1}$ to 1.5×10^7 $M^{-1}s^{-1}$ by the use of a radical clock reaction. An upper limit on the rate of rearrangement of the 2-cyanopropyl radical was found to be 3.65×10^3 s^{-1}.

A new compound (23) was prepared.

ACKNOWLEDGEMENTS

I am much indebted to Dr. J. Warkentin, my supervisor, for his continued guidance and encouragement during the course of this work.

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I. INTRODUCTION

I.1. Historical Development of Free Radical Chemistry

The first authentic free radical was discovered by Gomberg[1] in 1900. This lead to the reinterpretation of the kinetics of many chemical reactions. A radical chain process was suggested independently in 1918 by Christiansen,[2] Hertzfeld[3] and Polani[4] for the reaction of H_2 with Br_2.

Free radicals were later implicated in polymerization reactions, addition of halogens to olefins,[5] cyclizations,[6] autoxidation reactions,[7] and redox reactions[8] among others.

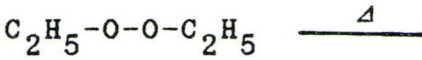
With the advent of electron spin resonance spectroscopy (ESR) in the 1950's, it became possible to study free radicals at the low steady state concentrations at which they often occur. Chemically induced dynamic nuclear polarization (CIDNP) and chemically induced dynamic electron polarization techniques, which were developed in the 1960's and 1970's, shed further light onto the reactions of free radicals.[9]

I.2. Generation of Free Radicals

Thermolysis

As the kinetic energy of a molecule is increased by raising the temperature, the vibrational amplitude increases and the bonds begin to stretch. Eventually, a bond will break and two free radicals will be produced. A typical C-C bond energy is about 90 kcal mol^{-1} and temperatures in excess of 450°C must be reached in order for thermal homolysis to occur.

However, the peroxy, perester, and the azo functional groups will fragment at lower temperatures to form radicals at a reasonable rate in the temperature range of normal solution chemistry.[10] Equations 1,2 illustrate peroxy and azo thermolysis.



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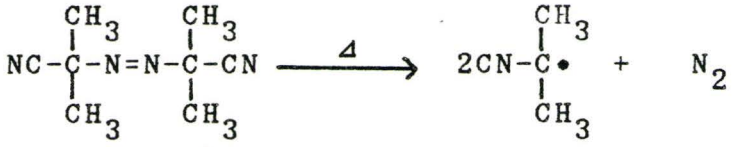

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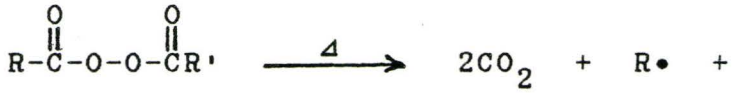
Peresters and azo compounds decompose readily due to the stable products which are formed. The formation of N_2 in the case of azo compounds and the formation of CO_2 in the case of peresters provides a strong driving force for the dissociation process (equations 3,4).



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(4)

Radicals can also be produced by molecule assisted homolysis (MAH),[11] by visible or ultraviolet radiation induced homolysis, or by electron transfer reactions such as the

Fenton reaction.[12,13] The action of γ-rays, X-rays or high energy electrons can produce radical ions which then decompose producing an ion and a free radical. The focus of this work will be on the generation of radicals by the thermolysis of azo compounds.

I.3. Free Radical Reactions.

I.3.1. Free Radical Addition Reactions.

The scheme for the addition of a free radical to an unsaturated system via a radical chain mechanism is shown below:

Scheme 1

Initiation

$$In \rightarrow In\bullet$$

$$In\bullet + XY \xrightarrow{k_1} X\bullet + InY$$

Propagation

$$X\bullet + CH_2{=}CH_2 \xrightarrow{k_2} XCH_2 - \dot{C}H_2$$

$$XCH_2 - \dot{C}H_2 + XY \xrightarrow{k_3} XCH_2CH_2Y + X\bullet$$

Termination

$$2X\bullet \xrightarrow{k_4} X_2$$

$$X\bullet + XCH_2CH_2\bullet \xrightarrow{k_5} XCH_2CH_2X$$

$$2XCH_2CH_2\bullet \xrightarrow{k_6} XCH_2CH_2CH_2CH_2X$$

The overall addition to an unsaturated compound can be represented as;

$$XY + A{=}B \rightarrow AXBY \qquad (5)$$

These radical addition reactions have great synthetic utility.[14-17] Reagents that can be added to an unsaturated system by a radical chain mechanism include halogens, HBr, hydrocarbons, polyhaloalkanes, amines, esters, alcohols, ketones, aldehydes, aliphatic acids, and compounds of sulfur, phosphorus, silicon, tin, and germanium.

There are two sites that the free radical can initially attack in an unsymmetric unsaturated system. This leads to two isomeric addition products.

$$X\bullet + CH_2{=}CHZ \xrightarrow{k_\alpha} XCH_2\text{-}\dot{C}HZ \qquad (6)$$

$$X\bullet + CH_2{=}CHZ \xrightarrow{k_\beta} \dot{C}H_2\text{-}CHXZ \qquad (6)$$

$$XY + XCH_2\text{-}\dot{C}HZ \rightarrow XCH_2\text{-}CHYZ \qquad (7)$$

$$XY + \dot{C}H_2\text{-}CHXZ \rightarrow YCH_2\text{-}CHXZ \qquad (8)$$

The ratio of isomeric products formed is called the orientation ratio (OR). The orientation ratio is defined as the ratio of the rate constant for addition to the most substituted end (β) compared to the rate constant for addition to the least substituted end (α).

$$OR = \frac{k_\beta}{k_\alpha} \qquad (9)$$

The predominant product formed in most radical additions is from initial attack at the least substituted end regardless of the nature of the radical or the substituent on the alkene. Studies of the OR for various free radical additions to alkenes suggest that both steric and polar factors are important in making the least substituted end the favoured site of initial attack.

I.3.2 Free Radical Substitution Reactions

Free radical substitution (S_H2) reactions are defined operationally as homolytic processes in which one atom or group of atoms in a molecule is replaced with another without regard to details of mechanism.

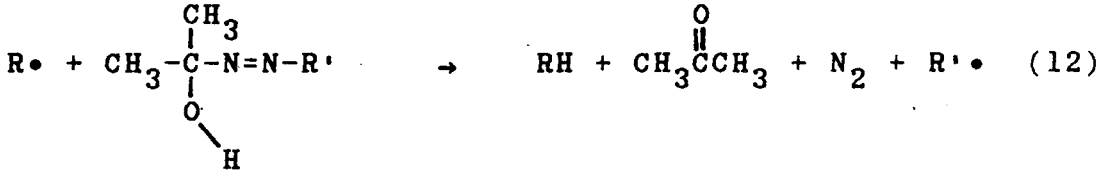
I.3.2.1 Substitution at Hydrogen

Radical substitution takes place at hydrogen during halogenation (eqn. 10), autoxidation (eqn. 11) and during oxidation.

$$X\bullet + RH \rightarrow XH + R\bullet \qquad (10)$$

$$ROO\bullet + RH \rightarrow ROOH + R\bullet \qquad (11)$$

A wide variety of radicals substitute at hydrogen in alcohols. These include alkyl,[21] alkoxy,[22] hydroxyl,[23] nitrogen[24] and sulfur[25] radicals. The radicals attack preferentially at the α-CH bond and generally not at the O-H bond. This is due to the lower bond dissociation energy of the C-H bond (90 kcal mol^{-1}) compared to the O-H bond (108 kcal mol^{-1}). Knittel and Warkentin,[26,27] found that a variety of radicals will abstract the hydroxylic hydrogen from a series of α-azocarbinols (equation 12) and oxadiazolines (equations 13,14,15).



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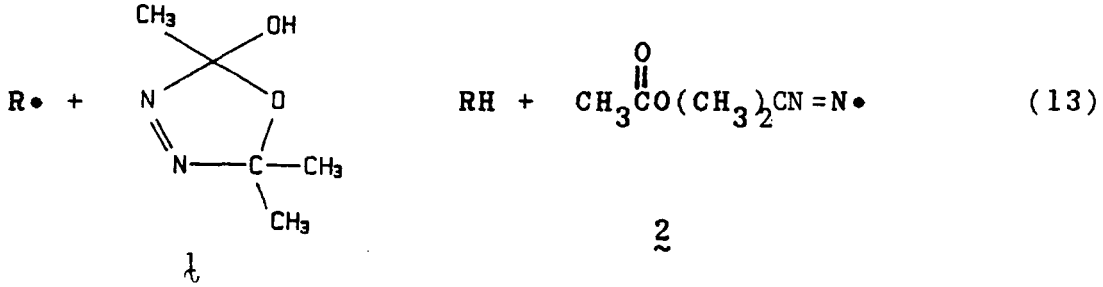

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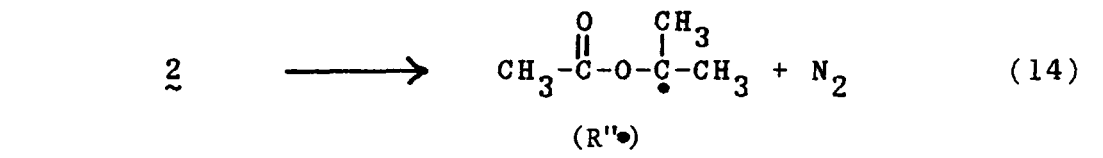

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I.3.2.2 Substitution at Oxygen

Evidence for a S_H2 reaction at oxygen comes from studies on the induced decomposition of peroxides.

$$ROOR' + R\bullet \rightarrow [RO....\underset{\underset{R'}{|}}{O}...R]\bullet \rightarrow RO\bullet + ROR' \quad (16)$$

This reaction is thermodynamically favourable since an O-O bond is being broken and a C-O bond is being made resulting in the substitution being about 45 kcal mol^{-1} exothermic. Labelling studies[28,29] have shown that the reaction is not a two-step addition-elimination but occurs by a S_H2 reaction at the peroxidic oxygen.

I.3.3 Autoxidation

Many organic compounds react with atmospheric oxygen to produce oxygenated compounds such as hydroperoxides, peroxides, alcohols, ketones, aldehydes, epoxides, and acids. The series of steps that lead to the formation of these products is called autoxidation. Autoxidation proceeds by the general Scheme shown below.

Scheme 2

Initiation: Production of radicals

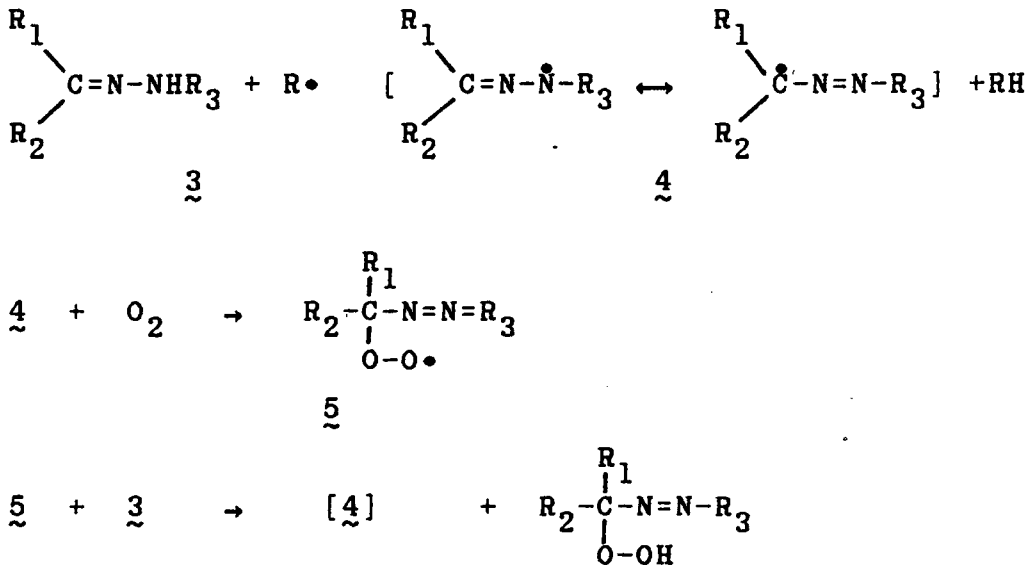
Propagation: $R\bullet + O_2 \rightarrow ROO\bullet$

$ROO\bullet + RH \rightarrow ROOH + R\bullet$

Termination: $2ROO\bullet \rightarrow$ non-radical products

Pausacker[30] and Criegee and Lohaus[31] were the first to suggest a radical chain mechanism for the autoxidation of hydrazones (Scheme 3).

Scheme 3



The first step in the autoxidation involves the hydrogen abstraction from the hydrazone by an initiator radical. The resonance stabilized hydrazyl radical reacts with oxygen to produce the α-azoperoxy radical which then abstracts hydrogen from the starting hydrazone producing the α-azohydroperoxide and another hydrazyl radical.

Autoxidation is often a spontaneous detrimental process by which new molecules are produced upon incorporation of atmospheric oxygen. Many antioxidants have been developed to prevent oxidative degradation. These antioxidants fall into

two categories. The first are chain breaking antioxidants. These are usually hindered phenols and aromatic amines which interrupt the radical chain process by scavenging chain propagating alkylperoxyl radicals.

$$ROO\bullet + AH \rightarrow ROOH + A\bullet \quad (17)$$

$$ROO\bullet + A\bullet \rightarrow ROOA \quad (18)$$

The second category are the preventative antioxidants which prevent or inhibit initiation of the radical chain reaction. Preventative antioxidants include metal ion deactivators, UV light deactivators such as o-methylbenzophenone and peroxide decomposers such as organic sulfur compounds.

I.3.4 Free Radical Rearrangements

Free radical rearrangement is the unimolecular reaction of organic radicals which leads to isomeric radicals. Radical rearrangements have been reviewed by Walling,[32] Freidlina,[33] and more recently by Wilt[34] and Surzur[35a], Beckwith[35b]. Rearrangements involving group migration will be discussed in this section.

I.3.4.1 Group Migrations

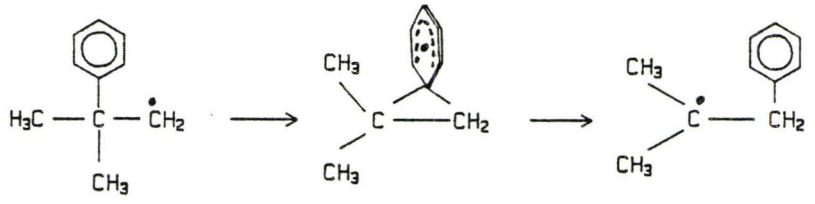
Group migrations may be represented by the general equation below.

$$ABC_n\overset{\bullet}{D} \longrightarrow \overset{\bullet}{B}C_nDA \qquad (19)$$

The most common migrations involve a 1,2-shift (n=0 in equation 19). Also known are 1,4-shifts (n=2) and 1,5-shifts (n=3). The activation energy for the rearrangement must be less than 15 kcal mol^{-1} in order for the migration to compete with other radical destroying processes. The direction of migration depends upon the thermodynamic stability of the rearranged versus the unrearranged species.

The 1,2-shifts are more common than the 1,3-, 1,4-, or 1,5-shifts. The highly strained 3-membered transition state in the 1,2-shift would tend to disfavour the 1,2-shift. The factor which overcomes the ring strain is the amount of time the reacting centers are in close proximity in a molecule that can undergo a 1,2-shift. The A-C distance in a molecule ABC is independent of conformation whereas the longer the acylic system is (as in the 1,3-, 1,4-, 1,5-systems), the larger the number of conformations which are available where the reacting centers will be too far apart.

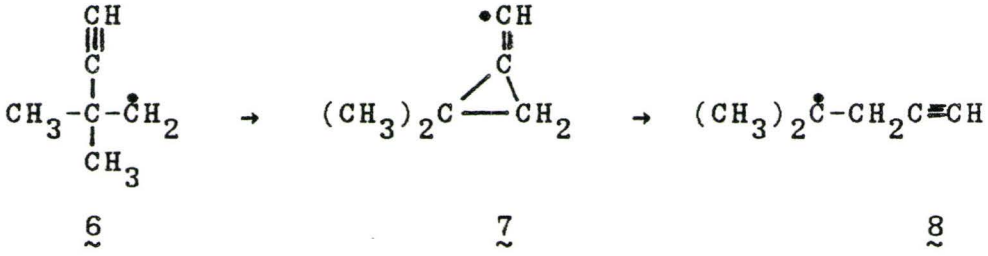
The first identified radical rearrangement was the neophyl rearrangement as studied by Urry and Karasch.[36]



(20)

The rearrangement has been shown to be intramolecular[37] although the spiro[2.5]octadienyl radical intermediate is so short-lived that it has not been observed.

Vinyl groups are known to migrate via a 1,2-shift. Warkentin and Ingold[38] studied the rearrangement of the 2,2-dimethyl-3-buten-1-yl radical(6) to the 1,1-dimethyl-3-buten-1-yl radical(8) via the cyclopropylcarbinyl radical(7) as an intermediate (equation 21).



(21)

6 7 8

The rate constant was found to be 4.3×10^7 sec^{-1} at 25°C. Such rearrangements are potential steps in synthetic sequences. The rate determination means that this system can be used as a "radical clock" for measuring the rates of other radical processes.

I.3.4.2 Free Radical Clocks

Radical isomerization reactions can be used to calculate the rate constants of radical-molecule reactions. If during a radical-molecule reaction there is a competing radical isomerization and the rate of isomerization is known then the rate constant of the radical-molecule reaction can be calculated by analysis of the ratio of the rearranged and unrearranged products. Griller and Ingold[39] have suggested that these rates of radical isomerization are in essence "radical clocks" that can be used to time the radical molecule reaction.

To avoid the problems associated with timing a 100 m dash with a calendar or the passage of years with a stopwatch, it was necessary that a whole class of radical clocks be available to cover a wide range of time scales. The order of magnitude of the clock must be suited to the estimated rate constant of the radical molecule reaction of interest. Griller and Ingold[36] have established the rate constants by which thirteen primary radicals isomerize. These rate constants at 25°C span more than seven orders of magnitude. The authors have called this calibrated collection of radical clocks a "horlogerie" which in French means a small store where clocks can be obtained. They have established another horlogerie containing secondary, tertiary and

heteroatom-centered radicals whose rate constants also span seven orders of magnitude. Mathew and Warkentin[40] have recently calibrated the cyclopropylmethyl to 3-buten-1-yl radical isomerization over the convenient temperature range of 30-89°C.

I.4. Organic Hydroperoxides

The synthesis of organic hydroperoxides has been extensively reviewed.[41] Organic hydroperoxides can be synthesized from alkanes using hydrogen peroxide, molecular oxygen, ozone, or by the hydrolysis of organic peroxides.

These compounds undergo five general types of homolytic reactions:

Unimolecular homolysis:

$$ROOH \xrightarrow{\Delta \text{ or } h\nu} RO\bullet + \bullet OH \qquad (22)$$

Bimolecular Homolysis:

$$\begin{array}{l} H\text{-}O\text{-}OR \\ \vdots \quad \vdots \\ RO\text{-}O\text{-}H \end{array} \rightarrow RO\bullet + H_2O + RO_2\bullet \qquad (23)$$

Molecule Assisted Homolysis (MAH)

$$A + ROOH \rightarrow \bullet AOH + RO\bullet \qquad (24)$$

Hydrogen abstraction:

$$R'\bullet + ROOH \rightarrow R'H + ROO\bullet \qquad (25)$$

Radical Substitution at Oxygen:

$$ROOH + R\bullet' \begin{cases} \rightarrow ROR' + \bullet OH \\ \rightarrow R'OH + RO\bullet \end{cases} \qquad (26)$$

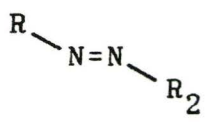
Research by Hiatt and Irwin[42] using hydroperoxides at low concentrations (0.01-0.001 M in toluene) indicated that the rate of unimolecular decomposition (equation 22) was very slow. The rate constant of t-BuOOH was found to be 2.6×10^{-5} sec^{-1} at 180°C. Hiatt[43] suggested that any decomposition that is faster than this would have to be due to some other reaction. The major process in the thermal decomposition of hydroperoxides at low concentrations is attack by free radicals at oxygen or hydrogen. At higher concentrations of hydroperoxide (>0.01 M in toluene), the major process becomes a bimolecular decomposition of the α-hydroperoxydiazene as shown in equation 23.

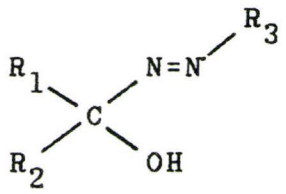
Organic hydroperoxides also undergo non-radical reactions including the oxidation of many organic compounds and the production of dialkyl and diacyl peroxides (Equation 27).

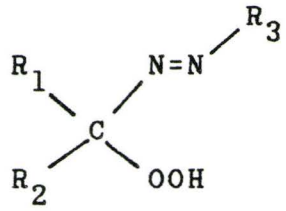
$$ROOH + R'X \rightarrow ROOR' + HX \qquad (27)$$

I.5. Azo Compounds

The chemistry of azo compounds dates back to 1909[44]. There have been a number of reviews on the chemistry of azo compounds published.[45-50] The categories of azo compounds that will be discussed are the following:

i)  acyclic azo alkanes

ii)  α-hydroxydiazenes (or α-azocarbinols)

iii)  α-hydroperoxydiazenes (or α-azohydroperoxides)

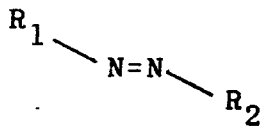
I.5.1 Acyclic Azoalkanes

Studies have been done to determine if acyclic azoalkanes decompose via a one-step process (equation 28) or by a two-step process (equation 29).

$$R\text{-}N{=}N\text{-}R' \rightarrow R\bullet + N_2 + R'\bullet \quad (28)$$

$$R\text{-}N{=}N{=}R' \rightarrow R\bullet + \bullet N{=}N\text{-}R' \rightarrow N_2 + R'\bullet \quad (29)$$

Ramsperger[57] made the first attempt to address this question of the mechanism of decomposition. He measured the activation energy of 9a and 9b. He then hypothesized that if the azo



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9a, $R_1=R_2=CH_3$; 9b, $R_1=R_2=iPr$; 9c, $R_1=CH_3$; $R_2=iPr$

alkane decomposed by a one-step mechanism then the activation energy of 9c should be between the activation energy of 9a and that of 9b. However, if the reaction proceeded by the two-step mechanism then the first bond to break would be the weaker isopropyl bond and the activation energy of 9c would be very close to that of 9b. The results of his studies are shown in Table 1.

Table 1

Energies of Activation for Decomposition of 9

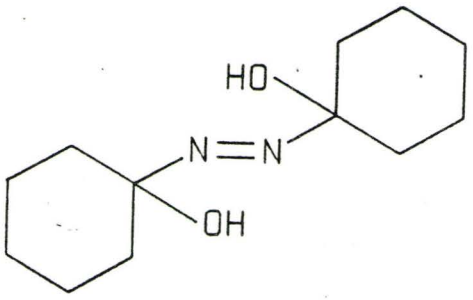
	R_1	R_2	E_a(kcal mol^{-1})[57]	Recent Value[52]
9a	CH_3	CH_3	51.2	
9b	i-Pr	iPr	40.9	47.9
9c	CH_3	i-Pr	47.5	

Ramsperger's results indicated a one-step decomposition. Recent work however, has shown that Ramsperger's energy of activation for 9b was incorrect. The best current value for the activation energy for 9b is 47.9 kcal mol^{-1}.[52] This

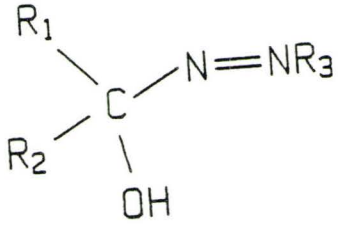
indicates that the mechanism of decomposition is a two-step process (equation 29). Research by Crawford,[53] Engel and Bishop,[54] Engel and Gerth,[55] and Seltzer[56] all fortify the position of a two-step mechanism for the decomposition of symmetrical and unsymmetrical acyclic azo compounds.

I.5.2 α-Hydroxydiazenes

α-Hydroxydiazenes (or α-azocarbinols) were first synthesized in 1963. Schmitz and co-workers[57] synthesized 1,1'-dihydroxyazocyclohexane. Studies[58] began in 1969



on the then rare α-monohydroxydiazenes (10).



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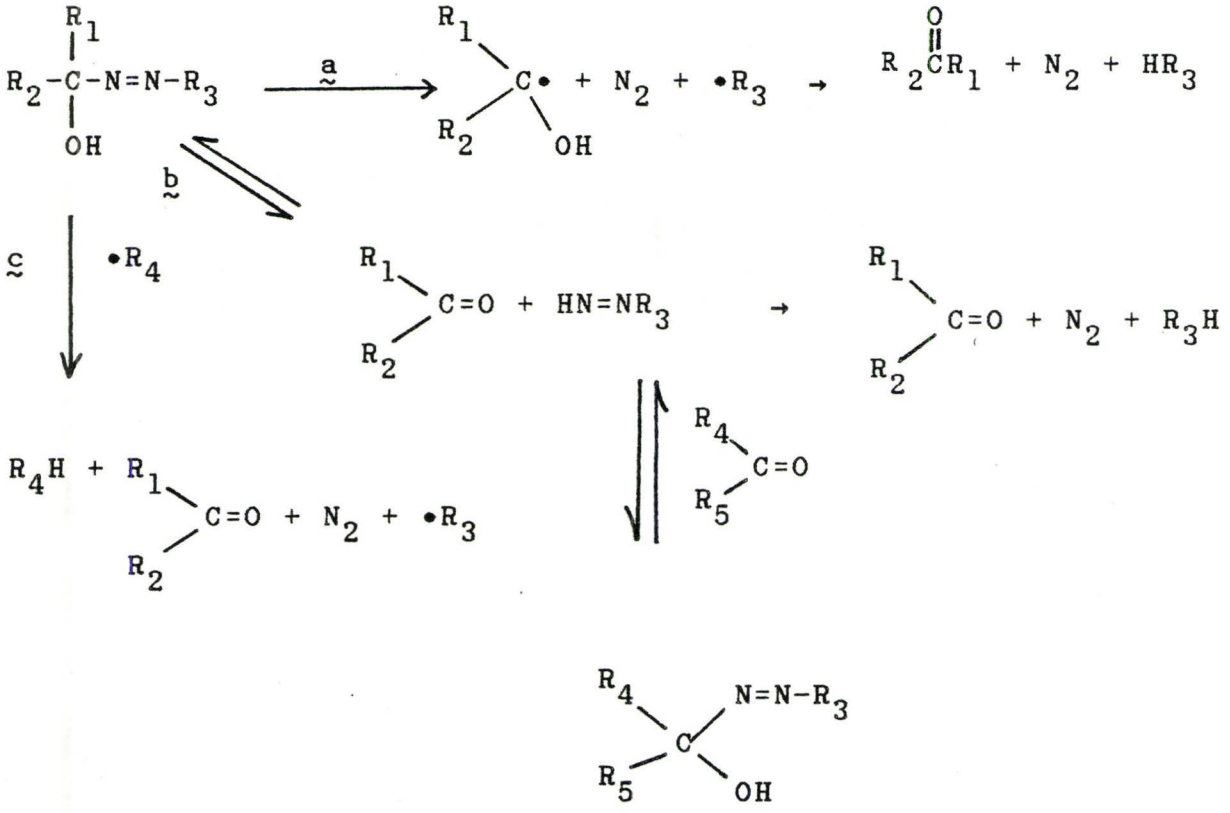
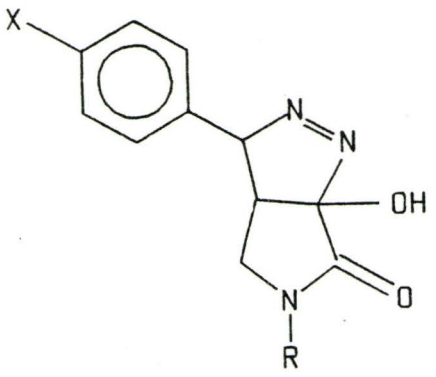
These compounds have been shown to undergo three main types of chemistry (Scheme 4).

Scheme 4



Southwick and co-workers[59] suggested that their compounds (11) underwent a normal unimolecular decomposition (mechanism a, Scheme 4) and produced ketyl radicals and alkyl (or aryl) radicals which disproportionated in the cage.



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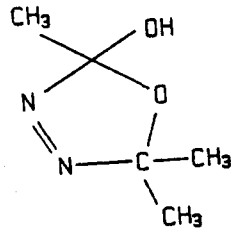
Hünig[58] demonstrated that α-hydroxydiazenes could undergo a reversible dissociation yielding carbonyl compounds and a diazene (mechanism b, Scheme 4). Under strongly alkaline conditions the intermediate diazene ($HN=NR_3$) can lose a proton becoming nucleophilic and can react with another ketone producing a new α-hydroxydiazene.

Warkentin and Knittel[26,60] studied the decomposition of 1.



$$+(CH_3)_2COCCH_3 \quad N_2 + (CH_3)_2CHOCCH_3 + (CH_3)_2COCCH_3 \qquad (30)$$

They proposed and proved that oxadiazoline 1 underwent a bimolecular decomposition induced by free radical attack at the hydroxyl hydrogen (mechanism c, Scheme 4). Evidence that a radical reaction was occurring included:

i) the reaction started when heated to 60°C, but could not be stopped by cooling back down to room temperature

ii) inhibition of the reaction by triphenylstannane, a known hydrogen donor;

iii) spin trapping of 2-acetoxy-2-propyl radical by nitrosobenzene;

iv) reaction of 1 with various alkenes lead to hydroalkylation products and;

v) the decomposition of 1 was initiated by stable free radicals.

Warkentin, Chang, and Profetto[60] showed that acyclic α-hydroxydiazenes also decompose by radical attack at the hydroxyl hydrogen. Ordinarily the abstraction of hydroxyl hydrogen in solution is difficult. It has been suggested[20,26,61,62] that these reactions are facilitated by the stability of molecular nitrogen and the stability of the carbonyl group which lowers the free energy of the transition state. It was proposed that the mechanism of induced homolysis must involve the concerted rupture of the hydrogen-oxygen and at least one of the carbon-nitrogen bonds.

The synthetic utility of the α-hydroxydiazenes has been demonstrated by the numerous hydroalkylations,[19,26,63] hydrophenylations and hydro-1-alkenylations[60] of olefinic substances. It is often impractical to add reagent X-Y to an unsaturated system due to the adverse thermochemistry of the chain carrying abstraction step. The first step in the addition of R-H to an alkene (Equation 31) involves the formation of a σ-bond and the loss of a π-bond. Consequently, this step is usually exothermic and fast.

$$R\bullet + CH_2{=}CHY \longrightarrow RCH_2\dot{C}HY \qquad (31)$$

$$RCH_2\dot{C}HY + H{-}R \longrightarrow RCH_2CH_2Y + R\bullet \qquad (32)$$

In equation 32 a σ-bond is being exchanged for another σ-bond. This step would be approximately thermoneutral. The product of hydroalkylation is often not obtained because other reactions such as β-scission, disproportionation, cyclization, and polymerization can compete with the hydrogen abstraction reaction. α-Hydroxydiazenes, however, can lead to greatly increased yields of the hydroalkylation product.

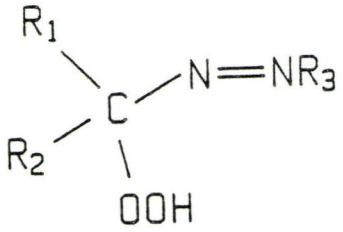
$$RCH_2\dot{C}HY + Me_2\underset{\underset{OH}{|}}{C}N{=}NR \longrightarrow RCH_2CH_2Y + CH_3\overset{\overset{O}{\|}}{C}CH_3 + N_2 + R\bullet \qquad (33)$$

The hydrogen abstraction, as shown in equation 33, is made much more favourable by the concerted formation of the C=O bond and the N≡N bond. The hydrogen abstraction step is now strongly exothermic and potentially fast. By using α-hydroxydiazenes there are lower amounts of the products from the competing reactions produced and more of the desired hydroalkylation product is formed.

I.5.3 α-Hydroperoxydiazenes

The structure of α-hydroperoxydiazenes (12) was first reported in 1951.[30,31] This class of chemical compounds has been used in aromatic hydroxylation reactions,[64,65] as an oxidizing agent for epoxidation of olefins[66] and in the

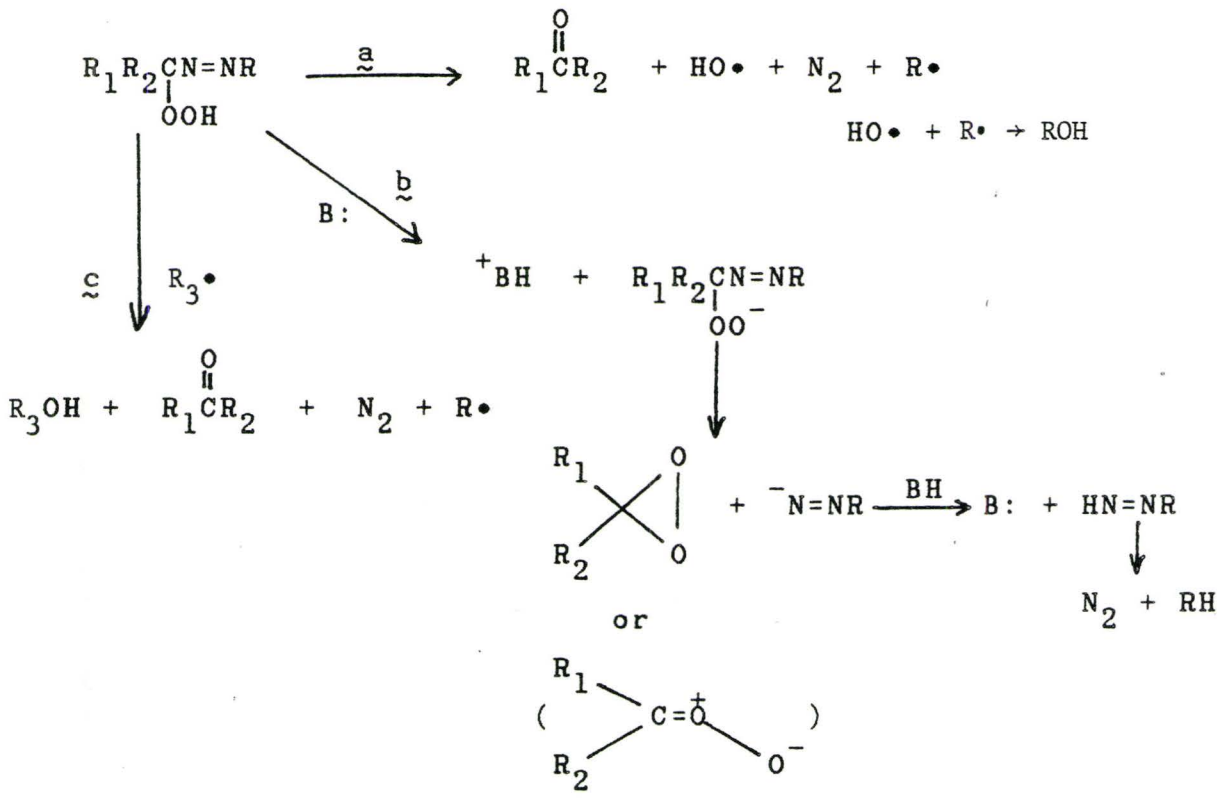
sulfoxidation of sulfides to sulfoxides.[67] α-Hydroperoxydiazenes can be reduced to α-hydroxydiazenes by the action of reducing agents such as triphenylphosphine,[68] lithium aluminium hydride[66] and the iodide ion.[69]



12

Three mechanisms have been proposed for the decomposition of α-hydroperoxydiazenes (Scheme 5). Tezuka[64,65] proposed a unimolecular route (mechanism a, Scheme 5). Tezuka also suggested that when the α-hydroperoxydiazene acted as an oxidizing agent in the epoxidation of olefins and in the sulfoxidation of sulfides, it decomposed via a base catalyzed route (mechanism b, Scheme 5). He has not, however, proved that the dioxirane (or carbonyl oxide) are the intermediates. Workers in this lab have independently suggested that

Scheme 5



α-hydroperoxydiazenes decompose by a unimolecular mechanism[70] and have also proposed and proved the radical chain abstraction of the hydroxyl group of the hydroperoxy functionality (mechanism c, Scheme 5). A fourth mechanism has also been proposed involving the radical chain abstraction of the hydroperoxyl hydrogen.

The induced decomposition of the α-hydroperoxydiazenes by radical chain abstraction of the hydroxyl group suggests that these compounds could be used as hydroxyalkylating agents for unsaturated systems, in an analogous manner to the way that α-hydroxydiazenes serve as hydroalkylating agents. In this work the hydroxyalkylation of various unsaturated systems by α-hydroperoxydiazenes was attempted.

II. RESULTS AND DISCUSSION

II.1 Hydroxyalkylation of Alkenes Using α-Hydroperoxydiazenes

α-Hydroperoxydiazene (15) was synthesized as shown in Scheme 6.

Scheme 6

$$NH_2NH_2 + CH_2{=}C(CH_3)CN \rightarrow NH_2NHCH_2CH(CN)CH_3 \quad (34)$$

(13)

$$13 + CH_3COCH_3 \rightarrow >NNHCH_2CH(CN)CH_3 \quad (35)$$

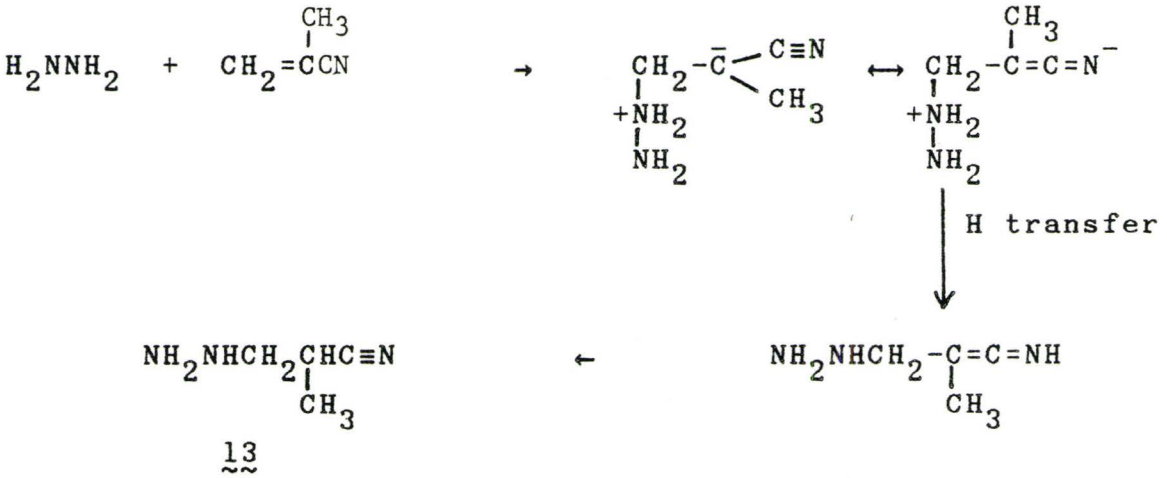
(14)

$$14 \xrightarrow[\text{benzene}]{O_2} Me_2C(OOH)N{=}NCH_2CH(CN)CH_3 \quad (36)$$

(15)

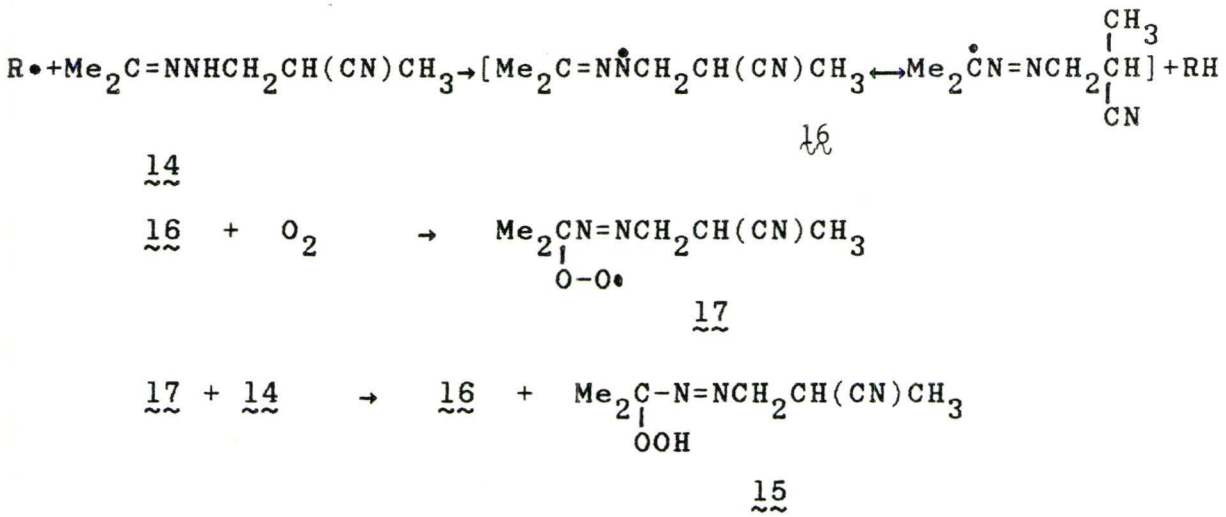
The formation of the 2-cyanopropylhydrazine (13) involves the Michael addition of hydrazine to methacrylonitrile (Scheme 7).

SCHEME 7



The formation of the α-hydroperoxydiazene (15) involves the autoxidation mechanism shown in Scheme 8.

Scheme 8



The spectral information and percent yields for compounds 13 through 15 are given in Table 2.

Table 2: ^{1}H NMR Spectra of Products 13 → 15

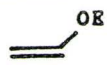
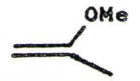
Compound	Yield (%)	^{1}H NMR[a]
$NH_2NHCH_2\underset{\underset{CN}{|}}{CH}CH_3$ 13	62	CH_3: 1.30 (d, 3H, J=7 Hz) $CH_2\underline{CH}$: 2.92 (m, 3H) NH : 3.55 (s, 3H)
$>C=NNHCH_2\underset{\underset{CN}{|}}{CH}CH_3$ 14 IR: CN at 2250 cm^{-1}	82	$CH\underline{CH_3}$: 1.30 (d, 3H, J=7 Hz) CH_3: 1.75 (s, 3H) CH_3: 1.93 (s, 3H) CH : 3.05 (m, 1H) CH_2: 3.25 (d, 2H, J=7 Hz) NH : 4.85 (s, br, 1H)
$\overset{CN}{\underset{|}{CH}}(CH_3)CH_2N=N-C(CH_3)_2OOH$ 15	76-95[b]	$CH-\underline{CH_3}$: 1.40 (s, 6H) CH_3: 1.45 (d, 3H, J-7 Hz) CH : 3·22 (sextet, 1H, J=7 Hz) CH_2: 4.0 (d, 2H, J=7 Hz) OOH : 8.60 (s, br, 1H)

[a] In $CDCl_3$ with internal Me_4Si. The numbers are δ values followed, in parenthesis, by the multiplicity, the relative signal intensity, and, where appropriate, by the coupling constants in Hertz.

[b] Based on iodometric titration of analogous α-hydroperoxydiazenes.[72]

α-Hydroperoxydiazene 15 was used to hydroxyalkylate ethyl vinyl ether and 2-methoxypropene. The results of these experiments can be found in Table 3.

Table 3: Products of Thermolysis of 15 in Ethyl Vinyl Ether and in 2-Methoxypropene.

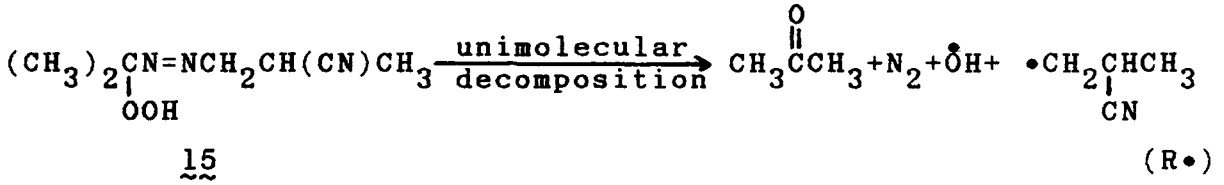
Reagent		
Structure of product	$CH_3\underset{\underset{CN}{|}}{CH}(CH_2)_2CHO$ **18**	$CH_3\underset{\underset{CN}{|}}{CH}(CH_2)_2COCH_3$ **19**
Yield (%)[a]	65	63
^1H NMR	1.32(d, 3H, J=7 Hz) 1.87(m, 2H) 2.67(m and t, 3H, $J_{triplet}$=7 Hz) 9.87(s, 1H)	1.27(d, 3H, J=7 Hz) 1.77(m, 2H) 2.13(s, 3H) 2.67(m and t, 3H, J_t=7 Hz)
MS(m/z)[b]	55[$(M-C_3H_3O)^+$]base peak 67[$(M-C_4H_5N)^+$] 82[$(M-CHO)^+$] 83[$(M-CO)^+$] 112[$(M+H)^+$]	46[$(M-C_3H_5N)^+$] 55[$(M-C_4H_6O)^+$] 58[$(M-C_4H_5N)^+$] 67[$(M-C_3H_6O)^+$] 126[$(M+H)^+$]
2,4-DNP mp (°C)	79-80°C	98-99°C
^1H NMR of 2,4-DNP	250 MHz 1.45(d,3H, J=5 Hz) 1.98(m, 2H) 2.72(m, 3H) 7.62(t, 1H, J=5 Hz) 7.81(d, 1H, J=9 Hz) 8.36(d, 1H, J=9 Hz) 9.12(s, 1H) 11.08(s, 1H)	1.43(d,3H, J=7 Hz) 2.02(m, 2H) 2.15(s, 3H) 2.67(m, 3H) 7.88(d, 1H, J=7 Hz) 8.36(m, 1H) 9.15(d, 1H) 11.05(s, 1H)
MS(m/z) of 2,4-DNP		55[$(M-C_{10}H_{10}N_4O_4)^+$] 305[M^+]

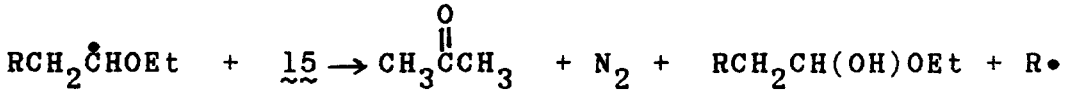
[a] Calculated by the addition of a standard to the reaction mixture followed by a comparison of the area under the peaks in the NMR spectrum.

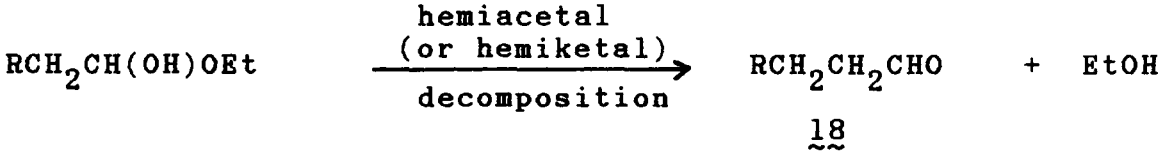
[b] Probable ion assignments in parenthesis; major ions are given.

Evidence that the addition proceeds by a radical chain mechanism includes the rapid decomposition at 50°C; the poor fit of kinetic data to the first order rate equation; the strong inhibition effect by 2,2,6,6-tetramethylpiperidin-N-oxyl;[70] the trapping of the intermediate radicals by 3,5-diphenyl-1-methyl-4-nitrosopyrazole (DMNP); and the characteristics of the products produced. Scheme 9 illustrates the mechanism of addition of 15 to the ethyl vinyl ether. The addition to the 2-methoxypropene would be similar.

Scheme 9







The α-hydroperoxydiazene undergoes unimolecular decomposition yielding R• which attacks the alkene, forming an adduct which then abstracts the hydroxyl group from 15. The hemiacetal (or hemiketal when the 2-methoxypropene is used) then decomposes giving the aldehyde (or ketone) product.

There is a possibility that the aldehyde (or ketone) products of the addition reaction could arise not from the hemiacetal (or hemiketal) decomposition but rather due to β-scission (equation 37).

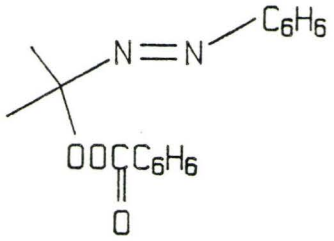
$$RCH_2\dot{C}HOEt \longrightarrow RCH_2\underset{\underset{O}{\|}}{CH} + \bullet CH_2CH_3 \qquad (37)$$

The ethyl radical formed would then attack the ethyl vinyl ether producing butyraldehyde (equation 38).

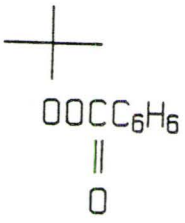
$$CH_3\dot{C}H_2 + CH_2{=}CHOEt \rightarrow CH_3(CH_2)_2\dot{C}HOEt \rightarrow CH_3(CH_2)_2\underset{\underset{O}{\|}}{CH} + \bullet CH_3CH_2 \qquad (38)$$

Butyraldehyde was not detected in the product mixture indicating that the aldehyde (or ketone) produced is formed by hemiacetal (or hemiketal) decomposition and not by β scission.

Warkentin and Nazran[7] studied the rates of thermal decomposition of compounds 20 and 21 in order to gain more



20



21

insight into the process of unimolecular decomposition of diazenes. If compound 20 decomposed by a process where the breaking of the peroxy O-O bond was the rate determining step, then it should have a rate constant of decomposition close to that of compound 21. The results of the experiment lead Warkentin and Nazran to estimate that at 10°C, compound 20 has a rate constant 10^8 times larger than that for 21. It was suggested that azoperesters must decompose by a concerted 2-bond or a concerted 3-bond mechanism to account for the greatly enhanced rate constant.

α-Hydroperoxydiazenes are also thought to decompose by a concerted 2-bond (equations 39,40) or a concerted 3-bond homolysis[72] (equation 41).

$$Me_2\underset{\underset{OOH}{|}}{C}N{=}NR \xrightarrow[\text{concerted}]{\text{slow}} CH_3\overset{\overset{O}{\|}}{C}CH_3 + \bullet OH + \bullet N{=}NR \qquad (39)$$

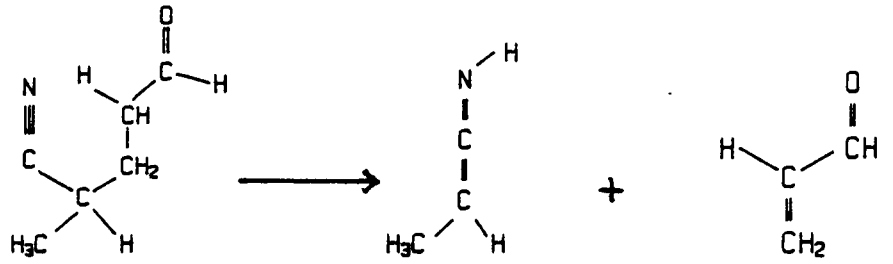
$$\bullet N{=}NR \xrightarrow{\text{fast}} N_2 + R\bullet \qquad (40)$$

The question as to whether the decomposition is 2-bond or 3-bond has not yet been fully settled.[73,74,75]

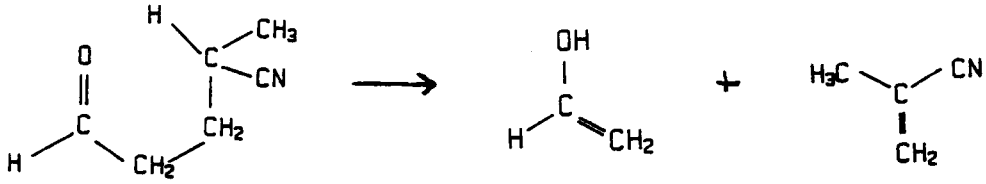
$$Me_2\underset{\underset{OOH}{|}}{C}N{=}NR \xrightarrow{\text{concerted}} CH_3\overset{\overset{O}{\|}}{C}CH_3 + \bullet OH + N_2 + R\bullet \qquad (41)$$

The abstraction of the hydroxyl group from the α-hydroperoxydiazene by the alkylated radical (see Scheme 9) leads to the induced decomposition of the α-hydroperoxydiazene. This is one of the chain carrying steps of the radical chain process. The rate of this step is greatly enhanced since it is a concerted 2-bond or 3-bond homolysis. A facile chain carrying step means that the chain length will be long which is desirable for a radical chain mechanism. A long chain length leads to low yields of unwanted termination products. The critical factor that makes the radical chain hydroxyalkylation possible is the enhanced rate of abstraction of the hydroxyl group during the chain carrying step.

The base peak at m/z 55, for aldehyde 18, is due to the McLafferty rearrangement of the compound (equation 42). The signal at m/z=67 can be explained in terms of a second McLafferty rearrangement (equation 43).

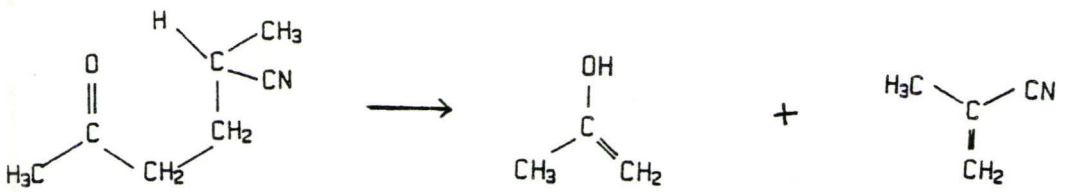


18 m/z=55 m/z=56 (42)



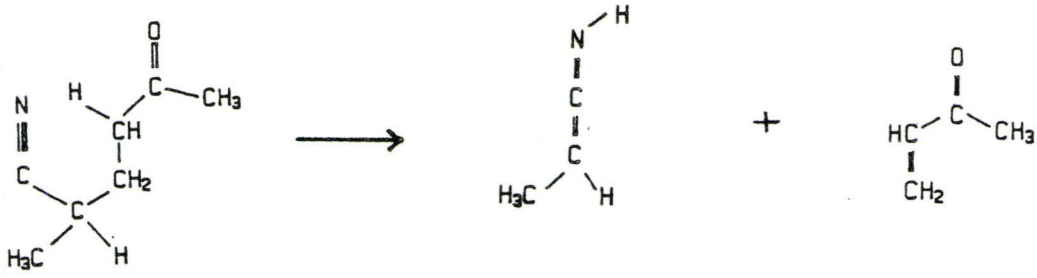
18 m/z=44 m/z=67 (43)

The signals in the mass spectrum for the ketone 19 at m/z=58,67,55 and 46 can also be explained in terms of the McLafferty rearrangement (equations 44,45).



(44)

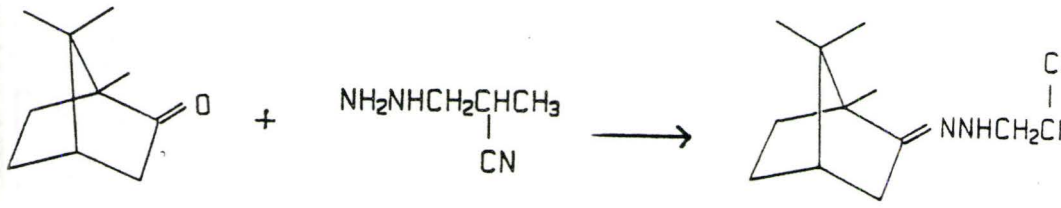
19 m/z=58 m/z=67



(45)

19 m/z=55 m/z=70

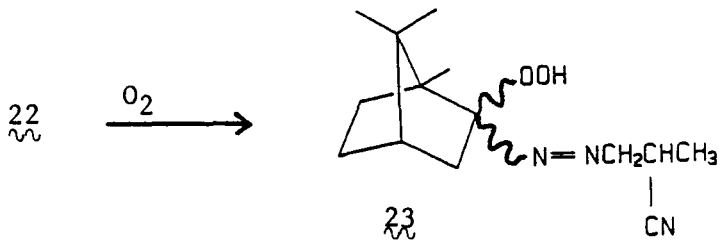
Compound 23 was synthesized (equation 46, 47) to see if it could hydroxyalkylate ethyl vinyl ether.



(46)

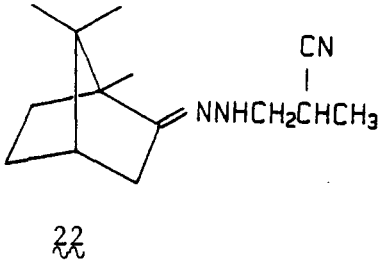
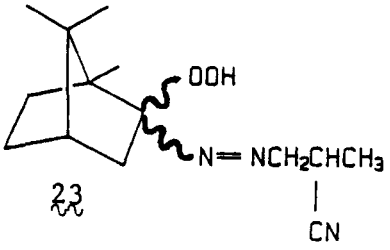
d-camphor 22

Compound 22 was converted to the hydroperoxide by autoxidation.



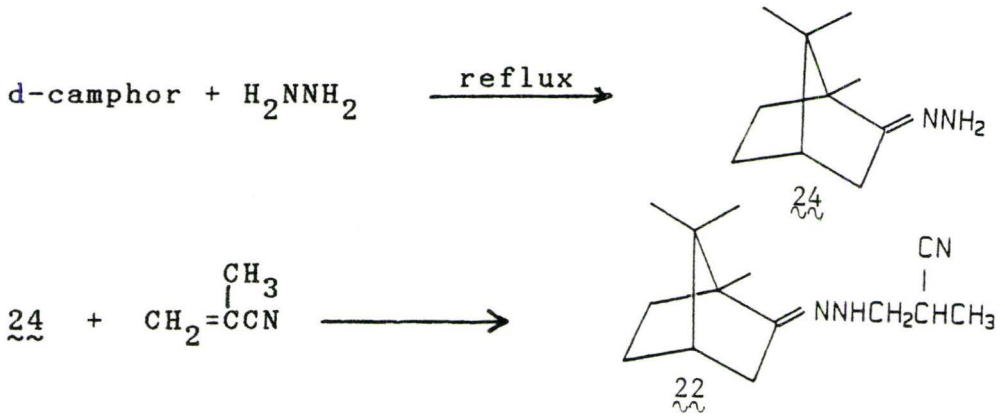
(47)

Table 4: ^{1}H NMR Spectra for Compounds 22, 23

Compound	^{1}H NMR
 22	0.75(s, 3H) 0.90(s, 6H) 1.26(d, 3H, J=7Hz) 1.65(m, 7H) 3.10(m, 3H) 4.55(br.s, 1H)
 23	0.74 (s, 1.5H) 0.76 (s, 1.5H) 0.85 (s, 1.5H) 0.95 (s, 1.5H) 1.12 (s, 1.5H) 1.20 (s, 1.5H) 1.36 (d, 3H, J=7 Hz) 1.90(m, 7H) 3.20 (m, 1H) 4.10 (d, 2H, J=7 Hz) 9.90 (br.s, 1H)

The low yield of hydrazone 22 (20%) suggested another route should be attempted to the hydrazone (Scheme 10).

Scheme 10



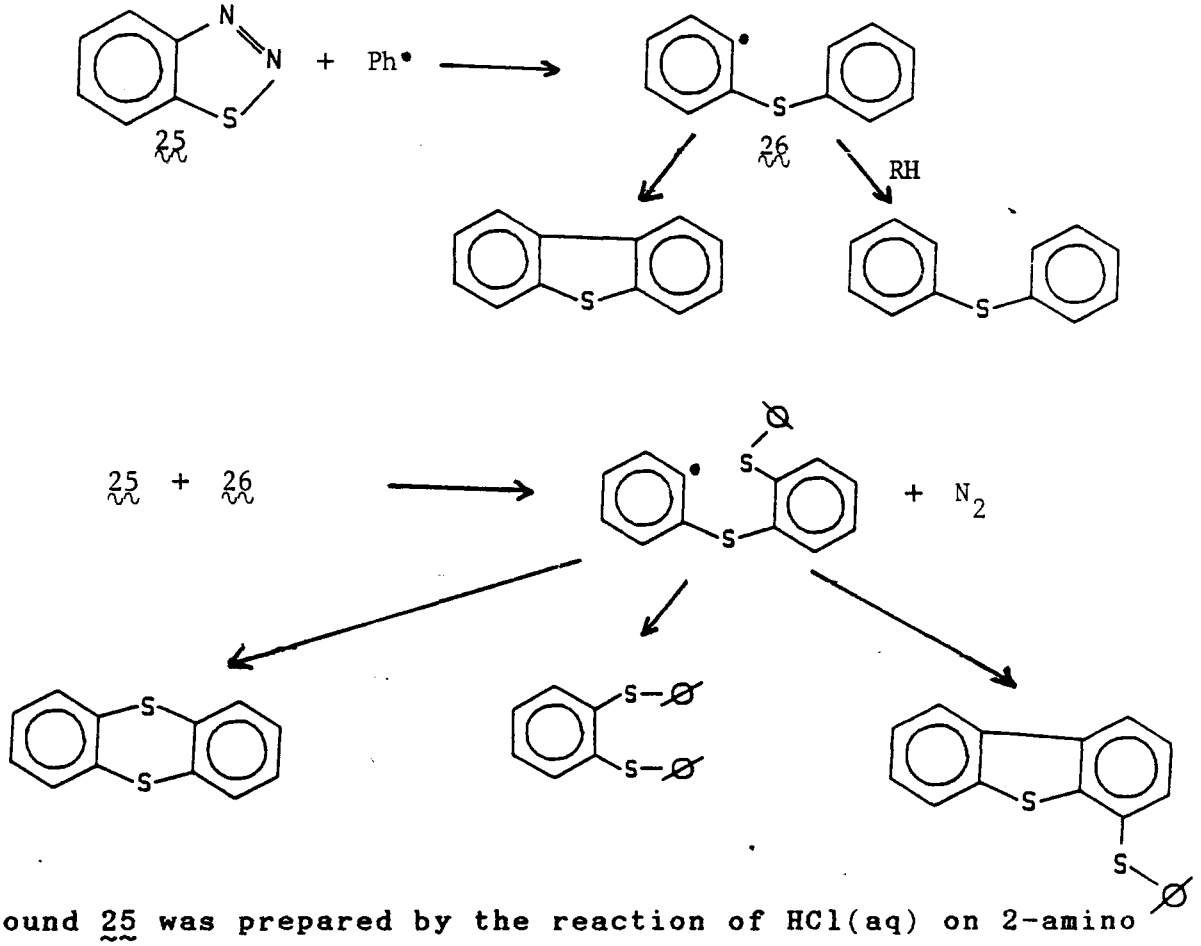
The camphor hydrazone (24) was produced in 67% yield: melting point 39-42°C (white crystals); ^1H nmr ($CDCl_3$) δ 0.75(s, 3H), 0.90(s, 6H), 1.65(m, 7H), 4.37(s, 2H). The first step of the synthesis was successful.

The synthesis of 22 by the Michael addition of 24 to methacrylonitrile was unsuccessful.

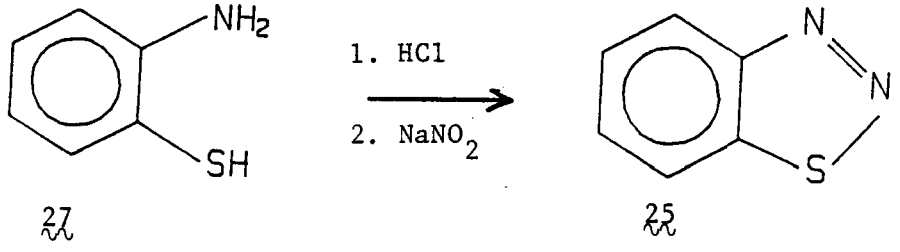
The thermolysis of 23 was run in ethyl vinyl ether at 80°C. A preparative GC collection was done on the reaction mixture. The major products were the expected aldehyde 18 (Yield 62%) and camphor. The mechanism of the hydroxyalkalation would be analogous to that shown in Scheme 9.

The hydroxyalkylation at a hetero atom double bond was also attempted. Compound 25 had been shown to undergo a radical chain addition according to Scheme 11.

Scheme 11



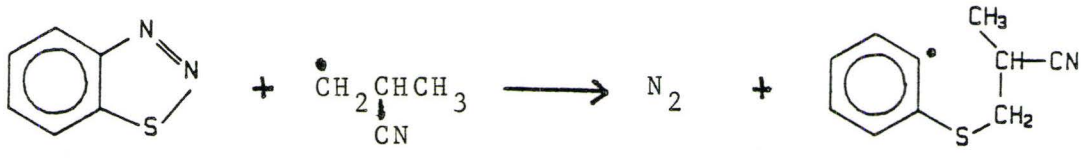
Compound 25 was prepared by the reaction of HCl(aq) on 2-amino thiophenol (27) followed by the addition of $NaNO_2$.



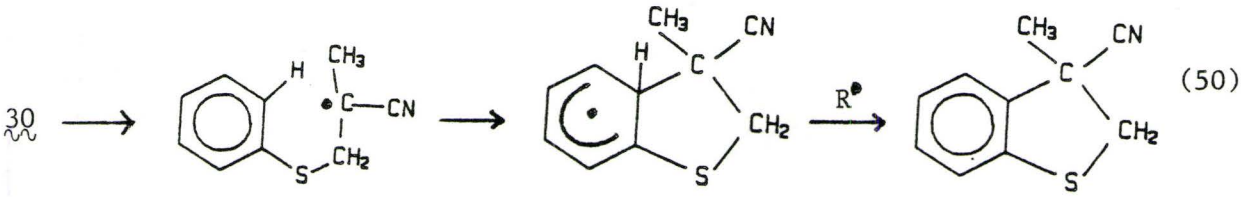
(48)

Compound 25 had a melting point of 35-36°C and the following ^1H nmr spectrum: δ7.60(m, 2H), 8.10(m, 1H), 8.60(m, 1H).

The addition reaction was attempted with α-hydroperoxydiazene 15 sealed in a tube with compound 25 dissolved in purified EtOAc. The tube was placed in the 80°C oil bath and analysis of the reaction mixture by analytical GC showed that the major product of the thermolysis was thianthrene 28. It was expected that the R group in 30 would cyclize to the aromatic ring according to equations 49, 50. Those reactions did not occur.



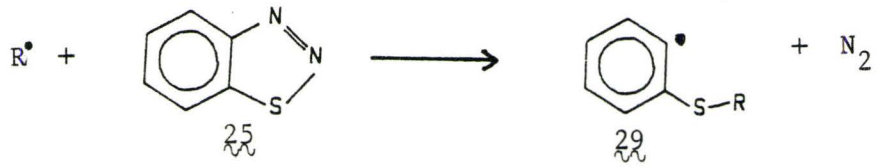
(49)

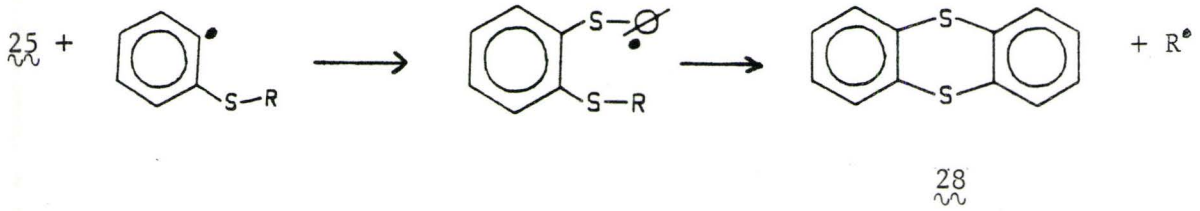


(50)

The preferred reaction under these conditions was the addition-elimination reaction of Scheme 12.

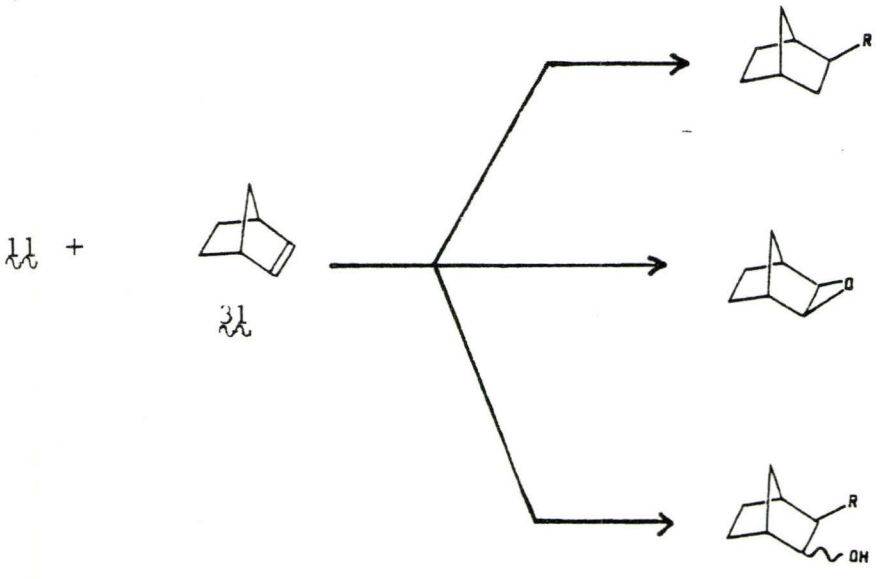
Scheme 12





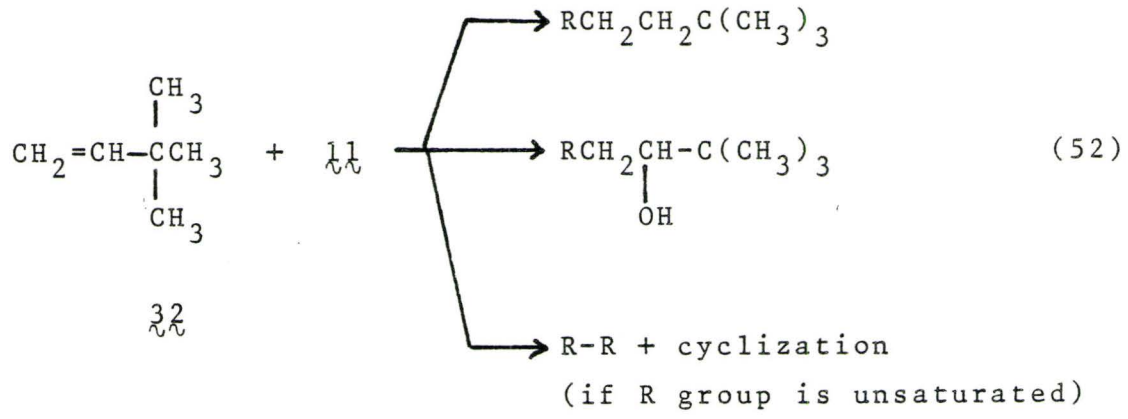
The radical (R•) presumably did add to compound 25 but was subsequently eliminated during the following addition-elimination reaction.

The hydroxyalkylation of norbornene (31) and t-butylethylene (32) by α-hydroperoxydiazenes was studied by Osei-Twum.[72] The following products were obtained (equations 51,52).



(51)

R = CH_2CF_3, $CH_2CH_2OCH_3$, $CH_2CH_2OC_6H_5$



(52)

The major product in the reaction of the α-hydroperoxydiazene with the norbornene was the hydroalkylation product, followed by large amounts of epoxide, and only small amounts (2-14%) of the hydroxyalkylation product. The major product in the reaction of the α-hydroperoxydiazene with t-butylethylene was the hydroalkylation product, followed by an appreciable amount of dimerization and cyclization products, and only about 5% hydroxyalkylation product. From the results of Osei-Twum's experiments and from the results of hydroxyalkylation of ethyl vinyl ether and 2-methoxyalkylation by 15, the following conclusions can be made about the hydroxyalkylation of alkenes using α-hydroperoxydiazenes:

1. For reactive, sterically unhindered alkenes there will be a high yield of hydroxyalkylation product;

2. For reactive, sterically hindered alkenes the reaction pathway is altered leading to hydroalkylation and epoxide formation;

3. For unreactive, sterically hindered alkenes there will be relatively high yields of hydroalkylation, cyclization, and dimerization products but only small amounts of hydroxyalkylation products. The hydroxyalkylation of olefins by α-hydroperoxydiazenes depends on the reactivity and structure of the olefin.

There are restrictions on the type of olefins that α-hydroperoxydiazenes can effectively hydroxyalkylate. Recently the synthetic utility of various α-hydroperoxy-diazenes was demonstrated as various olefins were hydroxyalkylated in yields of 65-75%.[70] α-Hydroperoxydiazenes have been found to be valuable synthetic agents, particularly on a small scale.

II.2 Rate Constant for H-Abstraction from an α-Hydroxydiazene

II.2.1 Introduction

α-Hydroxydiazenes have been used as initiators of free radical polymerizations.[71] They have also been used synthetically in the hydroalkylation or hydroarylation of alkenes by a radical chain mechanism.[18,19,61]

It is the relatively rapid rate of H-abstraction from the α-hydroxydiazene which makes these compounds good hydroalkylating reagents. The intermediate radical (*) can

Scheme 13

$$R\bullet + CH_2{=}CHY \rightarrow \underset{(*)}{RCH_2\dot{C}HY}$$

$$\underset{(*)}{RCH_2\dot{C}HY} + (CH_3)_2\underset{OH}{C}N{=}NR \rightarrow RCH_2CH_2Y + CH_3\overset{O}{\overset{\|}{C}}CH_3 + N_2 + R_2$$

$$RCH_2\dot{C}HY \longrightarrow \beta \text{ scission}$$

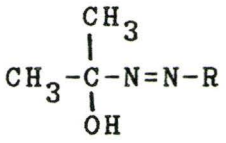
$$\longrightarrow \text{disproportionation}$$

$$\longrightarrow \text{cyclization (if R group is unsaturated)}$$

$$\longrightarrow \text{polymerization}$$

undergo four competing reactions. Only if the rate of H-abstraction is higher than the rate of the competing reactions will the desired hydroalkylation product be produced in good yield. If the rate constant of H-abstraction could be estimated, then hydroalkylation experiments could be better designed, using known rate constants for the likely competing reactions.

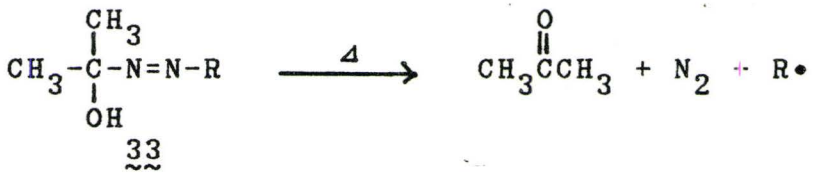
In order to determine the rate constant of hydrogen abstraction from an α-hydroxydiazene, an α-hydroxydiazene (33) was chosen so that there would be a competing reaction occurring by which the hydrogen abstraction could be timed.

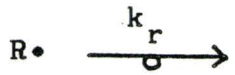


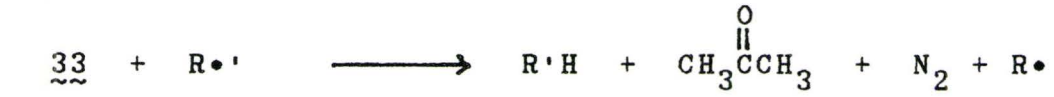
33

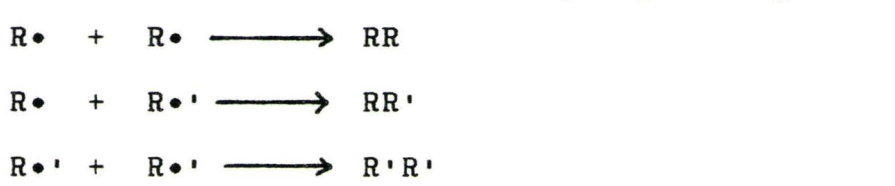
The competing reaction was the rearrangement of the abstracting radical.

Scheme 14









The rate of formation of RH would be

$$\frac{d[RH]}{dt} = k_H[R\bullet]\ [\underset{\sim\sim}{33}] \qquad (53)$$

The rate of formation of R'H would be

$$\frac{d[R'H]}{dt} = k_r[R\bullet] \qquad (54)$$

By combining equations 53 and 54

$$\frac{[RH\ ]}{[R'H]} = \frac{k_H[R\bullet]\ [\underset{\sim\sim}{33}]}{k_r[R\bullet]} \qquad (55)$$

or $$\frac{[RH]}{[R'H]} = \frac{k_H[\underset{\sim\sim}{33}]}{k_r} \qquad (56)$$

Solving for k_H;

$$k_H = \frac{k_r[RH]}{[R'H][\underset{\sim\sim}{33}]} \qquad (57)$$

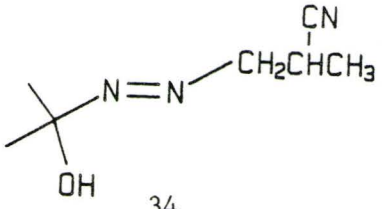
The rate constant for hydroxyl hydrogen abstraction from the α-hydroxydiazene could be determined if the following three general conditions could be met:

i) if the ratio of the unrearranged product to the rearranged product ($\frac{[RH]}{[R'H]}$) could be determined;

ii) if the concentration of the starting α-hydroxydiazene ([33]) was known and was kept fairly constant during the reaction; and

iii) if the rate constant for the rearrangement of the abstracting radical (k_r) was known or could be determined.

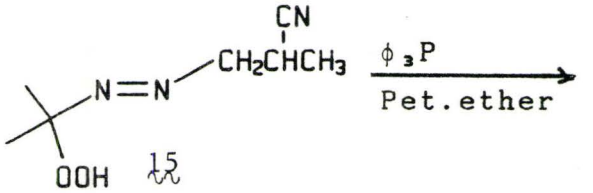
The specific α-hydroxydiazene (34) was chosen.



34

II.2.2 Synthesis

α-Hydroxydiazene 34 was synthesized by the action of triphenylphosphine on the α-hydroperoxydiazene 15. It has been suggested,[76,77] that this reaction proceeds via a polar rather than a radical mechanism.



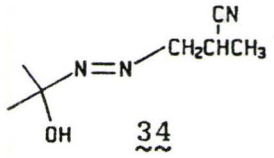
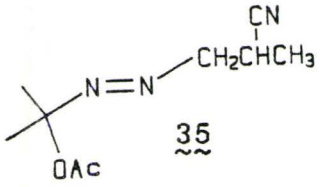
15

$$\xrightarrow[\text{Pet.ether}]{\phi_3P} \quad 34 + \phi_3P{=}O \qquad (58)$$

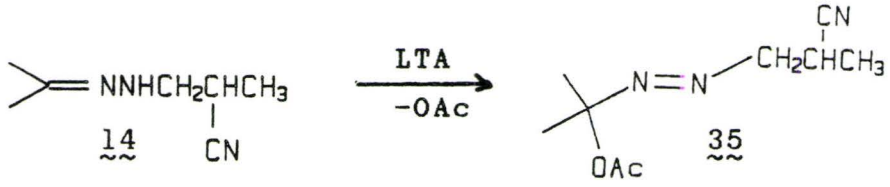
Attempts to synthesize 34 from 15 by the action of KI[69] proved unsuccessful. The ^1H NMR spectrum of the product indicated an impurity which could not be removed using bulb to bulb distillation, or column chromatography.

Another route to the α-hydroxydiazene was attempted where the acetone hydrazone (14) was converted to the corresponding azoacetate (35) by oxidation with lead tetraacetate (LTA) (equation 59). Table 5 contains spectroscopic data for compounds 34 and 35.

Table 5: Spectral Data for Compounds 34 and 35

Compound	H' NMR	% Yield	IR(cm^{-1})
 34	1.32(m,9H) 3.18(sextet,1H,J=7Hz) 3.98(d,s,3H,J_d=7Hz)	54[a]	3° alcohol: 3460, 1380, 1360, 1220 C≡N: 2200
 35	1.34(d,3H,J=7Hz) 1.50(s, 6H) 2.01(s, 3H) 3.13(sextet, 1H, J=7Hz) 3.95(d, 2H, J=7Hz)	71	

[a] Yield based on initial concentrations of the α-hydroperoxydiazene as calculated by analysis of the ^1H NMR spectrum of the α-hydroperoxydiazene/benzene solution.



(59)

The azoacetate 35 was then treated with CH_3Li in ether at -10°C followed by acidification with NH_4Cl solution. The expected α-hydroxydiazene was not obtained.

II.2.3 Thermolysis

When α-hydroxydiazene 34 was allowed to warm to room temperature or higher, it thermolyzed to give the products shown in equation 60.

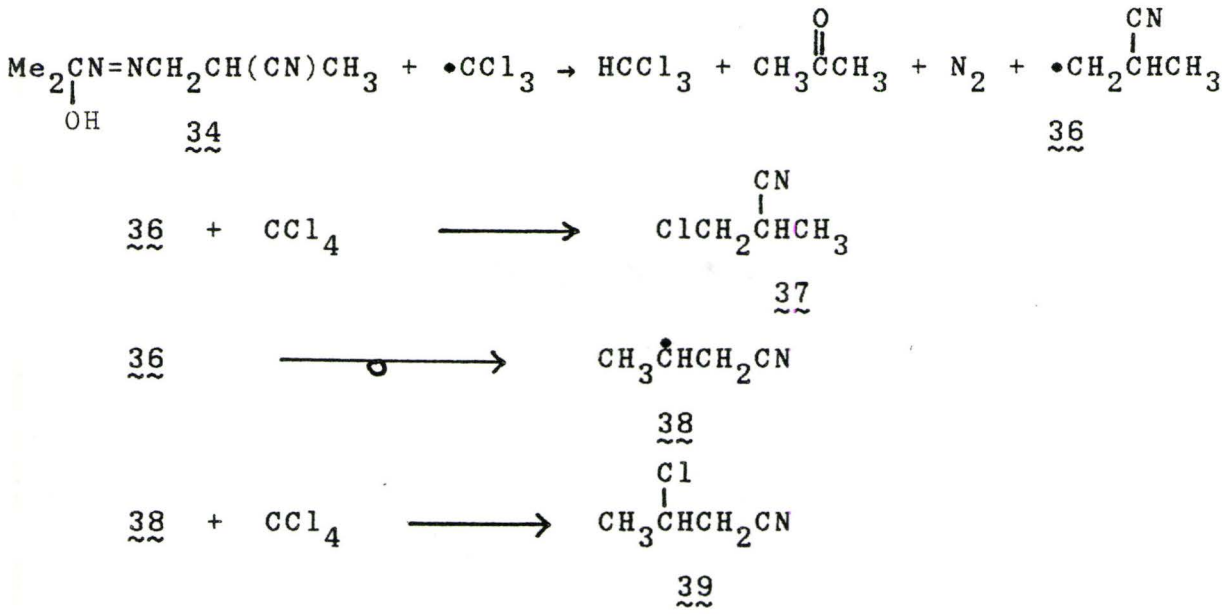
$$In\bullet + \underset{\underset{OH}{|}}{Me_2CN}{=}NCH_2CH(CN)CH_3 \xrightarrow[\Delta]{} InH + \underset{\underset{O}{\|}}{CH_3CCH_3} + N_2 + \bullet CH_2\underset{\underset{CN}{|}}{CH}CH_3 \qquad (60)$$

34 36

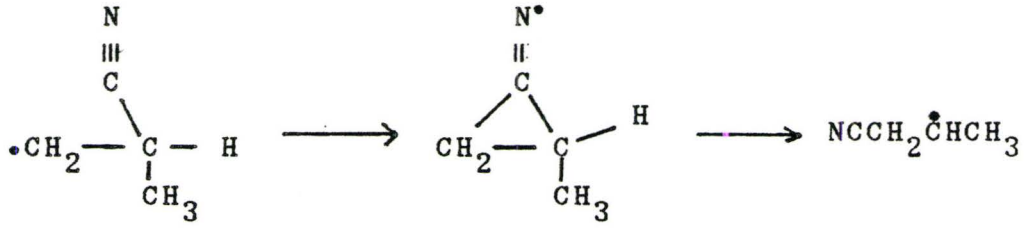
The 2-cyanopropyl radical (36) is very rare.[69] The usual location of the radical center in cyanoalkyl radicals is α to the cyano group because the effect of the cyano group is to lower the bond dissociation energy of the α C-H bond of a cyano alkane.[78] This bond would break preferentially during a radical hydrogen abstraction, placing the radical center α to, and not β to the cyano group, as it is in 36. The 2-cyanopropyl radical can be formed in this case because of the structure of α-hydroxydiazene 34.

There is a report[69] that when 34 was decomposed in CCl_4, two chlorine abstraction products were produced (Scheme 15).

Scheme 15



The 2-cyano propyl radical had apparently rearranged to produce the secondary radical (38) shown in equation 61.

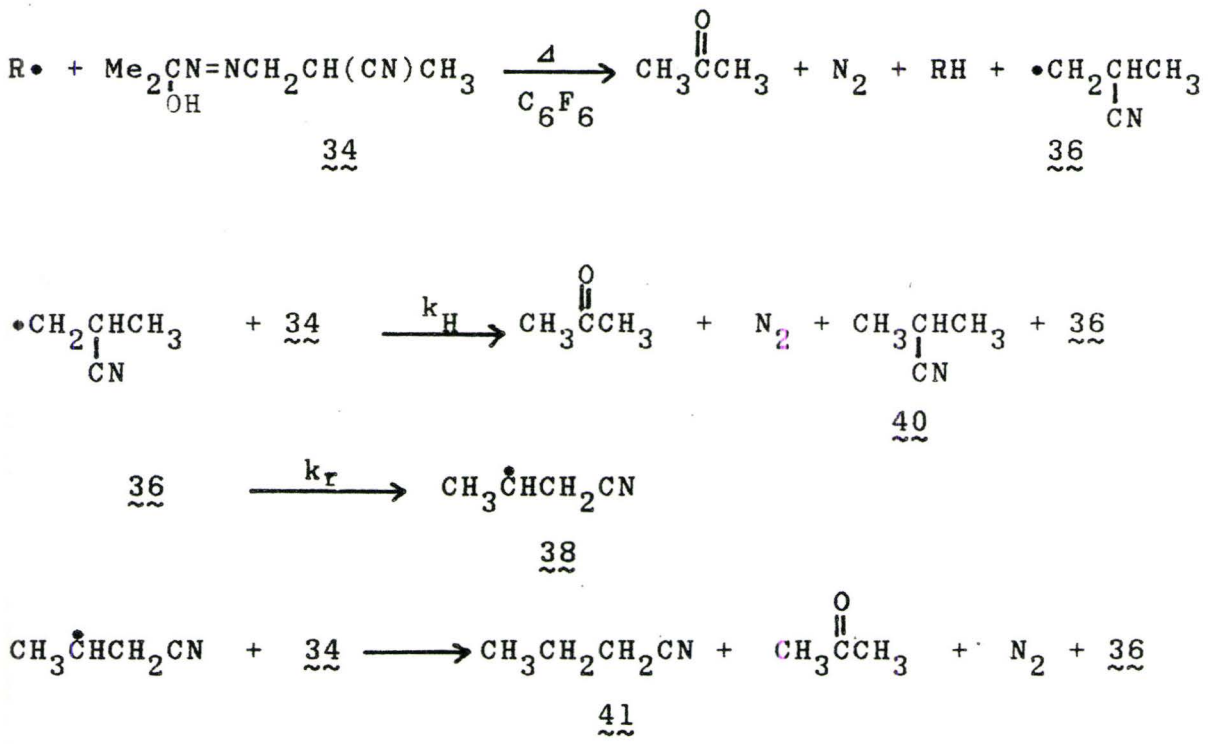


(61)

36 38

It was decided that the radical rearrangement (equation 61) might be used as the radical clock to determine the rate constant for hydrogen abstraction. α-Hydroxydiazene (34) was therefore thermolyzed in an inert solvent. The thermolysis was expected to proceed by Scheme 16.

Scheme 13



Certain conditions had to be met in order to use equation 57 to calculate k_H.

$$k_H = \frac{k_r[RH]}{[R'H][\underset{\sim\sim}{34}]} \qquad (57)$$

i) The ratio of the unrearranged product to the rearranged product had to be determined. This could be done by taking the ^1H NMR spectrum of the reaction products. Table 6 shows that the spectra of RH and R'H are distinguishable.

Table 6: ^{1}H NMR Spectra of 2-Cyanopropane (RH) and 1-Cyanopropane (R'H)

Compound	Boiling Point (°C)	^{1}H NMR
$CH_3CH(CH_3)CN$	102-104	1.30(d, 6H)
		2.69(m, 1H)
40 (RH)		
$CH_3CH_2CH_2CN$	115.5	1.07(t, 3H)
41 (R'H)		1.67(m, 2H)
		2.27(t, 2H)

The peaks that could be used to identify 40 in the reaction mixture would be the doublet at δ 1.30 (6H). The peaks that could be used to identify 41 would be the triplet at δ 2.27. There should be no interference from any of the other products of the reaction at these δ values.

In order to determine k_H it would be necessary to determine $\frac{[RH]}{[R'H]}$ as accurately as possible. The percent error would be reduced if the ratio were as near to 1 as possible. It can be seen from equation 57 that $\frac{[RH]}{[R'H]}$ is proportional to [34], and that the ratio of the products can be altered by changing the initial concentration of the α-hydroxydiazene.

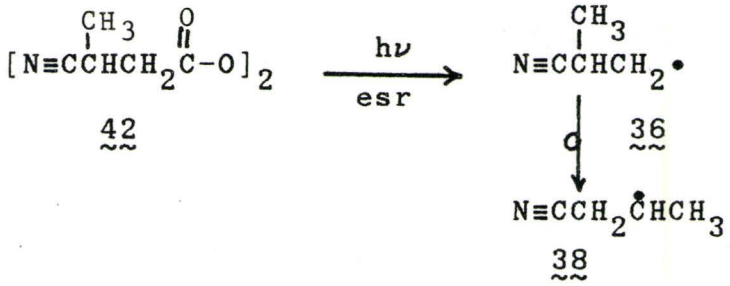
ii) The reaction would have to be run under pseudo first order conditions ([34] constant) for equation 57 to apply. In practice, a 10% variation in concentration is generally acceptable. In order to keep the reaction pseudo first order with respect to 34 the reaction was terminated after 10% completion.

NMR analysis of the peak heights of the products and the reactants would be used to determine when the thermolysis had reached 10% completion. When this point was reached the thermolysis would be quenched by the addition of an excess of $BrCCl_3$. The tube would be then resealed and the thermolysis continued. RH and R'H would not be formed after the addition of $BrCCl_3$ because the rate constant for Br extraction is much higher than that estimated for H–abstraction. After the addition of the $BrCCl_3$ any R• (or R•') formed would be scavenged as in equation 62.

$$R\bullet + BrCCl_3 \longrightarrow RBr + \dot{C}Cl_3 \qquad (62)$$

The RBr (or R'Br) would be higher molecular weight products which could be easily separated from the product mixture.

iii) If k_r could be determined then all four variables in equation 57 would be known and k_H could be determined. Electron Spin Resonance could be used to determine k_r. Compound 42 would rearrange in an ESR cavity as shown in equation 63.



(63)

At low temperatures the rearrangement of 36 → 38 would be very slow and the ESR spectrum would indicate that 36 was the main product. At high temperatures the rearrangement would be more facile and the ESR spectrum now would show 38 as the major product. The reaction could then be run at intermediate temperatures giving both spectra. By integrating the peak heights the ratio of 36:38 would be used to determine the rate constant for the rearrangement which would then serve as a radical clock to time the rate of hydrogen abstraction from the α-hydroxydiazene 34. The role of a competing intramolecular radical reaction as a radical clock has lately been studied intensively.[38-40,79-82] See the Introduction for more information on radical clocks.

The results for the thermolysis reactions are shown in Table 7.

Table 7: Results of Thermolysis Reactions in C_6F_6

Solvent	[34] initial (M)	Results[a]
C_6F_6	1.23	RH found, No R'H found
C_6F_6	0.602	RH found, No R'H found
C_6F_6	0.534	RH found, No R'H found
C_6F_6	0.390	RH found, No R'H found
C_6F_6	0.182	RH found, No R'H found

[a]Results based on GC, GC/MS, MS analysis of the reaction mixture. Authentic RH and R'H samples were co-injected into the analytical GC.

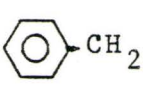
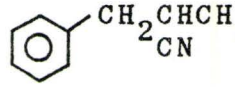
The initial concentration of the α-hydroxydiazene was lowered in steps from 1.23M to 0.182 M in an attempt to increase the concentration of R'H in the reactants (since $[R'H] \alpha \frac{1}{[34]}$). The rearranged hydrogen abstraction product was not found, even at 0.182 M in hexafluorobenzene. There was a lower limit on the initial concentration of 34 that could be used. It was necessary to have a low initial concentration of

34 in order to raise the concentration of R'H, however, this also lowered the concentration of the products. Since the reaction was only run to 10% completion and the products ideally would be in a 1:1 ratio, this meant that the expected concentration of RH and R'H would be 1/20th that of the initial concentration of the starting α-hydroxydiazene making it increasingly difficult to detect the small quantities of RH and R'H produced. The reaction was scaled to larger sealed tubes (in an attempt to increase the amount of RH and R'H produced) but still no R'H was detected. According to a previously published report[69] the radical 36 rearranged quickly in CCl_4. It should have rearranged under these conditions also.

The thermolysis was then carried out in purified benzene to see if it was the solvent (C_6F_6) that was interfering with the production of R'H. The results (Table 8) indicated that

Table 8: Results of Thermolysis Reactions in C_6H_6

Solvent	[34] initial (M)	Results
C_6H_6	0.065	RH; R• attack on benzene
C_6H_6	0.042	RH; R• attack on benzene

RH was produced (semi-preparative GC collection, followed by FT-NMR) and the product of attack of R• on the solvent (GC/MS m/z=91[]$^+$; m/z=145 []$^+$). Benzene was not an inert solvent for the thermolysis. The radical did not rearrange as it preferentially attacked the solvent.

It was decided to check the results of the report[69] that indicated that radical 36 rearranged in CCl_4 because the rearranged product had not been detected in reactions of 34 in either C_6F_6 or C_6H_6.

Samples of the unrearranged (37) and rearranged (39) chlorides were synthesized according to equations 64 and 65.

$$CH_2=C(CN)(CH_3) \xrightarrow[0°C]{HCl(g)} CH_2(Cl)-CH(CN)-CH_3 \qquad (64)$$

37

Compound 37 was produced by the anti-Markovnikov addition of HCl to methacrylonitrile. Table 9 lists the ^1H nmr spectra of 37 and 39.

$$CH_2=CHCH_2CN \xrightarrow[0°C]{HCl} CH_2(CN)-CH(Cl)-CH_3 \qquad (65)$$

39

Table 9: ^{1}H NMR For 1-Chloro-2-cyanopropane and 1-Cyano-2-chloropropane.

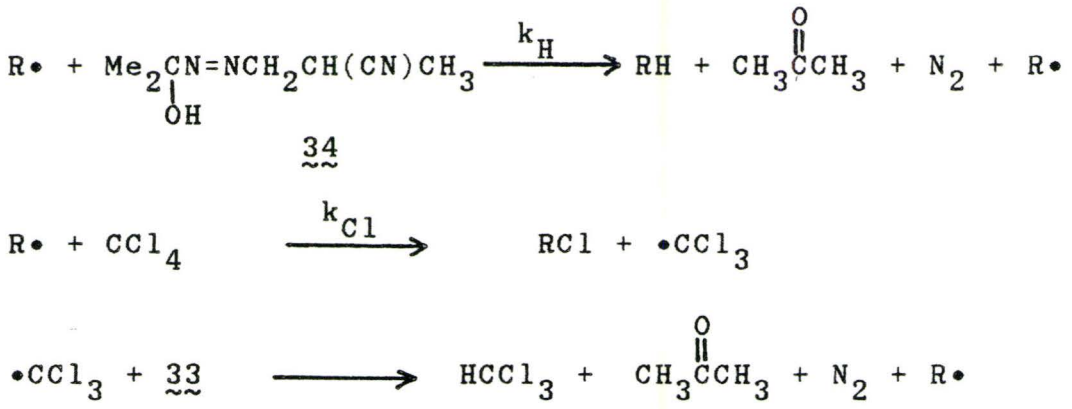
Compound	^{1}H NMR
$CH_2(Cl)-CH(CN)-CH_3$	1.44(d, 3H, J=7Hz)
	3.06(sextet, 1H, J=7Hz)
37	3.67(d, 2H, J=7Hz)
$CH_2(CN)-CH(Cl)-CH_3$	1.65(d, 3H, J=7Hz)
	2.77(d, 2H, J=7Hz)
39	4.23(sextet, 1H, J=7Hz)

Samples of 34 in CCl_4 (0.3136 M and 0.2839 M) were thermolyzed at 80°C to 100% completion. Analysis of the products indicated that 1-chloro-2-cyanopropane (RCl, 37) and 2-cyanopropane (RH, 39) were the major products in the ratio 1.7:1 (for 0.283 M).

It was shown, using these authentic samples, that the radical did not undergo rearrangement[70], as earlier published.[69] Since 36 did not rearrange under these conditions, it could not be used as a radical clock to time the rate of hydrogen abstraction. The rearrangement reaction (equation 61) was slowed down, possibly by the ring strain in the intermediate, and the competing process of hydrogen abstraction was much too fast to be timed by the very slow rearrangement clock.[70]

The value of k_H can be estimated by using the results of the previous experiment (Scheme 17).

Scheme 17



The ratio of RCl:RH was 1.7:1 at 80°C using an initial concentration of 34 of 0.283M. An expression for k_H can be determined as follows:

$$\frac{d}{dt}[RCl] = k_{Cl}[R\bullet][CCl_4]$$

$$\frac{d}{dt}[RH] = k_H[R\bullet][34]$$

$$\frac{RCl}{RH} = 1.7 = \frac{k_{Cl}[CCl_4]}{k_H[34]}$$

$$k_H = \frac{k_{Cl}[CCl_4]}{1.7[34]}$$

The rate of Cl abstraction from CCl_4 by the 5-hexenyl radical has been shown[79] to be 3.65×10^4 $M^{-1}s^{-1}$ at 80°C. The initial concentration of 34 was 0.283M and the reaction went to completion so an intermediate value of 0.141M was used for [34]. A value of 10 M was used for $[CCl_4]$.

$$k_H = \frac{k_{Cl}[CCl_4]}{1.7\,[34]}$$

$$= \frac{3.65 \times 10^4 \times 10}{1.7 \times 0.141} \qquad \left(\frac{M^{-1}s^{-1}M}{M}\right)$$

$$= 1.5 \times 10^6\ M^{-1}s^{-1} \quad \text{at } 80°C$$

There is an error associated with this value for k_H due to the average value assigned for [34]. Taking this uncertainty into account the value of k_H would lie between 1.5×10^5 $M^{-1}s^{-1}$ and 1.5×10^7 $M^{-1}s^{-1}$. This range of values for k_H is in agreement with the rate of H-abstraction from another α-hydroxydiazene.[80] The estimated value of k_H is large indicating that α-hydroxydiazene 34 would probably react cleanly with at least some olefins to give hydroalkylation products.

An upper limit can be placed on the rate of rearrangement of the 2-cyanopropyl radical. There was no R'Cl detected in the reaction mixture from thermolysis of 34 in CCl_4. This means that the ratio of RCl/R'Cl must have been $\geq$ 100 based on the detection limit of the GC at 1%. An equation for k_r can be developed (Scheme 18).

Scheme 18

$$R\bullet \xrightarrow{k_r} R\bullet'$$

$$R\bullet + CCl_4 \xrightarrow{k_{Cl}} RCl + \bullet CCl_3$$

$$R\bullet' + CCl_4 \longrightarrow R'Cl + \bullet CCl_3$$

$$\frac{RCl}{R'Cl} \geq 100 = \frac{k_{Cl}[R\bullet][CCl_4]}{k_r[R\bullet]}$$

$$k_r \leq \frac{k_{Cl}[CCl_4]}{100}$$

$$k_r \leq \frac{3.65 \times 10^4 \times 10}{100} \ (M^{-1}s^{-1} \times M)$$

$$k_r \leq 3.65 \times 10^3 s^{-1} \quad \text{at } 80°C$$

This sets an upper limit on the rate of rearrangement of the 2-cyanopropyl radical at 3.65×10^3 s^{-1}. Ingold and others[83] suggest that from theory the rate of a 1,2-cyano shift would be closer to 0.9 s^{-1} at 25°C.

III. EXPERIMENTAL

III.1 General

Melting points were determined on a Thomas-Hoover Capillary Melting Point apparatus. All values reported are uncorrected.

Proton magnetic resonance spectra were obtained on either a Varian EM-390, a Bruker WP-80, or a Bruker EM-250 spectrometer. $CDCl_3$ was used as the solvent unless otherwise indicated. Tetramethylsilane was used as the internal reference.

Electron impact mass spectra were recorded on a VG 7070 mass spectrometer (VG Micromass, Altricham, U.K.). Samples were introduced via a direct insertion probe system or through a gas chromatograph via a jet separator. The ion source temperature was 200°C. The spectra were obtained at an accelerating voltage of 4kV and electron energy of 70 eV with emission of 100 μa. The spectra were acquired and processed with a VG 2035 data system.

The solvent for infrared analysis was CCl_4. The spectra were obtained on a Perkin-Elmer model 283 spectrophotometer using 0.5 mm KBr cells. Only major and diagnostic bands (transmittance) are reported.

Gas chromatographic analyses were done on a Varian VISTA 6000 gas chromatograph equipped with an off-column flash injector at 220°C and a flame ionization detector (FlD) at 300°C. The column (glass, 2.5 m x 2 mm I.D.) was packed with 3% OV-17 (phenyl silicone) on 80/100 mesh Chromosorb W. Nitrogen was the carrier gas at a flow rate of 25 mL min^{-1} The column oven temperature was programmed from 40°C to 280°C at 5° min^{-1} (unless otherwise specified). Data were acquired and processed with a Varian VISTA 402 chromatographic data system. Semi-preparative gas chromatographic analyses were performed on a Varian Aerograph A90-P3 instrument equipped with a thermal conductivity detector (T.C.D.) at 300°C and an off-column flash injector at 250°C. The column (steel, 1.8 m x 4 mm I.D.) was packed with 10% Carbowax 20M on 80/100 Chromosorb W. The carrier gas was helium at a flow rate of 20 mL min^{-1} and the chromatograph was operated at column oven temperatures between 40°C and 300°C.

Chemicals were purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin), J.T. Baker (Phillipsburg, New Jersey), British Drug Houses (Poole, England), Fisher Chemical Co. (Toronto, Ontario), and Matheson (Whitby, Ontario). Chromatographic supplies were obtained from Chromatographic Specialities (Brockvillle, Ontario). Solvents were supplied by Caledon (Georgetown, Ontario). The reagents were used without purification unless otherwise specified. Solvents were purified by distillation and stored over molecular sieves.

III.2 Synthesis

2-Cyanopropylhydrazine (13)

Methacrylonitrile (48g, 0.72 mol) was dropped very slowly into an ice cold, stirring solution of excess hydrazine monohydrate (67.6 g, 2.1 mol) in 100 mL of methanol over a period of 1h. The reaction mixture was left to stir for an additional 6h and then placed in a freezer overnight. The bulk of the methanol was removed by evaporation and then the reaction mixture was distilled under vacuum. Pure substituted hydrazine (44 g, 62%) was collected at 100°C at 1.0 mm of Hg. The substituted hydrazine was a very pale yellow viscous liquid. Table 2 contains the spectral data.

2-Cyanopropylhydrazone of Acetone (14)

An excess of acetone (75 mL, 1.27 mol) was slowly added with stirring and cooling to 10 g (0.10 mol) of substituted hydrazine 13. The solution was then brought to room temperature and the excess acetone was removed by evaporation. The reaction product was then distilled under vacuum and the substituted hydrazine (11.4 g, 0.082 mol, 82%) was collected at 86°C at 3.0 mm of Hg. It was a clear colourless liquid. For spectral information refer to Table 2.

2-Cyanopropyl[1-hydroperoxy-1-methylethyl]diazene (15)

Distilled substituted hydrazone 14 autoxidized spontaneously as a solution in benzene. The reaction flask was cooled and it was taped to reduce the amount of light entering the flask. The substituted hydrazone 14 (3.0 g, 0.022 mol) was dissolved in 100 mL of benzene (benzene has been used as a solvent for autoxidation[30]), and was exposed to oxygen from a gas burette. There was no induction period. When the oxidation was complete (as indicated by a constant gas volume for 4h or longer) an aliquot containing about 15 mg of the hydroperoxide was removed. The benzene was evaporated by passing a stream of nitrogen gas over the surface of the solution with the flask in an ice water bath. The ^{1}H NMR spectrum of the product (Table 2) indicated that the autoxidation was complete because the E- and Z-methyl signals of the starting material had disappeared. See Table 2 for spectral information.

Caution: These hydroperoxides are known to be explosive when isolated. Use proper safety equipment and only work with small quantities.

2-Cyanopropylhydrazone of d-Camphor (22)

A mixture of d-camphor (15.5 g, 0.1 mol), 2-cyanopropyl hydrazine 13 (3.3 g, 0.03 mol), ethylene glycol (20 mL), and ethanol (5 mL) was refluxed for 20 h. The cooled solution was poured into distilled water (150 mL) and extracted with

benzene: hexane (1:1, 3 x 40 mL). The combined organic phase was washed with H_2O (2 x 10 mL) and then ice cold water (10 mL) containing concentrated HCl (10 mL). The aqueous phase was separated as quickly as possible into water (120 mL) containing K_2CO_3 (40 g). This was then extracted with benzene: hexane (1:1, 4 x 50 mL). The mixture was dried over $MgSO_4$ and the solvents were evaporated. The residue was then evacuated under a higher vacuum to remove the last traces of solvent.

The residue was then purified using a continuous vacuum, bulb to bulb distillation. The first fraction (20°C @ 1 x 10^{-3} mm of Hg) contained unreacted camphor, as did the second fraction (60°C @ 1 x 10^{-3} mm of Hg). The third fraction was brought over by quite severe heating of the pot with a heat gun at 1 x 10^{-3} mm of Hg. This fraction contained the camphor, 2-cyanopropyl hydrazone 22 (2.0 g, 32%). For spectral information see Table 4.

2-Cyanopropyl[1-hydroperoxy-1-d-camphoryl]diazene (23)

The 2-cyanopropylhydrazone of camphor 23 (1 g, 3x10^{-3} mol) was dissolved in benzene and placed on the autoxidation unit. The oxygen uptake stopped after 48h. An aliquot was removed and the solvent was evaporated as in an earlier autoxidation procedure (Caution). See Table 4 for NMR details.

d-Camphor Hydrazone (24)

d-Camphor (15.5 g, 0.10 mol) and hydrazine hydrate (14g, 0.44 mol) in diethylene glycol (20 mL) and ethanol (4 mL) were heated under reflux for 10h. The cooled solution was poured into water (150 mL) and extracted with benzene-hexane (1:1, 3 x 40 mL). The combined organic phase was washed with H_2O (2 x 10 mL) and then ice cold water (50 mL) containing concentrated HCl (10 mL). The aqueous phase was separated as quickly as possible into H_2O (120 mL) containing K_2CO_3 (40 g) and covered with a layer of benzene-hexane (1:1). The organic phase was separated, dried over K_2CO_3, filtered,and evaporated to give d-camphor hydrazone, 11.19 g, white crystals, melting point 39°-42°C, 73%.

Attempted Michael Addition of d-Camphor Hydrazone 24 to Methacrylonitrile

Camphor hydrazone (10.69 g, 0.0694 mol) was stirred in 40 mL of MeOH under a N_2 blanket. To this was added dropwise 4.7 g (0.079 mol) of methacrylonitrile in 5 mL of MeOH at room temperature. The mixture was stirred overnight. An aliquot was removed after 20 h of stirring and the solvent was evaporated. The NMR spectrum indicated that the reaction had not occurred. The reaction mixture was heated at reflux over night and the reaction mixture was checked again by ^1H NMR. The reaction had not occurred. Another 4.7 g (0.07 mol) of methacrylonitrile was added to the reaction mixture and it was

refluxed overnight. The mixture was checked again by ^{1}H NMR and it still contained only the starting materials. Another 4.7 g (0.07 mol) of methacrylonitrile was added and the mixture was refluxed for 3 days. When the reaction had still not occurred, this synthetic approach was abandoned.

Compound 25

Concentrated HCl (51 mL) was added to 51 g of ice. To this was added 2-aminothiophenol (25g, 0.20 mol). The mixture was then stirred and cooled in an ice bath. Sodium nitrite (14.2 g, 0.20 mol) in 28 mL of icewater was added to the reaction mixture with stirring. The flask was allowed to return to room temperature after the addition was complete. Steam distillation afforded a yellow oil that settled to the bottom of the water layer. The yellow oil was distilled under vacuum. A yellow liquid was collected at 95.5°C at 4 mm of Hg. This liquid solidified (17.4g, 64%) upon cooling to room temperature (m.p. = 35-36°C).

2-Cyanopropyl[1-hydroxy-1-methylethyl]diazene (34)

To 175 mL of the α-hydroperoxydiazene 15 benzene solution (about 2.6 g of sample, 0.015 mol) was added triphenyl phosphine (5.5 g, 0.012 mol) with cooling and stirring for 2h. The solvents were evaporated and the residue was subjected to a vacuum distillation (20°C at 2 x 10^{-3} mm of Hg) with the receiver immersed in a liquid nitrogen bath. The distillate was the α-hydroxydiazene 34. See Table 5 for spectral details.

Attempted KI Reduction of 15

KI solution (70 g in 700 mL of H_2O) was added slowly with stirring to the cold α-hydroperoxydiazene 15 benzene solution. When the bubbling stopped, 10 mL of a $NaHCO_3$ solution was added. The reaction mixture was extracted with cold CH_2Cl_2. The solvents were then removed by evaporation. ^1H NMR indicated that an impurity was present in the products of the reaction.

Attempted Purification of the KI Reduction Product.

A column was packed with activated aluminum oxide (activated basic CAMAG, 95% + Al_2O_3, 60 mesh). The packing was made activity grade III by the addition of 6% (w/w) of water. The column was loaded with 1 g of the crude reaction mixture in 0.5 mL of CH_2Cl_2. The sample was then eluted with hexanes (2 x 40 mL); 5% EtOAc in hexanes (2 x 40 mL); 7% EtOAc in hexanes (3 x 40 mL); 10% EtOAc in hexanes (3 x 40 mL); 10% EtOAc, 1% MeOH in hexanes (3 x 40 mL); 10% EtOAc, 5% MeOH in hexanes (3 x 40 mL); and finally 10% EtOAc, 10% MeOH in hexanes (5 x 25 mL). Twenty four fractions were collected. Only the ^1H NMR of fraction #21 indicated the α-hydroxydiazene. The mass of the sample was about 30 mg. This indicated that the compound must have decomposed on the column and the lighter decomposition products were removed during the vacuum concentration procedure.

2-Cyanopropyl[1-acetoxy-1-methylethyl]diazene (35)

Cyanopropylhydrazone 14 (7 g, 0.05 mol) dissolved in 50 mL of CH_2Cl_2 was added dropwise to a stirred and cooled solution of lead tetracetate (22.0 g, 0.05 mol) in 100 mL of CH_2Cl_2 under an atmosphere of nitrogen. CH_2Cl_2 was added periodically to replace amounts that were lost due to evaporation caused by the nitrogen passing over the surface. After the addition, the flask was stoppered and stirred at room temperature for 0.5 h. H_2O (200 mL) was added and the mixture was stirred. The CH_2Cl_2 layer was then extracted with H_2O and washed with a $NaHCO_3$ solution until no more white precipitate formed. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated. A bulb to bulb distillation afforded the acetate 35 (7.0 g, 71%) as a clear yellow liquid. See Table 5 for spectral information.

Attempted Deacylation of (35) to (34).

Methyl lithium in ether (8.5 mL of a 1.2 M solution, 4 equivalents) was added dropwise with stirring to a cooled (-10°C) solution of the acetate 35 (0.500 g, 0.0025 moles) in ether under an atmosphere of nitrogen. The ether was previously dried over $MgSO_4$. The mixture was stirred at -10°C for 10 minutes. A cold (-10°C) saturated solution of NH_4Cl (30 mL) was then added dropwise with stirring. The organic layer was separated and the aqueous fraction was extracted two times

with ether. The combined etheral solutions were then dried over $MgSO_4$ and then concentrated on the rotary evaporator (cold bath). The ^1H NMR indicated that the α-hydroxydiazene 34 had not been formed. The starting material was recovered.

1-Chloro-2-cyanopropane (37)

Cold methacrylonitrile (2-cyanopropene) (5 g, 0.07 mol) was added to 5 mL of anhydrous diethyl ether. The mixture was cooled to 0°C and dry HCl gas was passed through a frit into the solution. The frit was used to decrease the size of the bubbles so as to increase the reacting surface area of the gas. Bubbling was continued for 15 minutes after the exhaust gas from the reaction flask tested acidic with wet litmus paper. The flask was then stoppered, cooled, and the contents were stirred continuously for 12 h with resaturation with $HCl_{(g)}$ every 3 h. The solvent was removed by distillation and the residue was shown by NMR (Table 6) to be 1-chloro, 2-cyanopropane (37) (5.6g, 73%).

1-Cyano-2-chloropropane (39)

Freshly distilled allyl cyanide (5 g, 0.07 mol) was added to 8 mL of anhydrous diethyl ether. The mixture was cooled to 0°C. Dry HCl was passed through a frit and then bubbled through the solution. The exhaust gas was tested with

wet litmus paper every hour to ensure that the solution was saturated with $HCl_{(g)}$. The reaction mixture was washed with an aqueous solution of $NaHCO_3$. It was then extracted with ether three times. The ether layer was dried over $MgSO_4$, filtered, and then distilled. The second fraction (4.8g, 62%), was collected at 3mm of Hg while heating with a hot air gun. The 1-cyano-2-chloropropane (39) was a colourless liquid. See Table 6 for spectral data.

Purification of Ethyl Acetate

The water, ethanol, and acid impurities were removed by washing the ethyl acetate with 5% (w/w) aqueous sodium carbonate, then saturated calcium chloride followed by drying over anhydrous potassium carbonate. The ethyl acetate was then distilled from P_2O_5 at 77°C at 760 mm of Hg.

Purification of Benzene

Benzene was shaken twice in a separatory funnel with concentrated sulfuric acid (100 mL $H_2SO_{4(aq)}$/L of benzene). The benzene was washed three times with distilled water, dried over $CaCl_2$ and was then distilled. The azeotrope of benzene/water, which distilled at 69°C (760 mm/Hg), was discarded. The fraction boiling at 80°C (760 mm/Hg) was collected and stored over molecular sieves 4A.

III.3. Thermolysis Reactions

III.3.1 Thermolysis of α-Hydroperoxydiazenes 15 in Ethyl Vinyl Ether and 2-Methoxypropene

In a typical addition procedure, the α-hydroperoxydiazene was isolated as mentioned previously (CAUTION) and was added to 4 mL of the unsaturated substance in a large thick walled tube. The tube was then put through the freeze-pump-thaw cycle three times, sealed, and placed in an 80°C oil bath for 24h. The contents were then frozen and the tube was opened. Excess alkene was removed and the reaction products were isolated and collected using a semi-preparative gas chromatograph. A small portion of the reaction mixture underwent a GC/MS analysis. The collected aldehyde or ketone was characterized by MS, ^{1}H NMR, and DNP derivative (melting point, probe MS, and ^{1}H NMR). The % yield values were obtained by GC analysis after addition of an internal standard

III.3.2 Thermolysis of α-Hydroxydiazene 34

In a typical thermolysis reaction, the α-hydroxydiazene 34 was dissolved in C_6F_6 to make solutions of 0.182 M, 0.390 M, 0.534 M, 0.602 M, 1.23 M or in C_6H_6 0.065 M, 0.042 M. The solution was degassed using freeze-pump-thaw cycles and the reaction tube was sealed. The sealed tubes were heated at 50° or 80°C for 5 min. to 24 h.

If the reaction was to be stopped at 10% completion then it was followed carefully by NMR spectroscopy. The appearance of the peak due to acetone at 2.1δ indicated the extent of the conversion. When the NMR spectrum indicated 10% conversion, the tube was frozen, opened, and excess $BrCCl_3$ was added to scavange any further radicals produced. The tube was then placed back in the oil bath for approximately 14 h. The contents of the tubes were then analyzed by GC/FID, GC/MS and NMR.

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