THE PREPARATION AND CHEMISTRY OF OXADIAZOLINONES AND OXADIAZOLINES

By

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PREPARATION AND CHEMISTRY OF OXADIAZOLINONES AND OXADIAZOLINES

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SCOPE AND CONTENTS:

The objectives of this work were fourfold. Firstly, the oxidation of semicarbazones with lead tetraacetate was examined from the point of view of products and of mechanism, as related to the mechanisms of other lead tetraacetate oxidations of carbonyl derivatives. Secondly, the chemistry of the acetone semicarbazone oxidation product, 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one was investigated. Thirdly, the chemistry of the methyl lithium addition product of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one, 2-hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline, was studied mainly from the aspect of its novel radical chain thermal decomposition. Fourthly, a general principle regarding radical pathways was put forward.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. J. Warkentin, for his continued assistance and encouragement throughout the course of this work.

I am deeply indebted to my wife, Cathy, for her diligent examination of this thesis for correct English and for insistence on perfection. Also, I would like to thank her for our many stimulating discussions on the relevance of science to everyday life, which allowed me to view my work from the proper perspective. It was Cathy's patience, love, understanding and encouragement that resulted in the completion of this work.

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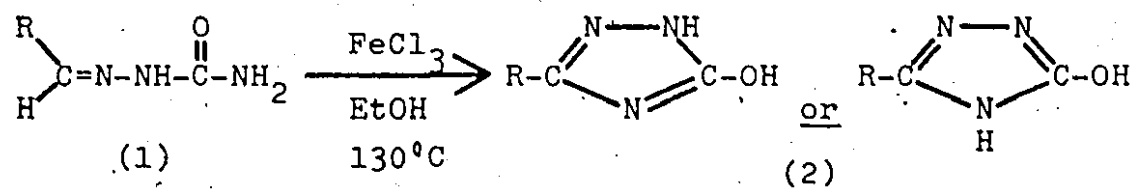
INTRODUCTION

I. OXIDATION OF SEMICARBAZONES

A) ALDEHYDE SEMICARBAZONES

The oxidation of aldehyde semicarbazones (1) has been examined in considerable detail by various workers since the turn of the century. The earliest reported work on the oxidation of (1) appears to be that of Young and co-workers in 1900 and 1901. In 1900, Young and Whitham[1] prepared a series of hydroxytriazoles (2) by oxidizing aryl semicarbazones (1, R = C_6H_5, m-$O_2NC_6H_4$, $C_6H_5CH{=}CH$) with ferric chloride (eq. 1).

[1]

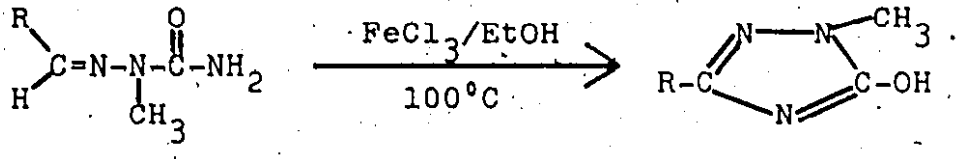


The reaction conditions were somewhat drastic requiring heating of an alcoholic solution to 130°C in a sealed tube. The original authors advanced no mechanism for this transformation. However, in 1962 Gibson[13] stated that the oxidation of Young and Whitham "probably proceeded by a radical mechanism".

Using a very similar oxidation procedure (ferric chloride in ethanol at 100°C in a sealed tube), Young and Oates[2] in 1901 succeeded in preparing a series of 1-methyl-

5-hydroxytriazoles (4) from 2-methylsemicarbazones (3) (eq. 2). Again mechanistic information was not included. Isomerization

[2]



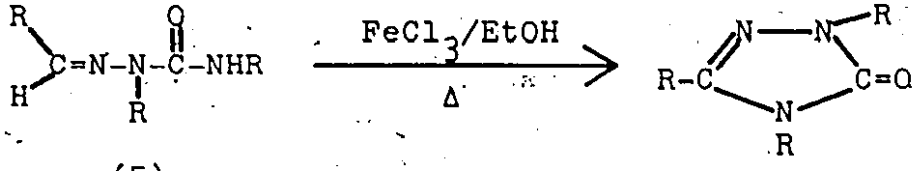
(3) (4)

R = C_6H_5, m-$O_2NC_6H_4$, $C_6H_5CH{=}CH$.

of (4) to the triazolone was not reported and various derivatives prepared by Young and Oates indicated that (4) was the correct structure of the oxidation product.

In 1903 Busch and Walter[3] used the oxidation conditions of Young and co-workers[1,2] to oxidize the 2,4-diphenylsemicarbazone of benzaldehyde (5) (eq. 3). They obtained the analogous product, the 1,3,4-triphenyl-1,2,4-triazolone (6).

[3]

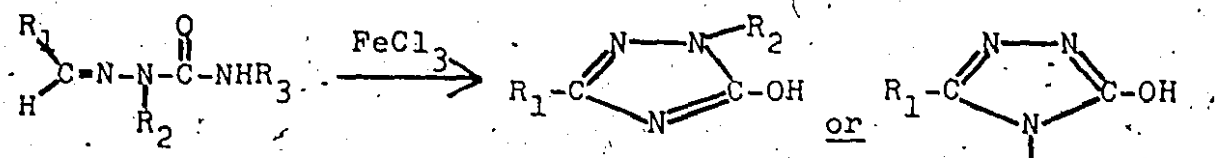


(5) (6)

R = C_6H_5

Backer and Mulder[4] employed the method of Young and Oates[2] to oxidize various 2- and 4-substituted semicarbazones. In so doing, they obtained the 3-hydroxy-1,2,4-triazoles (7)

(eq. 4). The purpose of preparing compounds (7) was to study their nitration with sodium nitrite.



[4]

R_1 = p-$CH_3OC_6H_4$, $CH_2O_2C_6H_3$, C_6H_5, C_6H_5

R_2 = CH_3, CH_3, C_6H_5, H

R_3 = H, H, H, C_6H_5

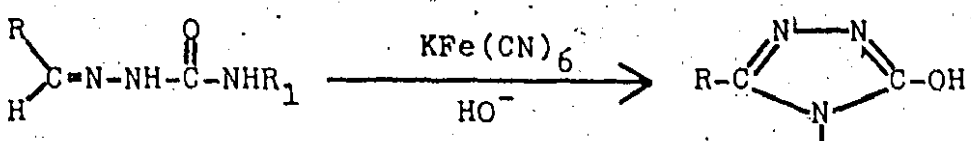
(7)

An attempt to prepare the hydroxytriazole (2, R = C_6H_5), by oxidation of benzaldehyde semicarbazone with nitric acid, was reported in 1917[5]. These authors claimed that the semicarbazone reacted, but they were unable to identify the products.

The next paper on the oxidation of aldehyde semicarbazones (1) was published by Hoggarth[6] in 1949. Using the conditions of Young and Whitham[1], he prepared a series of hydroxytriazoles (2, R = C_6H_5, p-ClC_6H_4, p-$CH_3OC_6H_4$) from the corresponding semicarbazones. He noted that considerable amounts of the corresponding azines were also formed as by-products of the oxidation.

In 1959 two Indian workers reported[7] a simpler, more efficient preparation of hydroxytriazoles from semicarbazones. Ramachander and Srinivasan found that oxidation of 4-aryl-semicarbazones (8) with alkaline potassium ferricyanide led to the 4-aryl-5-hydroxytriazoles (9) (eq. 5). In a later

paper Srinivasan and co-workers[8] reported the preparation of a variety of (9) by oxidation of (8) with alkaline potassium ferricyanide. The ultraviolet and infrared spectra of the products (9) were discussed in detail in this later paper.



[5]

(8) (9)

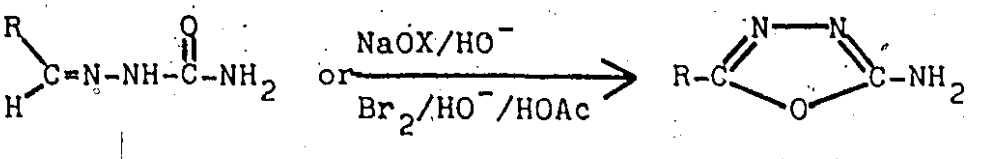
R = C_6H_5, p-$H_3CC_6H_4$.

R_1 = C_6H_5, p-$CH_3OC_6H_4$, m-$O_2NC_6H_4$.

A report on the photooxidation of semicarbazones (1) was published in 1960. Using porphyrin photosensitizers, Sharp[9] oxidized a wide variety of organic substrates, including aldehyde semicarbazones. The resulting products were not described in the abstract.

The first mention of products other than the triazole derivatives from semicarbazone oxidation was in a publication in 1952. Italian researchers[10] prepared 2-amino-5-phenyl-1,3,4-oxadiazole (10, R = C_6H_5) from benzaldehyde semicarbazone using hot alkaline sodium hypobromite or hypoiodite (eq. 6). In a later and more extensive study[11], these workers reported the generalization of the preceding oxidation. Using a different oxidant, namely bromine in alkaline solution added to the semicarbazone in acetic acid, they prepared a large number of

2-amino-1,3,4-oxadiazoles (10) (eq. 6). In neither of these two papers was a mechanism suggested for the oxidation.



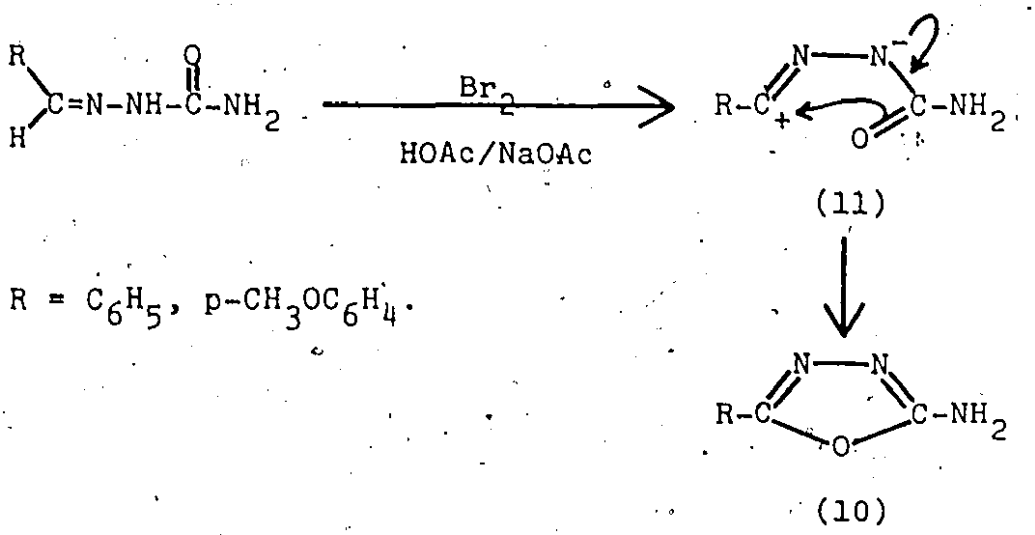
[6] (X = Br, I). (10)

R = C_6H_5, p-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 3,4-$CH_2O_2C_6H_3$, $C_6H_5CH{=}CH$, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$.

The first reported oxidation of aliphatic aldehyde semicarbazones appeared in 1962. Gehlen and Möckel[12] used iodine in sodium carbonate solution to oxidize a variety of aliphatic and aromatic aldehyde semicarbazones. They found that the products were the oxadiazoles (10) and that the yield from aliphatic aldehyde semicarbazones was only 10-20% while that from the aromatic analogues came to 80-90%. They also observed that, in some cases, bromine was a better oxidizing agent than iodine.

Up to this point in time, the reports on oxidation of aldehyde semicarbazones were purely synthetic in nature with little or no reference to the mechanisms involved. In 1962, Gibson[13] synthesized two oxadiazoles (10) by oxidation of the semicarbazones of benzaldehyde and p-anisaldehyde with bromine in acetic acid containing sodium acetate (eq. 7). He claimed that his reaction conditions encouraged the "in situ" formation

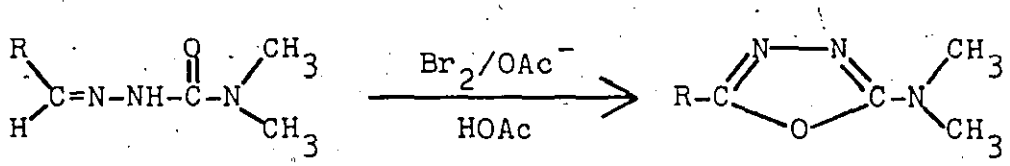
of a nitrilimine intermediate (11) which subsequently closed to the 5-substituted-2-amino-1,3,4-oxadiazole (10). He found support for this mechanism in the fact that oxidations under conditions not amenable to nitrilimine formation (eg. ferric chloride oxidation which Gibson[13] claimed proceeded by a radical mechanism) invariably led to triazoles (2) rather than to oxadiazoles (10).



[7] R = C_6H_5, p-$CH_3OC_6H_4$.

The preparation of 2-dimethylamino-1,3,4-oxadiazoles (13) was first reported in 1964. Najer and co-workers[14] oxidized benzaldehyde 4,4-dimethylsemicarbazone (12, R = C_6H_5) using the conditions of Gibson[13]. In a later study[15], they prepared a variety of oxadiazoles (13) by oxidizing several aromatic aldehyde 4,4-dimethylsemicarbazones (12) with Gibson's procedure (eq. 8). They found, however, that p-chlorobenzaldehyde 4,4-dimethylsemicarbazone (12, R = p-ClC_6H_4) did not oxidize to (13, R = p-ClC_6H_4), but gave instead the 1-(α-bromo-

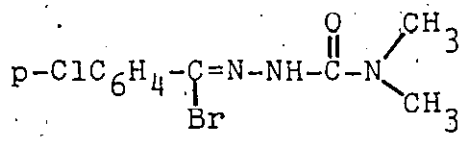
p-chlorobenzylidene)-4,4-dimethylsemicarbazide (14). An



[8] (12) (13)

R = C_6H_5, p-$CH_3OC_6H_4$, o-$CH_3OC_6H_4$, m-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$.

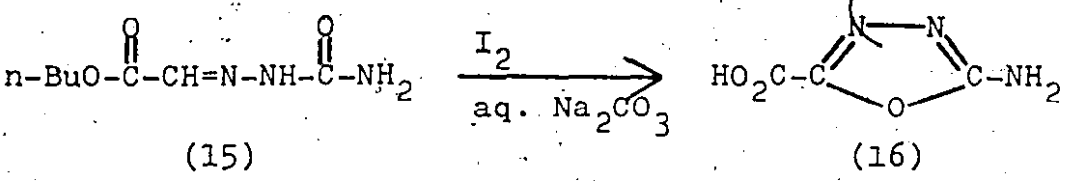
explanation for this anomaly was not given. The compounds (13) were prepared to study their anti-inflammatory activity in biological systems.



(14)

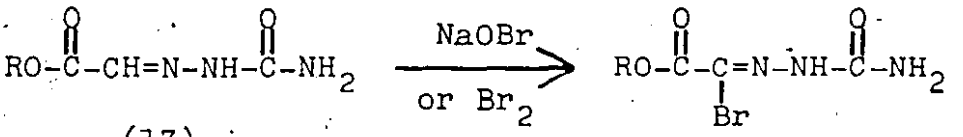
The oxidation of semicarbazones (1) where R is neither alkyl nor aryl was first published in 1966 by Werber and Buccheri[16]. Using iodine in aqueous sodium carbonate, they oxidized n-butylglyoxylate semicarbazone (15) to the 2-amino-5-carboxy-1,3,4-oxadiazole (16) (eq. 9). Hydrolysis of the ester presumably occurred during workup. Decarboxylation of (16) was accomplished by heating in water.

In a later paper[17], Werber and co-workers used both sodium hypobromite and bromine plus anhydrous sodium acetate

[9] 

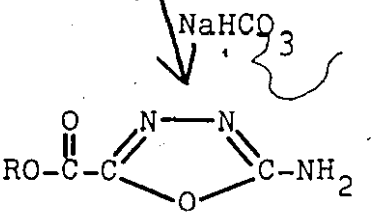
(15) (16)

in acidic solution to oxidize alkyl glyoxylate semicarbazones (17) (eq. 10). They found, however, that the oxadiazoles were not formed directly as when iodine was used (eq. 9).



(17) (18)

[10] R = $CH_3CH_2CH_2CH_2$, CH_3CH_2, CH_3.



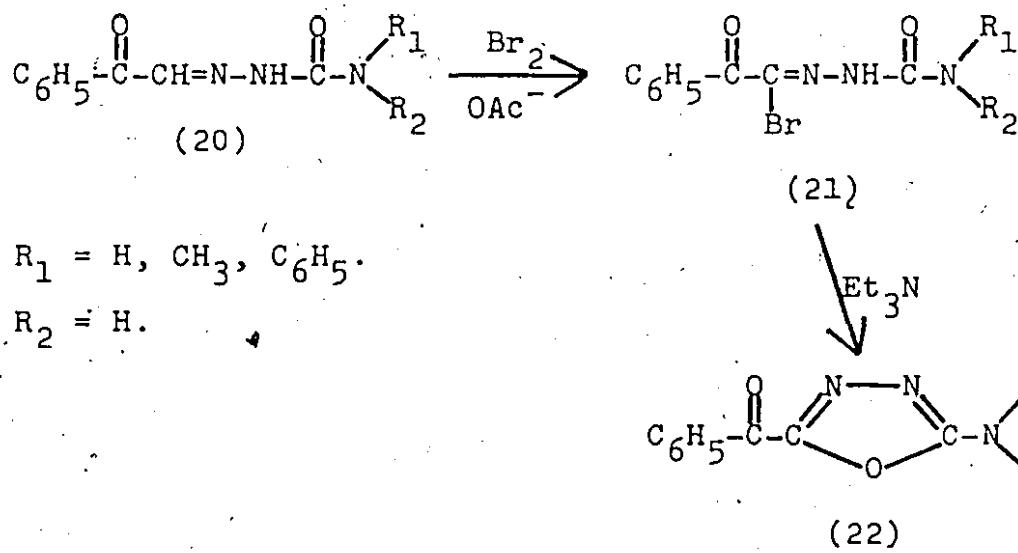
(19)

Instead, they found that a bromide (18) was formed and that this bromide could be converted to the oxadiazole (19) with sodium bicarbonate.

Werber and co-workers published a paper[18] in 1969 disputing the work of Najer and co-workers[15] (see page 6). They reported that oxidation of p-chlorobenzaldehyde 4,4-dimethylsemicarbazone (12, R = p-ClC_6H_4) under Gibson's[13] conditions gave a perbromide rather than (14) as reported by

Najer. This perbromide, when dissolved in methanol, gave the hydrobromide of 2-dimethylamino-5-p-chlorophenyl-1,3,4-oxadiazole (13, R = p-ClC_6H_4) as well as the free base. Similarly, these authors prepared a series of (13) with R = o-BrC_6H_4, m-BrC_6H_4, p-BrC_6H_4, o-ClC_6H_4, m-ClC_6H_4.

Werber and co-workers[19] also oxidized phenylglyoxal semicarbazones (20). With bromine and sodium acetate in acidic solution they obtained the corresponding bromides (21) (eq. 11). These bromides were then cyclized to the oxadiazoles (22) with triethylamine. In the case of (20, R_1=R_2 = CH_3), oxidation gave (22, R_1=R_2 = CH_3) directly.

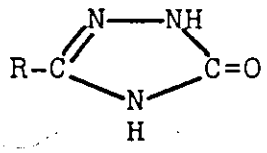


(20) (21) (22)

[11] R_1 = H, CH_3, C_6H_5.
R_2 = H.

Gibson's theory[13] of the nitrilimine intermediate (11) (see page 6) was revived and supported in a series of papers published by Butler and co-workers[20-24] between 1970 and 1972. These authors[20,21] used bromine as the oxidizing agent on

arylaldehyde semicarbazones (1, R = aryl). Using two sets of reaction conditions they obtained two different products. In one case, they used anhydrous acetic acid as the solvent and isolated the triazolones (23). These arose from cyclization to the terminal nitrogen of the semicarbazones. When they



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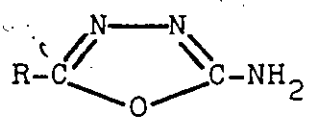


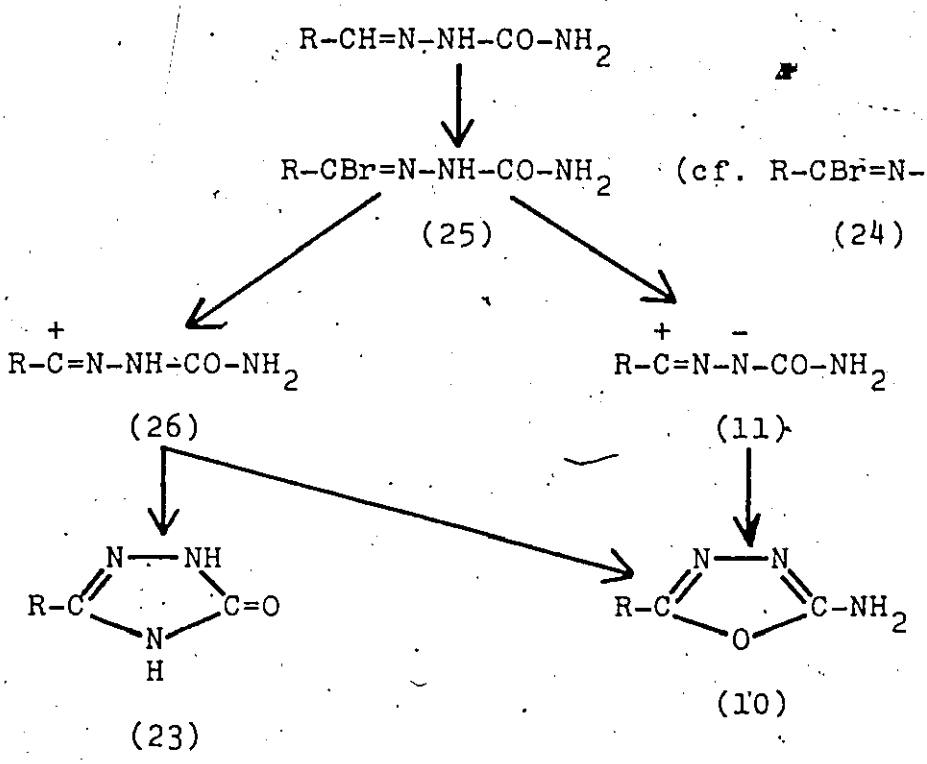
(10)

used acetic acid containing either water or sodium acetate as the solvent, the products were the 2-amino-1,3,4-oxadiazoles (10) (see page 5). The same authors also reported[22] the formation of the oxadiazoles (10) when using lead tetraacetate in anhydrous acetic acid as the oxidizing agent.

To explain the formation of products (23) and (10), they proposed a mechanistic scheme involving hydrazidic bromides and nitrilimine intermediates (Scheme I). Citing the fact that hydrazonyl halides of the type (24) had been isolated by reaction of halogens with arylhydrazones of aldehydes[23], they assumed that a similar species (25) was formed from aldehyde semicarbazones and bromine. However, no such species was isolated. Hydrazonyl halides (24) had also been reported[24] to undergo hydrolysis via nitrilimines like (11) or carbonium ions, depending on the pH of the medium. Butler

and co-workers cited this work to substantiate their claim that the supposed intermediate (25) would also hydrolyze via the nitrilimine (11) or the carbonium ion (26).

Scheme I

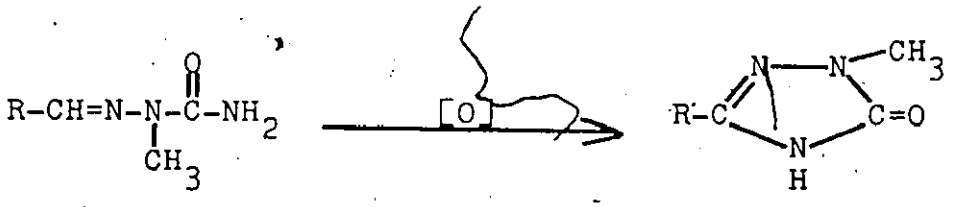


To account for the formation of (23) they proposed that, in anhydrous acetic acid, species (25) ionized exclusively to give (26). The triazolone (23) then resulted from nucleophilic attack of the terminal nitrogen at the carbonium ion site. Some oxadiazole (10), resulting from oxygen attack, was also formed in low yield. Formation of (10), in acetic acid containing water or sodium acetate, was explained as follows. The species (25) was said to undergo a 1,3-dipolar

elimination to give the nitrilimine (11), which was then presumed to do an intramolecular 1,5-dipolar cycloaddition to give (10).

The result of the oxidation of 2-methylsemicarbazones (27) (eq. 12) by the same authors[20,21] was cited as further proof of the proposed mechanisms in Scheme I. In this case, nitrilimine formation was structurally prohibited, whereas carbonium ion formation was not. Under conditions where oxadiazoles (10) normally formed, (27) did not react. However, using conditions which previously led to the triazolones (23); (27) gave the triazolones (28). This tends to support the inter-

[12]



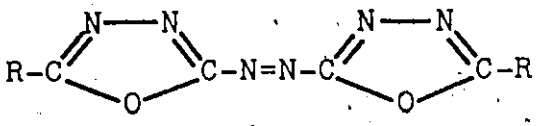
(27) (28)

mediacy of carbonium ions in the formation of triazolones, but does not prove that nitrilimines are necessary for the formation of oxadiazoles (10). It should be noted here, however, that similar systems such as amides and ureas, undergo electrophilic attack at oxygen[25,26] not nitrogen as Butler claims for his intramolecular cyclization of (26) to (23).

It is interesting to note that both Najer[15] and Werber[17,19] had reported the isolation of hydrazidic halides of the type (25) before Butler and co-workers postulated them

as intermediates in semicarbazone oxidation. However, it seems that Butler and co-workers were not aware of this earlier work.

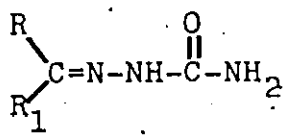
Further oxidation of the oxadiazoles (10) is possible and was in fact reported[27] as early as 1929. The products obtained were the azo-1,3,4-oxadiazoles (29). For a more detailed account of the chemistry of oxadiazoles, the reader is referred to a review on the subject by Russian authors[28].



(29)

B) KETONE SEMICARBAZONES

The oxidation of unsubstituted ketone semicarbazones (30) has received little or no attention in past literature. Oxidations have been limited to 2- or 4-substituted semicarbazones (31) and semicarbazones of α-functionalized ketones (32).



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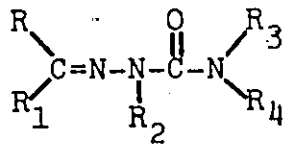

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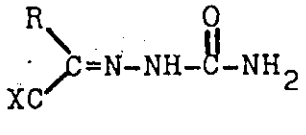
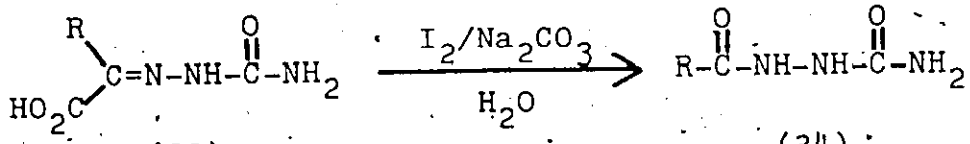


(32)

The earliest reports on ketone semicarbazone oxidation

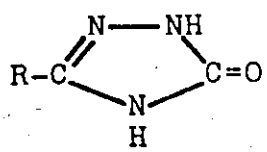
appear to be those of Bougault. In a series of papers[29-32] published between 1916 and 1929, he reported the results of oxidizing α-keto acid semicarbazones (33) with iodine in aqueous sodium carbonate (eq. 13). Initially he reported[29,30] the oxidation products to be the acylsemicarbazides (34) on the basis of a single analysis and a comparison of melting points with those of known acylsemicarbazides. These melting points differed from his by 15 to 25 degrees. In 1919 Bougault published[31] a correction stating that the product of the oxidation was not (34), but rather a compound with a formula that differed from formula (34) by a molecule of water. At



[13] (33) (34)

R = $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, C_6H_5, $(CH_3)_3C$.

this point he made no mention of what the product might be, but in a later paper[32], he suggested that the oxidation products might be the triazolones (35).



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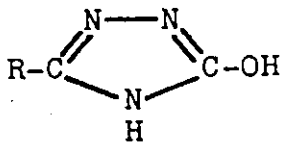

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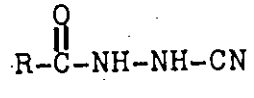


(37)

In 1941 another French worker confirmed that the products of Bougault's oxidation (eq. 13) were the triazolones (35). Girard[33,34] claimed that, on treatment with alkali, (35) tautomerized to the hydroxytriazoles (36) reported earlier[1].

All of the aforementioned results of oxidation of (33) were disputed in 1949 by Gehlen[35]. He claimed that the products obtained by Bougault were the β-N-cyanohydrazides (37). This claim was based on the melting points of Bougault's products mixed with authentic samples of (37), prepared from the reaction of hydrazides with cyanogen bromide. There was no depression of melting points; so, Gehlen assigned structure (37) to Bougault's oxidation products. To explain the work of Girard, he pointed out that alkaline treatment of (37) would lead, via the acylhydrazides (34), to the triazolones (35) which could then tautomerize to the hydroxytriazoles (36).

In 1960 Maggio and co-workers[11] oxidized the semicarbazones of phenylpyruvic acid and benzylpyruvic acid with iodine in aqueous sodium carbonate. By comparison with authentic samples, they concluded that the products obtained were the 2-amino-1,3,4-oxadiazoles (10). They went on to say that Bougault's products also had the structure (10) and that Girard's alkaline treatment led to the triazolones (35) via the acylhydrazides (34).

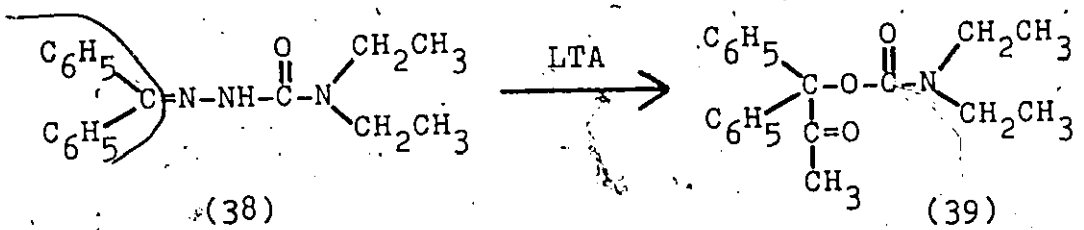
It appears then, that the structure of the products obtained from the oxidation of α-keto acid semicarbazones (33)

remains in doubt.

Photooxidation of ketone semicarbazones (30) was reported[9] in 1960 but the products were not described.

Oxidation of substituted semicarbazones (31) was first reported by Iffland and co-workers[36] in 1963. These workers reacted benzophenone 4,4-diethylsemicarbazone (38) with lead tetraacetate (LTA) and isolated 2-oxo-1,1-diphenylpropyl diethylcarbamate (39) in high yield (eq. 14). The same result was obtained with the morpholine derivative of benzophenone semicarbazone which gave 2-oxo-1,1-diphenylpropyl 4'-morpholine carboxylate. These results were in contrast to those obtained with the corresponding hydrazones which were converted to azoacetates under the same conditions[37].

[14]

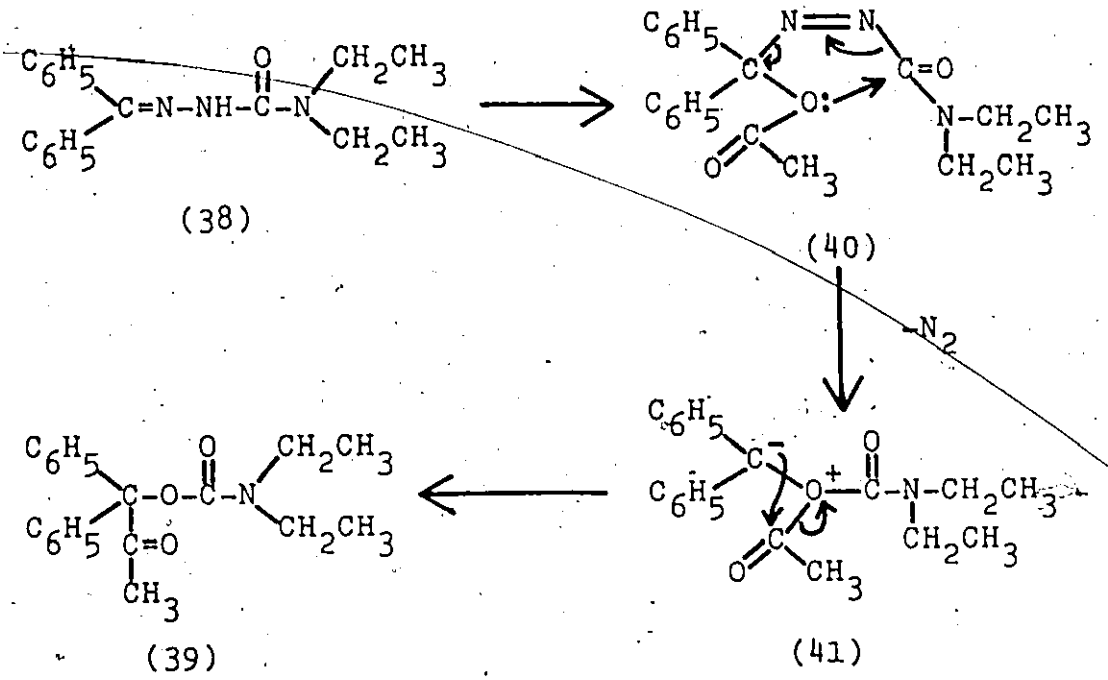


(38) (39)

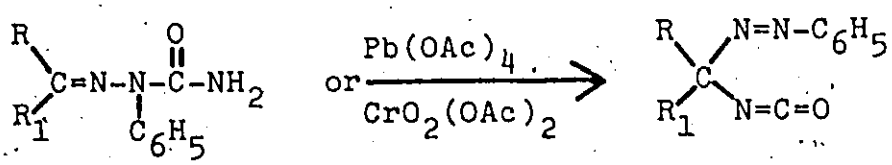
The mechanism put forward for this novel rearrangement was as follows (Scheme II). The semicarbazone (38) was converted by the LTA to the azoacetate (40). This azoacetate subsequently rearranged to the intermediate (41) by intramolecular nucleophilic displacement at the amide carbonyl and by loss of nitrogen from the quasi five membered ring. By a 1,2 shift analogous to the Stevens rearrangement, (41) went

on to give the carbamate (39).

Scheme II

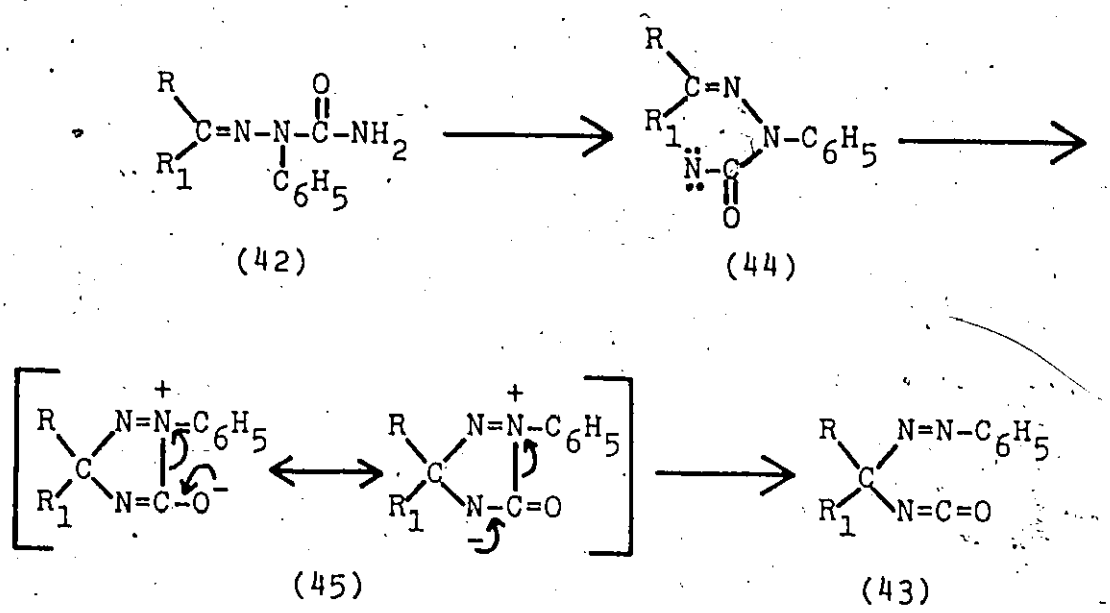


The oxidation of 2-phenylsemicarbazones (42) was examined in some detail by three separate research groups in 1968. Schildknecht and Hatzmann[38] reported the formation of phenylazomethyl isocyanates (43) on oxidation of (42) with chromyl acetate or lead tetraacetate (eq. 15). According to

[15] 

these authors, the semicarbazone (42) was oxidized to the nitrene (44) which then rearranged via a five membered ring (45) to the isocyanate (43) (Scheme III).

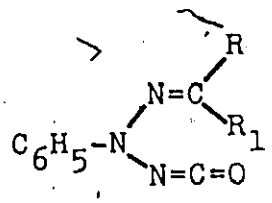
Scheme III



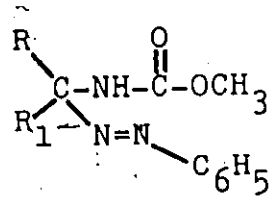
The oxidation of (42) with iodine was also reported at about the same time by Blackstock and Happer[39]. However in this case, the products were reported to be the triazane derivatives (46) rather than the isocyanates (43). Reaction mechanisms were not suggested and the structures of (46) were based on analysis, infrared and nuclear magnetic resonance spectroscopic data.

The last researcher to examine 2-phenyl semicarbazones (42) was Schantl[40]. He used mercuric oxide as the oxidizing agent and came to the conclusion, as had Schildknecht and

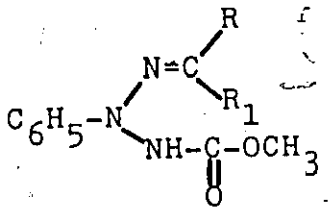
Hatzmann[38], that the products of the oxidation of (42) were the phenylazomethyl isocyanates (43). Schantl repeated the oxidations reported in references 38 and 39. Then, he reacted the product from the oxidation with mercuric oxide, lead tetra-acetate or chromyl acetate with alcohol and obtained the urethane (47). He also found that the product from iodine oxidation of (42), when reacted with alcohol, gave (47) and not urethane (48), which would have been expected had the triazane isocyanate (46) been the product of iodine oxidation[39].



(46)



(47)



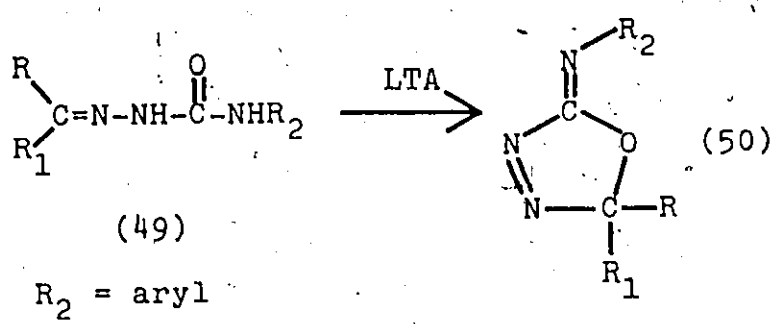
(48)

Furthermore, he found that oxidation of (42) with both iodine and bromine in the presence of sodium alkoxides led directly to the urethane (47) rather than (48). Thus it appears that Blackstock and Happer[39] were in error.

The oxidation of 4-arylsemicarbazones of ketones (49, R_2 = aryl) was examined in considerable detail by earlier workers[41] in this laboratory. By reacting (49) with lead tetraacetate, they prepared a series of oxadiazolines (50) (eq. 16). The structure (50) was assigned on the basis of analytical data, molecular weights, spectra and chemical behaviour. Analogy to products obtained from the earlier

oxidation of ketocarbohydrazones[42] helped to establish (50) as the correct structure. Furthermore, an X-ray crystal structure[43] firmly established the oxadiazoline ring system as well as the Z-geometry at the exocyclic imino group.

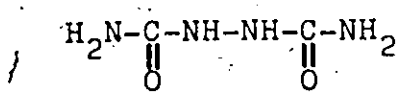
[16]



(49)

R_2 = aryl

The earliest mention of oxidation of unsubstituted ketosemicarbazones came in 1961[44]. Reaction of aliphatic ketosemicarbazones (30, $R=R_1$ = alkyl) with peracetic acid resulted in cleavage to the hydrazodicarbonamide (51), nitrogen, and the original carbonyl compound. Similar treatment of aromatic ketosemicarbazones (30, $R=R_1$ = aryl) gave no products and only starting materials were recovered. Mechanisms were not advanced.

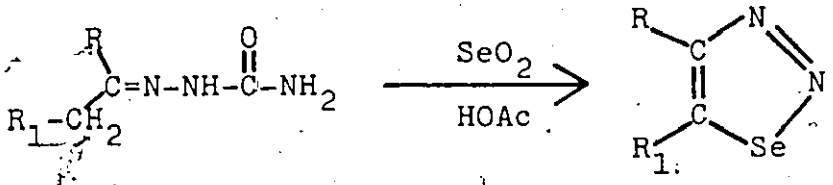


(51)

Results similar to the preceding were reported in 1969 by Bird and Diaper[45]. They used ceric ammonium nitrate with (30) and isolated the original carbonyl compounds.

A specific mechanism for this conversion was not put forward; however, a similar conversion of oximes was explained in mechanistic terms. This work was also mentioned in a review on oxidation in 1973[46].

The most recent reports[47,48] of oxidation of keto-semicarbazones were those of Lalezari and co-workers who used selenium dioxide as the oxidizing agent. The products in this case were the novel heterocyclic ring systems, incorporating selenium, called 1,2,3-selenadiazoles (52) (eq. 17).

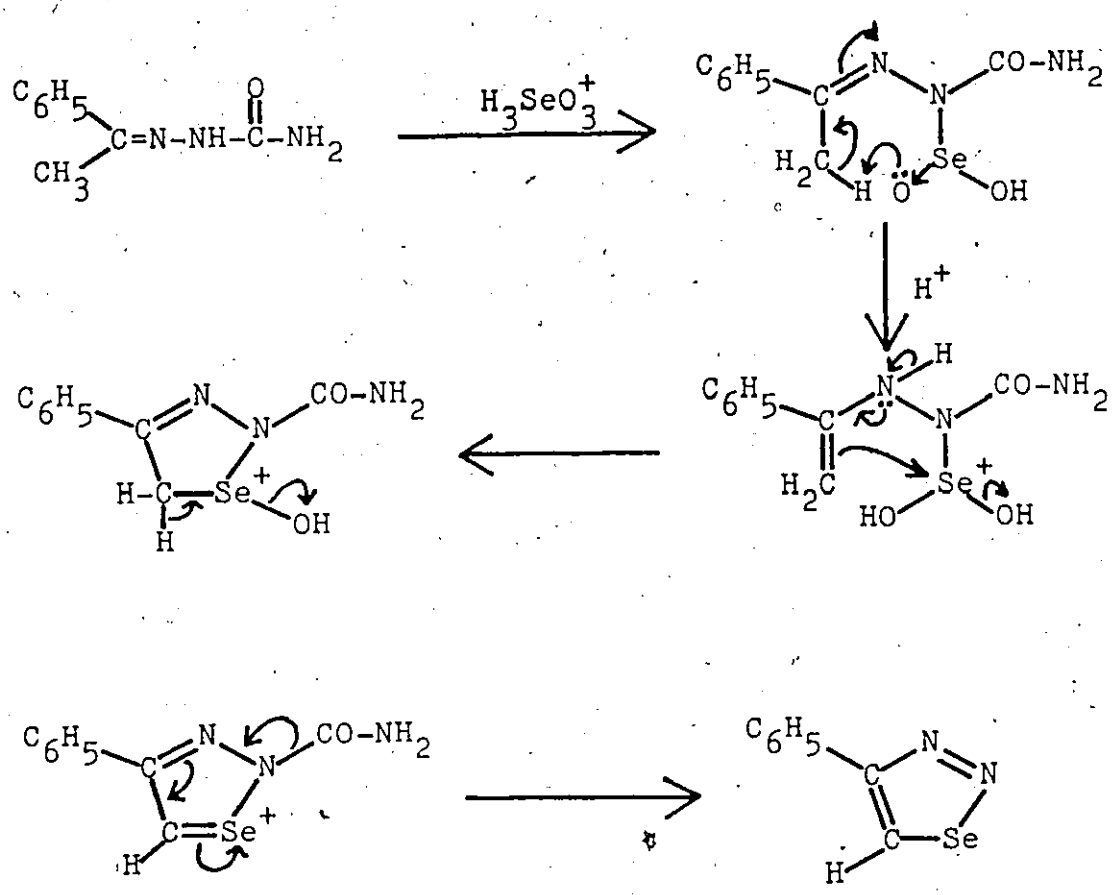
[17] 

(52)

A mechanism for this conversion was suggested by the authors, and is as shown in Scheme IV for acetophenone semicarbazone.

In 1974, the selenium oxidation of semicarbazones was employed by Caplin[49]. He synthesized a variety of selenadiazoles (52) in order to study their proton magnetic resonance spectra.

Scheme IV


C6H5
C=N-NH-C-NH2
CH3
O
H3SeO3+
CO-NH2
H2C
Se
OH
H+
HO
H-C
H

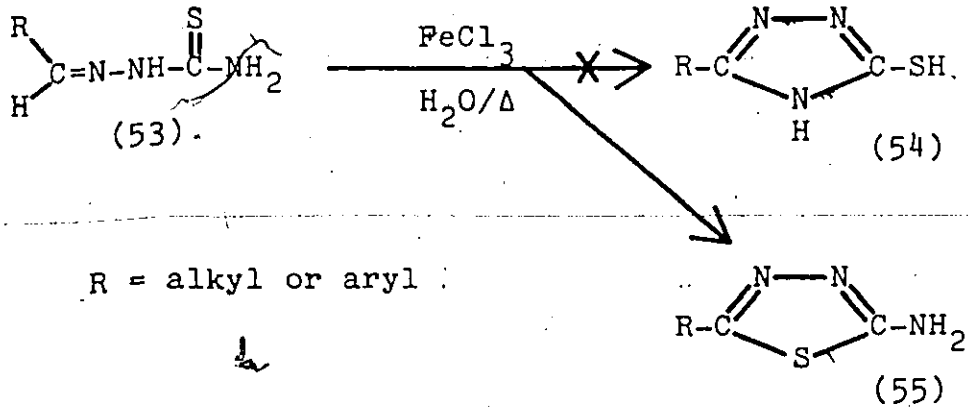
C6H5
CO-NH2
Se+
OH
H

II .OXIDATION OF THIOSEMICARBAZONES

The oxidation of thiosemicarbazones, which are closely related to semicarbazones, has also been extensively studied since the turn of the century. As in the case of semicarbazones, the aldehyde derivatives have received considerably more attention than the ketone analogues.

A) ALDEHYDE THIOSEMICARBAZONES

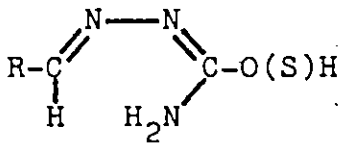
It appears that the earliest work with aldehyde thiosemicarbazones (53) was carried out in 1901 by Young and Eyre[50]. They reported the oxidation of benzaldehyde thiosemicarbazone (53, R = C_6H_5) with warm aqueous ferric chloride (eq. 18). They expected the product to be the mercaptotriazole (54), analogous to the hydroxytriazole (2) obtained earlier[1] from benzaldehyde semicarbazone (see page 1); instead, they found it to be 5-phenyl-2-amino-1,3,4-thiadiazole (55).



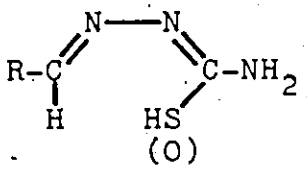
[18]

R = alkyl or aryl

The apparent discrepancy observed was explained by assuming that semicarbazones and thiosemicarbazones could exist in two stereoisomeric forms (56) and (57). Semicarbazones were thought to exist primarily in the form (56) leading to hydroxytriazoles (2) on closure. Conversely, thiosemicarbazones were believed to be primarily in the form (57), with subsequent closure giving the thiadiazole (55). There was never any evidence for such stereoisomerism and this explanation is no longer given serious consideration.

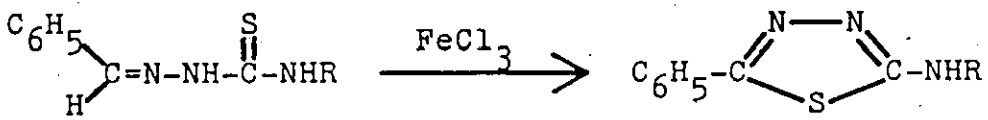


(56)



(57)

Young and Eyre[50] also oxidized 4-phenyl and 4-methyl-thiosemicarbazones of benzaldehyde; (58) and (59), respectively. The products, (60) and (61), were analogous to those from the unsubstituted thiosemicarbazones (eq. 19).



[19]

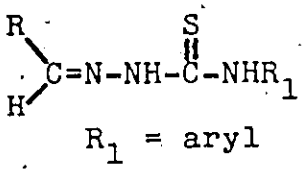
(58) and (60), R = C_6H_5

(59) and (61), R = CH_3

The results of Young and Eyre[50] were disputed in 1926.

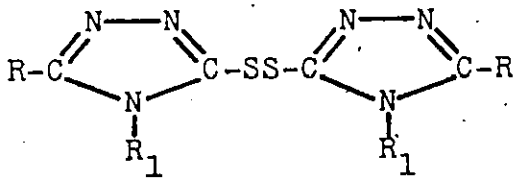
Fromm[51] claimed that since the products of benzaldehyde thiosemicarbazone oxidation did not react with mustard oil, they were not the thiadiazoles (55) but rather the mercaptotriazoles (54).

In 1928 two Indian workers reported[52] the oxidation of aldehyde 4-arylthiosemicarbazones (62) and benzaldehyde thiosemicarbazone with both ferric chloride and hydrogen peroxide. These authors were interested in producing mercaptotriazoles similar to (54). With ferric chloride they obtained only thiadiazoles similar to (55). However, with hydrogen peroxide they claimed to have isolated a derivative of the mercaptotriazoles, namely a disulfide with the structure (63). They also found that with excess hydrogen peroxide a sulfur free compound (64) could be isolated. The compound (64) was presumed to arise from further oxidation of (63) to sulfur dioxide and (64). Detailed information on the formation of (64) and (63) was not given.

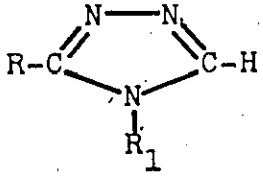


R_1 = aryl

(62)



(63)

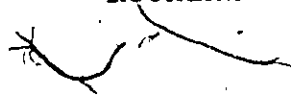


(64)

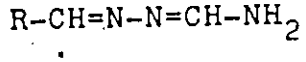
Another report on the oxidation of thiosemicarbazones with hydrogen peroxide appeared in 1937. Kitamura[53] added hydrogen peroxide to an alkaline alcoholic solution of alde-

hyde thiosemicarbazones and found that the corresponding semicarbazones precipitated out. A mechanism for this apparent desulfurization was not suggested.

The work of De and Roy-Choudhury[52] was re-examined in 1951 by Hoggarth[54,55]. By oxidizing unsubstituted aldehyde thiosemicarbazones, he prepared two novel compounds (65, R_1 = H) and (66). The oxidant was hydrogen peroxide in cold acetic acid. The two products (65) and (66) are derivatives of 2,3-diazabuta-1,3-diene. Products (66) were unstable and were isolated as their picrates. Hoggarth claimed that the product (64) described by De and Roy-Choudhury[52] was actually the product (66). Oxidation of 4-methylthiosemicarbazones resulted only in the isolation of product (65, R_1 = CH_3). Again, mechanisms were not formulated.



(65)

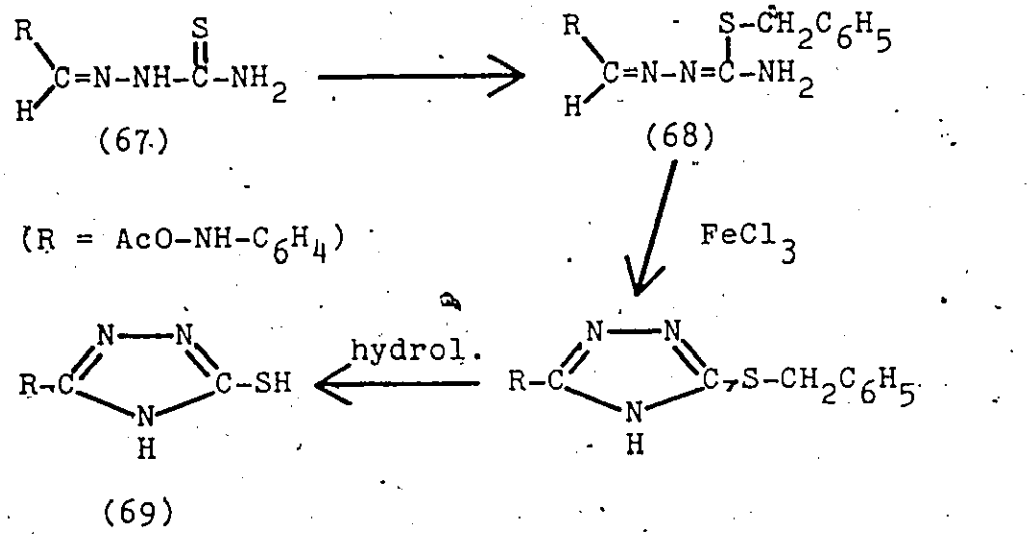


(66)

In 1951, Bernstein and co-workers[56] reported the oxidation of p-methoxy and p-aminobenzaldehyde thiosemicarbazones. Using the conditions of Young and Eyre[50], they isolated the corresponding 5-(p-methoxyphenyl)- and 5-(p-aminophenyl)-1,3,4-thiadiazoles. These compounds were prepared in order to test their antituberculosis activity.

The formation of triazole (69) from 4-acetamidobenz-

aldehyde thiosemicarbazone (67) was reported in 1951 by Duschinsky and Gainer[57]. These workers did not oxidize the thiosemicarbazone directly with ferric chloride. Instead, they used the S-benzyl derivative (68) as the substrate for oxidation (eq. 20). By blocking the sulfur of the thiosemicarbazone (67), they achieved closure through nitrogen to the triazole (69). Mechanistic information was not included.



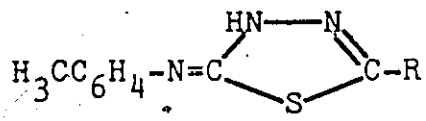
[20]

The earlier work of Young and Eyre[50] was confirmed by Holmberg[58] in 1955. Using ferric chloride in alcohol with a wide variety of aldehyde thiosemicarbazones, he demonstrated that in all cases the products were the thiadiazoles (55).

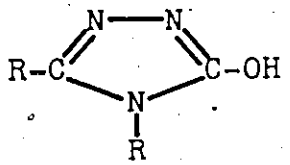
Two methods for the preparation of 2-iminoaryl-1,3,4-thiadiazolines (70) were reported in 1955. Das and Rout[59] treated a variety of 4-p-tolylthiosemicarbazones with either iodine or alkaline potassium ferricyanide, causing them to undergo cyclization to (70). This was in contrast to findings

of earlier workers[50,52,54,55,58] who in similar oxidations reported thiadiazole products. The authors did not explain this discrepancy.

In 1959 two Indian workers[7] repeated the oxidation of 4-arylthiosemicarbazones with alkaline potassium ferricyanide. In addition to product (70), they isolated a high-melting, alkali-soluble substance. Further analysis indicated that this was the 5-hydroxy-3,4-diaryl-1,2,4-triazole (71). The



(70) R = aryl



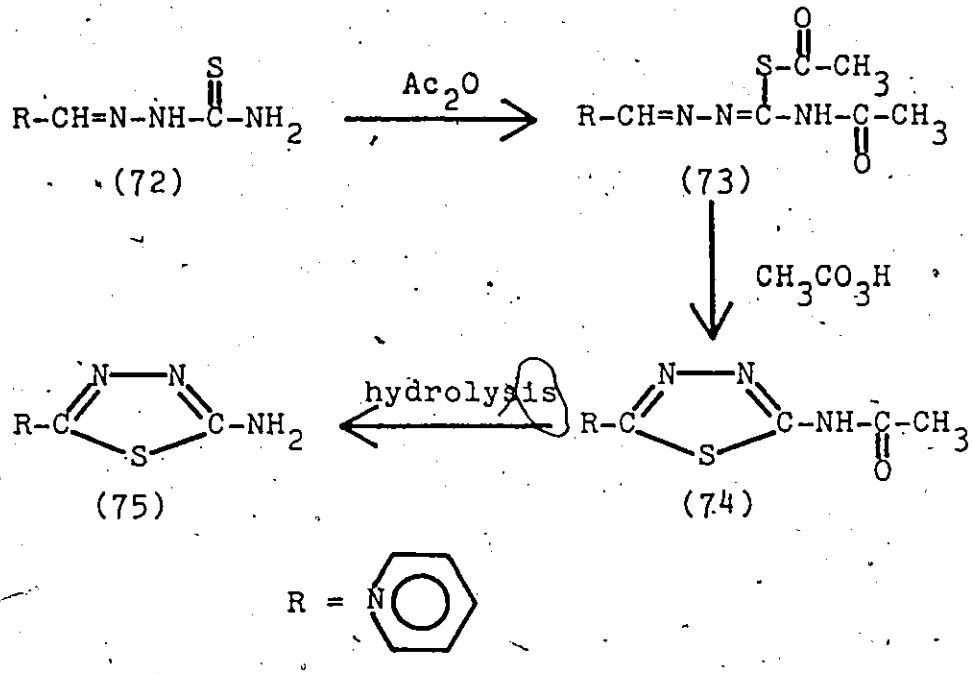
(71) R = aryl

products (71) apparently resulted from desulfurization of the thiosemicarbazone by the alkaline ferricyanide and subsequent oxidation of the semicarbazone to the hydroxytriazole (71). These findings were confirmed when 4-arylsemicarbazones, oxidized with ferricyanide, also yielded (71) (see page 3). Mechanisms for the preceding conversions were not given.

The preparation of 5-(4-pyridyl)-2-amino-1,3,4-thiadiazole (75) was reported in 1958 by Hemmerich and co-workers[60]. Rather than directly oxidizing pyridine-4-aldehyde thiosemicarbazone, these workers chose instead to oxidize the diacetyl derivative (73) formed by the action of acetic anhydride on (72). By oxidizing (73) with peracetic acid, they isolated

(74) which was then hydrolyzed to (75) (eq. 21).

[21]



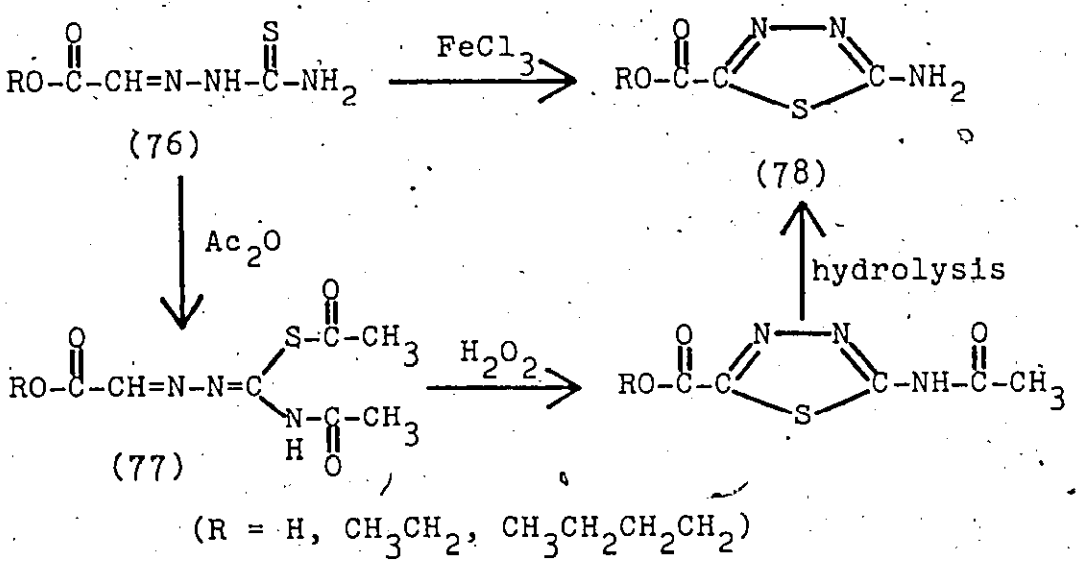
The oxidation of pyridine-4-aldehyde thiosemicarbazone (72) was re-examined in 1961 by Sadler[61]. This author claimed, however, that (72) could be converted to the thiadiazole (75) by direct oxidation with ferric chloride. The compound (75) was prepared for the purpose of testing its antivaccinal activity in biological systems.

Jones and co-workers[62] again investigated the oxidation of (72) in 1965. They disputed the report of Sadler[61], that oxidation of (72) with ferric chloride led to (75), and claimed instead to have obtained only the hydrochloride of (72) from the oxidation. They did report, however, that by treating quinoline-4-aldehyde thiosemicarbazone with ferric chloride, they obtained the thiadiazole derivative.

Werber and co-workers, in a series of papers[63-65]

between 1959 and 1963, reported the ferric chloride oxidation of thiosemicarbazones of glyoxylic acid and some of its esters (76). In the first paper[63], they reported the oxidation of both the thiosemicarbazones and the acetylated derivatives (77) to the thiadiazoles (78) (eq. 22).

[22]



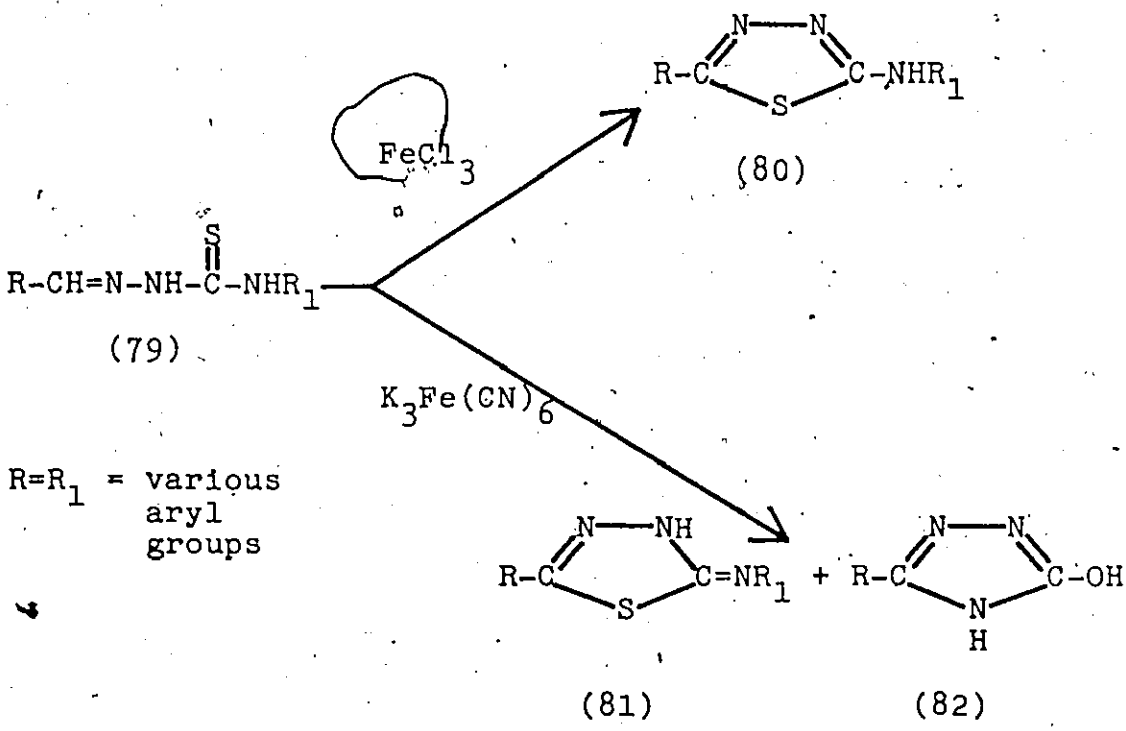
In the two subsequent papers[64,65], Werber and co-workers extended their oxidation to include 4-methyl and 4-phenylthiosemicarbazones of butyl glyoxylate as well as the unsubstituted, 4-methyl and 4-phenylthiosemicarbazones of glyoxylic acid. In all cases the products were the corresponding thiadiazoles.

The photooxidation of thiosemicarbazones was reported in 1960 by Sharp[9]. However, information concerning the products of the oxidations was not given.

In a series of reports between 1962 and 1964, Srinivasan and co-workers[66-69] reported the oxidation of arylalde-

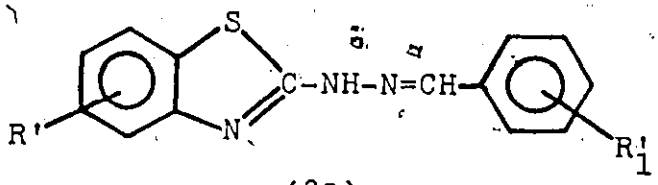
hyde 4-arylthiosemicarbazones (79) (eq. 23). With ferric chloride[66,67] they isolated the 2-arylamino-5-aryl-1,3,4-thiadiazoles (80), and with alkaline potassium ferricyanide they obtained[66,68] the 2-arylimino-5-aryl-Δ^4-1,3,4-thiadiazolines (81) as well as trace amounts of the 3,4-diaryl-5-hydroxy-1,2,4-triazoles (82) (compare reference 7). All the products were well characterized[66] and tested for their "in vitro" inhibitory effect on the growth of Mycobacterium tuberculosis.

[23]

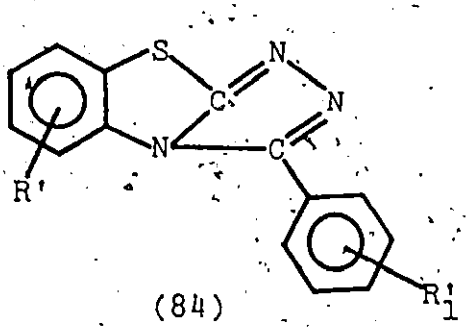


When these workers[69] used bromine in chloroform as the oxidizing agent, they found that (79, R = $R'C_6H_4$, R_1 = $R_1'C_6H_4$) were converted to 1-arylidene-2-(2'-benzothiazolyl)-

hydrazones (83). Further oxidation of the hydrazone (83) to the benzthiazoles (84) was achieved with ethanolic ferric chloride. However, an attempt to oxidize (79, R = $R'C_6H_4$, $R_1 = R_1'C_6H_4$) directly to (84) using a stronger oxidant, namely bromine in pyridine, failed and the products were the thiadiazoles similar to (80).

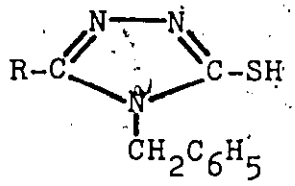


(83)

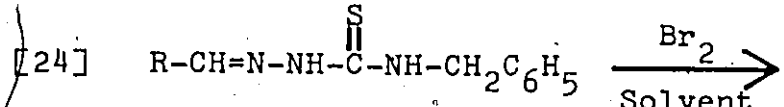


(84)

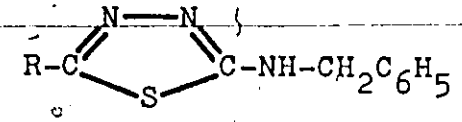
In 1966 and 1969 Srinivasan and co-workers[70,71] reported the oxidation of arylaldehyde 4-benzylthiosemicarbazones (85) with bromine (eq. 24). They found that the products obtained depended on the solvent used for the oxidation.



(86)

[24] 

(85)

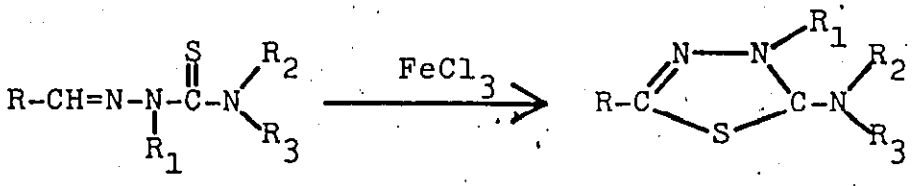


(87)

By using chloroform as solvent they isolated 50-80% of the 3-mercapto-4-benzyl-5-aryl-1,2,4-triazoles (86) and 10-30% of the 2-benzylamino-5-aryl-1,3,4-thiadiazoles (87). Carbon tetrachloride gave 55-80% of (87) and 1-30% of (86), while oxidation in acetic acid led to 60-90% of (86) and no (87). When N-bromosuccinimide in carbon tetrachloride was used as the oxidizing agent, the thiadiazoles (87) were the sole products. These results are in contrast to earlier ones (see reference 69 and page 31) where oxidation of 4-arylthiosemicarbazones (79), unlike (85), gave the hydrazones (83) and not triazoles or thiadiazoles.

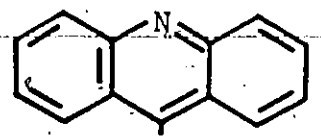
Ioffe and Tomchin[72], in 1969, published the ferric chloride oxidation of 9-acridinealdehyde thiosemicarbazone (88, $R_1=R_2=R_3$ = H), 2-methylthiosemicarbazone (88, R_1 = CH_3, $R_2=R_3$ = H) and 4,4-dimethylthiosemicarbazone (88, R_1 = H, $R_2=R_3$ = CH_3). In each case the product was the 5-(9-acridine)-1,3,4-thiadiazole derivative (eq. 25). These thiadiazoles

[25]



(88)

R =



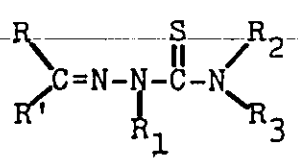
were prepared in order to study their electronic absorption

spectra. It was found that cyclization of (88) to the thiadiazoles led to a bathochromic shift of the spectrum, due presumably to lengthening of the chain of conjugation.

The most recently published oxidation of aldehyde thiosemicarbazones appears to be that of Tsurkan and Tsurkan[73]. By using ethanolic ferric chloride on the thiosemicarbazones, these workers synthesized a variety of 5-substituted-2-amino-1,3,4-thiadiazoles (55, R = $C_6H_5CH{=}CH$, 3,4-$(CH_3O)_2C_6H_3$, 4-BrC_6H_4, 4-$CH_3OC_6H_4$, C_6H_5, 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$). These compounds were used for detailed interpretations of infrared and ultraviolet spectra.

B) KETONE THIOSEMICARBAZONES

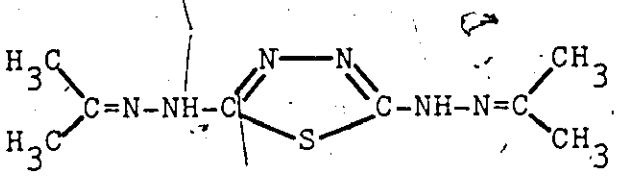
The first oxidation of ketone thiosemicarbazones (89) appears to be that of De and Roy-Choudhury[52] in 1928. They oxidized acetone thiosemicarbazone (89, R=R' = CH_3, R_1=R_2=R_3 = H), 4-phenylthiosemicarbazone (89, R=R' = CH_3, R_1=R_2 = H, R_3 = C_6H_5), and 4-p-tolylthiosemicarbazone (89, R=R' = CH_3, R_1=R_2 = H, R_3 = $H_3CC_6H_4$) with alcoholic hydrogen peroxide. The reported products were (90) from the unsubstituted thiosemicarbazone and (91) from the 4-substituted analogues. The products (90)



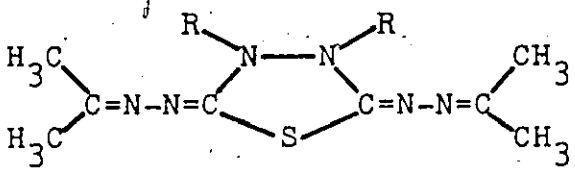
(89)

$R=R'=R_1=R_2=R_3$ = alkyl or aryl

and (91) were thought to arise from two molecules of thiosemicarbazone similar to the proposed formation of thiadiazole



(90)

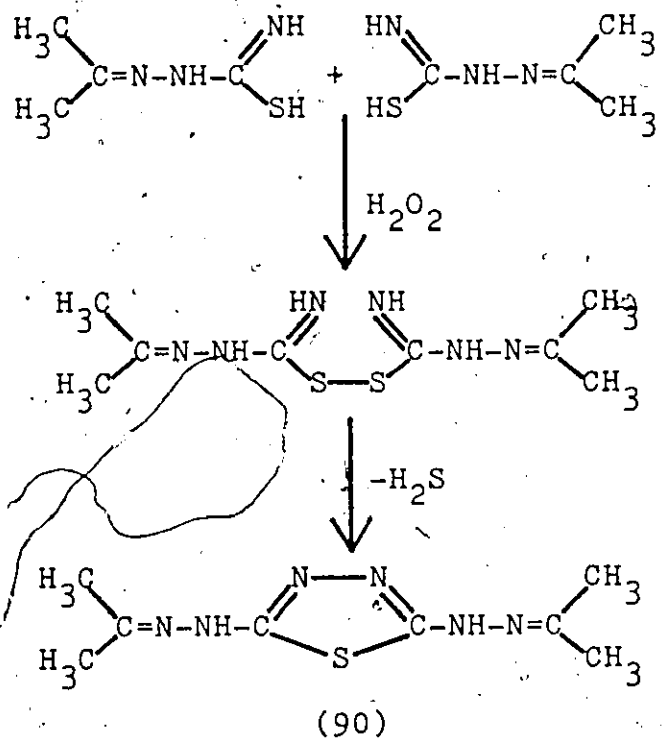


(91)

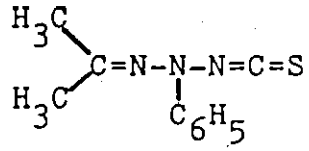
R = C_6H_5, p-$H_3CC_6H_4$.

derivatives from substituted arylthioureas[74]. The mechanism indicated for formation of (90) and (91) is shown in Scheme V.

Scheme V



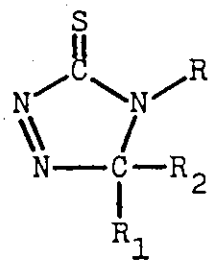
In 1968, Blackstock and Happer[39] published a report on the oxidation of acetone 2-phenylthiosemicarbazone (89, R=R' = CH_3, R_1 = C_6H_5, R_2=R_3 = H). These workers used iodine as the oxidizing agent and obtained the isothiocyanate (92) as the product. The thiosemicarbazone was assumed to rearrange via a Hofmann rearrangement to (92). They claimed this to be the first known case of a Hofmann rearrangement in thioamide systems. A similar rearrangement was claimed for acetone 2-phenylsemicarbazones (see page 18).



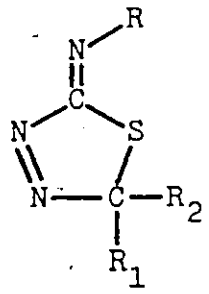
(92)

The oxidative cyclization of 4-methyl and 4-arylketo-thiosemicarbazones was reported by Landquist[75] in 1970. He found that these 4-substituted thiosemicarbazones underwent oxidative cyclization on chromatographic alumina to give the Δ^1-1,2,4-triazoline-5-thiones (93). On oxidation with manganese dioxide, he isolated the 5-imino-Δ^3-1,3,4-thiadiazolines (94). The oxidations appeared to be strongly influenced by steric factors. Steric hindrance retarded or prevented cyclization to the triazolinethiones (93) but appeared to have no effect on cyclization to thiadiazolines (94). The steric hindrance arose from substituents on the 4-aryl moiety.

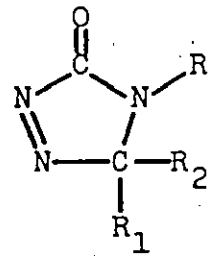
With mercuric acetate, the products (93) could be converted to the triazolinones (95), which were sometimes formed as well during the cyclization reaction on the alumina. The formation of (93) was explained in terms of the initial formation of triazolidinethiones (96) from addition of the terminal nitrogen to the double bond in the thiosemicarbazone. This process was facilitated by the solid alumina which held the thiosemicarbazone in a suitable configuration for closure. Then oxidation by dissolved oxygen was thought to lead to (93). The mechanism of cyclization over manganese dioxide was not indicated.



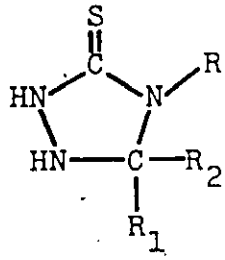
(93)



(94)



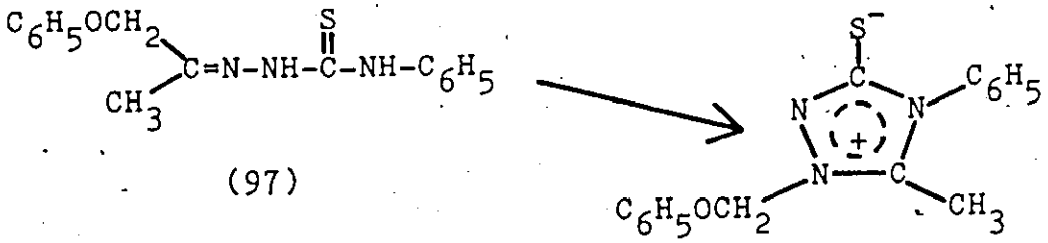
(95)



(96)

Landquist also reported[76] the oxidation of phenoxy-

acetone 4-phenylthiosemicarbazone (97) on alumina and with manganese dioxide. Along with the expected products (page 37), he also isolated an isomer of (93, R = C_6H_5, R_1 = CH_3, R_2 = $C_6H_5OCH_2$). This product was found to be the 3-mercapto-5-methyl-1-phenoxymethyl-4-phenyl-1,2,4-triazolinium hydroxide inner salt (98). The product (98) was thought to arise from a rearrangement of the intermediate triazolidinethione (96) (see page 37) through a 1,2 shift to an electron-deficient centre (ie. the nitrogen) formed during the oxidation.

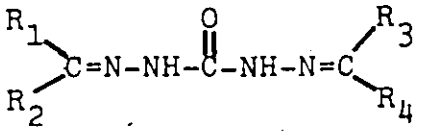


(97)

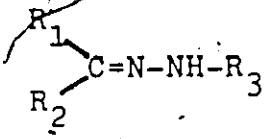
(98)

III OXIDATION OF CARBOHYDRAZONES AND HYDRAZONES

Carbohydrazones (99) and hydrazones (100) are derivatives similar to semicarbazones. Their oxidation has been studied in great detail, particularly that of hydrazones.



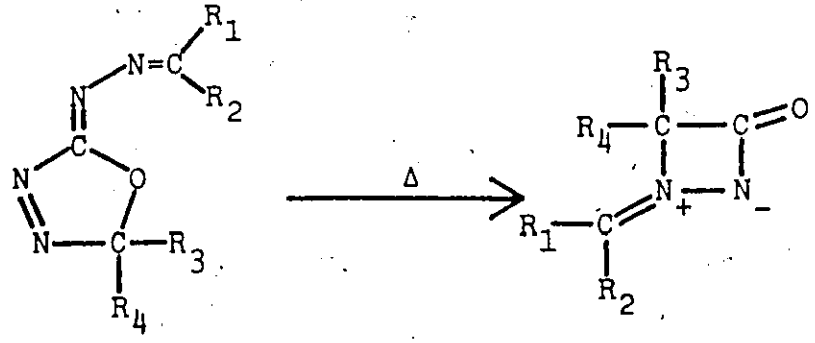
(99)



(100)

When carbohydrazones (99) were oxidized[42,77], they generally gave products of the type (101), 2-alkylidene-hydrazono-Δ^3-1,3,4-oxadiazolines. On heating, (101) were converted to the cyclic azomethine imines (102) in a new synthetic procedure[78] (eq. 26).

[26]



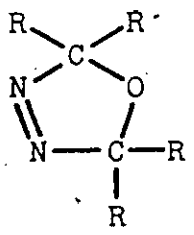
(101) (102)

A wide variety of hydrazones (100) have been oxidized, resulting in a vast number of products. Some examples are: the oxidation of phenylhydrazones of levulinanilide, levulinic acid and various other acids to substituted lactones with lead tetraacetate[79]; the oxidation of benzophenone carbethoxyhydrazones with lead tetraaacetate to give acetoxydiphenylmethylazocarboxylate and acetyldiphenylmethyl ethyl carbonate[80]; the oxidation of ketohydrazones to azoacetates[37].

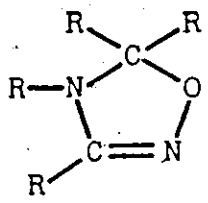
A more exhaustive review of hydrazone and carbohydrazone oxidation is not necessary here since several reviews of the subject already exist. The reader is referred in particular to three of these[81,82,83].

IV Δ^3-1,3,4-OXADIAZOLINES

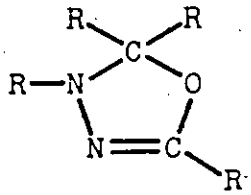
The Δ^3-1,3,4-oxadiazoline ring system (103) has been known for approximately sixty years. In addition to (103), several isomers are known as well. Some of these are: the Δ^2-1,2,4- (104), the Δ^2-1,3,4- (105), the Δ^3-1,2,4- (106), the Δ^4-1,2,4- (107), and the Δ^4-1,2,3-oxadiazolines (108).



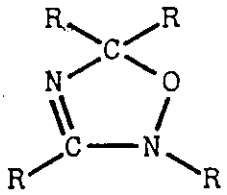
(103)



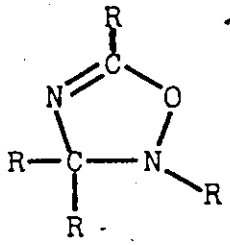
(104)



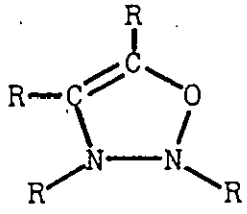
(105)



(106)



(107)

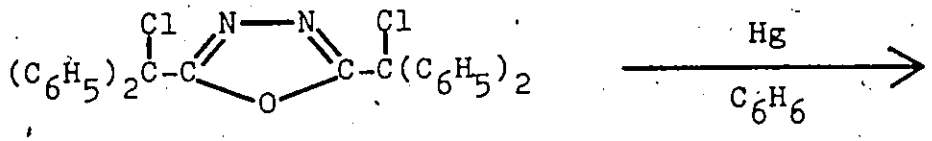


(108)

These isomers have been well catalogued in the literature and will not be mentioned any further.

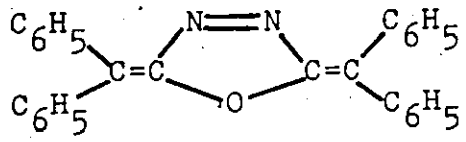
It appears that the earliest reported Δ^3-1,3,4-oxadiazoline system was that of Stollé and Laux[84] in 1911. They

obtained the compound (110) by treatment of bisdiphenylchloromethylfurodiazole (109) with mercury in benzene (eq. 27). The name assigned to (110) was bisdiphenylmethylenedihydrofurodiazole.



(109)

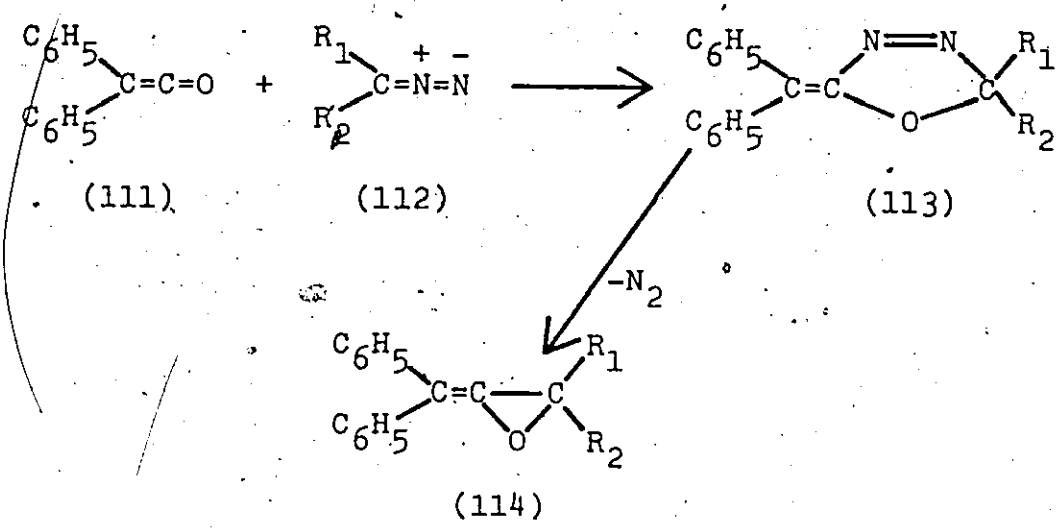
[27]



(110)

The oxadiazoline system was next reported in 1921 by Staudinger and Reber[85], who postulated it as a reaction intermediate. On reacting diphenylketene (111) with several diazomethane derivatives (112), they isolated the epoxides (114) as the major products (eq. 28). They indicated that (114) might arise from the intermediate Δ^3-1,3,4-oxadiazoline (113), as shown in eq. 28. In the case where $R_1 = C_6H_5$ and $R_2 = p\text{-}CH_3OC_6H_4$, they isolated a yellow solid which they believed to be (113, $R_1 = C_6H_5$, $R_2 = p\text{-}CH_3OC_6H_4$).

In two earlier reports[86,87], Staudinger and co-workers had reported that reaction of (111) with (112) gave a compound with structure (115). They later showed this to be in error[85].



(111) (112) (113)

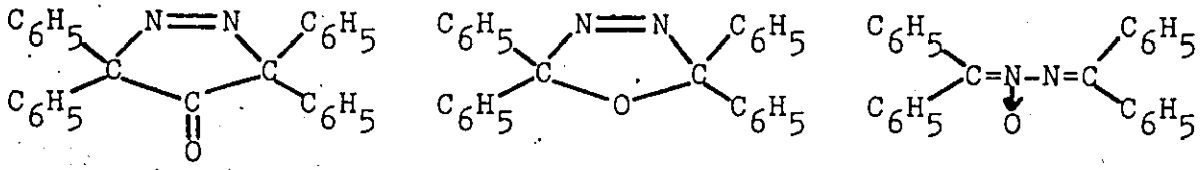
[28]

(114)

R_1 = H, C_6H_5, H, C_6H_5, C_6H_5.

R_2 = $CO_2CH_2CH_3$, C_6H_5, H, C_6H_5CO, $CH_3OC_6H_4$.

Schönberg and Barakat[88] suggested in 1938, that 2,2,5,5-tetraphenyl-Δ^3-1,3,4-oxadiazoline (116) was the product of the oxidation of benzophenone oxime with potassium ferricyanide. Auwers, who had carried out the original oxidation of benzophenone oxime[89,90] disputed[91] their findings and claimed that the product was the diphenylketazinoxide (117).



(115) (116) (117)

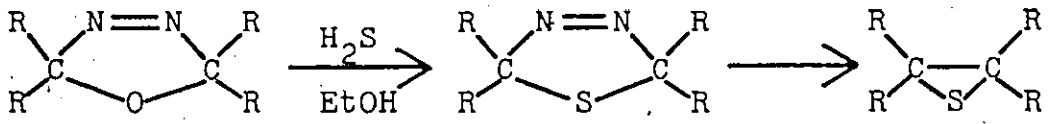
Futhermore, Auwers oxidized[92] p-methyl, o-methyl and p-chlorobenzophenone oximes, as well as acetophenone oxime, t-butyl phenyl ketoxime and dibenzyl ketoxime. In all cases he claimed

formation of the ketazinoxide.

Auwers' claim was supported in 1933 and 1942 by Dyer and co-workers[93,94]. These workers oxidized benzophenone oxime with potassium ferricyanide, iodine and silver oxide. In each case they claimed (117) as the product.

Schönberg and Barakat[88] also indicated that the thermal decomposition of what they believed to be (116) led to benzophenone and diphenyldiazomethane. The diphenyldiazomethane was reported to decompose further to benzophenone azine and nitrogen.

In 1939, Schönberg and Barakat[95] published the oxidation of di-p-tolyl ketoxime and p,p'-dimethoxybenzophenone oxime with potassium ferricyanide. In both cases, the product was claimed to be the 2,2,5,5-tetraaryl-Δ^3-1,3,4-oxadiazoline. They also reported that treatment of this oxadiazoline with hydrogen sulfide in boiling ethanol led to the tetraarylethylene sulfides (119) via the intermediate thiadiazoline (118) (eq. 29).



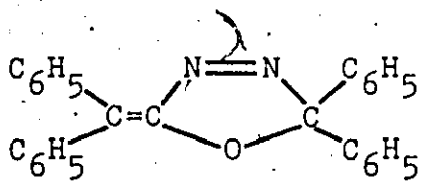
[29]

R = p-$H_3CC_6H_4$, p-$CH_3OC_6H_4$

The next mention in the literature of Δ^3-1,3,4-oxadiaz-

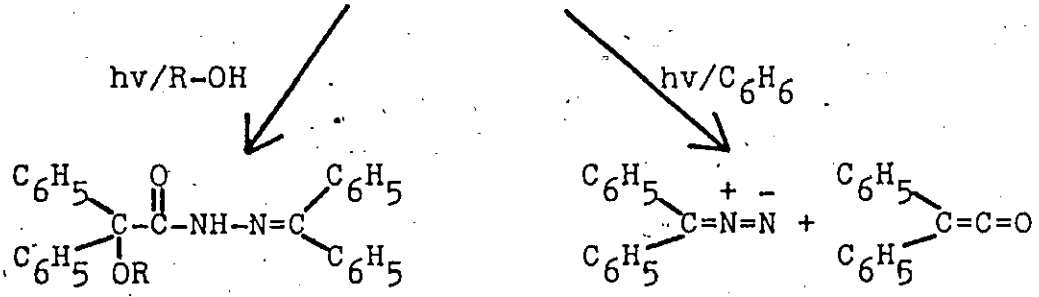
olines appeared in 1952. Offe and co-workers[96] tested what they believed to be (116) and similar systems for their activity against Mycobacterium tuberculosis.

The photolysis of oxadiazolines (110) and (113, $R_1=R_2 = C_6H_5$) was studied by Kirmse[97] in 1960. He found that, while (110) was stable to ultraviolet light, (113, $R_1=R_2 = C_6H_5$) was not. In hydroxyl free solvents such as benzene, (113, $R_1=R_2 = C_6H_5$) decomposed to diphenyldiazomethane and diphenylketene. However, in hydroxylic solvents such as acids or alcohols, addition products were obtained (eq. 30). Mechanisms were not given.



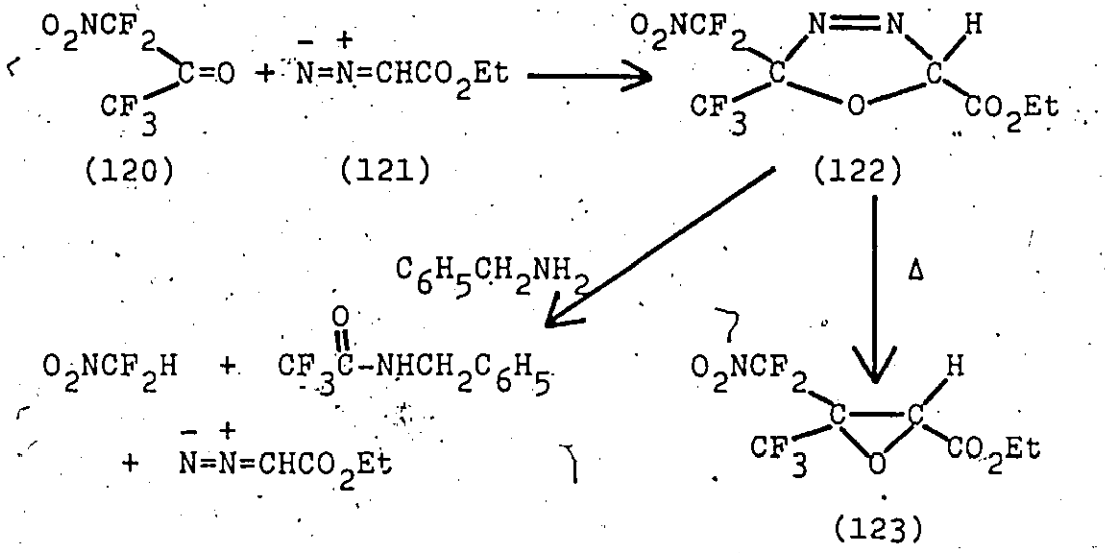
(113, $R_1=R_2 = C_6H_5$)

[30]



Preparation of a fluoro-substituted oxadiazoline was accomplished by Russian workers[98] in 1964. By reacting the ketone (120) with the diazo compound (121), they obtained the oxadiazoline (122) (eq. 31). On thermolysis, compound (122) gave the epoxide (123). Reaction of (122) with benzylamine

resulted in difluoronitromethane, N-benzyltrifluoroacetamide and ethyl diazoacetate (eq. 31).

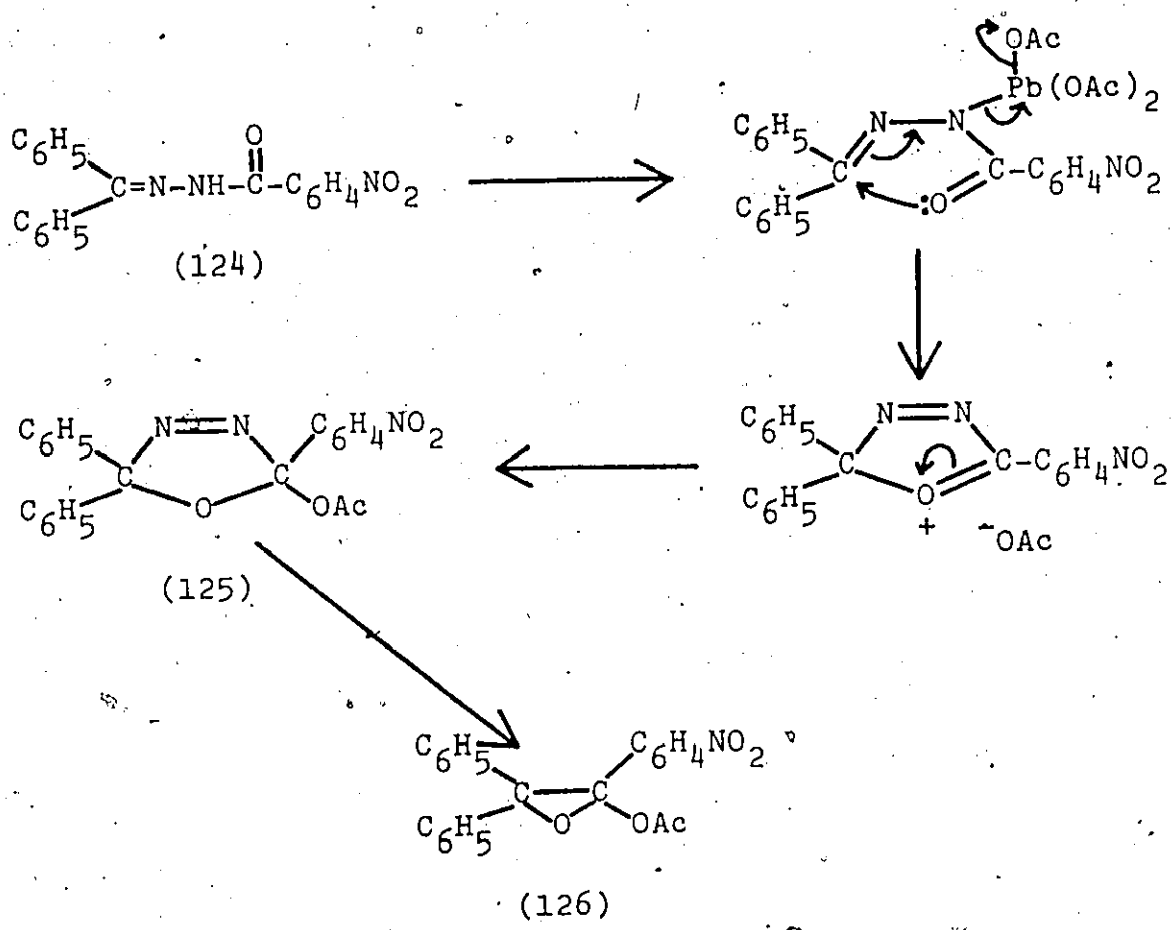


[31]

An oxadiazoline (125) was postulated in 1966 as an intermediate in the oxidation of benzophenone p-nitrobenzoylhydrazone (124) with lead tetraacetate. Gladstone and Norman[99] explained the formation of the epoxide (126) in this oxidation as shown in Scheme VI.

In a series of papers published between 1966 and 1968, Hoffman and Luthardt discussed the synthesis of oxadiazolines from benzoylhydrazones[100,102], mechanisms of formation[101,102], and subsequent reactions[103]. On oxidizing the benzylhydrazones (127) with lead tetraacetate, they obtained the oxadiazolines (129) (eq. 32). The reaction was carried out at -70°C to -40°C, at which temperatures an intermediate azoacetate (128) was observed. On warming to -20°C, they observed the formation

Scheme VI

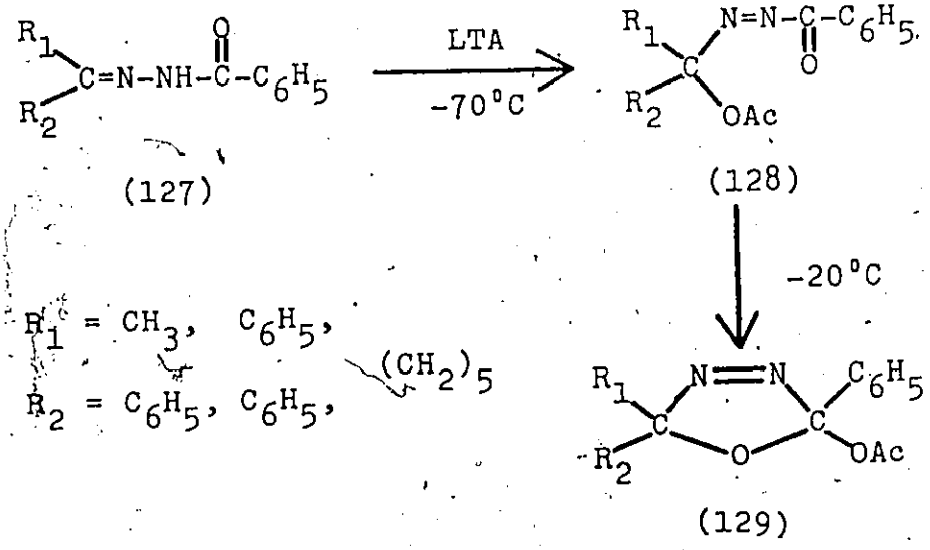


(124)

(125)

(126)

of (129) (eq. 32).



(127)

(128)

(129)

[32]

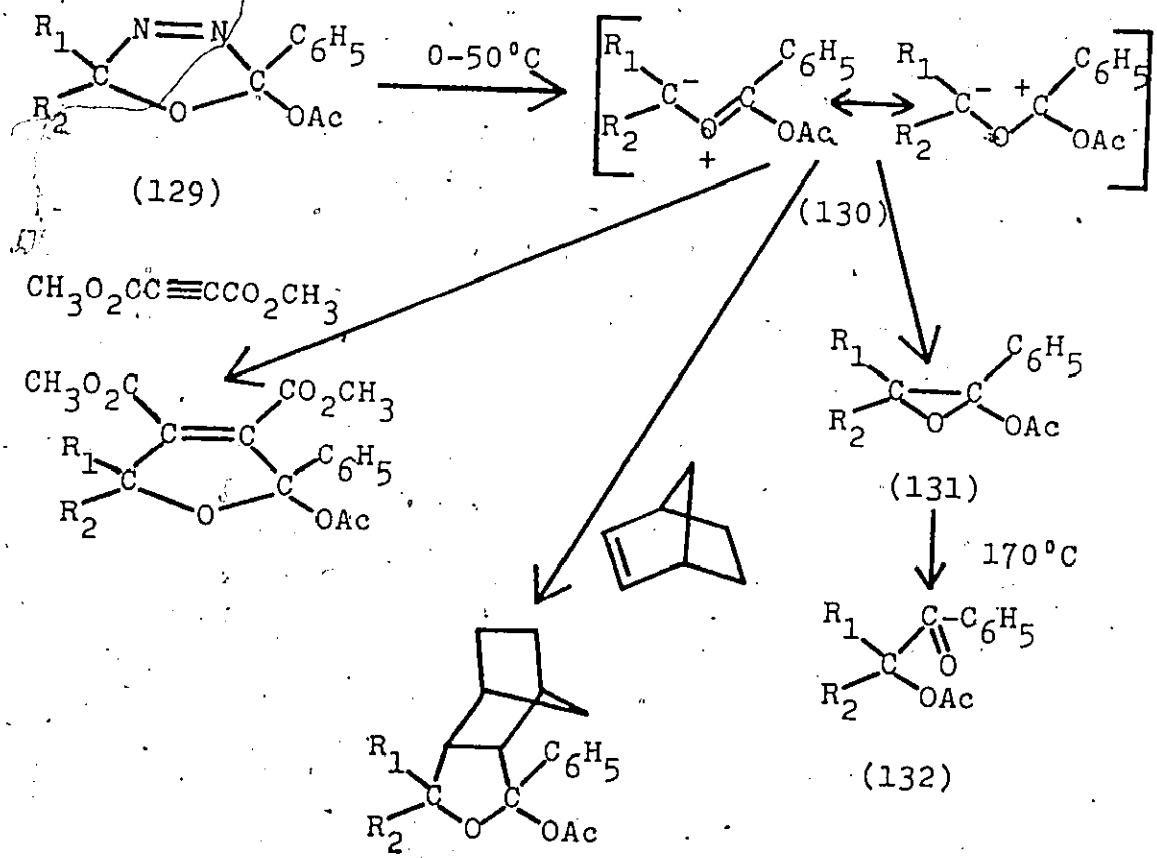
R_1 = CH_3, C_6H_5,

R_2 = C_6H_5, C_6H_5, $(CH_2)_5$

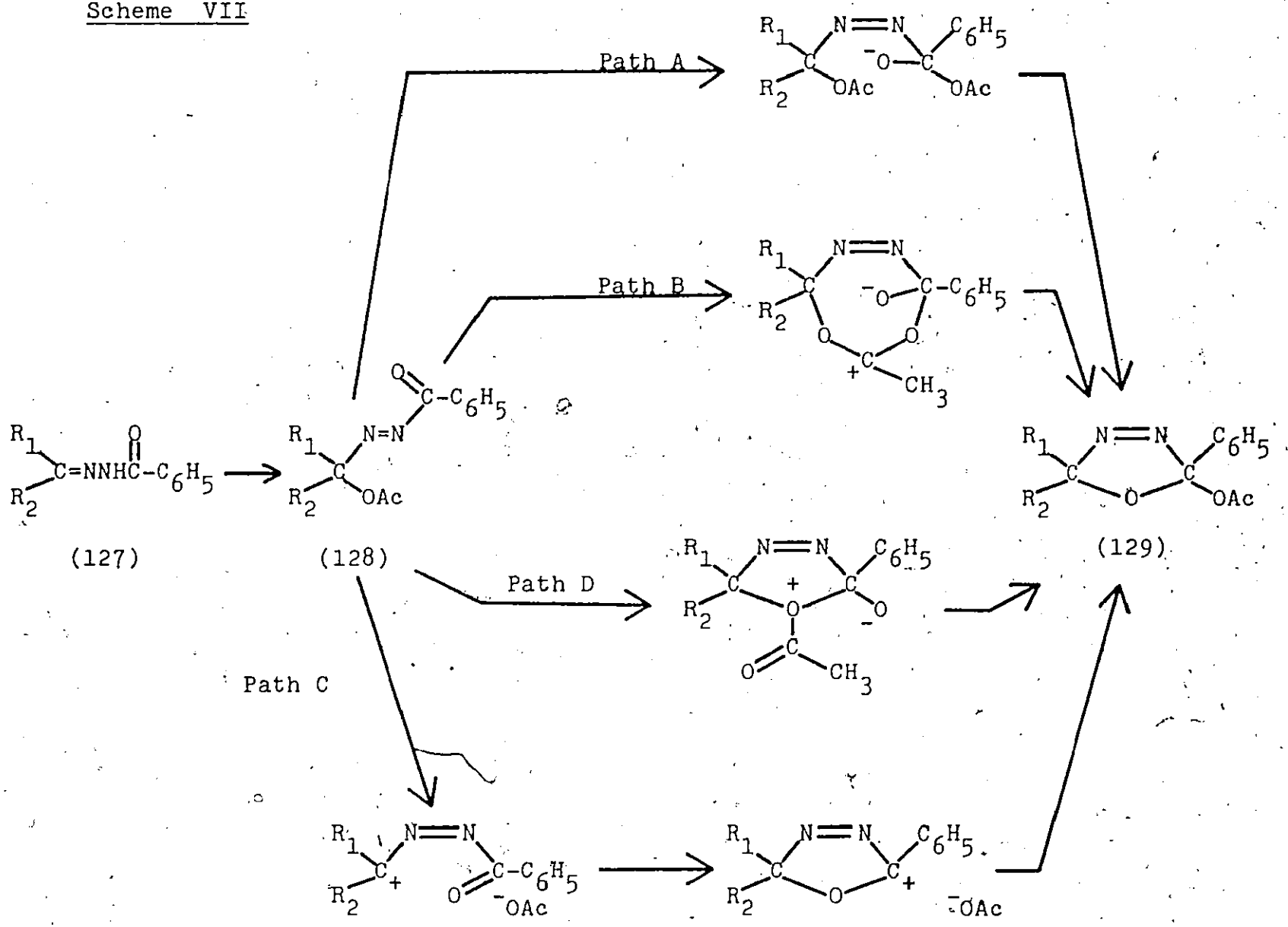
The mechanism of formation of (129) was examined in detail by Hoffman and Luthardt. From the several possibilities available (Scheme VII), they chose path C as the most likely mechanism.

It was found that oxadiazolines (129) were thermally unstable and decomposed to the epoxyacetates (131) which, on heating, gave the α-acetoxy ketones (132) (eq. 33). The decomposition of (129) to (131) was explained by postulating a carbonyl-ylide intermediate (130), formed by loss of nitrogen from (129), which subsequently closed to give (131). The existence of (130) was confirmed by trapping experiments with norbornene and dimethylacetylenedicarboxylate (eq. 33).

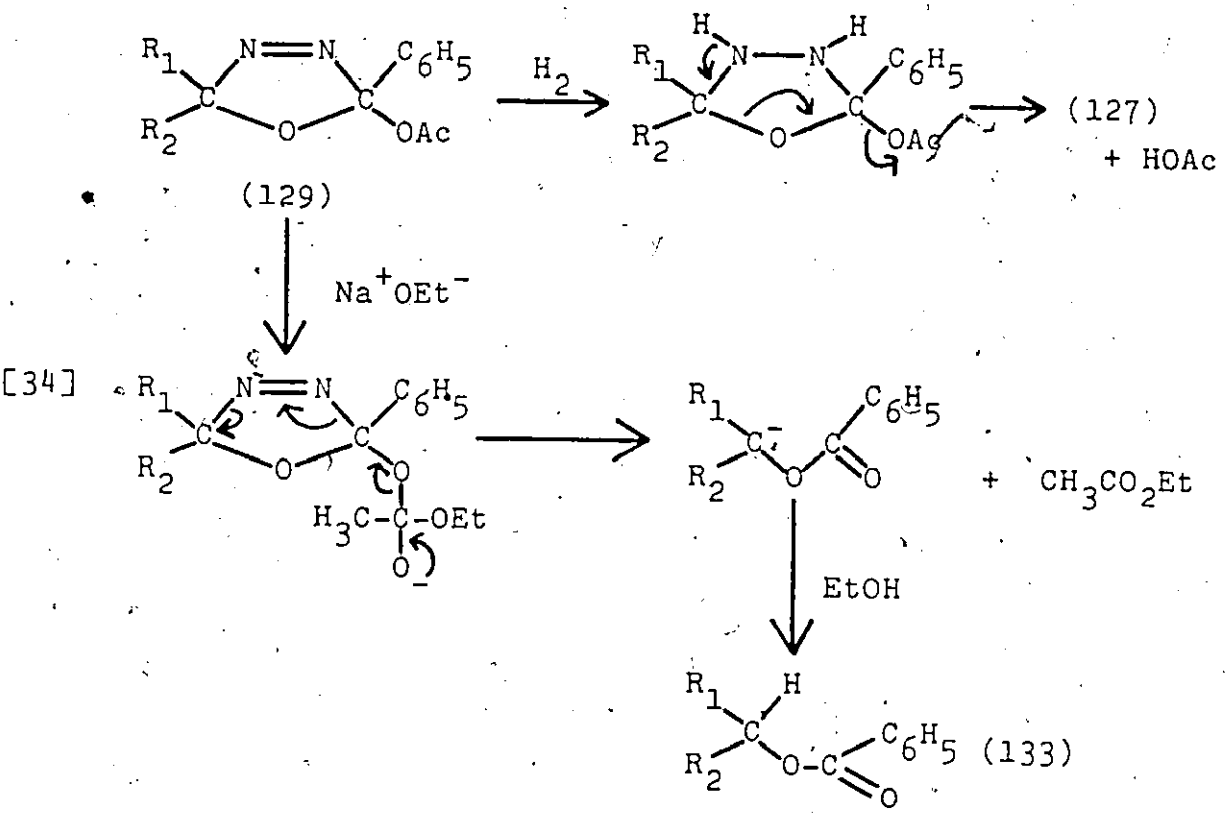
[33]



Scheme VII

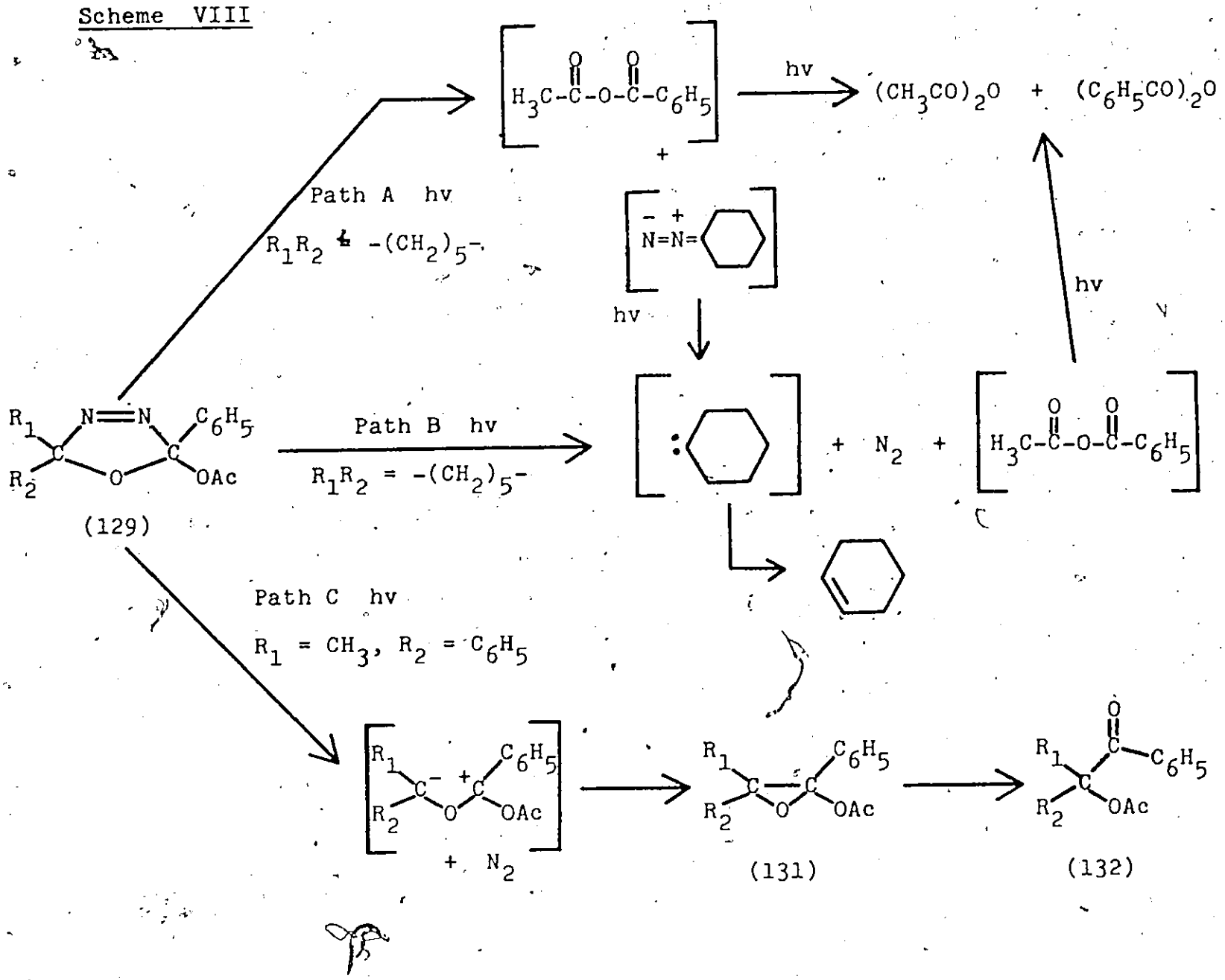


The oxadiazoline (129) was hydrogenated, resulting in the original hydrazone (eq. 34). Treatment of (129) with sodium ethoxide led to the ester (133) (eq. 34).



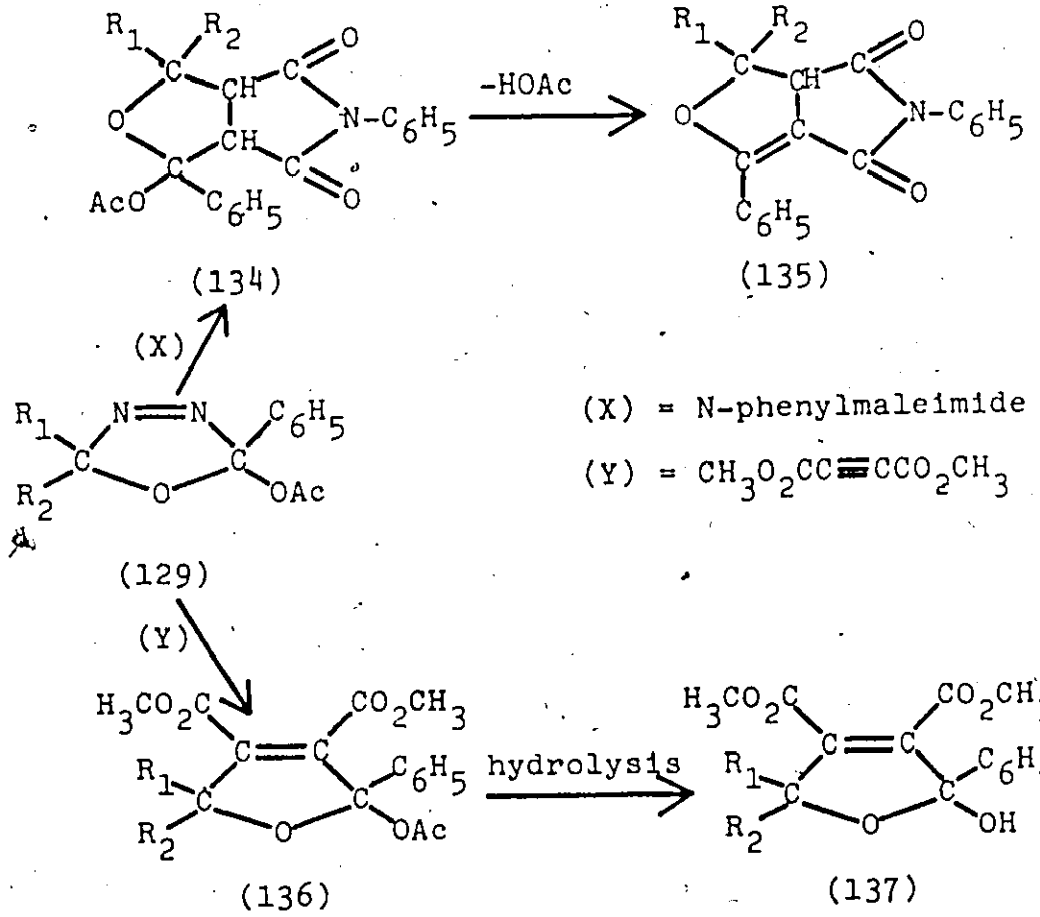
The photolysis of (129) was also studied. It appears that the mechanisms of the photolytic reactions were dependent on the nature of R_1 and R_2 (Scheme VIII). When R_1 = CH_3, R_2 = C_6H_5, the photolysis products were nitrogen, the epoxide (131) and the α-acetoxy ketone (132) (Path C, Scheme VIII). When R_1R_2 = $-(CH_2)_5-$, the products were cyclohexene, nitrogen and a mixture of acetic and benzoic anhydride (Path A or B, Scheme VIII). Path A in Scheme VIII had precedence in the literature (see page 45 and reference 97).

Scheme VIII


Path A hv
R_1R_2 = $-(CH_2)_5-$
Path B hv
R_1R_2 = $-(CH_2)_5-$
Path C hv
R_1 = CH_3, R_2 = C_6H_5
hv
hv
hv
+ N_2 +
+ N_2
(129)
(131)
(132)

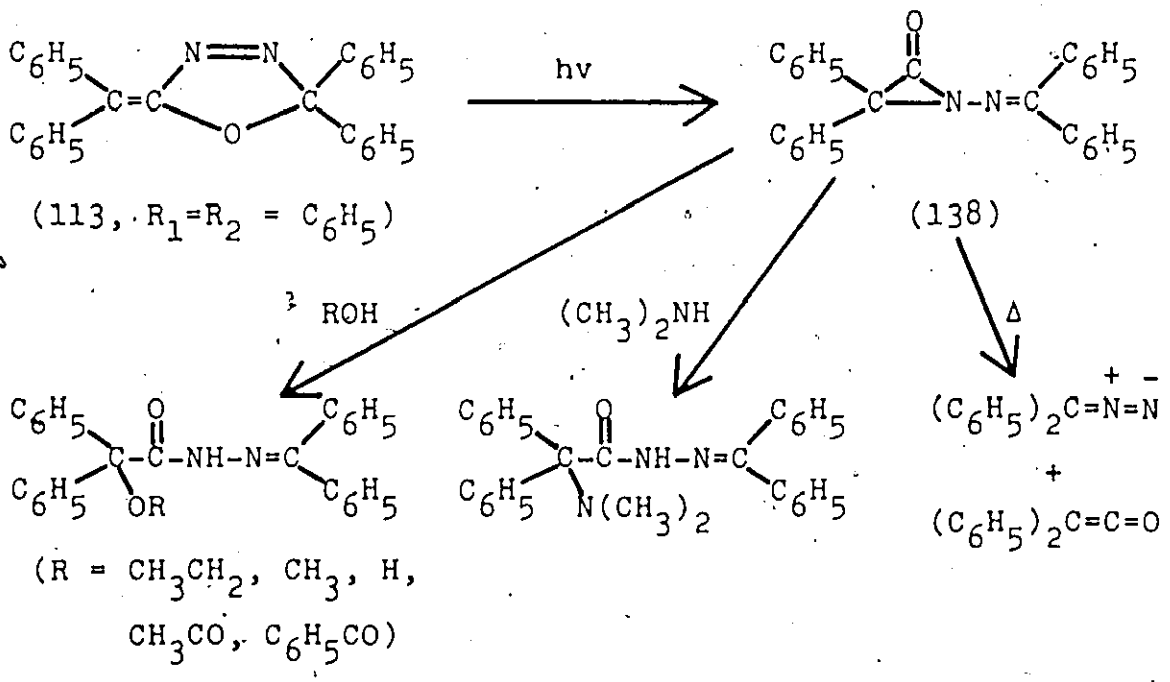
In 1967, Rajagopalan and Advani[104] reported the 1,3 cycloaddition reactions of the carbonyl-ylides resulting from the mild thermolysis of the oxadiazolines (129). Using N-phenylmaleimide and dimethylacetylenedicarboxylate as traps, they succeeded in isolating adducts similar to those reported by Hoffman and Luthardt (see page 48 and reference 103). With N-phenylmaleimide the product was not the expected adduct (134) but rather (135), resulting from (134) by loss of acetic acid (eq. 35). Also in the case of dimethylacetylenedicarboxylate, they obtained the hydroxy derivative (137) and not the expected product (136) (eq. 35).

[35]



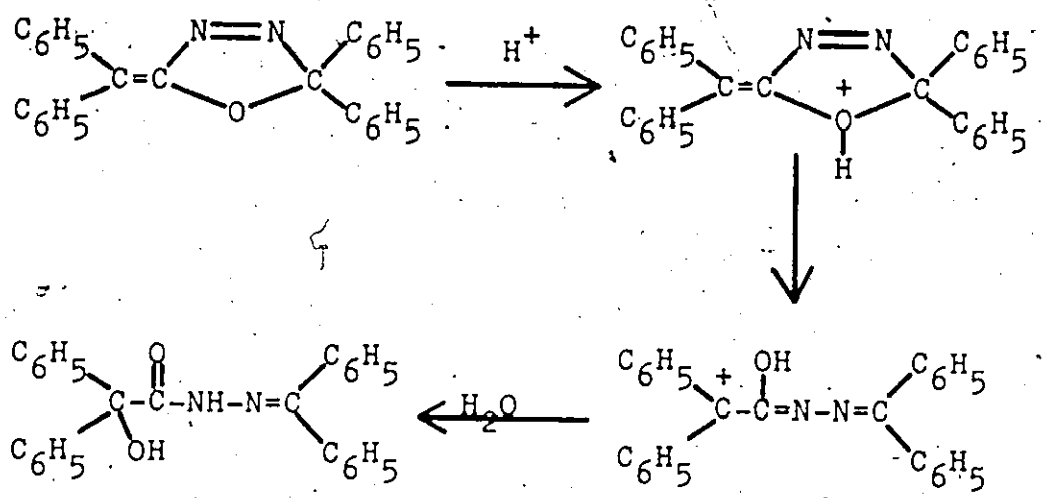
Interest in the 2,2-diphenyl-5-diphenylmethylene-Δ^3-1,3,4-oxadiazoline (113, $R_1=R_2 = C_6H_5$) (see page 43) of Staudinger[85] and Kirmse[97] was revived in 1968 by Michejda[105]. This worker reviewed the work of Kirmse[97] and suggested a mechanistic scheme to account for the observed results of the photolysis of (113, $R_1=R_2 = C_6H_5$) (Scheme IX). To explain the production of ketene and diazoalkane, he claimed the existence of an intermediate α-lactam (138). By photolysis in the presence of hydroxylic compounds or dimethylamine, he stated that he had trapped the α-lactam as it decomposed (Scheme IX).

Scheme IX



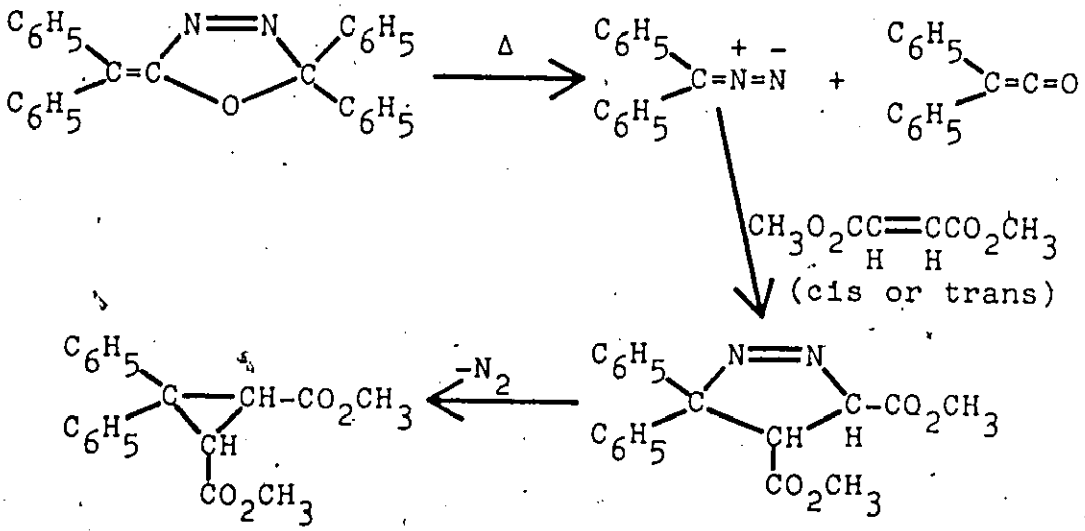
Michejda also described the acid catalyzed hydrolysis

of (113, $R_1=R_2 = C_6H_5$) (eq. 36), as well as its thermal



[36]

decomposition in the presence of dimethyl fumarate or maleate to cyclopropanes (139) (eq. 37).

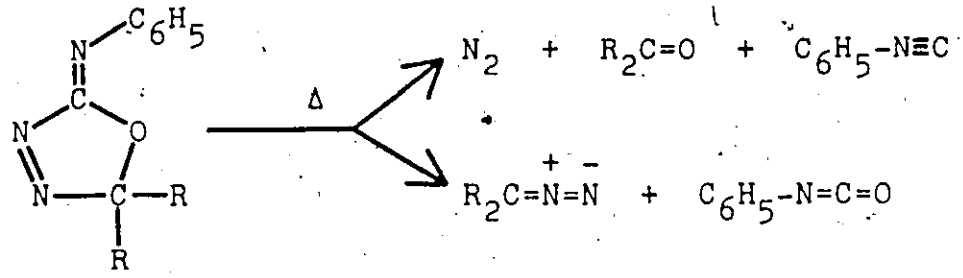


[37]

(139)

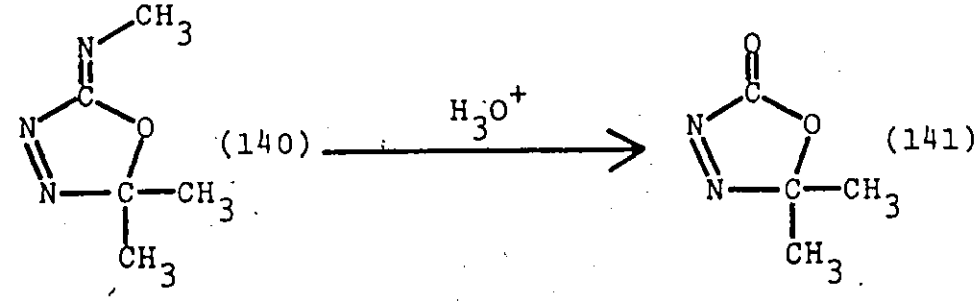
In 1966 and 1968 previous workers[42,77] in this laboratory reported the formation of Δ^3-1,3,4-oxadiazolines (101)

from the oxidation of ketocarbohydrazones (99) (see page 39). They also reported[41] the synthesis of 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines (50) by oxidation of 4-arylsemicarbazones (49) with lead tetraacetate (see page 19). West and Warkentin[106] published a report on the thermolysis of (50) in 1969. They claimed that (50) decomposed by a duality of pathways (eq. 38).

[38] 

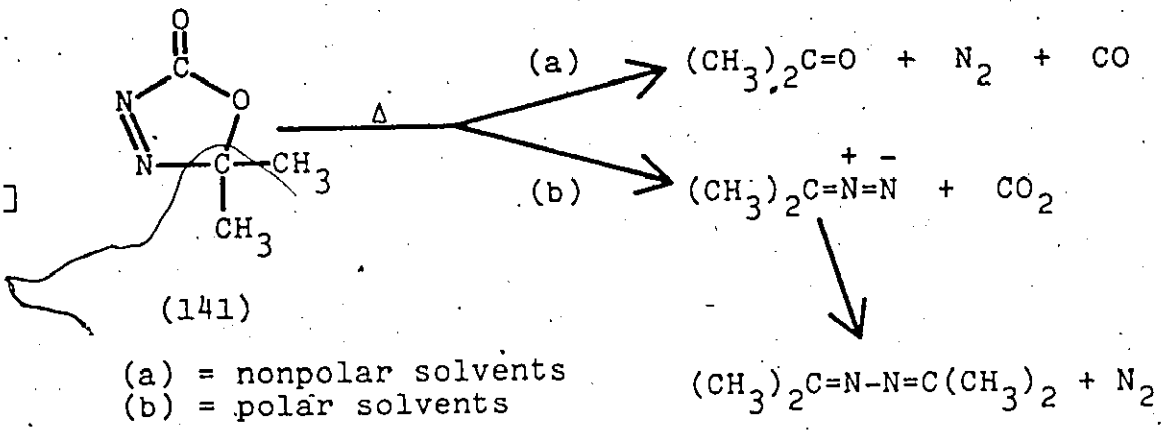
(50)

In 1970, Warkentin and co-workers[107] reported the hydrolysis of 5,5-dimethyl-2-methylimino-Δ^3-1,3,4-oxadiazoline (140) obtained by oxidation of acetone 4-methylsemicarbazone. In acid media (140) gave the 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (141) (eq. 39). The 5-ethyl-5-methyl- compound was also prepared in a similar fashion. In 1972, the same workers

[39] 

published a paper[108] describing the thermolysis of (141). Depending on the solvent used, decomposition of (141) proceeded predominantly via one of two pathways (eq. 40).

[40]



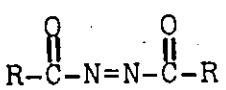
(141)

(a) = nonpolar solvents
(b) = polar solvents

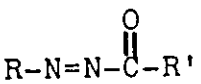
The oxadiazolines discussed in this chapter appear then to be the only cases of syntheses and reactions of Δ^3-1,3,4-oxadiazolines known prior to the work described in this thesis.

V α-CARBONYL AZO COMPOUNDS

The chemistry and spectral properties of azo compounds have been well documented in the literature[109, 110, 111]. However, the chemistry of α-carbonyl azo compounds does not appear to have received as much attention. The only extensive report on α-carbonyl azo compounds seems to be a review, published in 1966 by Fahr and Lin[112], concerned almost entirely with α,α'-dicarbonyl azo compounds (142). These authors cover in detail the synthesis, structure, spectroscopic behaviour and reactions of most of the known types of α,α'-dicarbonyl azo compounds.



(142)



(143)

R&R' = alkyl, aryl or alkoxy.

This discussion will be limited to a very brief description of the thermal decomposition and nucleophilic addition reactions of (142) with a more thorough investigation of the same reactions of α-carbonyl azo compounds (143).

There is a considerable difference in the chemistries of (142) and (143). It is well known that compounds (142)

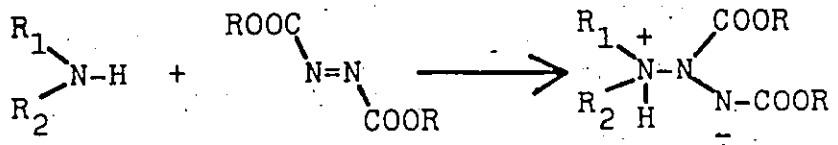
are more reactive towards nucleophiles than are compounds (143), and in some cases are also less thermally stable. However, certain compounds (143) are quite reactive and very thermally unstable.

Some compounds (142), such as diesters of azo dicarboxylic acids (142, R = alkoxy), have high thermal stabilities. Decomposition occurs only above 100°C, and then, with explosive force. However, diacylazo compounds (142, R = alkyl) and their cyclic analogues (142, RR = $-(CH_2)_n-$) are much more unstable and can react in one of two ways. Either they decompose at 0°C or lower to give nitrogen and carbonyl compounds; or they undergo polymerization on loss of nitrogen. Diaroylazo compounds (142, R = aryl) decompose on heating to nitrogen and aroyl radicals, which go on to give subsequent products.

Nucleophilic attack on (142) seems to occur almost exclusively at nitrogen. The only reported cases of nucleophilic attack at carbonyl involve primary amines as the nucleophiles[113]. In these cases the products were the azodicarbonamides (142, R = R_1NH) from the azo carbonyls (142, R= OR).

Secondary amines were reported[114] to attack at nitrogen to give the triazanes (145), presumably via the betaine (144) (eq. 41). Aromatic amines such as aniline, o-toluidine and p-toluidine behave like secondary aliphatic amines and yield triazanes with (142)[113]. However, other aromatic amines such as α- and β-naphthylamine yield ring substitution products[113] (eq. 42). Both of the preceding reactions occur

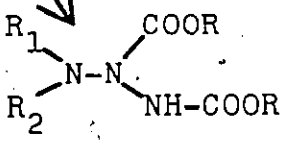
simultaneously with 2,5-dimethylaniline[113]. Aromatic compounds



(144)

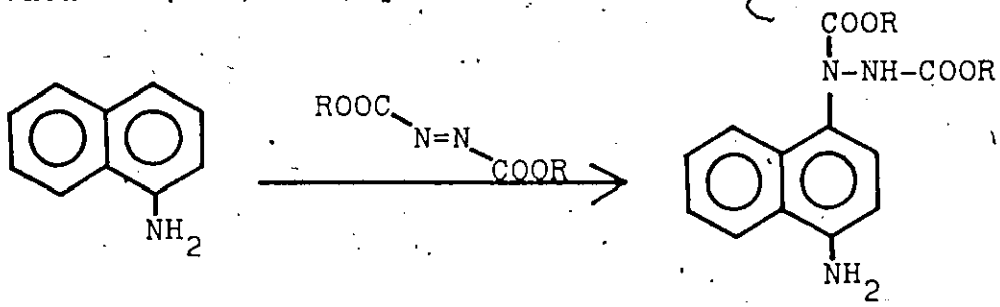
[41]

R_1=R_2 = alkyl or aryl

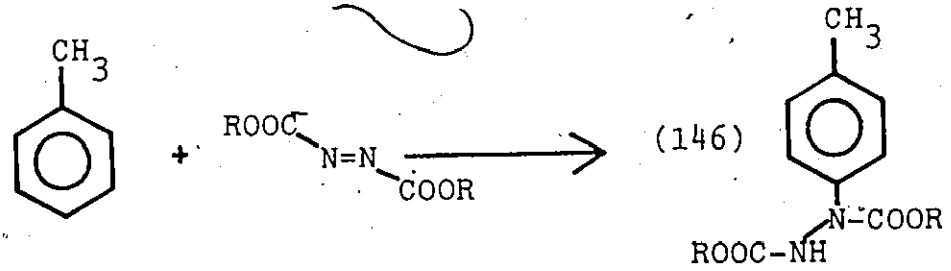


(145)

such as toluene also attack (142) to give hydrazinedicarboxylic acid derivatives (146)[115] (eq. 42).



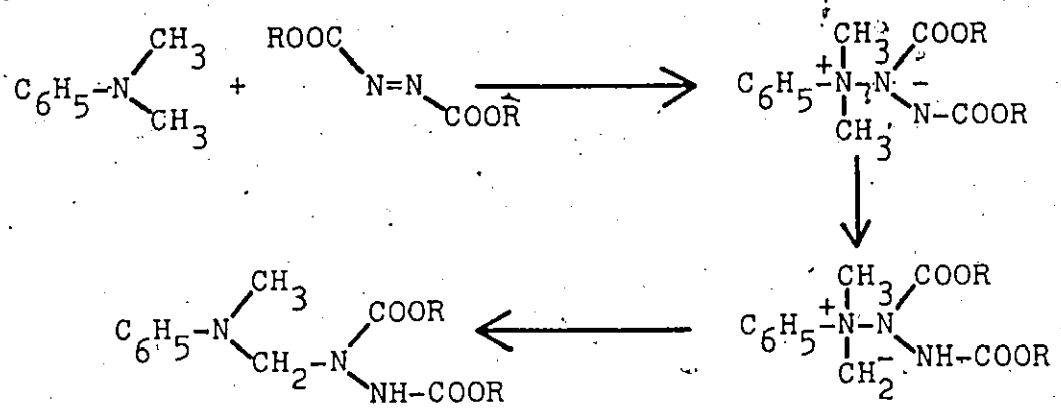
[42]



(146)

Tertiary amines also add to the nitrogen of (142). Treatment of (142) with N,N-dimethylaniline leads to the hydrazinedicarboxylic acid derivatives (148) possibly via

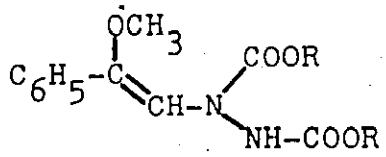
ylide rearrangement of the intermediate (147)[113,114] (eq. 43). The rate of reaction increases with the basicity of the amine.



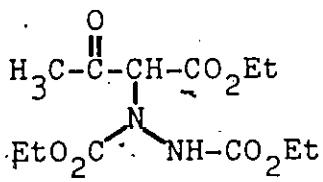
[43]

(148) (147)

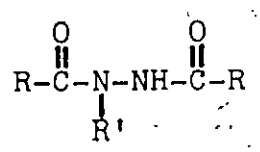
Vinyl ethers react with esters of azodicarboxylic acids to give the hydrazine derivatives (149)[116]. Sodium salts of acetoacetic ester, cyanoacetic ester and acetylacetone, when treated with (142) yield substituted hydrazines[117]. For example, diethyl azodicarboxylate and sodium acetoacetate gave (150). Grignard reagents react with (142) to form substituted hydrazides (151) via a 1,4-addition[118].



(149)



(150)

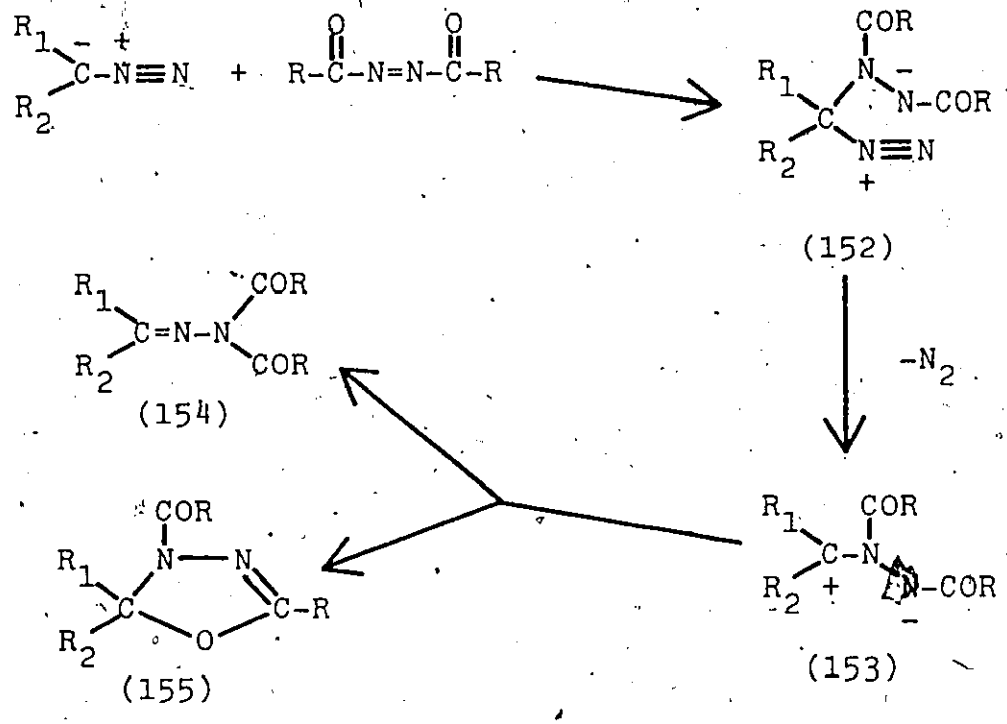


(151)

Compounds (142), such as azodicarboxylic ester, azo-

dibenzoyl and azodiacetyl, react with diazoalkanes or diazoacetic ester to give hydrazones (154) or oxadiazolines (155)[119] (eq. 44). The diazo compound attacks the azo compound giving the diazonium intermediate (152) which then decomposes to (153). Subsequent reactions of (153) depend on the nature of R, R_1 and R_2, as well as on the reaction conditions[112].

[44]

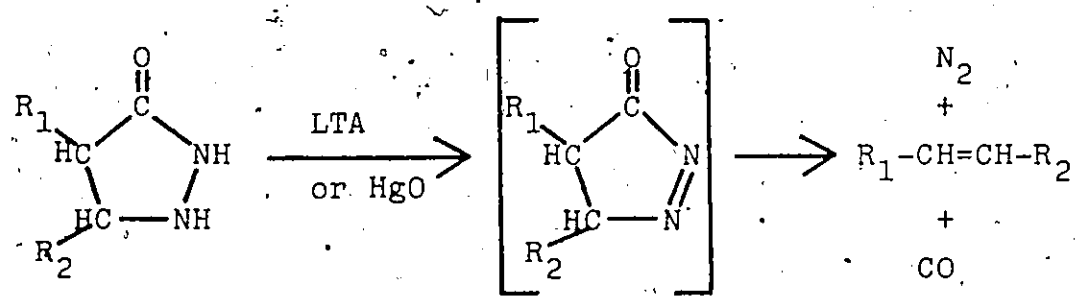


A very thorough search of the chemical literature revealed that compounds (143) have not been studied in much detail. In fact, apart from methods of preparation, little seems to have been reported about them. In general, it appears that (143, R = alkyl) are very unstable and cannot be isolated. This also seems to be true of most cyclic compounds (143, RR = $-(CH_2)_n-$). The most commonly known α-carbonyl azo compounds (143)

are those with R = aryl, aryloxy or alkoxy. These are reported to be relatively stable and can be made to react with nucleophiles.

The thermal decomposition of (143) has not been reported in any great detail. Thus no consistent modes of decomposition can be observed, and the products vary depending on the compound (143) studied. Certain cyclic compounds (157) have been postulated[120, 121] as intermediates in the oxidative fragmentation of 3-pyrazolidinones (156) to olefins (eq. 45).

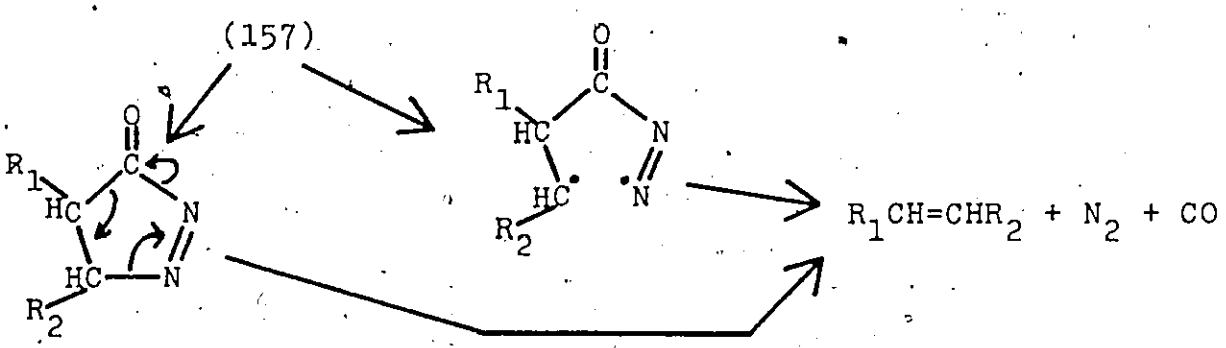
[45]



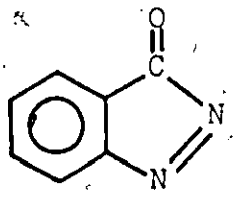
(156) (157)

The decomposition of (157) was believed to occur via a radical cleavage[120,121] or via a concerted opening[121] (Scheme X).

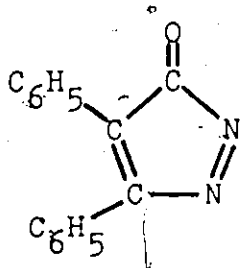
Scheme X



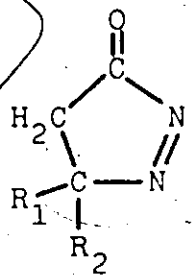
Other cyclic azocarbonyl compounds such as (158)[122] and (159)[123] are remarkably stable. It has been indicated[121] that this may be due to their increased resonance stabilization as compared with (157). The pyrazolinone system (160) has been found[124] to be somewhat more stable than (157). The compounds (160) can be prepared and stored at temperatures below -20°C but decompose violently above 0°C to give nitrogen, carbon monoxide and an olefin.



(158)



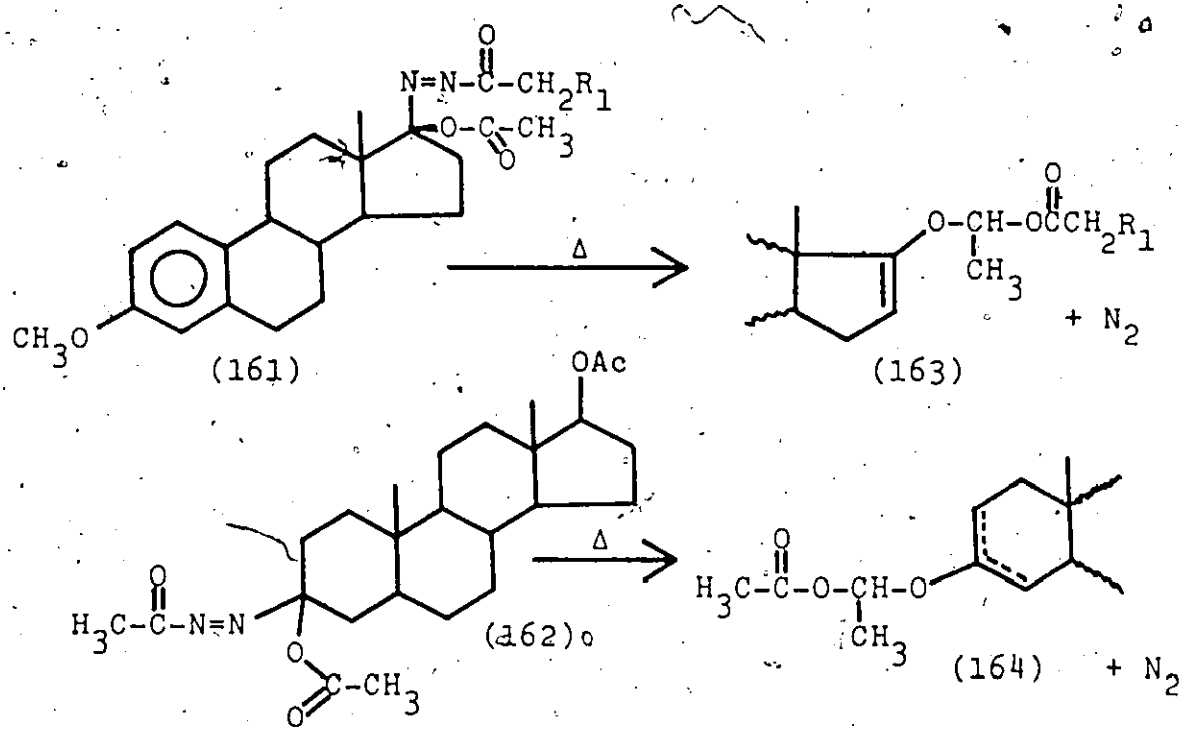
(159)



(160)

The pyrolysis of acyclic compounds (143) was reported by Pitt[125]. He prepared the compounds (161) and (162) and found them to be relatively stable. On pyrolysis these azo compounds gave the products (163) and (164), respectively, (eq. 46). In addition (161) gave estrone 3-methyl ether (41%) and biacetyl. This was attributed to the sterically crowded environment at C-17 which makes the acetate carbonyl less accessible for attack (Scheme XI), or to the difficulty of forming the Δ^{16} double bond. The formation of (163) and (164) was explained as shown in Scheme XI.

[46]

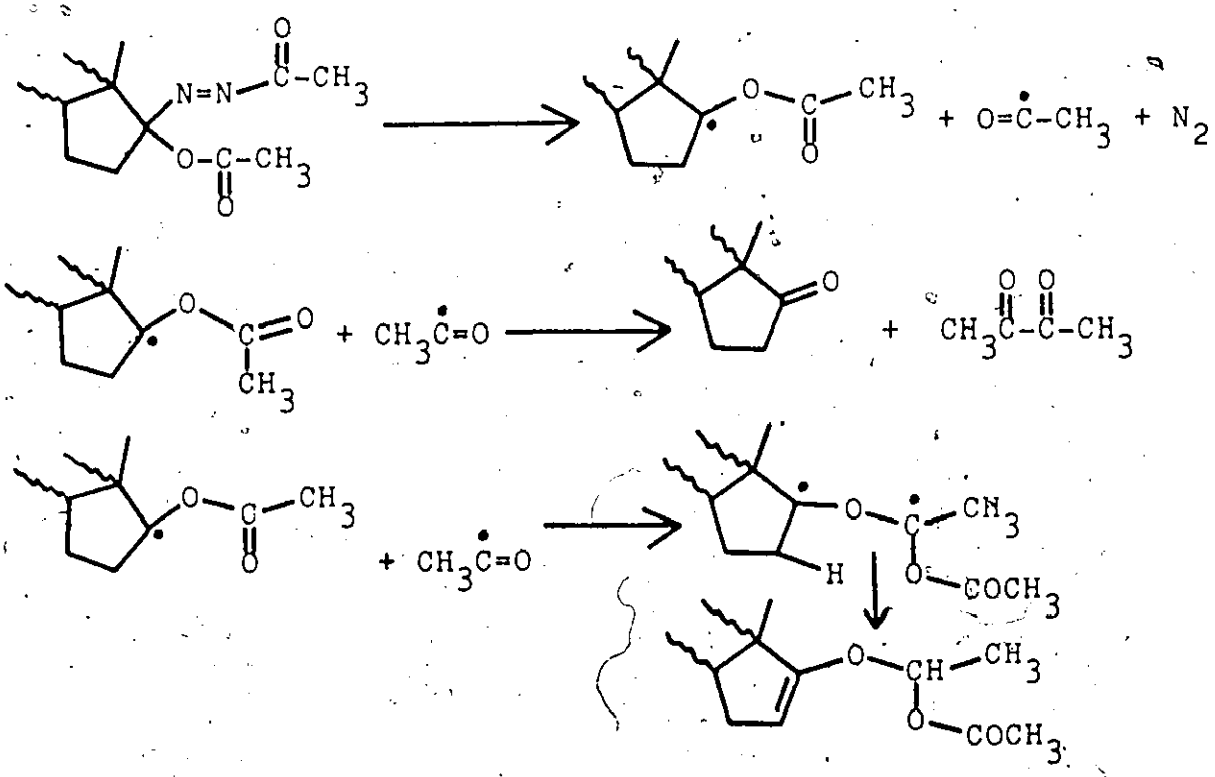


(161) (163)

(162) (164) + N_2

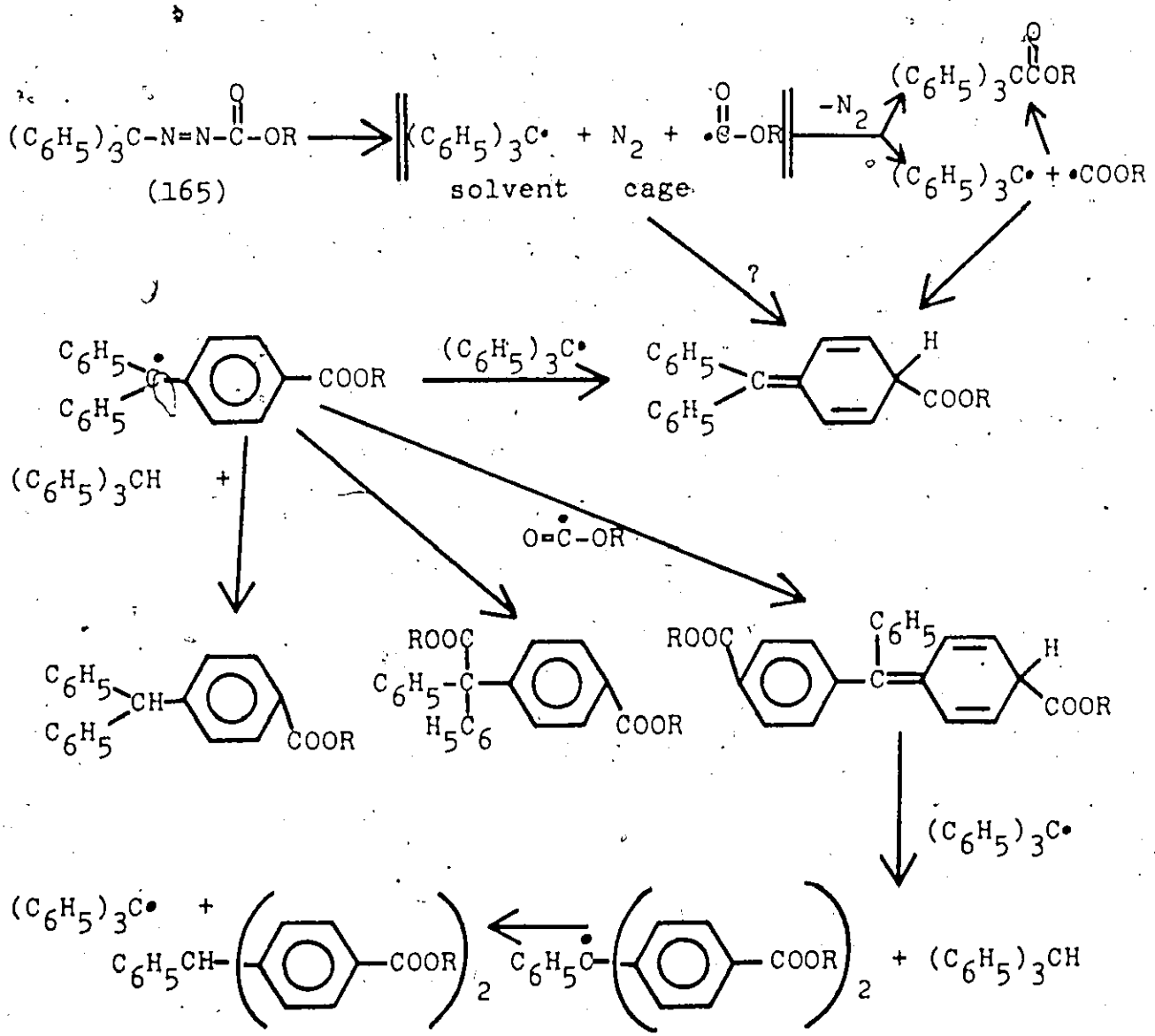
Another example of the study of the thermal decomposition of (143) is that of Zabel and Trahanovsky[126]. These

Scheme XI



workers decomposed methyl and phenyl triphenylmethylazocarboxylates (165) in benzene and cumene in order to produce alkoxycarbonyl radicals under mild conditions. They found (165) to be a good, high-yield source of alkoxycarbonyl radicals. A mechanism for the decomposition was given (Scheme XII).

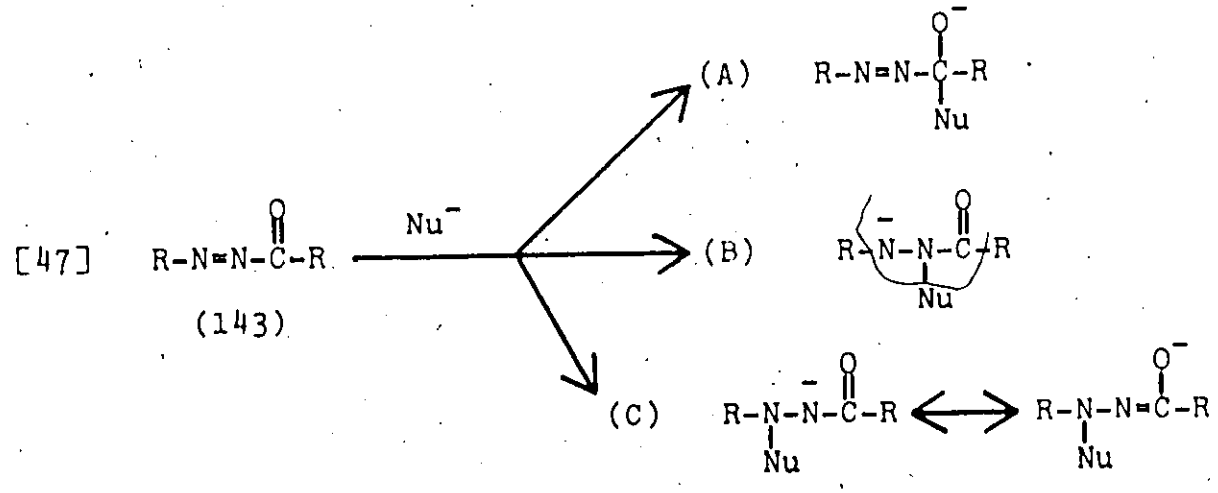
Scheme XII



Nucleophilic attack on compounds (143) is not surprising, in view of the high carbonyl stretching frequency. Unlike α,β-unsaturated carbonyl compounds which absorb at 1665-1685 cm^{-1}, α-carbonyl azo compounds (143) absorb at 1800-1840 cm^{-1}. This indicates a strong electron withdrawing of the azo function that tends to render the carbonyl carbon more electron deficient than normal and thus, very susceptible to nucleophiles.

Nucleophilic addition to compounds (143) can occur at three different positions (eq. 47): at the carbonyl carbon (A), at the nitrogen alpha to the carbonyl (B) or at the beta nitrogen (C). Of these, attack at the alpha nitrogen would appear the least likely due to electronic and resonance considerations. All three types of addition have been reported in the literature and examples are presented and discussed below.

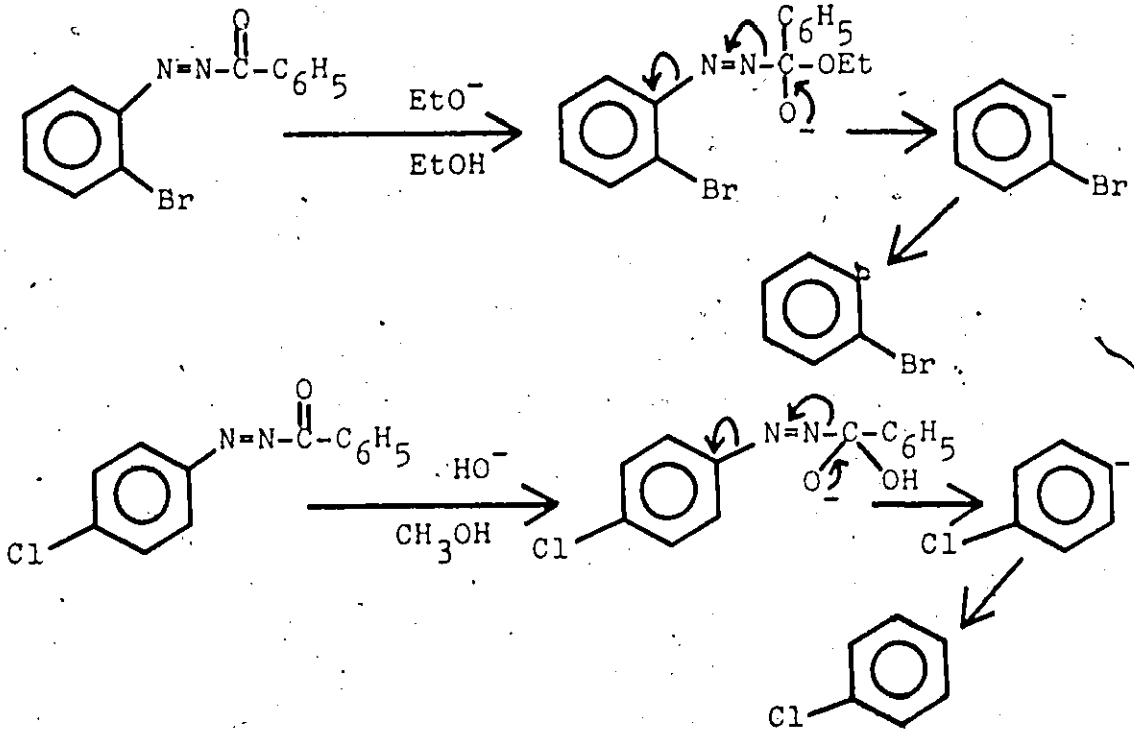
[47]



Of the relatively few reported cases of nucleophilic attack on (143), almost all occur at the carbonyl group.

Hoffmann and co-workers[127,128] reported the base catalyzed fragmentation of two α-carbonyl azo compounds (eq. 48). This was essentially a nucleophilic attack by the base on the carbonyl resulting in subsequent cleavage. In another paper[129] Hoffmann and Eicken reported the reaction of sodium ethoxide with the azocarbonyl compounds (166) (eq. 49) and (167) (eq. 50).

[48]

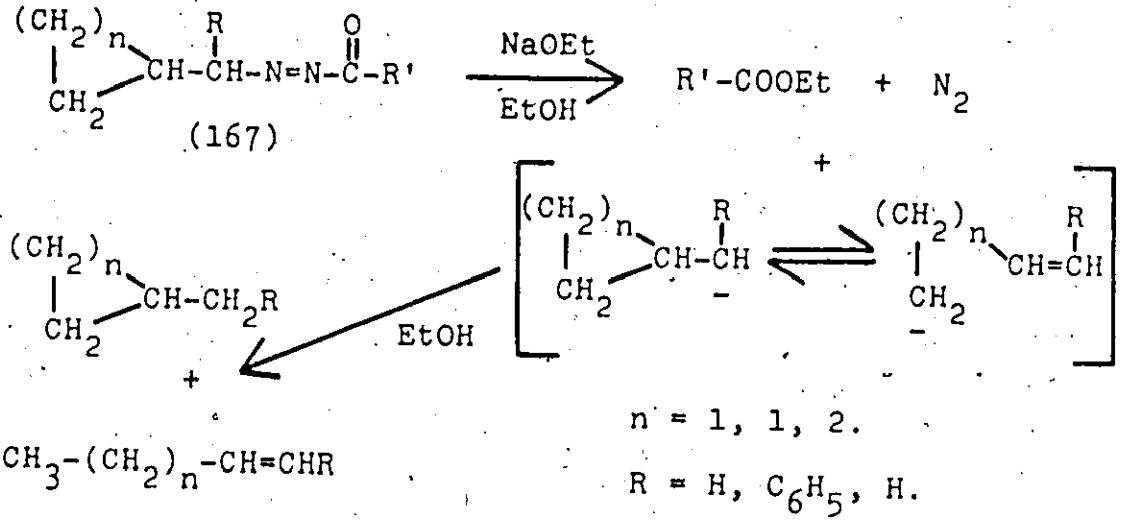


In both cases, attack occurred at the carbonyl carbon giving

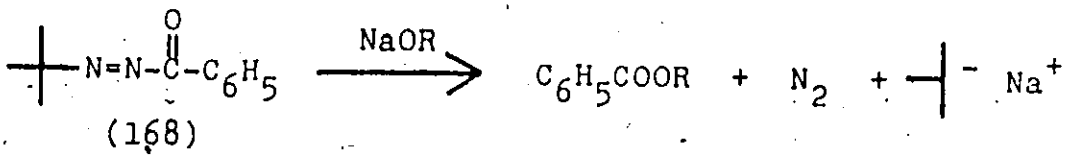
[49] $$R\text{-}\underset{\underset{CH_3}{|}}{CH}\text{-}N{=}N\text{-}\overset{\overset{O}{\|}}{C}\text{-}R \xrightarrow[EtOH]{NaOEt} R\text{-}COOEt + N_2 + R\text{-}CH_2CH_3$$

(166) $(R = C_6H_5)$

esters as products. In the case of (167), the products were more complex due to the possibility of two anions (eq. 50).



Fraenkel and Pecchold[130] reported in 1969 the alkoxide cleavage of benzoyl-t-butyldiimide (168) (eq. 51). They also used hydroxides, amides, phenoxides and sodium oxide as the nucleophiles, and obtained similar results.

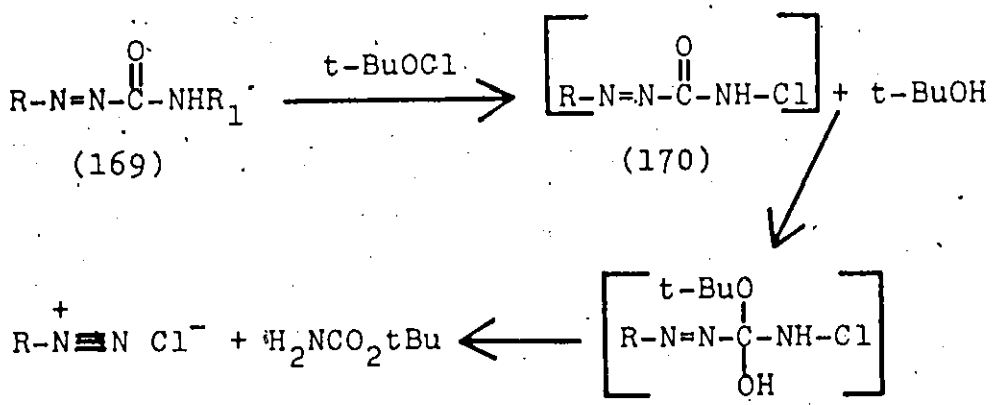


All the nucleophilic attacks and decompositions discussed up to this point were explained as shown in eq. 48.

Bock and co-workers[131] showed in 1966 that (143, R = C_6H_5, R' = OCH_3) behaved as normal esters. When carried out under normal conditions, ammonolysis and hydrolysis gave the

amide and the acid salt, respectively. Again, this represents nucleophilic attack at the carbonyl group but in these cases azo nitrogen was retained.

The reaction of N-chloro-azocarbonamides (170) with t-butanol was examined in 1971 by Ohme and co-workers[132]. On reacting phenylazocarbonamide (169, R = C_6H_5, R_1 = H) with t-butylhypochlorite, they obtained phenyldiazonium chloride and the t-butyl ester (171) (eq. 52). The products were thought to have arisen by attack of t-butanol on (170) and subsequent fragmentation. With R = C_6H_5, R_1 = CH_3CH_2 the same result was claimed. With R = $-(CH_2)_6-$, R_1 = H the products were (171), nitrogen and cyclohexyl chloride.



[52]

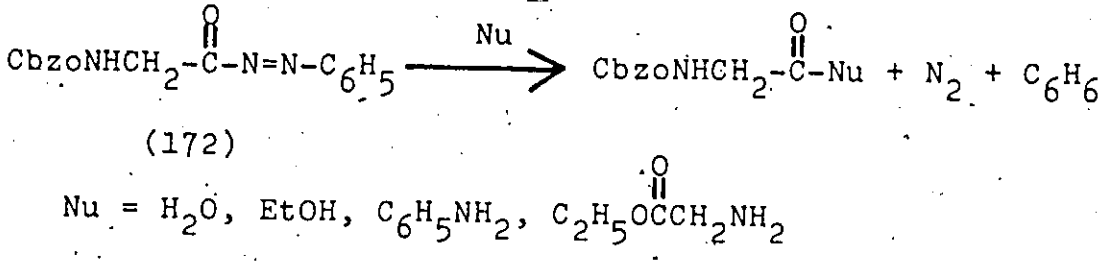
R = C_6H_5, C_6H_5, C_6H_{11}.

R_1 = H, CH_3CH_2, H.

Milne and Kilday[133] prepared carbobenzoxyglycinephenyldiimide (172) and studied the attack of nucleophiles on it (eq. 53). With water they obtained carbobenzoxyglycine; with

ethanol they got carbobenoxyglycine ethyl ester; with aniline they isolated benzyloxycarbonylglycylanilide and with glycine ethyl ester they obtained a peptide, carbobenzoxyglycylglycine ethyl ester. Similar observations were made by Kelly[134] who claimed that oxidation of phenylhydrazides to carboxylic acids occurred via a phenylazo compound (143, R' = C_6H_5) which was attacked by water to give the carboxylic acid.

[53]



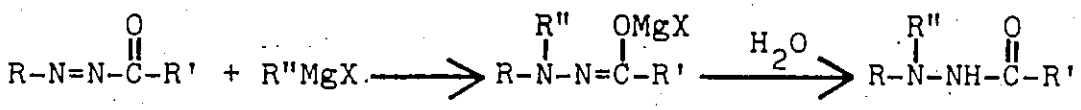
(172)

Nu = H_2O, EtOH, $C_6H_5NH_2$, $C_2H_5OCCH_2NH_2$

In a series of papers[135-137] published between 1964 and 1966, Cohen and Nicholson discussed the methanolysis of N-phenyl-N'-benzoyldiimide (143, R=R' = C_6H_5). They indicated that acid or base catalyzed attack of methanol on (143) led to methyl benzoate and phenyl diimide[135,136]. The phenyl diimide was then thought to decompose to nitrogen and phenyl radicals. They also found[137] that ferric ion in methanol led to more efficient conversion of (143) to products.

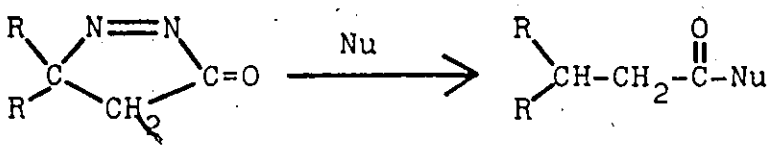
All the preceding cases of nucleophilic attack on (143) have been either nucleophilic displacements or substitutions. There appear to be only two cases of nucleophilic addition to (143) reported in the literature. The first is that of Stolle and co-workers[138] who reacted benzoylazobenzene

(143, R=R' = C_6H_5) with Grignard reagents (eq. 54). In one of the few cases of attack at beta nitrogen in the systems (143), 1,4-addition of the Grignard gave the substituted hydrazides (173) on hydrolysis.

[54] 

R = C_6H_5 (173)

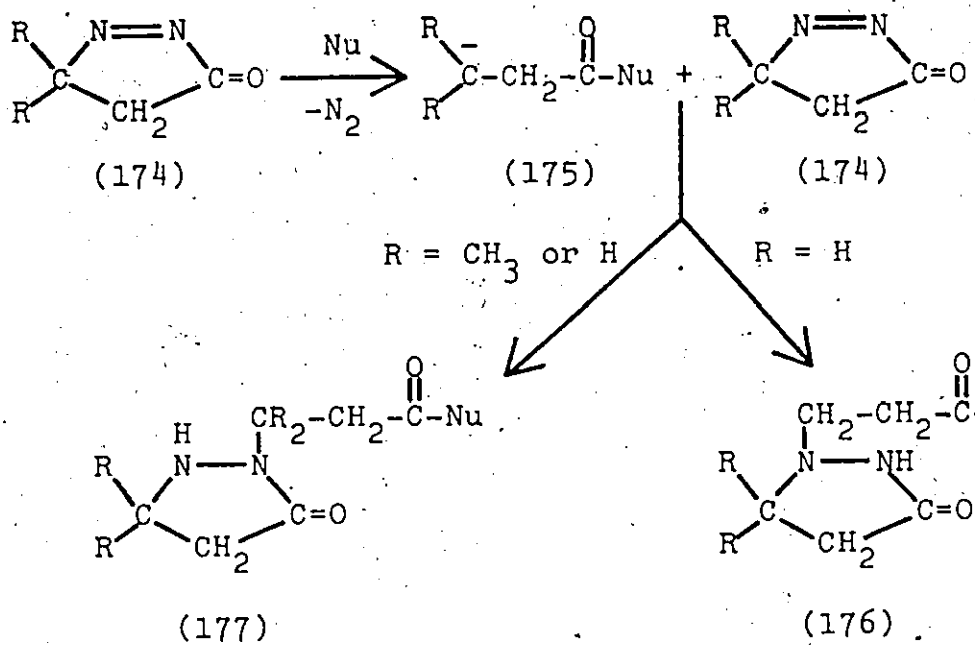
Finally, the work of Nagata and Kamata[124] on 1-pyrazolin-3-one derivatives (174) appears to be the most extensive work covering nucleophilic attack on α-carbonyl azo compounds (143). These authors found that nucleophilic attack with hydroxide, methoxide, ethanol, aniline and pyrazolidin-3-one resulted in substitution at the carbonyl group to give propane derivatives (eq. 55). They also found that treatment of (174)

[55] 

(174) (R = H or CH_3)

with ethanol, methanol, aniline, N-methylaniline and 2-dimethylaminoethanol led to initial substitutive attack on (174) to give the anion (175). This subsequently reacted at either nitrogen of more (174) by nucleophilic addition, and depending

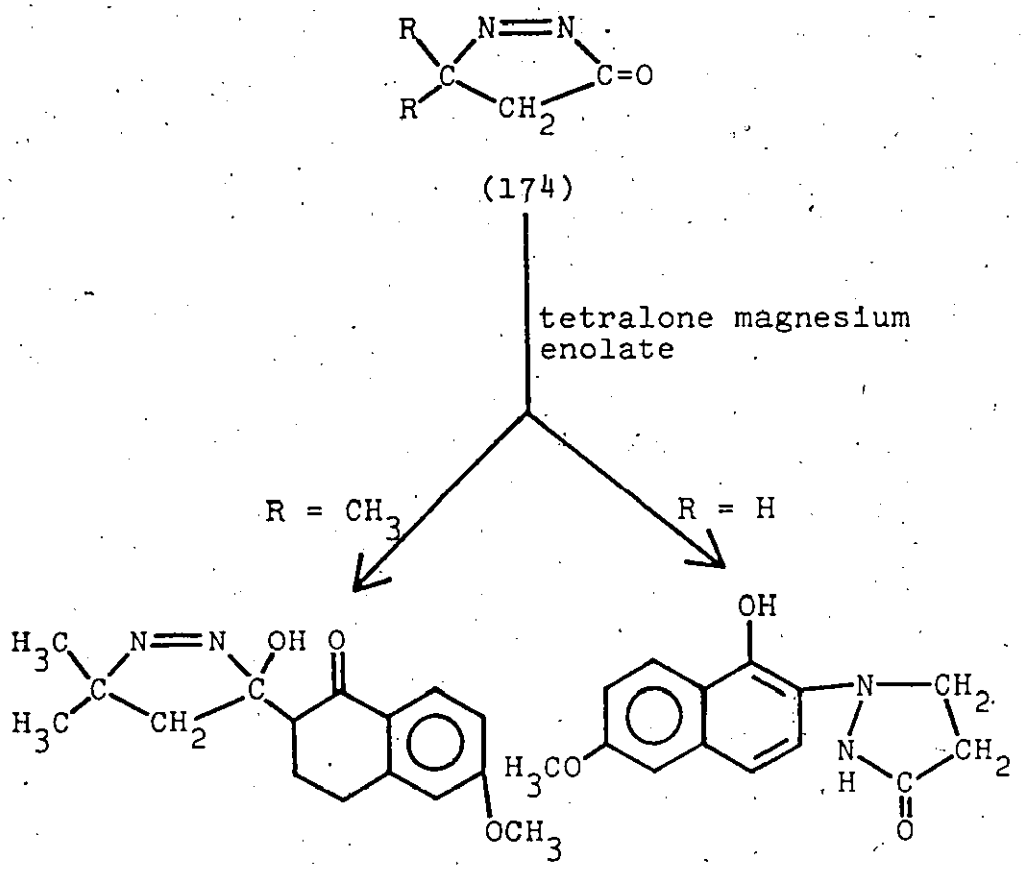
on R, gave products (176) and/or (177) (eq. 56).



[56]

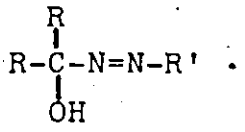
Nagata and Kamata[124] also reacted (174) with the Grignard reagent, ethylmagnesium bromide, and with 6-methoxy-1-tetralone magnesium enolate. With the former, (174, R = CH_3 or H) led to a complex mixture from which only the product from attack at the β-nitrogen was isolated. However, with the latter, (174, R = H) gave in low yield only the β-nitrogen addition product (178), whereas (174, R = CH_3) gave, as the major product, the carbonyl addition product (179) (eq. 57).

[57]


R
N=N
C
C=O
R
CH2
(174)
tetralone magnesium enolate
R = CH3
R = H
H3C
N=N
OH
O
C
H3C
CH2
H3CO
OCH3
OH
N
CH2
N
H
CH2
C
O
(179)
(178)

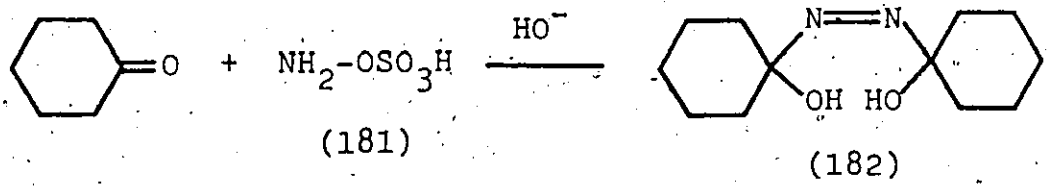
VI α-HYDROXY AZO COMPOUNDS

Compounds of the type (180) with a hydroxyl group alpha to the azo function are quite rare and appear to have been prepared and studied by only five research groups. The rarity of compounds (180) is perhaps due to their thermal instability. Although the five groups have proposed several different names for compounds of the type (180), such as α-hydroxyazoalkanes, α-hydroxyalkyldiazenes, semiaminals of diimide, and α-azocarbinols, for convenience in this discussion only the name α-azocarbinols will be used in general reference to compounds of the type (180).



(180)

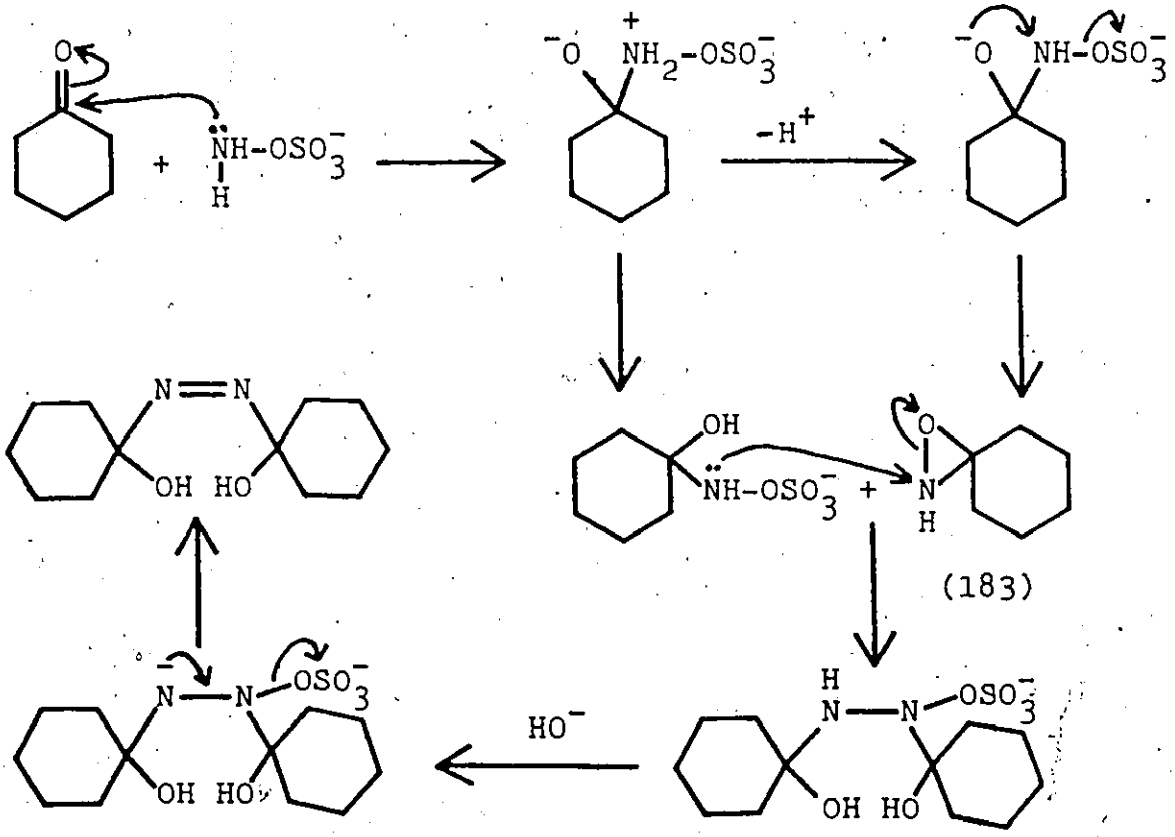
It appears that the first α-azocarbinol was prepared in 1963 by Schmitz and co-workers[139], but it was not until 1967 that these workers published a more extensive report[140] on the synthesis and properties of 1,1'-dihydroxyazocyclohexane (182). Treatment of hydroxylamine-O-sulfonic acid (181) with cyclohexanone in alkaline solution at 10°C yielded a crystalline solid (182) (eq. 58).

[58] 

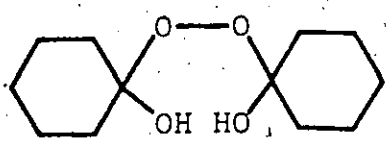
(181) (182)

A mechanism for the formation of (182) was advanced by Schmitz and co-workers[140]. As shown in Scheme XIII, the initial product was thought to be the iso-oxime of cyclohexanone (183). This was assumed to lead to (182) by subsequent nucleophilic attack as indicated in Scheme XIII.

Scheme XIII



The azocarbinol (182) was stable for several days at -15°C, in the absence of oxygen. However, with air present, (182) was converted to the peroxide (184) after several days.

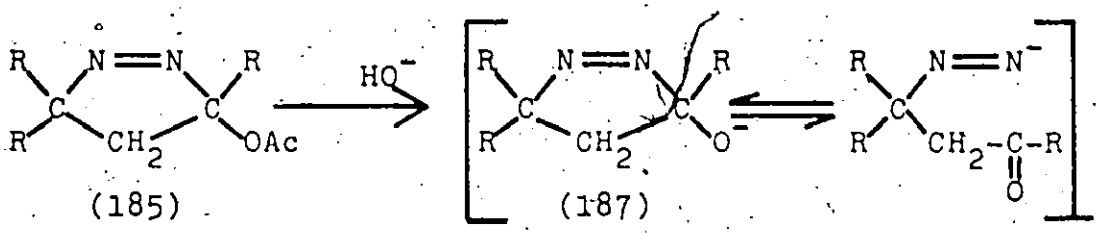


(184)

Compound (182) was thermally unstable and at room temperature decomposed to nitrogen, hydrazine and cyclohexanone in a 1:1:4 ratio. In the presence of acid or base, the decomposition rate increased and these results were thought to indicate that thermal decomposition was a polar process in such media. Decomposition in neutral media led to the formation of cyclohexanol and was accounted for by proposing a radical cleavage. Confirmation of the radical nature came from decomposition in carbon tetrachloride, which led to hydrazinehydrochloride, and from decomposition in the presence of acrylonitrile, which led to polymeric products.

In 1966, Freeman and Plonka[141] attempted to prepare an α-azocarbinol (186) by hydrolysis of 3-acetoxy-3,5,5-trimethyl-Δ^1-pyrazoline (185). Although they did not isolate (186), they postulated its anion (187) as an intermediate in the hydrolysis of (185), which led to isobutyl methyl ketone and pinacolone (eq. 59).

Freeman and Rathjen[142] succeeded in 1969 in preparing the azocarbinol (186), 3-hydroxy-3,5,5-trimethylpyrazoline,

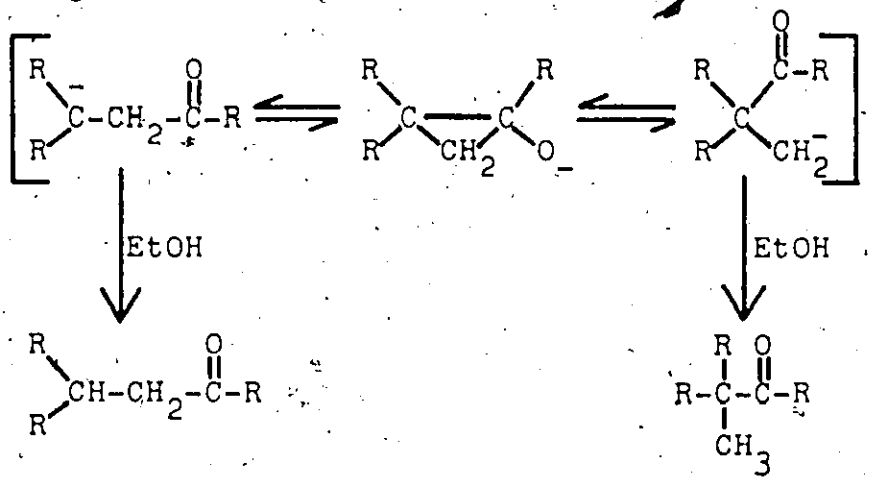


(185)

(187)

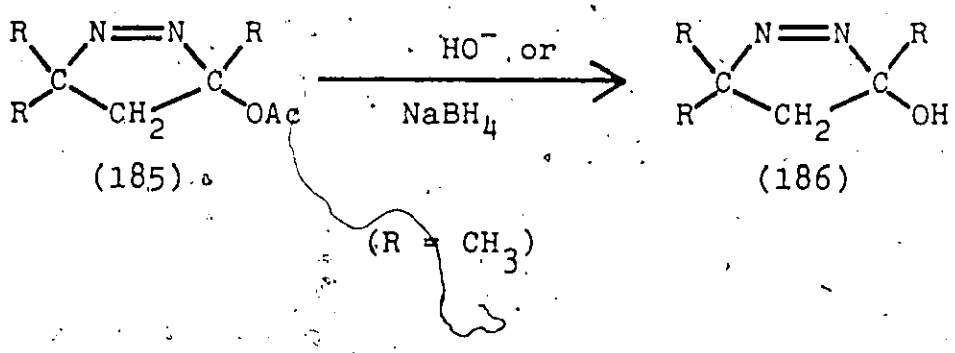
(R = CH_3)

[59]



by controlled hydrolysis of (185) (eq. 60). They found that (186) was remarkably stable and that the previous assumption of its intermediacy in the hydrolysis of (185) was in error. They also found that the azocarbinol (186) could be obtained by hydrogenolysis of (185) with sodium borohydride (eq. 60).

[60]



(185) (186)

(R = CH_3)

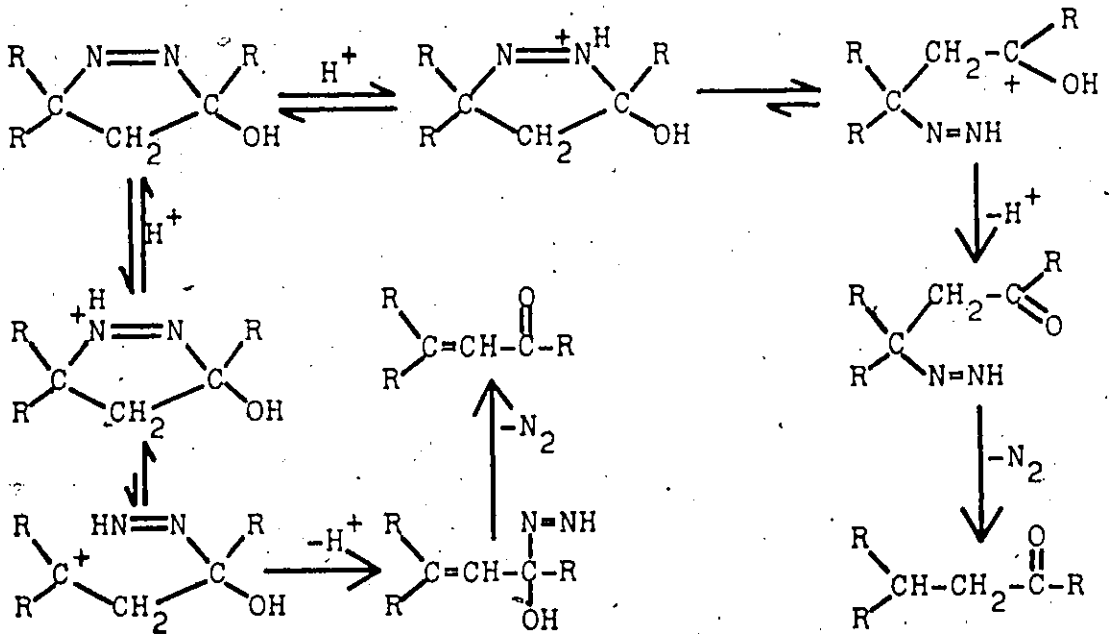
In a later and more extensive study[143], Freeman and co-workers prepared a variety of (186) and examined their

chemistry. On treatment with acid, the principal reaction was ring opening to produce a mixture of saturated and unsaturated ketones, the former predominating (eq. 61). It is interesting to note that acid catalyzed decomposition was

[61] (186) $\xrightarrow{H^+}$ N_2 + $R_2CH-CH_2-C(=O)-R$ (major) + $R_2C=CH-C(=O)-R$ (minor)

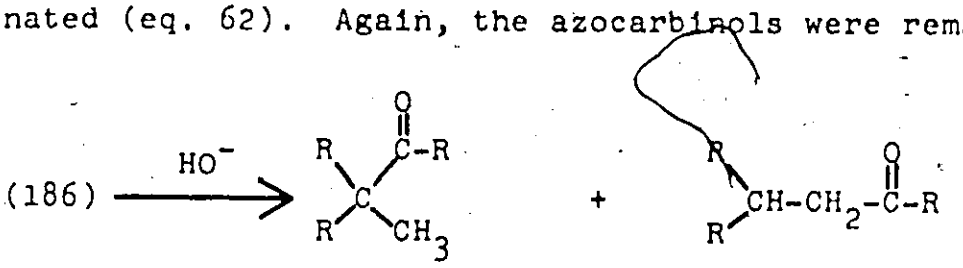
very slow and up to 80% of the azocarbinol could be recovered after one hour of refluxing in 50% methanolic HCl. The products of the hydrolysis were accounted for as shown in Scheme XIV.

Scheme XIV



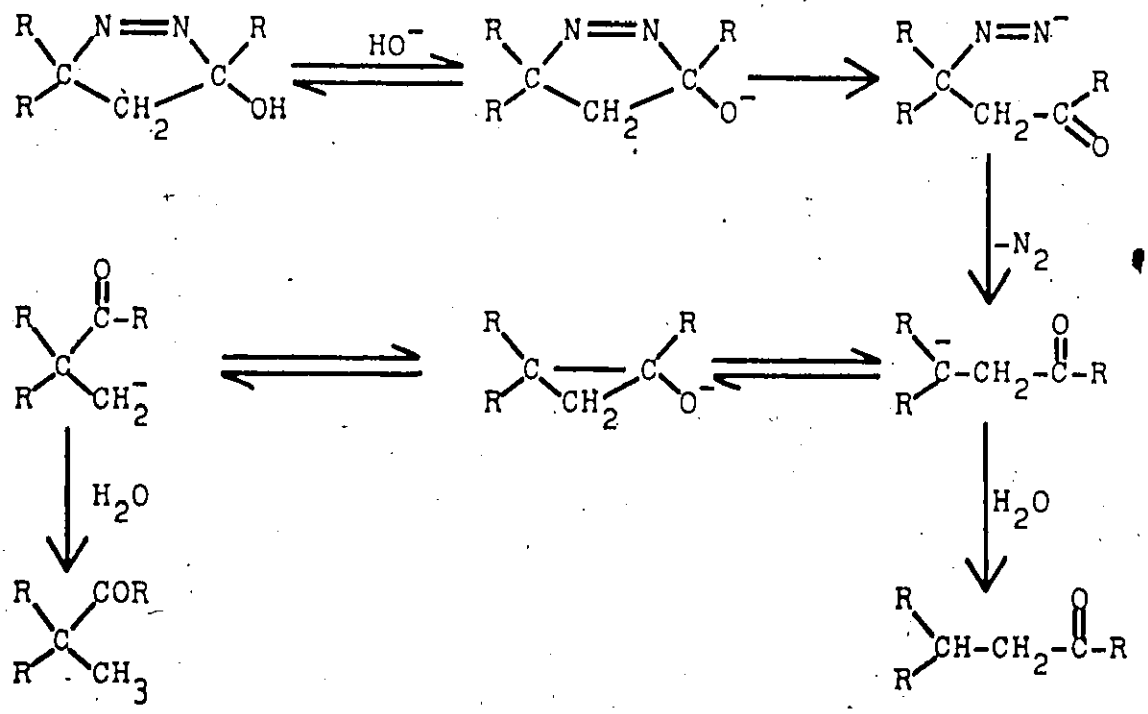
(R = CH_3)

Base catalyzed cleavage of the azocarbinols (186) was also studied by Freeman and co-workers. On treatment with an equimolar amount of methanolic sodium hydroxide under reflux, the azocarbinols yielded a mixture in which rearranged ketones predominated (eq. 62). Again, the azocarbinols were remark-

[62] 

ably stable to base and decomposed very slowly. The reported mechanism for this decomposition is given in Scheme XV.

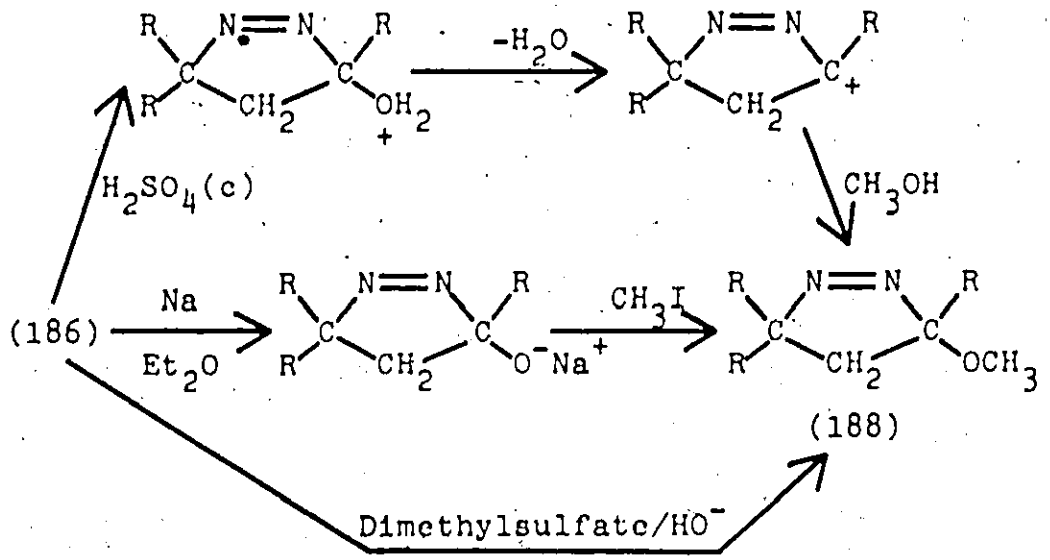
Scheme XV



(R = CH_3)

Esterification of the azocarbinols (186) to the 3,5-dinitrobenzoates was also reported. Using a variety of methods, etherification of (186) to (188) was accomplished as well (eq. 63). Treatment of the sodium salt of the azocarbinol with methyl iodide was found to be the best method for etherification.

[63]

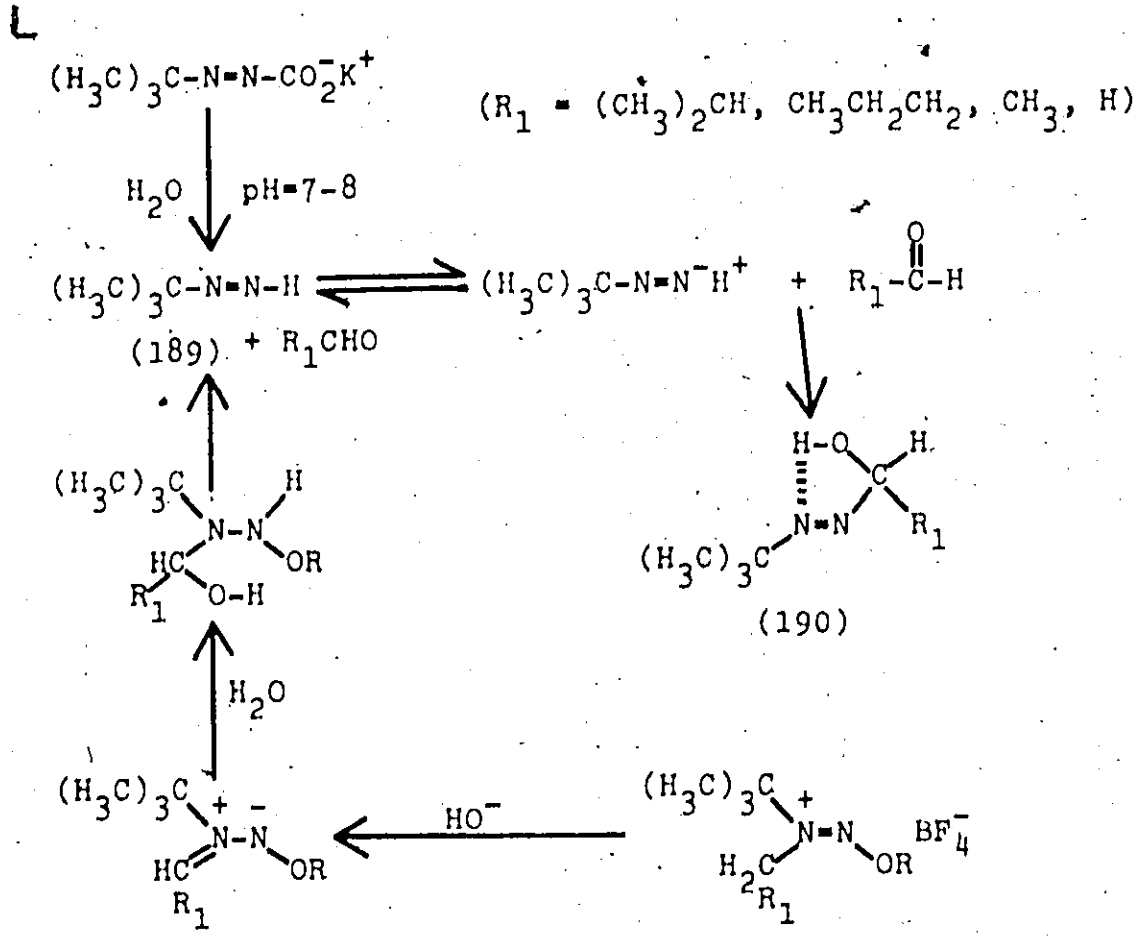


The compounds (186) were found to be quite thermally stable. But, heating at high temperatures for extended periods resulted in decomposition to ketonic products.

The third group of researchers to study α-azocarbinols reported their work in a series of publications[144-148] which appeared between 1968 and 1971. In a communication in 1969, Hünig and Büttner[145] reported the synthesis of four t-butyl-α-hydroxyalkyldiazenes (190). Preparation of t-butyldiazene (189) "in situ" by two methods and subsequent trapping by

aldehydes led to the hydroxydiazenes (190), which were relatively stable yellow liquids (eq. 64).

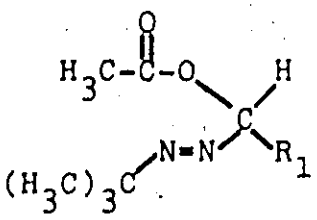
[64]



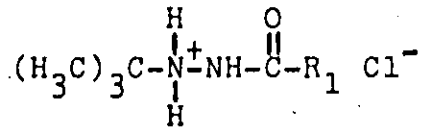
Reaction of (190) with acetic anhydride in pyridine led to the acetates (191), and treatment of (190) with hydrogen chloride in ether gave the hydrazidehydrochlorides (192). The trans configuration of the azo group was confirmed by ultraviolet spectroscopy; the intramolecular hydrogen bond was established by infrared studies.

Furthermore, the detection of azocarbinols (193) and (194) in solution by Hünig and Büttner indicated that alkyl-

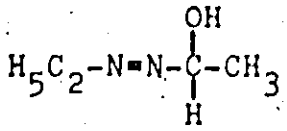
diazenes, with both an α-methylene group and cis azo configuration, could be formed "in situ" and trapped by aldehydes. Compounds (193) and (194) were very unstable and could not be isolated.



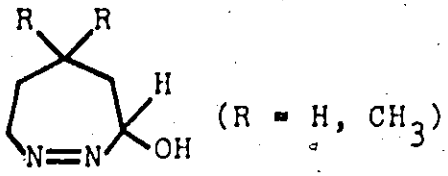
(191)



(192)



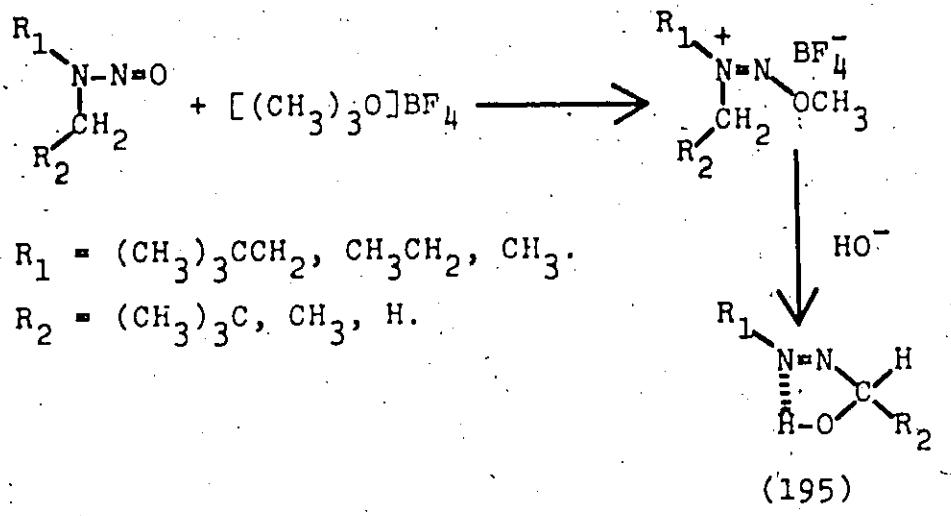
(193)



(194)

In a more detailed report in 1971[146], Hünig and Büttner extended the synthesis of azocarbinols with reasonable stability to include groups other than t-butyl on the carbon bearing the hydroxyl. They prepared a variety of trans-α-hydroxydialkyldiazenes (195) (eq. 65) and compiled a thorough study of their chemistry. The structures (195) were analyzed with infrared, ultraviolet and nuclear magnetic resonance spectroscopy, all of which confirmed the trans, hydrogen-bonded natures of (195).

In addition to the esterification and isomerization discussed earlier, they examined the thermal decomposition of (195). They found that (195) decomposed thermally at room

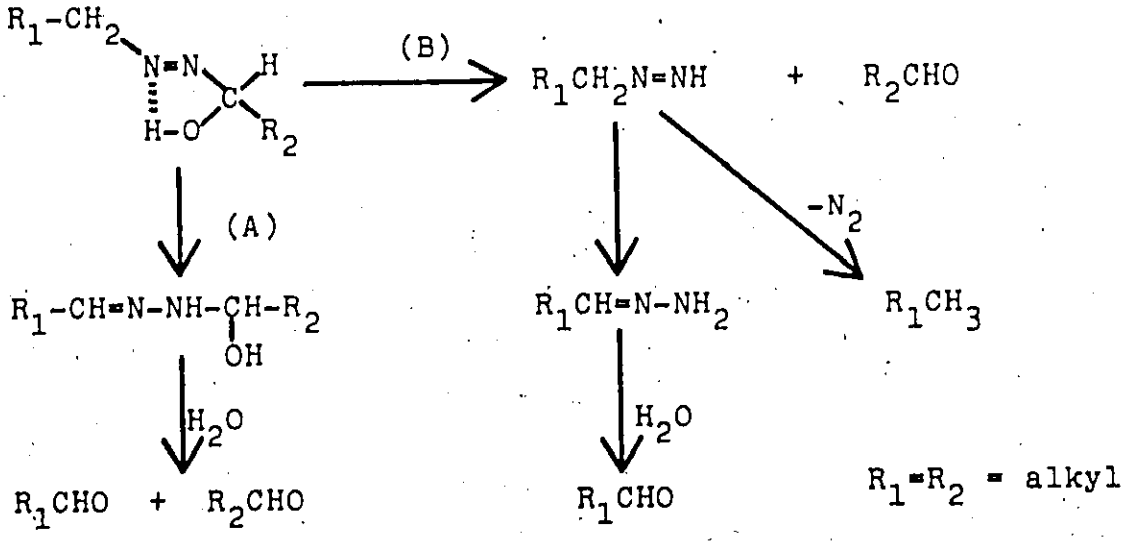


[65] R_1 = $(CH_3)_3CCH_2$, CH_3CH_2, CH_3.
R_2 = $(CH_3)_3C$, CH_3, H.

(195)

temperature to give a mixture of aldehydes. This result was accounted for as indicated in Scheme XVI. Path (B) was considered more likely than path (A).

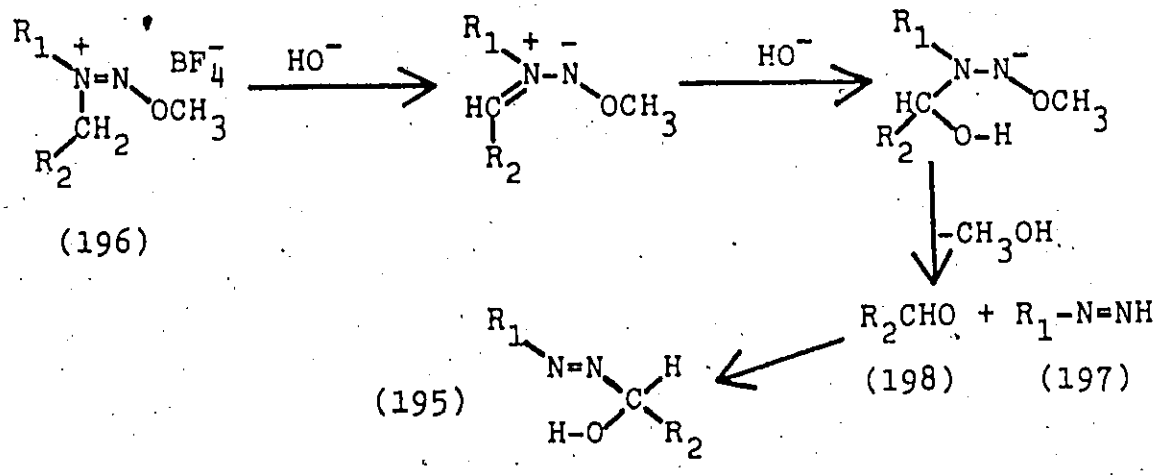
Scheme XVI



The mechanism of formation of the azocarbinols (195)

from alkoxydiazenium salts (196) was studied in detail by Büttner and Hünig in 1971[147]. They claimed that (196), on treatment with base, rearranged to the free alkyldiazene (197) and the aldehyde (198) (Scheme XVII). The existence of the free diazenes was supported by the formation of (195) by reaction of aldehydes with alkyldiazenes liberated from azocarboxylic acids. Support for the mechanism given in Scheme XVII was obtained from two other experiments. Addition of

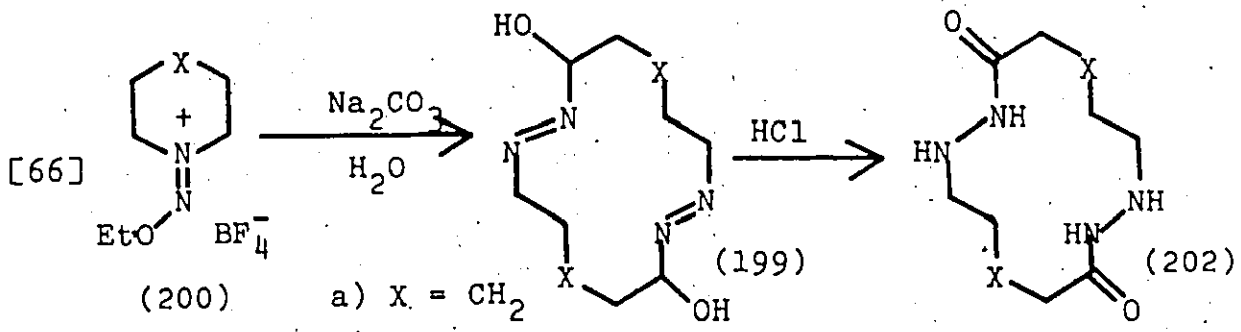
Scheme XVII



a new aldehyde to the reaction mixture resulted in its incorporation into the product (195). Introduction of a different dialkyldiazene led to a similar result. These two experiments then supported the formation of free diazenes and aldehydes in the course of formation of (195) from (196).

In 1968 Hünig and Cramer[144] reported the synthesis of 1,2,8,9-tetraaza-1,8-cyclotetradecadiene-3,10-diol (199a)

and its 5,12-dioxa- analogue (199b). Treatment of the methylene-2-ethoxydiazenium tetrafluoroborate (200) with an aqueous sodium carbonate solution gave (199) (eq. 66), and not (201) as had been earlier reported by Hünig and co-workers[144a].



[66]

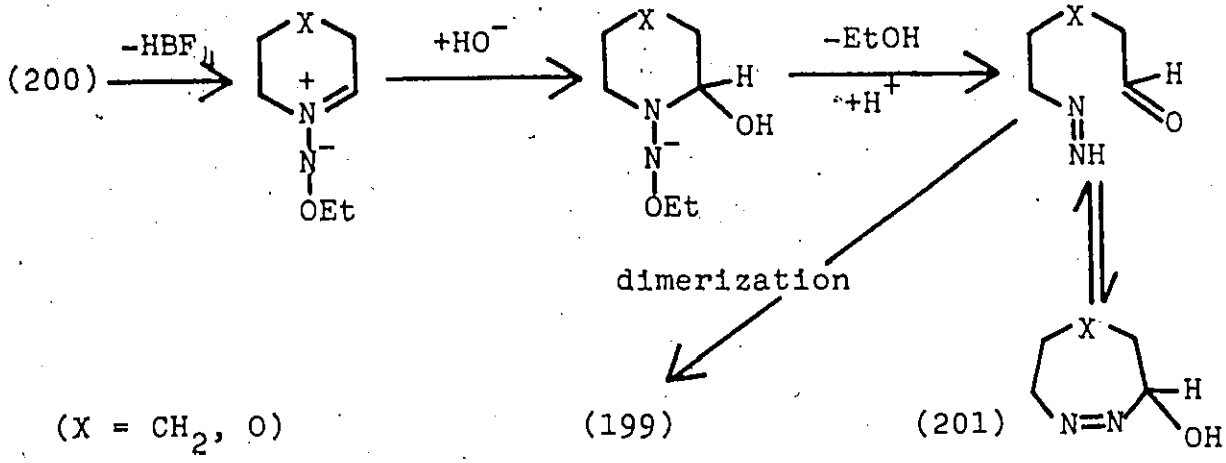
(200) a) X = CH_2 b) X = O

(199)

(202)

The proposed mechanism for this transformation is shown in Scheme XVIII. The cis-hydroxydiazene (201) was not isolable.

Scheme XVIII



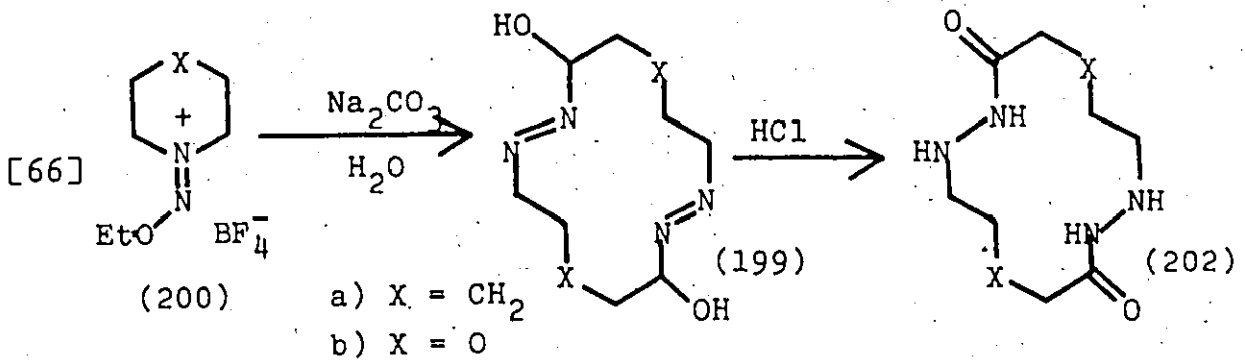
(X = CH_2, O)

(199)

(201)

Compounds (199) could be acetylated with acetic anhydride in pyridine. Isomerization of (199) with hydrogen chloride led to the hydrazides (202) (eq. 66).

and its 5,12-dioxa- analogue (199b). Treatment of the methylene-2-ethoxydiazenium tetrafluoroborate (200) with an aqueous sodium carbonate solution gave (199) (eq. 66), and not (201) as had been earlier reported by Hünig and co-workers[144a].

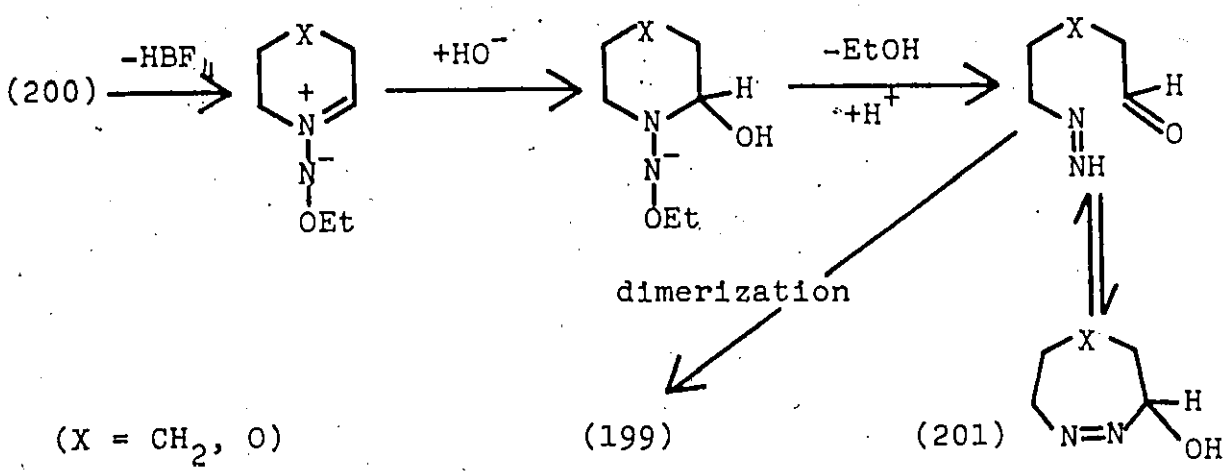


[66]

(200) a) X = CH_2 b) X = O

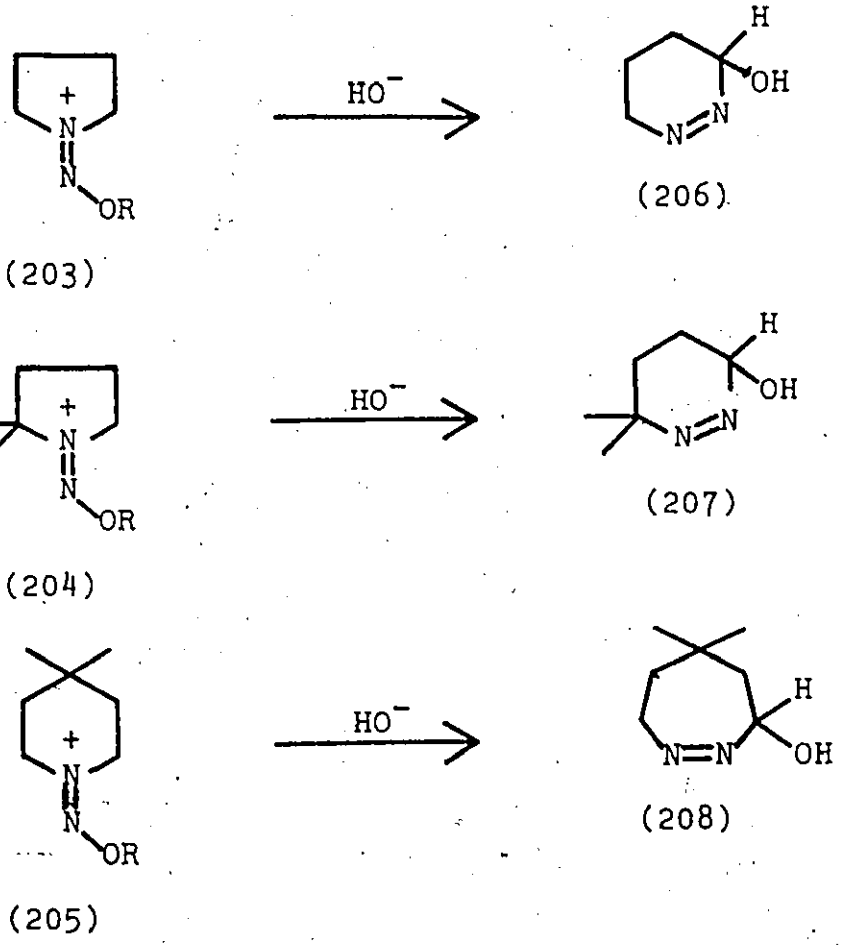
The proposed mechanism for this transformation is shown in Scheme XVIII. The cis-hydroxydiazene (201) was not isolable.

Scheme XVIII[144a]



Compounds (199) could be acetylated with acetic anhydride in pyridine. Isomerization of (199) with hydrogen chloride led to the hydrazides (202) (eq. 66).

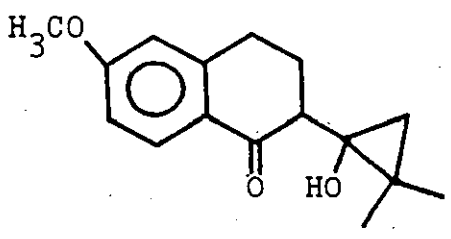
Buttner and co-workers[148], in 1971, published an attempt to prepare cis α-hydroxydialkyldiazenes. The acyclic α-hydroxydialkyldiazenes were isolable only in the trans form. The cis isomer could be observed only in solution on irradiation of the trans isomer. These workers thought that perhaps cyclic alkoxydiazenium salts (203), (204), (205) would give the cis-α-hydroxydialkyldiazenes (206), (207), and (208) on treatment with hydroxide (eq. 67). Although (206), (207) and (208) were detected by ultraviolet spectroscopy during the course of the reaction, they could not be isolated, and decomposed rapidly in the solution in which they were formed.



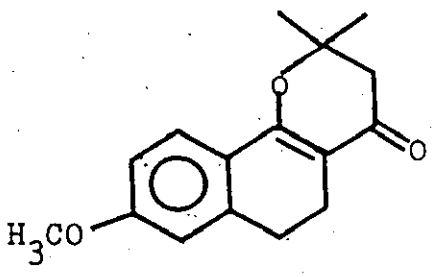
[67]

As mentioned earlier, attempts to isolate the seven-membered ring cis compounds (201) again failed, and they dimerized with remarkable ease to the fourteen-membered ring trans-α-hydroxydiazenes (199).

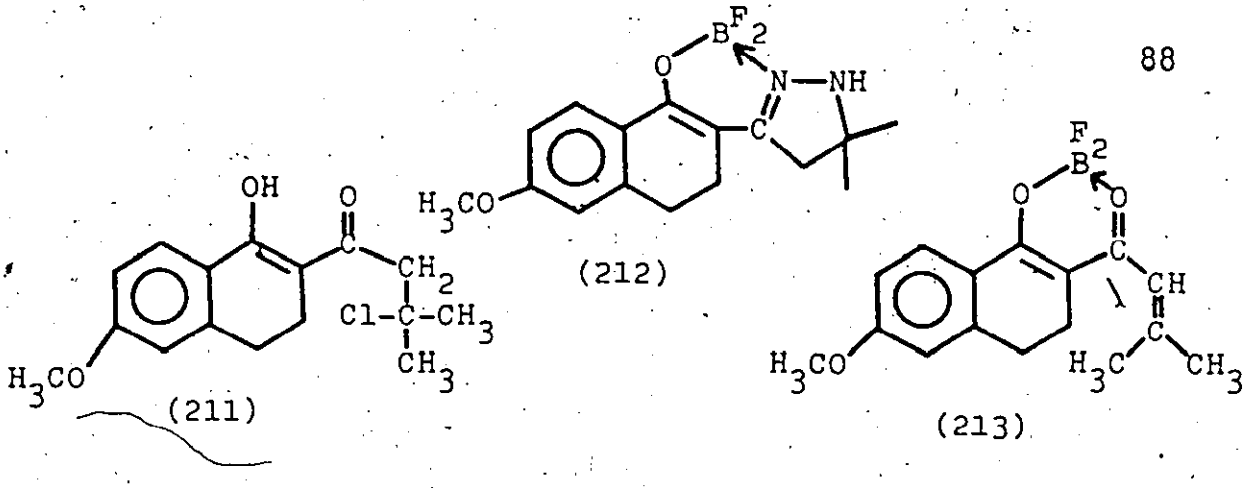
Another publication on the preparation of an α-azo-carbinol appeared in 1970. Nagata and Kamata[124] reported the synthesis of 2-(5,5-dimethyl-3-hydroxy-1-pyrazolin-3-yl)-6-methoxy-1-tetralone (179) (see page 73). On reacting 5,5-dimethyl-1-pyrazolin-3-one (174, R = CH_3) with the bromomagnesium enolate of 6-methoxy-1-tetralone, they isolated (179) (see page 73, eq. 57). Compound (179), on treatment with base, reverted completely to 6-methoxy-1-tetralone. Refluxing (179) in 2,4,6-collidine resulted in loss of nitrogen and in the formation of the cyclopropanol derivative (209). When copper (II) chloride was added prior to refluxing, the product was the cyclic enol ether (210). Treatment of (179) with cupric chloride in bis(2-methoxyethyl) ether at room temperature yielded (211). The attempted elimination of the azo group of (179) with the Lewis acid, boron trifluoride-etherate, led to (212) and (213).



(209)



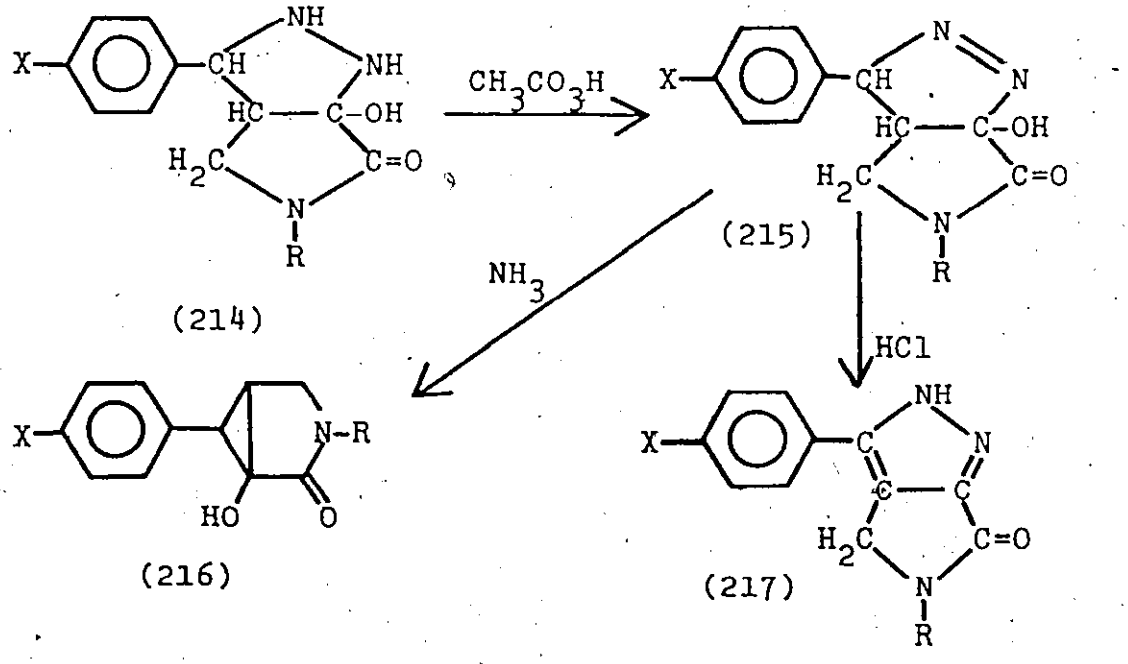
(210)



(211) (212) (213)

In 1970, Southwick and co-workers[149] reported the synthesis of an α-azocarbinol (215) with a cis azo linkage by oxidation of the pyrazole (214) with peracetic acid (eq. 68). Treatment of (215) with weak bases at or below room temperature led to the cyclopropanol derivatives (216). Similarly, dissolving (215) in aprotic solvents, heating in neutral solvents (benzene or carbon tetrachloride) or heating in the dry state led to (216). Reaction of (215) with hydrogen chloride gave the pyrazoles (217).

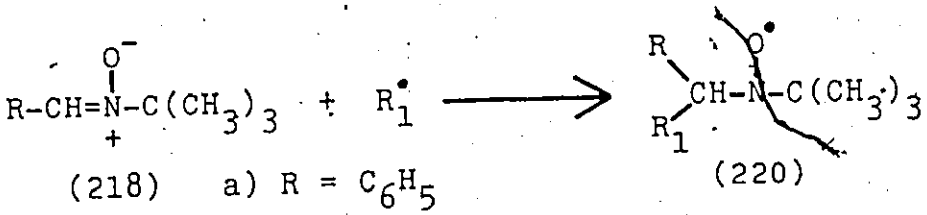
[68]



(214) (215) (216) (217)

It becomes apparent, in summary, that due to the rarity of α-azocarbinols, little is known about their general properties. Likewise, consistent patterns of reactivity and thermal stability have not yet been determined.

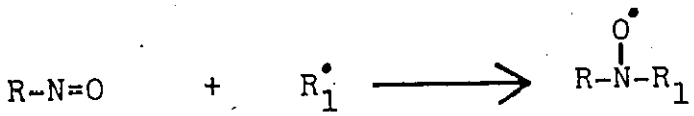
used as spin traps are nitroso-t-butane (219a), 2-methyl-2-nitroso-3-butanone (219b) and nitrosobenzene (219c). Both types of traps react with reactive free radicals in an addition reaction to give nitroxide radicals (220) and (221) (eq. 69).



(218) a) R = C_6H_5
b) R = H

(220)

[69]



(219) a) R = $(CH_3)_3C$
b) R = $CH_3COC(CH_3)_2$
c) R = C_6H_5

(221)

The nitroso compounds (219) are the most useful spin traps because information concerning the original radical structure is more easily obtainable, due to the fact that the new radical site is closer to the previous radical site. However, as Janzen points out at length in his review, there are both advantages and disadvantages inherent in the use of either nitrones (218) or nitroso compounds (219) as spin traps.

A paper describing the use of hindered phenols as spin traps was published in 1972 by Camaggi and Perkins[159].

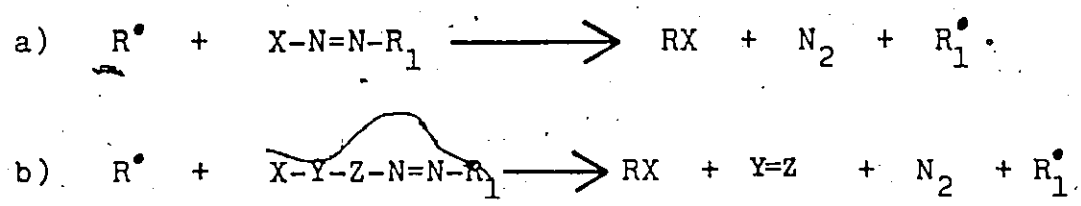
The electron spin resonance spectra of nitroxide free radicals were discussed at length by Leaver and Ramsay[155,156], and also by Griffith and Waggoner[160]. The latter authors discussed the use of nitroxide free radicals in a procedure called spin labelling. This procedure is similar to spin trapping in that it utilizes "planted" nitroxide radicals in macro molecules of living systems to allow their study by electron spin resonance spectroscopy.

VIII RADICAL CHEMISTRY

A) INDUCED DECOMPOSITION

Azo compounds have long been known to decompose thermally or photochemically to produce nitrogen and free radicals. However, the induced decomposition of azo compounds to free radicals is rare. Possible mechanisms for induced decomposition are given in eq. 70. One reason for the rarity of the

[70]



radical substitution reactions of eq. 70 could be the relative rarity of azo compounds with sites X, capable of participating in radical substitutions. Azo compounds with site X, amenable to radical substitution of the type shown in eq. 70a, have been reported in the literature and include those with: X = H[161,162], X = RCO[163], X = RSO_2[164], X = RCO_2[165], X = ArS[166], X = CH_3O[167], X = Cl[168]. It is very possible that the decomposition of these compounds could have occurred via radical substitution at X.

A few cases of possible induced decomposition of the type shown in eq. 70b have also been reported[169,140]. An

example is given in eq. 71. This is the observation of Bensen and co-workers[169] that HCl accelerates the thermal decomposition of azo isobutane.

$$(CH_3)_3C^{\bullet} + HCl \longrightarrow (CH_3)_3CH + Cl^{\bullet}$$

[71] $$Cl^{\bullet} + (CH_3)_3CN{=}NC(CH_3)_3 \longrightarrow HCl + {}^{\bullet}CH_2(CH_3)_2CN{=}NC(CH_3)_3$$

$$^{\bullet}CH_2(CH_3)_2CN{=}NC(CH_3)_3 \longrightarrow CH_2{=}C(CH_3)_2 + N_2 + (CH_3)_3C^{\bullet}$$

B) RADICAL ADDITION

The addition of suitable reagents across the double bond of olefins by a free radical chain reaction provides a useful synthetic method for the preparation of small molecules. A wide variety of reagents such as halogens, hydrogen bromide, alkyl polyhalides, aldehydes, alcohols, amines, mercaptans, thiols, esters, acids, ethers, acetals as well as certain phosphorus and silicon compounds can undergo radical addition to suitably reactive olefins.

Radical addition occurs when a radical A$^{\bullet}$, produced from a molecule A-B by some initiation process (photolysis, thermolysis or chemical initiation), attacks the double bond of an olefin producing a new radical, A-CH_2-$\dot{C}$HR. This radical in turn attacks molecules A-B to give A-CH_2-CBHR and radical A$^{\bullet}$. Radical A$^{\bullet}$ again attacks the olefin and the process is repeated. The overall addition of A-B across the double bond (eq. 72) occurs through a complex sequence of steps as shown (eqs. 73-78). In this sequence equation 73 represents initiation,

equations 74 and 75 represent propagation; equations 76 to 78 represent termination. The reactions represented in equations 74 and 75 are the important steps in determining the product, since A is consumed (eq. 74) and regenerated (eq. 75), and many such cycles can occur for every radical A introduced into the system.

[72] $A\text{-}B + CH_2{=}CHR \longrightarrow ACH_2CHBR$

[73] $A\text{-}B + In^{\bullet} \longrightarrow A^{\bullet} + BIn$

[74] $A^{\bullet} + CH_2{=}CHR \longrightarrow A\text{-}CH_2\text{-}\dot{C}HR$

[75] $ACH_2\dot{C}HR + A\text{-}B \longrightarrow ACH_2CHBR + A^{\bullet}$

[76] $2A^{\bullet} \longrightarrow A\text{-}A$

[77] $2ACH_2\dot{C}HR \longrightarrow ACH_2CHR\text{-}CHRCH_2A$

[78] $A^{\bullet} + ACH_2\dot{C}HR \longrightarrow ACH_2CHAR$

The overall reaction rate and the kinetic chain length (molecules of product produced per initiator radical) which determine the yield of product depend on each of the three processes: initiation, propagation, and termination. The rate of initiation can be controlled by adjustment of experimental conditions. The rate of termination is not controllable and thus imposes a serious limitation on the usefulness of the addition process. The reactions represented in equations 76 to 78 have very high rate constants ($\sim 10^7$ l/mole/sec.) with the time interval between initiation and termination being of the order of only a second. In order for a large number of

propagation steps (eqs. 74&75) to occur in this time interval, it becomes obvious that they must be very rapid, low activation energy processes.

The overall rates and yields of addition (eq. 72) are also dependent on the structures and reactivities of A-B and the olefin. The overall reaction (eq. 72) is, in general, exothermic by approximately 20 Kcal./mole (assuming that A is a hydrocarbon radical). However, for high yields this energy must be suitably divided between the two propagation steps (eqs. 74&75) and neither can be significantly endothermic. How this energy is divided between steps 74 and 75 is determined by the stability of radicals $A^{\bullet}$ and $ACH_2\dot{C}HR$. For exothermicity in the addition reaction (eq. 74), radical $A^{\bullet}$ should be unstable relative to $ACH_2\dot{C}HR$, since the resonance energy of $A^{\bullet}$ is lost while that of $ACH_2\dot{C}HR$ is gained. In order for the chain transfer reaction (eq. 75) to be exothermic, the loss of the resonance energy of $ACH_2\dot{C}HR$ should be compensated for by the resonance energy of $A^{\bullet}$ plus the energy of formation of ACH_2CHBR. An example of the dependence of this division of energies on the structure of A-B is the case of HCl and HBr addition to olefins. In the case of HBr, both propagation steps are low energy and the addition proceeds in high yield. However, in the case of HCl, although the overall reaction is exothermic, the chain transfer reaction (eq. 75) where A-B = Cl-H is appreciably endothermic and the radical chain addition of HCl to olefins is not an efficient process.

Other processes, such as, disproportionation (eqs. 79-81), chain transfer with solvent (eqs. 82-84), telomer formation (eqs. 85-87), allylic attack (eqs. 88&89), and rearrangement (eqs. 90&91), can compete with radical addition to affect seriously the yield of the desired 1:1 adducts. These processes are usually dependent on specific features of a given reaction.

[79] $2ACH_2\dot{C}HR \longrightarrow ACH{=}CHR + ACH_2CH_2R$

[80] $A^\bullet + ACH_2\dot{C}HR \longrightarrow ACH{=}CHR + AH$

[81] $A^\bullet + A^\bullet \longrightarrow C + D$

[82] $ACH_2\dot{C}HR + SS \longrightarrow ACH_2CHSR + S^\bullet$

[83] $S^\bullet + CH_2{=}CHR \longrightarrow SCH_2\dot{C}HR$

[84] $SCH_2\dot{C}HR + SS \longrightarrow SCH_2CHSR + S^\bullet$

[85] $ACH_2\dot{C}HR + CH_2{=}CHR \longrightarrow ACH_2CHR\text{-}CH_2\dot{C}HR$

[86] $ACH_2CHRCH_2\dot{C}HR + A\text{-}B \longrightarrow ACH_2CHRCH_2CHBR + A^\bullet$

[87] $ACH_2CHRCH_2\dot{C}HR + CH_2{=}CHR \longrightarrow ACH_2CHRCH_2CHR\text{-}CH_2\dot{C}HR$

[88] $A^\bullet + CH_2{=}CHCH_2R' \longrightarrow CH_2{=}CH\dot{C}HR' + AH$

[89] $A\text{-}B + CH_2{=}CH\dot{C}HR' \longrightarrow A^\bullet + CH_2{=}CHCHBR'$

[90] $ACH_2\dot{C}HRR' \longrightarrow ACH_2CHR'\dot{C}R$

[91] $ACH_2CHR'\dot{C}HR + A\text{-}B \longrightarrow ACH_2CHR'CHBR + A^\bullet$

For a more thorough discussion of radical addition chemistry, the reader is referred to several good books[170, 171, 172] and review articles[173, 174].

DISCUSSION

A) LEAD TETRAACETATE OXIDATION MECHANISMS OF SEMICARBAZONES AND SIMILAR CARBONYL DERIVATIVES

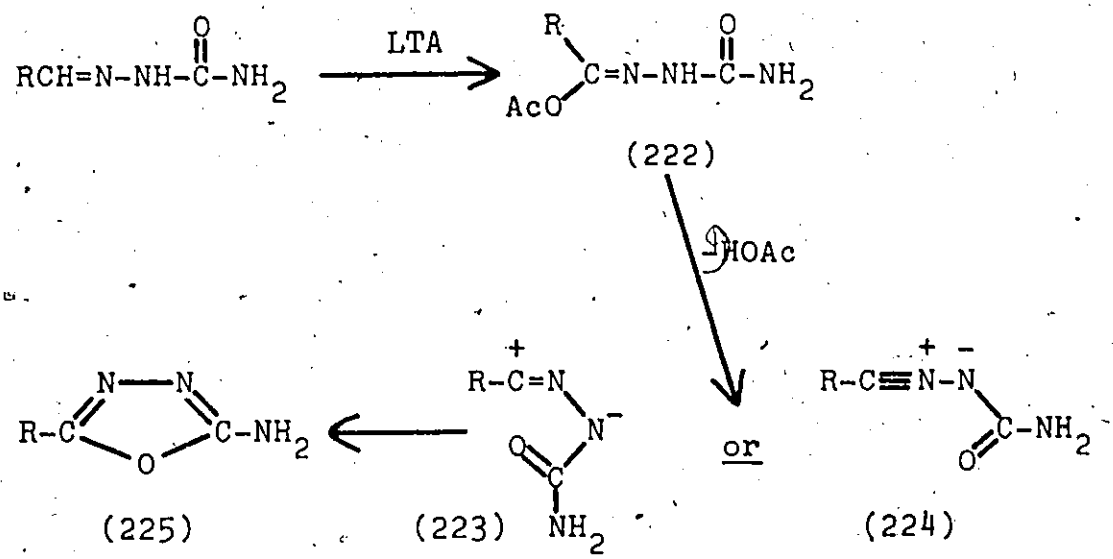
Although the products of the lead tetraacetate oxidation of carbonyl derivatives are different chemical compounds, they all exhibit the same arrangement of atoms in a five-membered ring. Therefore it seems reasonable that a common mechanism should be able to account for all the observed results of such oxidations.

One of the aims of our work was to examine the reported lead tetraacetate (LTA) oxidations and, by analyzing them in relation to our results on the LTA oxidations of semicarbazones, come up with a mechanistic scheme that would account for most or all of the observed results. Such a scheme was prepared and is shown in Scheme XXI (see pages 106 and 107).

Several other authors have proposed mechanisms for the LTA oxidation of various carbonyl derivatives, but none of these mechanisms account for all of the observed results. Butler[22] explained the LTA oxidation of aldehyde semicarbazones in acetic acid to 2-amino-1,3,4-oxadiazoles (225), in terms of a nitrilimine intermediate (Scheme XIX). This mechanism left a lot to be desired since the acetate (222) was not isolated and it is unlikely that the nitrilimine

would assume the favorable geometry (223) required for closure. It is more likely to have the positive charge distributed between carbon and nitrogen and this requires a linear geometry (224).

Scheme XIX



Hoffmann and Luthardt[101,102] rationalized the formation of oxadiazolines from benzoylhydrazones by LTA oxidation as shown in Scheme VII (page 49). Their explanation required the formation of an acyclic azoacetate which subsequently closed to the oxadiazoline. The evidence for the existence of the azoacetate was weak and inconclusive, since the compound was unstable and unisolable. Iffland and co-workers[37] isolated stable acyclic azoacetates produced by LTA oxidation of phenylhydrazones. The disagreement as to the stability of

acyclic azoacetates seems to cast some doubt on their existence in Hoffmann's case.

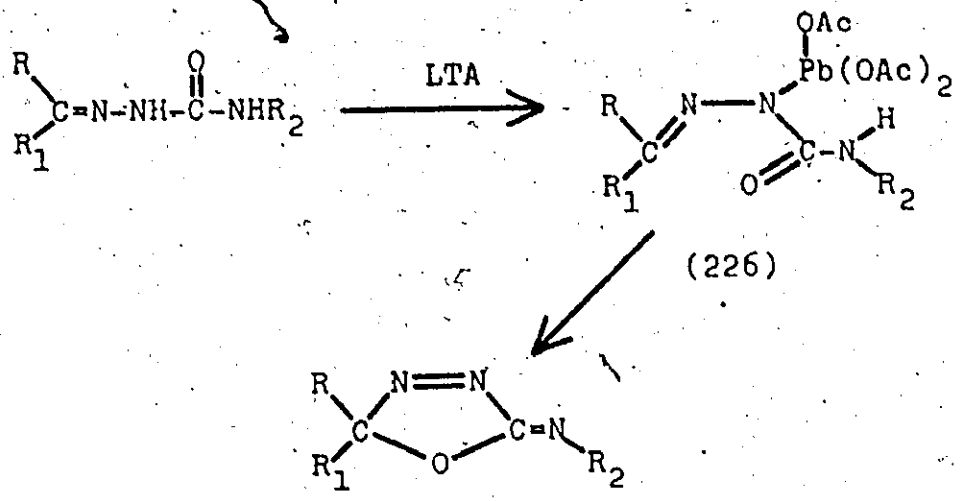
Iffland and co-workers[36] also postulated azoacetate intermediates in the oxidation of 4,4-diethylsemicarbazones with LTA (Scheme II, page 17). Rabjohn and Chaco[80] explained the LTA oxidation of carbethoxyhydrazones to acetyldiphenylmethyl ethyl carbonate in a similar fashion. In neither case was the azoacetate isolated or evidence for its existence produced.

Norman and Gladstone[99] suggested a mechanism (Scheme VI, page 47) for the formation of an epoxide (126) from 4-p-nitrophenylhydrazone (124) by oxidation with LTA, which is similar to the one given in Scheme XXI. Their mechanism involved cyclization of a 2-nitrogen lead complex to an oxadiazoline and subsequent loss of nitrogen to give the epoxide (126).

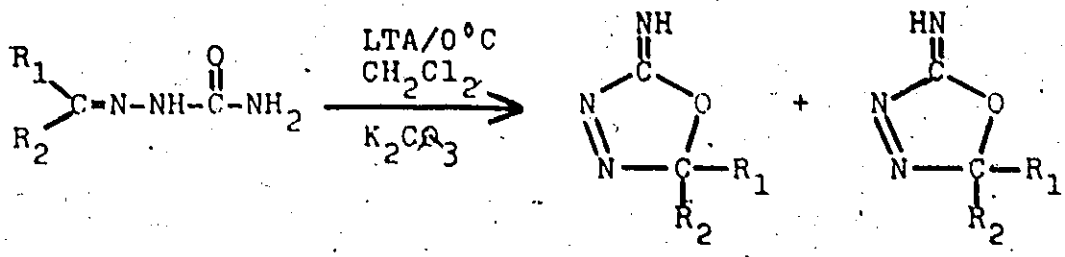
A mechanism similar to Norman's was proposed by Cameron[175] for the oxidation of 4-substituted semicarbazones with LTA which resulted in selective formation of only one of two possible isomers, the Z-isomer (see page 20). This selectivity could not be explained by the Hoffmann-Luthardt mechanism. Cameron's proposed mechanism is shown in Scheme XX. The 2-nitrogen lead complex (226) has steric requirements which force the terminal nitrogen to orient itself in such a way as to minimize steric hindrance, that is, the bulkiest group (R_2) must be away from the lead and rotation about the

C-N bond is effectively prohibited. Closure of the complex in this orientation results in the Z-isomer exclusively.

Scheme XX



We carried out the LTA oxidations of unsubstituted ketone and aldehyde semicarbazones. Oxidation of ketone semicarbazones in methylene chloride, containing anhydrous potassium carbonate to remove the acetic acid formed during the oxidation, resulted in high yields of the 2-imino-Δ^3-1, 3,4-oxadiazolines (227) (eq. 92). Although the substituted 2-imino analogues are known (see page 55), (227) have not been reported to date, and this appears to be the first preparation of them. In the benzylmethyl case, two imino signals were observed in the p.m.r. spectrum. The fact that hydrolysis of the mixture gave the corresponding oxadiazolinone suggests that those signals came from the E- and Z-isomers of the imine. The compounds (227) were purified by sublimation and the structure supported by microanalysis.



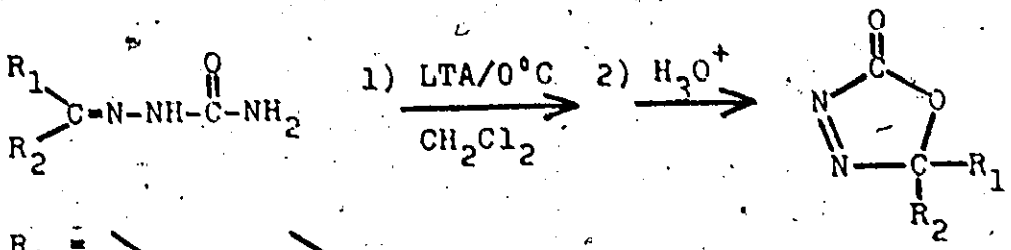
[92]

Z (227) E

R_1 = CH_3, CH_3, CH_3, $(CH_2)_5$

R_2 = CH_3, $(CH_3)_2CH$, $C_6H_5CH_2$,

Our main interest in ketone semicarbazone oxidation, apart from the mechanistic aspect, was the preparation of 5,5-disubstituted-Δ^3-1,3,4-oxadiazolin-2-ones (228)[176]. Compounds of the type (228) were first prepared in this laboratory[107] by hydrolysis of 2-methylimino-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines (140) in dilute acid media (see page 55). We found that LTA oxidation of unsubstituted ketone semicarbazones in methylene chloride followed by "in situ" dilute acid hydrolysis of the imino compounds (227), provided a simpler, more readily accessible route to (228) for two reasons. Firstly, unsubstituted semicarbazones are more readily available than the 4-methyl analogues and secondly, "in situ" hydrolysis results in higher yields. The procedure for the preparation of (228) is outlined in eq. 93. Purification for analytical purposes was achieved by sublimation for the solid products, and by vacuum distillation for the liquid products, with average yields of 40-50%. Compounds (227) could be converted to (228) by dilute acid hydrolysis.

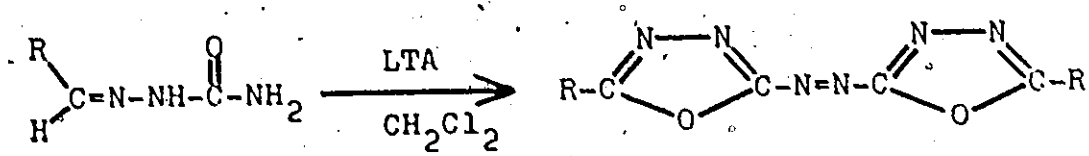


[93] R_1 = R_2 = $(CH_2)_5$, $(CH_2)_4$, (228)

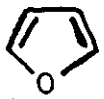
R_1 = CH_3, $(CH_3)_2CH$, $CH_3CH_2CH_2$, $C_6H_5CH_2$, $(CH_3)_2CH$.

R_2 = CH_3, CH_3, CH_3, CH_3, $(CH_3)_2CH$.

The oxidation of aldehyde semicarbazones in methylene chloride with LTA resulted in the formation of 5,5'-disubstituted-azo-1,3,4-oxadiazoles (29) (eq. 94). Compounds of the type (29) had been reported[27] as products of the oxidation of 2-amino-1,3,4-oxadiazoles (225), but were never obtained directly from oxidation of aldehyde semicarbazones. In order



[94] (29)

R = o-ClC_6H_4, o-$CH_3OC_6H_4$, $C_6H_5CH{=}CH$, $(CH_3)_2CH$, 

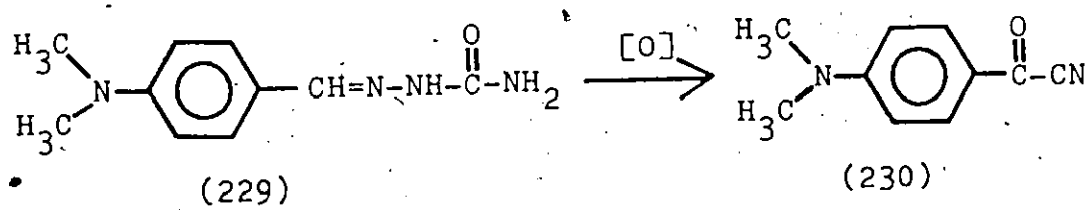
to demonstrate that (29) are the same products as those obtained from the oxidation of (225) and that (225) are intermediates in the above oxidation, two compounds (225, R = o-ClC_6H_4, $C_6H_5CH{=}CH$) were prepared by Gibson's[13] method and oxidized under the same conditions used for the aldehyde

semicarbazones (eq. 94). The products obtained were identical to (29).

Since (29) is a product of the further oxidation of (225), it is suprising that Butler[22] did not observe it. The fact that he used acetic acid instead of methylene chloride (this work) as solvent may be important. Protonation of (225) in acetic acid must reduce the concentration of free amine. If the rate-determining step of coupling is an S_N2 reaction between free amine (RNH_2) and a lead derivative ($RNHPb(OAc)_3$), then the rate of coupling depends on the square of the concentration of free base. Halving the concentration of free base would therefore reduce the rate of coupling fourfold.

During the course of our oxidations of aldehyde semicarbazones, we obtained one anomalous result. Oxidation of p-dimethylaminobenzaldehyde semicarbazone (229) (eq. 95)[177] under identical conditions to those used for other aldehyde semicarbazones (eq. 94), led to a quantitative yield of p-dimethylaminobenzoyl cyanide (230) (eq. 95). The product

[95]



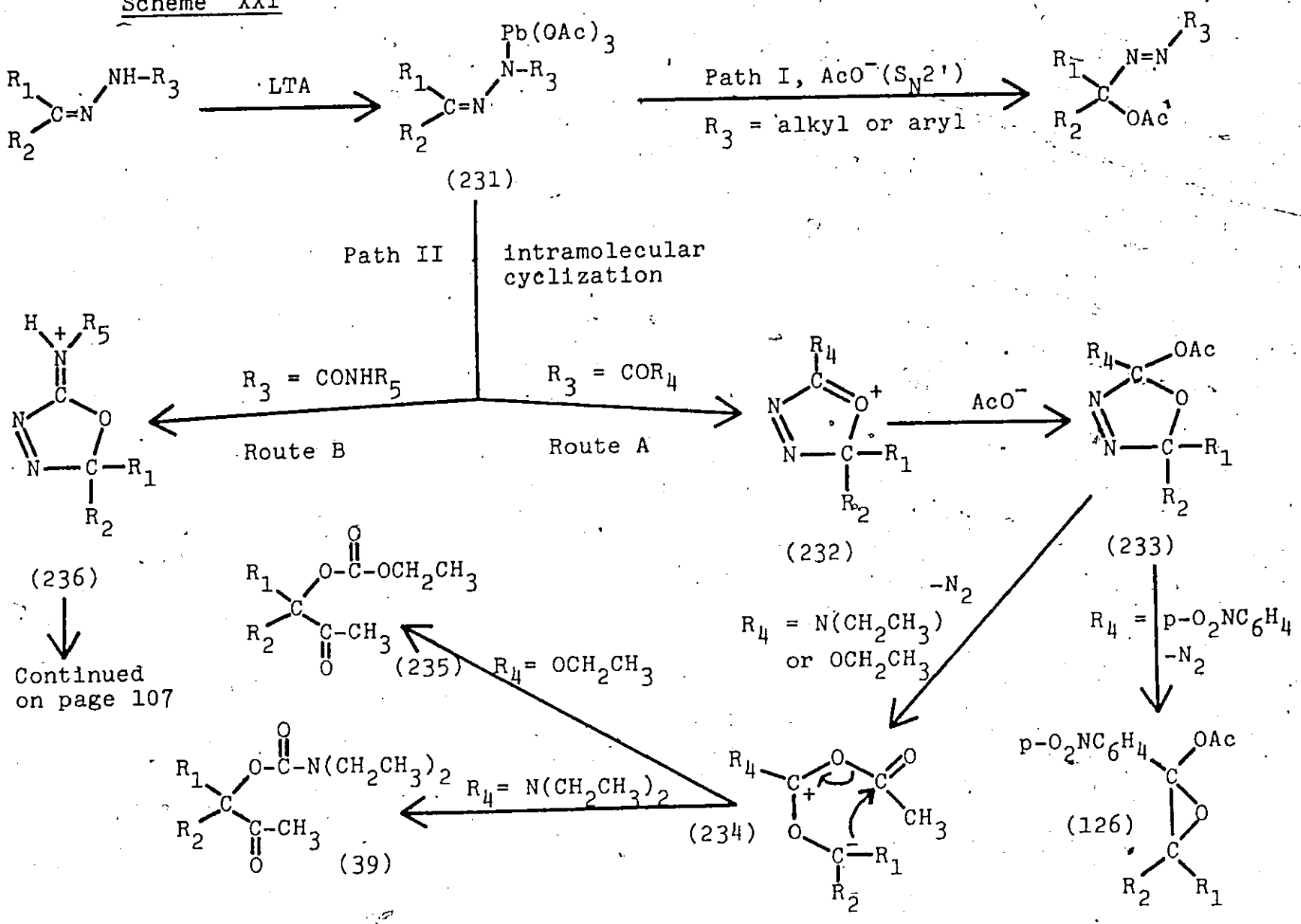
(229) (230)

(230) was identified by microanalysis, spectra, comparison of properties to those reported[178] as well as base hydrolysis to the known p-dimethylaminobenzoic acid[179] and cyanide ion.

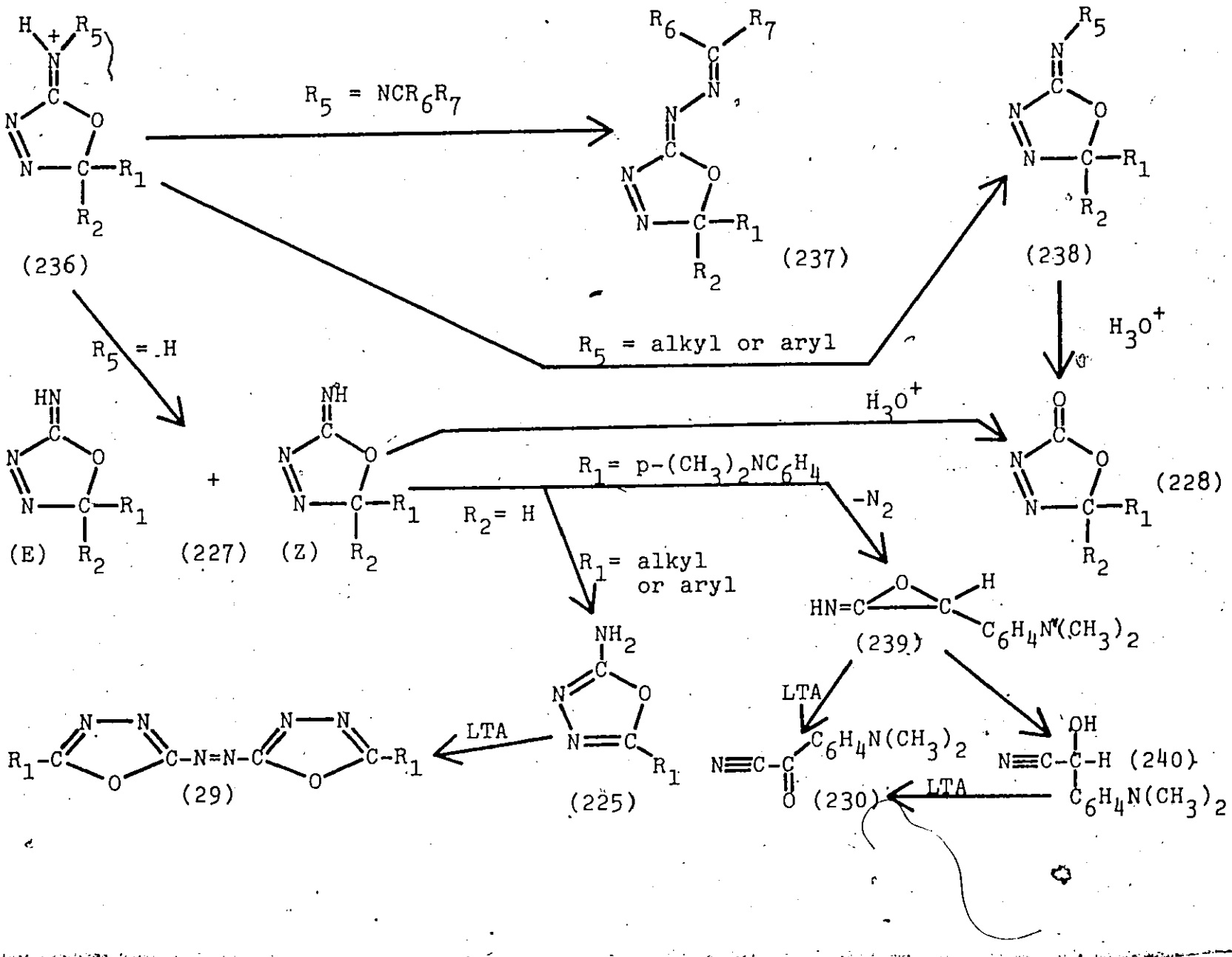
We believe that the oxidation of carbonyl derivatives with LTA can be explained by a single mechanism closely related to Cameron's and our proposed mechanism is shown in Scheme XXI. The initial step in the oxidation involves reaction of the carbonyl derivative with the LTA to give a complex (231), in which the lead is attached to the 2-nitrogen. If the carbonyl derivative is an aryl or alkyl hydrazone, then azoacetate formation occurs (Path I) since cyclization is not possible. Thus Iffland's[37] azoacetate product can be accounted for. When the carbonyl derivative has a carbonyl group in the 3-position, intramolecular cyclization occurs (Path II).

Depending on R_3, Path II can branch into two routes, A and B. When $R_3 = COR_4$, cyclization leads (Route A) to the charged species (232) which then adds acetate to give the oxadiazoline (233). This is Hoffmann's product with $R_4 = C_6H_5$ and by this route its formation is explained without invoking an acyclic azoacetate. If $R_4 = p\text{-}O_2NC_6H_4$, then (233) is the same as Norman's intermediate which loses nitrogen to form the epoxide (126). Iffland's carbamate, from the oxidation of 4,4-diethylsemicarbazone, can also be explained by Route A. The intermediate (233, $R_4 = N(CH_2CH_3)_2$ can lose nitrogen to give the dipolar species (234) which can rearrange to the carbamate (39). A similar explanation accounts for the formation of acetyldiphenylmethyl ethyl carbonate (235) from the carbethoxyhydrazone observed by Rabjohn and Chaco. The intermediate (233, $R_4 = OCH_2CH_3$) loses nitrogen to give (234)

Scheme XXI


LTA
Pb(OAc)3
Path I, AcO⁻(SN2')
R3 = alkyl or aryl
(231)
Path II
intramolecular cyclization
R3 = CONHR5
R3 = COR4
Route B
Route A
AcO⁻
(232)
(233)
(236)
Continued on page 107
(235)
R4= OCH2CH3
-N2
R4 = N(CH2CH3)
or OCH2CH3
R4 = p-O2NC6H4
-N2
(234)
R4= N(CH2CH3)2
(39)
(126)

Scheme XXI (cont'd)



which rearranges to the carbonate (235).

In the case of monosubstituted and unsubstituted ketone semicarbazones, where R_3 = $CONHR_5$, cyclization leads (Route B) to the charged species (236). Depending on R_5, (236) can deprotonate to give three products. If R_5 = NCR_6R_7, then deprotonation leads to the product (237) and the oxidation of carbohydrazones[77] is accounted for. If R_5 = alkyl or aryl groups, then deprotonation yields the z-isomer of 2-alkyl or aryliminooxadiazolines (238) exclusively. This selectivity was explained by Cameron and the explanation is summarized on page 100.

Finally, our results can be accounted for in the following way. When R_5 = H, deprotonation of (236) leads to a mixture of E and Z isomers of 2-iminooxadiazoline (227). This is reasonable in light of Cameron's argument since when the steric requirements of both substituents on the 4-nitrogen are equal, one should obtain both isomers. Acid hydrolysis of both (238) and (227) leads to the oxadiazolin-2-ones (228).

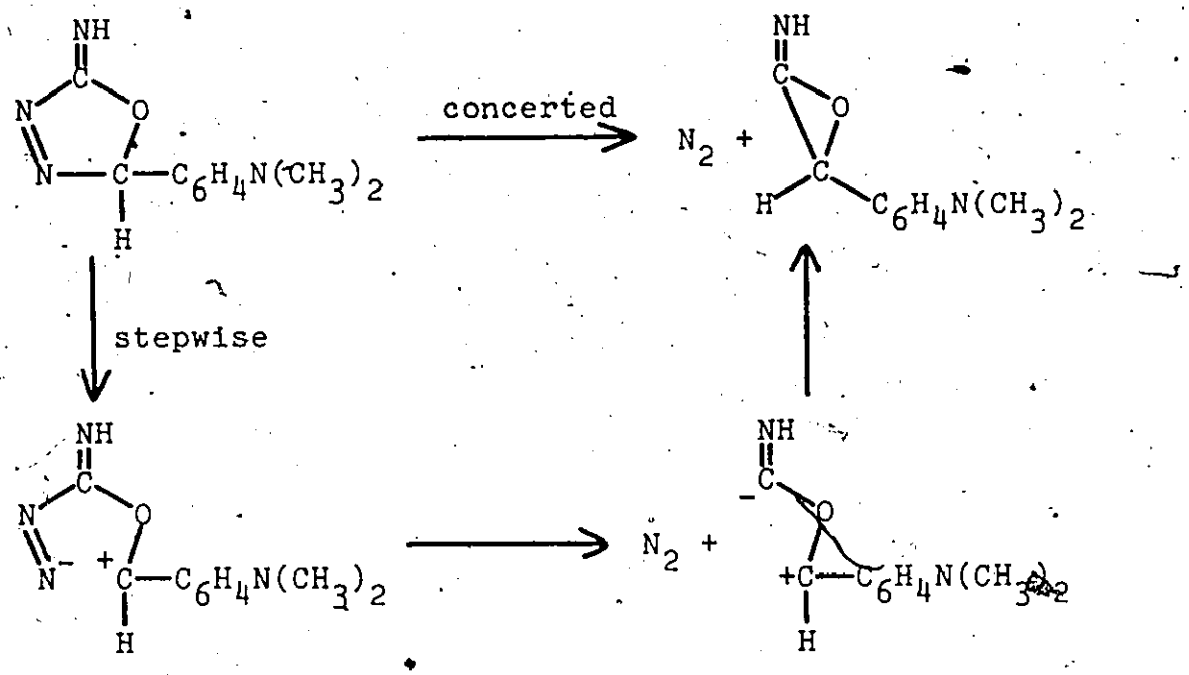
In the case of aldehyde semicarbazones, oxidation leads by Path II, Route B to the intermediate (227, R_2 = H). This can then, depending on R_1, undergo either of two transformations. For groups R_1 other than p-$(CH_3)_2NC_6H_4$, (227, R_2 = H) isomerizes to the 2-amino-1,3,4-oxadiazoles (225). Thus Butler's products can be accounted for without resorting to nitrilimine intermediates. Under our conditions (225) are oxidized further to the azooxadiazoles (29).

When R_1 = p-$(CH_3)_2NC_6H_4$, the intermediate (227, R_2 = H) loses nitrogen to give the iminooxirane (239), which can be subsequently oxidized by LTA to the benzoyl cyanide (230), or it can isomerize to the cyanohydrin (240) which is then oxidized by LTA to (230). It can be seen that, to explain the formation of (230), the imino compound (227) must be formed as an intermediate. With Butler's nitrilimine mechanism it is not possible to account for the C-C bond formation required to form (230).

The anomalous effect of the p-dimethylaminophenyl group can be explained in the following manner. The strong electron donating property of p-dimethylaminophenyl, by supporting the developing positive charge at the 5-carbon, would tend to encourage C-N bond cleavage, as opposed to isomerization which occurs in the case of other groups R_1. The result is loss of nitrogen, giving the iminooxirane (239) by either a stepwise process or a concerted process with a polar transition state (Scheme XXII). With groups R_1 other than p-dimethylaminophenyl, isomerization is the fastest process effectively preventing loss of nitrogen. Here the result is formation of the 2-aminooxadiazoles (225).

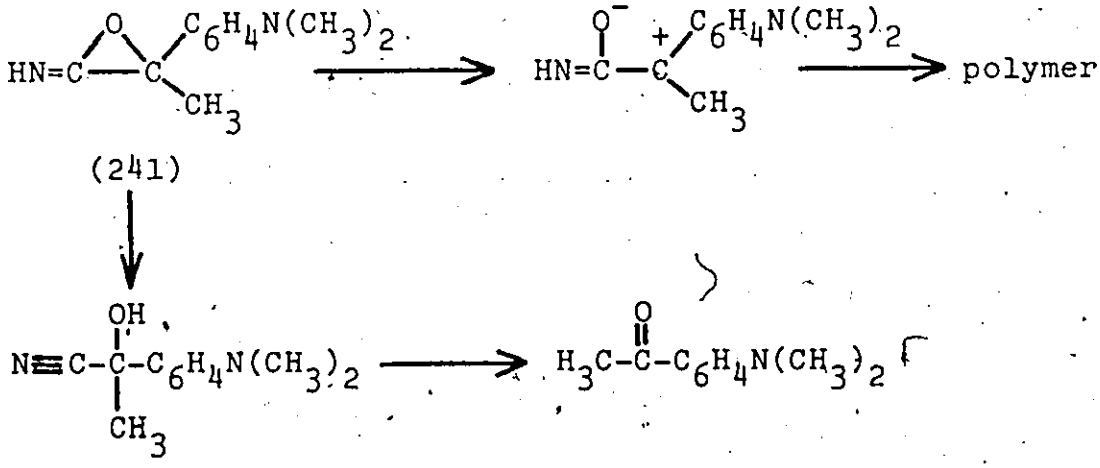
Support for the existence of an iminooxirane (239) intermediate came from the oxidation of p-dimethylaminoacetophenone semicarbazone, which led to a polymer and p-dimethylaminoacetophenone. In this case, the intermediate iminooxirane (241) (Scheme XXIII) cannot be oxidized; therefore, it either

Scheme XXII



opens and polymerizes, a known facile reaction of α-lactones[180], or it isomerizes to the cyanohydrin which hydrolyses to the ketone during workup (Scheme XXIII).

Scheme XXIII



The proposed mechanism in Scheme XXI accounts, then, quite adequately for all the recorded observations and appears to be a general mechanism for LTA oxidations of carbonyl derivatives.

B) SPECTROSCOPIC AND CHEMICAL PROPERTIES OF THE OXIDATION PRODUCTS

5,5'-DISUBSTITUTED-AZO-1,3,4-OXADIAZOLES (29).

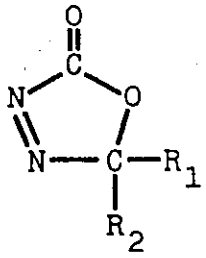
The products (29) are essentially azo dyes and are highly coloured. Once in the solid form, they are extremely insoluble and, as such, are very difficult to analyze. Prolonged refluxing in hexachlorobutadiene, for instance, was necessary to give a concentrated enough solution for n.m.r. analysis.

The compound (29, R = o-ClC_6H_4) was analyzed by microanalysis, by molecular weight determination, and through its n.m.r. and ir. spectra. The other structures were assigned by analogy. In the case of R = $C_6H_5CH=CH$, two products were obtained. Both were azo compounds, and it is possible that one was the product of the further oxidation of the cinnamyl double bond by LTA.

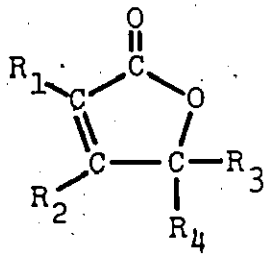
The compounds (29) are all very high melting, very stable and do not react with acid or base. Due to their insolubility, to their unreactivity and to the fact that they were already known, the chemistry of (29) was not examined. It is possible that they may have some utility as dyes, since their insolubility would make them colour-fast once in the fabric.

2) 5,5-DISUBSTITUTED-Δ^3-1,3,4-OXADIAZOLIN-2-ONES (228).

The compounds (228) are α,β-unsaturated-α,β-diaza-γ-lactones and, as such, can be compared to α,β-unsaturated-γ-lactones (242). The infrared carbonyl frequencies of (228) occur at 1835 cm^{-1}, while those of (242) come at about 1750 cm^{-1}. The discrepancy appears to be due to the strong electron withdrawing effect of the azo group of (228). This influence is probably exerted at the carbonyl carbon, where



(228)



(242)

sp^2 nitrogen acts inductively to withdraw electrons, and indirectly at the γ-carbon, which transmits an inductive effect to the ether oxygen. This γ-effect is also known in (242). γ-Acetoxy-γ-valerolactone absorbs at 1797 cm^{-1}, about 30 cm^{-1} higher than γ-valerolactone[181]. Compounds (228), like γ-lactones, do not have altered carbonyl frequencies due to spirocyclic geometry (228, $R_1R_2 = (CH_2)_4$ or $(CH_2)_5$) where extra rigidity is imposed. Another infrared band of (228) at 1540 cm^{-1} is attributable to the azo group[182] and is comparable to the N=N stretching frequency of 3-acetoxy-1-pyrazolines at 1565 cm^{-1} [183].

The ultraviolet spectra of (228) consist of a medium-intensity $\pi-\pi^*$ band near 217 nm and a low-intensity $n-\pi^*$ band near 370 nm. The former is red-shifted in polar solvents as is common for $\pi-\pi^*$ bands[184]. The $n-\pi^*$ band is also red-shifted in polar solvents, in contrast to the $n-\pi^*$ band of ketones which is blue-shifted due to decreased polarity of the excited state relative to the ground state[184]. In the case of (228), the red shift of the $n-\pi^*$ band indicates increased excited state polarity and suggests that the $n-\pi^*$ band is due to the n-electrons from nitrogen rather than from the carbonyl carbon.

The compounds (228) exhibit n.m.r. spectra characteristic of alkyl groups with protons on carbons directly attached to electronegative atoms. In some cases, complex spectra are obtained due to chirality from unsymmetrical substitution at C-5.

Oxadiazolin-2-ones (228) are white solids or clear, colourless liquids depending on the groups R_1 and R_2. They have a pungent odour reminiscent of onions and are relatively volatile. At 0°C under anhydrous conditions they are stable indefinitely, but in the presence of water or at room temperature they slowly decompose. The solids are low-melting (50-80°C) and can be recrystallized from petroleum ether (30-60°C). Thermal decomposition of (228), by heating to 100°C, results in a mixture of ketone and ketazine.

3) 5,5-DISUBSTITUTED-2-IMINO-Δ^3-1,3,4-OXADIAZOLINES (227).

All compounds (227) prepared are white solids with melting points in the range from 50 to 90°C. Their spectra are similar to those of the corresponding oxadiazolin-2-ones (228), with the infrared exhibiting a strong exocyclic imino absorption at about 1705 cm^{-1}. Additional properties were not determined, although microanalysis of the 5,5-dimethyl compound was obtained to ensure that the assigned structures (227) were correct.

C) CHEMISTRY OF 5,5-DIMETHYL-Δ^3-1,3,4-OXADIAZOLIN-2-ONE (243)

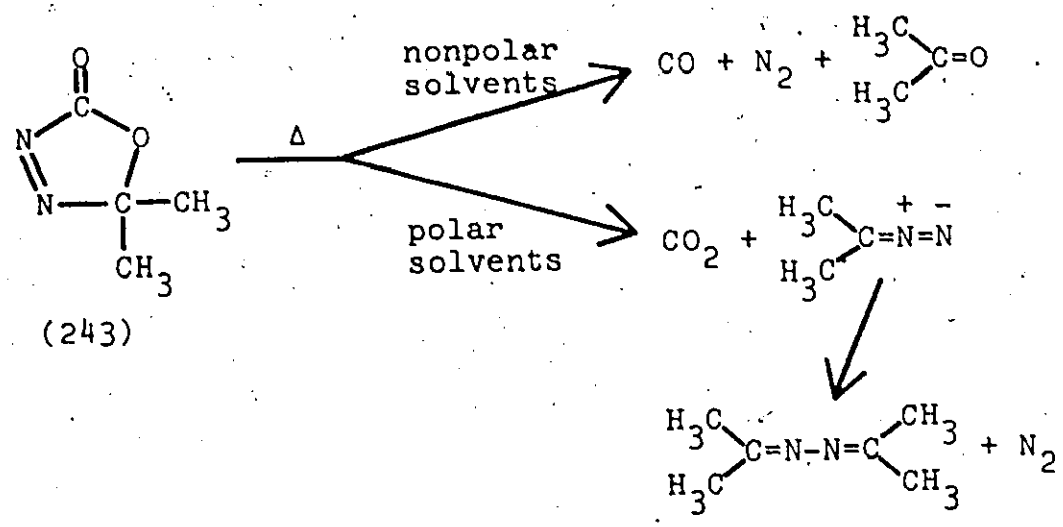
In general, systems containing two nitrogen atoms directly bonded by a double bond are potentially reactive and synthetically useful. Their reactivity arises from the possibility of thermal or photochemical cleavage of the molecule, producing a stable nitrogen molecule as well as other fragments, which can, in turn, be useful intermediates for synthesis. The formation of nitrogen tends to lower the activation energy of the decomposition, thereby enhancing the reactivity.

Oxadiazolinones (228) contain not only the azo function referred to above, but also the lactone function. Their chemistry was therefore expected to be interesting, complex, and possibly useful. Although eight members of the family were synthesized, only the 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243) was studied since it promised the simplest n.m.r. spectra for materials potentially available from various chemical reactions.

The thermal decomposition of (243) was first examined by Lee, Cameron and Warkentin[108]. They found that the molecule does indeed cleave, and furthermore, does so by a duality of pathways. In nonpolar solvents, such as carbon tetrachloride, the decomposition leads primarily to carbon monoxide, nitrogen and acetone. This route has little synthetic signif-

icance. However, in polar solvents, such as methanol, decomposition leads mainly to carbon dioxide and 2-diazopropane (eq. 96) which, if no reactive trap is present, goes on to acetone azine.

[96]

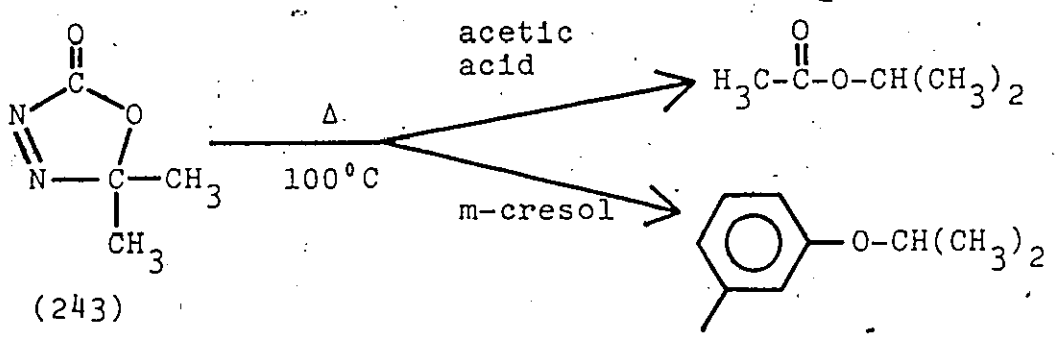


(243)

Given the presence of a suitable reagent during formation, it seemed likely that the 2-diazopropane could be trapped. If this should prove to be the case, the decomposition of oxadiazolinones (228) promised a simple route to usable complex diazoalkanes. Fairly complex diazoalkanes are, in general, difficult to prepare due to three factors: firstly, the usual route involving oxidation of the hydrazone requires 1:1 condensation of ketone with hydrazine, and results in traces of metallic impurities which can catalyze decomposition[185]; secondly, hydrazones tend to disproportionate to azines and hydrazines[186]; thirdly, some diazoalkanes react rapidly with themselves to form azines[187].

On decomposing (243) at 100°C in excess glacial acetic acid in a sealed tube, we found that the 2-diazopropane could indeed be trapped and converted to isopropyl acetate in about 20% yield (eq. 97). Similarly, decomposition of (243) in m-cresol yielded m-tolyl isopropyl ether (eq. 97). Decomposition of (243) in phenol resulted in phenyl isopropyl ether.

[97]



(243)

To establish the generality of the reaction for all (228), we decomposed cyclopentanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one) (228, $R_1R_2 = (CH_2)_4$) in glacial acetic acid and obtained cyclopentyl acetate.

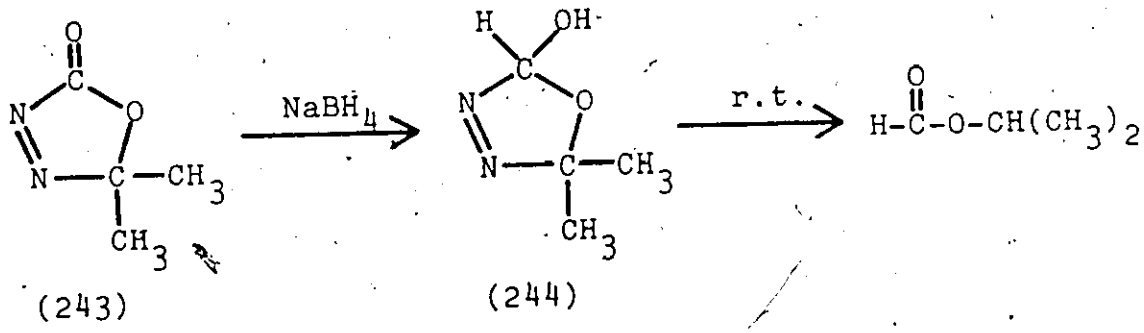
Although the yields are low, the decomposition of (228) appears to provide an easy route to fairly complex diazoalkanes. Apart from the fact that this method is cheap and does not require synthesis of halides or tosylates for the S_N reactions, it provides for esterification and etherification of various substrates through use of the appropriate ketone.

Diazoalkanes also react with aryl isocyanates to form

oxindole derivatives and hydantoins[188]. Oxadiazolinones (228) may be excellent sources of diazoalkanes for these syntheses.

It was also of interest to examine the reactivity of (243) towards nucleophiles as well as other reagents. This reactivity was expected to be fairly high, in view of the elevated carbonyl stretching frequency of (243) at 1835 cm^{-1}. Although oxadiazolinone (243) is similar to an α,β-unsaturated ester, it has, in some instances, the chemistry of α,β-unsaturated ketones. Treatment of (243) with sodium borohydride in methanol or water resulted in 5,5-dimethyl-2-hydroxy-Δ^3-1,3,4-oxadiazoline (244) in good yield (eq. 98). The product

[98]



(243) (244)

(244) was identified by n.m.r. but, due to its thermal instability, further analysis was not possible. Thermal decomposition occurs at room temperature and leads quantitatively to isopropyl formate (eq. 98), identified by comparison of spectra with those reported in the literature[189].

Since normal esters are inert to sodium borohydride[190], the reduction of (243) was unexpected. However, the fact that ketones are reduced by sodium borohydride allows one to infer

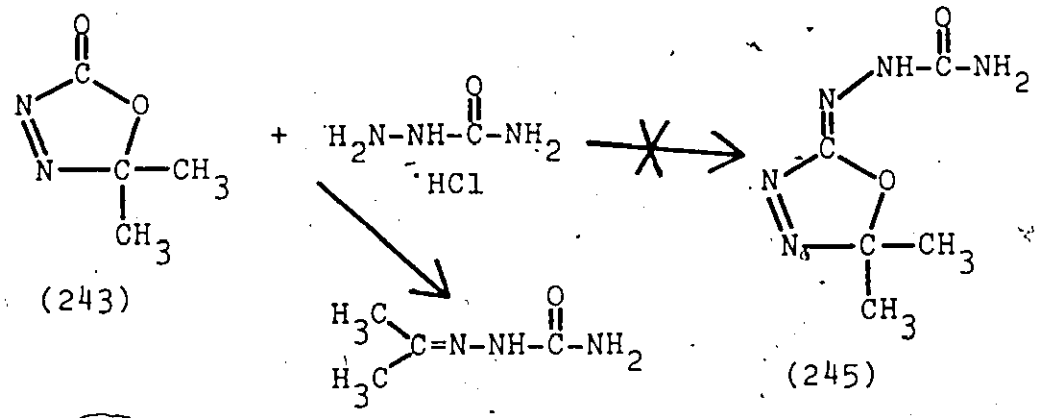
that (243) behaves more like a ketone than an ester towards reducing agents. The ketone-like behaviour of ester carbonyls has been noted by other workers. Dean and Park[191] came to the conclusion that the presence of electronegative substituents on the α-carbon of an ester tends to give the carbonyl group ketone-like qualities. In (243) a strongly electronegative group, the azo function, is present and is directly bonded to the carbonyl carbon. By analogy to Dean and Park's theory, the ketone-like behaviour of (243) becomes explainable. To ascertain whether the ketone-like behaviour of (243) was general, we examined several other typical ketone reactions.

Treatment of (243) under conditions leading to ketal formation (methanol and acid) did not result in reaction, and (243) was recovered quantitatively. When (243) was treated with sodium cyanide in water or methanol with traces of acid, cyanohydrin formation did not occur. But in this case, a violent reaction ensued on mixing the reagents and the only isolable product was hydrazobisisobutyronitrile. How this arises is unclear, but it could be due to cyanide attack on acetone azine, a decomposition product of (243). The reason why cyanide enhances the rate of decomposition of (243), normally very slow at room temperature in water or methanol, remains a mystery.

A similar, violent reaction was observed when (243) was treated with semicarbazide hydrochloride under normal conditions for semicarbazone formation. Instead of the

expected semicarbazone (245) (eq. 99), acetone semicarbazone was isolated. Again, it appears that semicarbazide hydrochoride in some way enhances the rate of decomposition of (243) to acetone azine or acetone, and subsequently reacts with the product to give the semicarbazone.

[99]

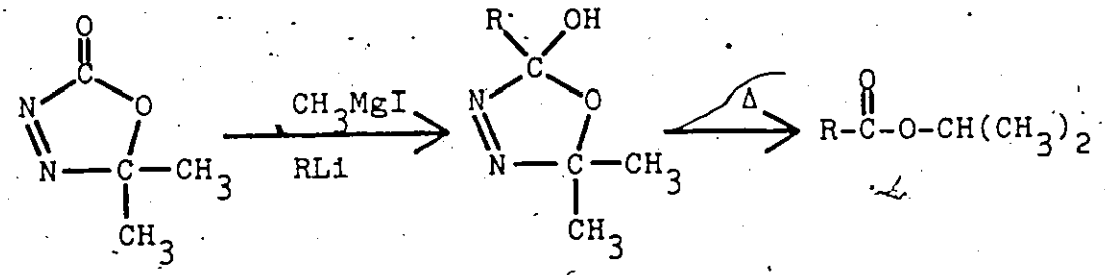


(243) (245)

5,5-Dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243) was also treated with organometallic reagents. Treatment of (243) with methyl magnesium iodide, methyl lithium, t-butyl lithium, isopropyl lithium and n-propyl lithium yielded the carbonyl addition product (246) (eq. 100), which could be isolated. However, reaction of (243) with phenyl lithium resulted in isolation of isopropyl benzoate, which is the thermal decomposition product of (246, R = C_6H_5). All the products (246) were unstable, and on heating we obtained the appropriate isopropyl esters.

For convenience of analysis and handling of products, further studies were conducted with (243) and methyl lithium.

[100]

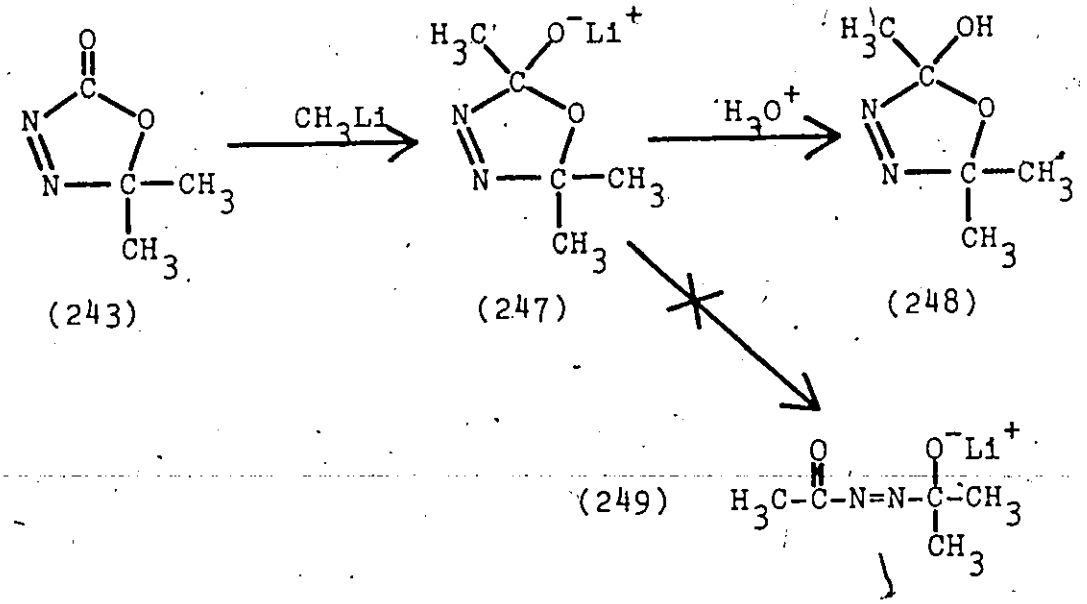


(243) (246)

R = CH_3, $(CH_3)_3C$, $(CH_3)_2CH$, $CH_3CH_2CH_2$

Treatment of (243) with methyl lithium in ether at 0°C led[192] to the lithium salt (247) which could be isolated and stored, or hydrolyzed directly to 2-hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (248) (eq. 101). The formation of (248) was a somewhat suprising result since, unlike acyclic esters and most lactones which consume two equivalents of methyl lithium[193] giving a tertiary alcohol product, (243) consumed only one

[101]



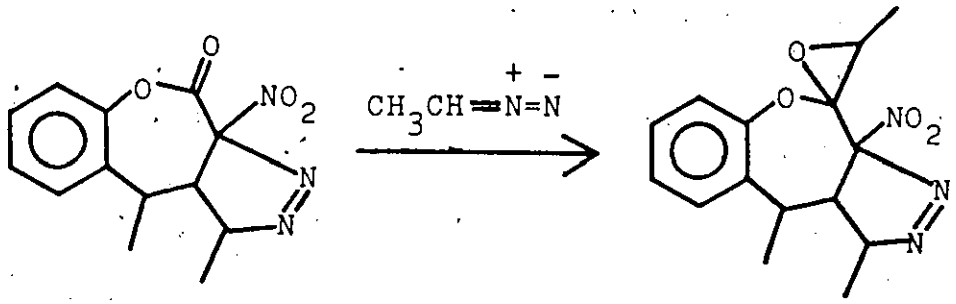
(243) (247) (248)

(249)

equivalent of methyl lithium even when the reagent was in huge

excess. This result can be attributed to the strong electron withdrawing inductive effect of the azo group, which serves to make ring opening of the lithium salt (247) to the azo carbonyl compound (249) (eq. 101) unusually endothermic. The strong electron withdrawing effect of the azo function is indicated by the high carbonyl frequency (1835 cm^{-1}) of (243) and of other azo carbonyl systems[142]. Substituent constants (σ_p = 0.35 and σ_p^- = 0.70) for the phenylazo group also attest to the same polar effect of the azo group[194].

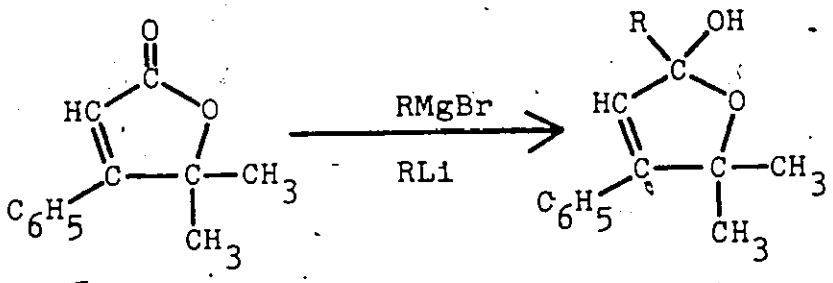
Nucleophilic attack on a cyclic ester system with electron withdrawing α-substituents has been reported[191]. Here attack occurred at the carbonyl carbon to give an epoxide (eq. 102), rather than the ring expansion product. For the same reason mentioned in the preceding paragraph, this result may be due to the nitro group which makes ring opening an unfavorable process.

[102] 

Not necessarily all lactones add two equivalents of organometallic reagents. An unusual reaction of a carbon analogue of (243) with organometallic reagents was reported recently[195]. The α,β-unsaturated-γ-lactone (250), when reacted

with phenylmagnesium bromide, p-tolylmagnesium bromide or organolithium compounds, was reported to give the cyclic hydroxy compounds (251) (eq. 103). This is a somewhat suprising result since, α,β-unsaturated lactones normally undergo

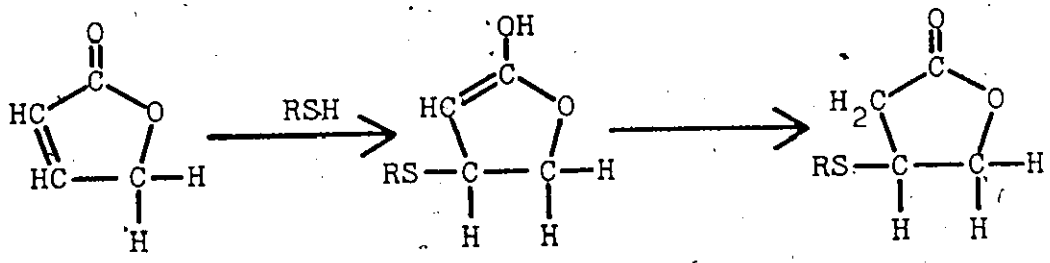
[103]



(250) (251)

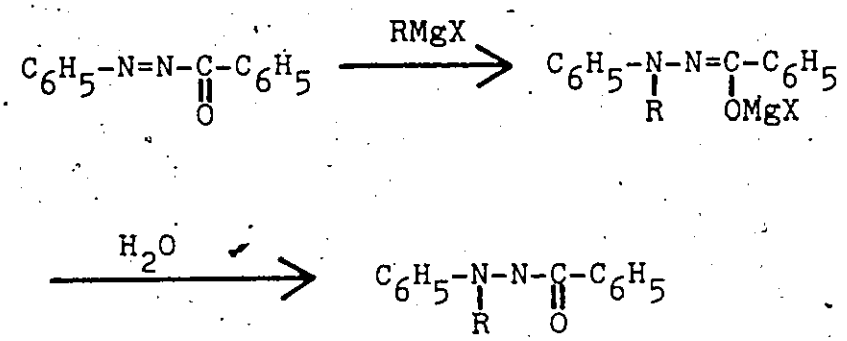
nucleophilic attack in a 1,4 sense at the β-carbon rather than at the carbonyl carbon. An example of this 1,4 attack is the reaction of lactone (252) with thiols[196] (eq. 104).

[104]



(252)

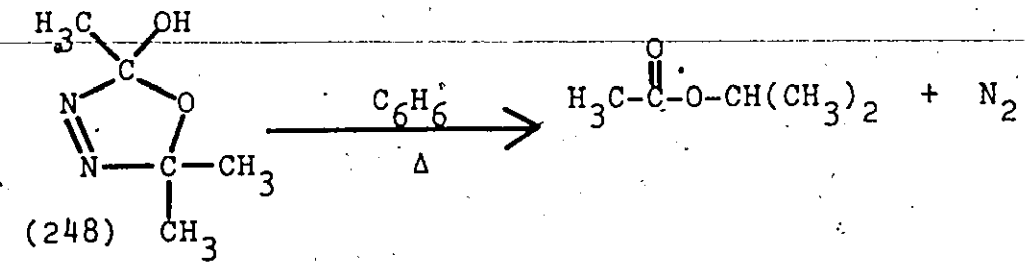
It is also true, in some cases, that α-carbonyl azo systems add nucleophiles in a 1,4 sense. Acyclic α-carbonyl azo compounds were reported[118] to add Grignard reagents to give the β-substituted hydrazides (eq. 105). Similarly,



[105]

cyclic azo carbonyl compounds were reported[124] to undergo 1,4 attack with ethyl magnesium bromide (see page 72). However, with tetralone magnesium enolate, formation of a hydroxy compound analogous to (248) was reported[124] (see page 73).

The hydroxy compound (248) (eq. 101) was too unstable to be isolated analytically pure, but its structure was readily established from spectra and decomposition products. The n.m.r. consisted of three sharp singlets at high field, equivalent to three protons each, and a broad low field singlet, equivalent to one proton, which disappeared on addition of D_2O. The infrared contained bands at 3550 cm^{-1}, indicating a free O-H; at 3350 cm^{-1}, indicating hydrogen-bonded O-H; and at 1565 cm^{-1}(weak), indicating a cis azo linkage. Thermal decomposition led to isopropyl acetate quantitatively, indicating a C-O-C skeleton (eq. 106).



[106]

(248)

D). CHEMISTRY OF 2-HYDROXY-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINE (248)

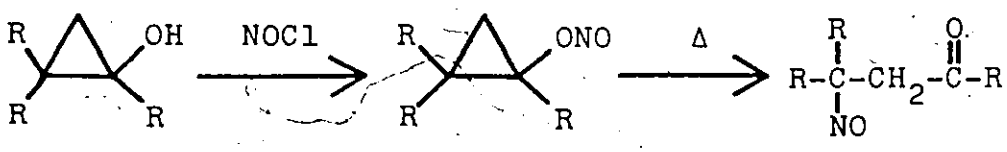
Since (248) is an azo compound, which also has three heteroatoms bonded to the 2-carbon, its chemistry was expected to be interesting.

As mentioned before, (248) decomposes cleanly to give isopropyl acetate, an unusual result in view of the fact that other similar systems, such as those of Hoffmann[100-104] and Nagata[124], gave epoxides on heating. The reasons for this unusual mode of decomposition were examined in detail.

From several observations it became clear that the process in eq. 106 was radical in nature. Decomposition of (248) in such solvents as carbon tetrachloride and chloroform, which can participate in or interfere with radical reactions, led to very complicated, unassignable n.m.r. spectra; whereas decomposition in an inert solvent, such as benzene, resulted in a clean n.m.r. spectrum of isopropyl acetate. Some freshly prepared samples of (248) decomposed spontaneously, while others were stable for some time at room temperature. Heating of an aliquot of (248) in benzene to 55°C initiated decomposition--observable by bubbling--which could not be stopped on cooling and (248) proceeded to decompose completely to isopropyl acetate. Yet in the same time, the rest of the same sample, from which the aliquot was taken, did not decompose appreciably.

The radical nature of the process (eq. 106) was confirmed by heating a sample of (248) in the presence of nitrosobenzene, a known spin trap[158]. The e.s.r. spectrum of this sample showed a strong triplet signal with g = 2.007 and a_N = 11.78 G. There was no observable signal from an identical solution containing undecomposed (248). The observed e.s.r. signal is characteristic of a nitroxide radical, produced from a trapped tertiary radical, with the only splitting being due to nitrogen. The trapped tertiary radical had to be the 2-acetoxy-2-propyl radical, since only this radical can lead to isopropyl acetate under normal decomposition in benzene.

It was also found that (248) could be stabilized in benzene solution by triphenylstannane, a known radical chain inhibitor. The radical nature of the decomposition of (248) was also established by analogy to the work of DePuy[197] on cyclopropanols. DePuy had reported the formation of cyclopropyl nitrites from cyclopropanols and their subsequent thermal decomposition to nitroso compounds (eq. 107).

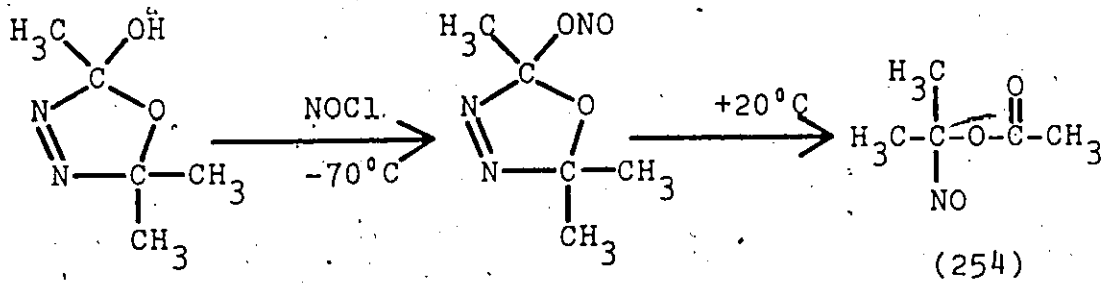
[107] 

Decomposition of nitrites to oxy radicals and nitroso radicals is well known (eg. Barton reaction), and DePuy claimed that

his nitrites also decomposed by radical mechanisms.

The reaction of nitrosyl chloride with (248) under DePuy's conditions was followed by n.m.r., where it was possible to observe the conversion of (248) to the nitrite (253). Heating to 20°C from -70°C resulted in a deep blue solution, due to formation of the nitroso compound (254) (eq. 108). This nitroso compound decomposed further to an unidentifiable yellow oil. Just as DePuy had postulated a

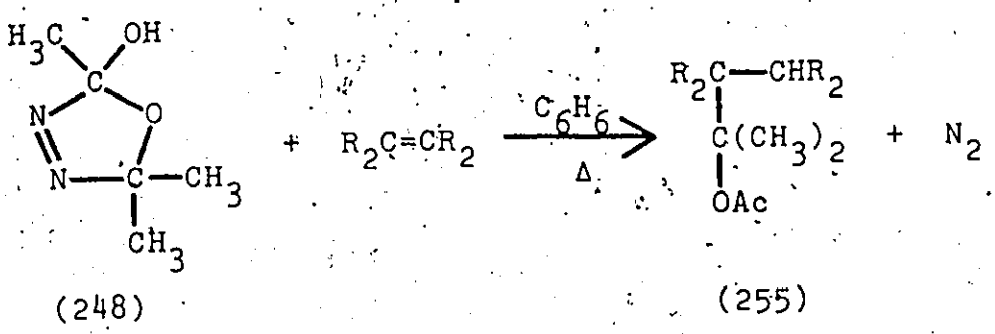
[108]



(248) (253) (254)

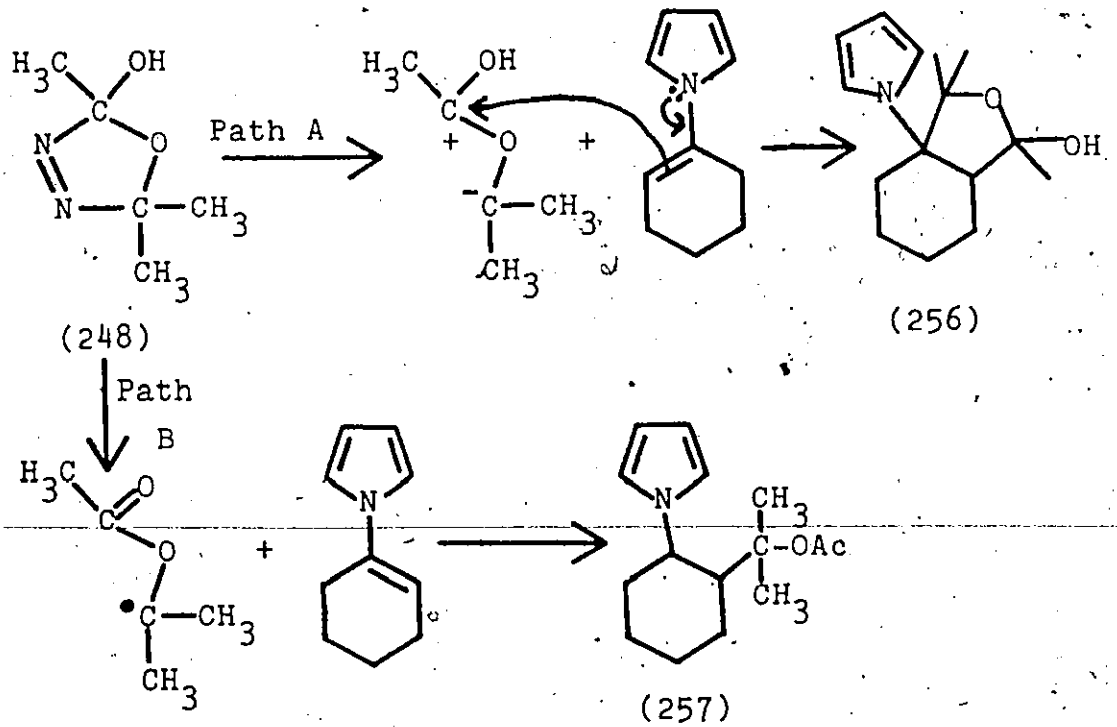
radical decomposition for his nitrites, we also assumed a similar decomposition for our nitrite (253) and, by analogy, for (248) where NO is replaced by H.

Finally, the addition of a 2-acetoxy-2-propyl moiety to olefins, when (248) was decomposed in their presence, helped to establish the radical nature of the decomposition of (248) (eq. 109). The result obtained from the decomposition of (248) in the presence of 1-(pyrrolidino)-1-cyclohexene, which normally adds dipolar species to give bicyclic compounds due to assistance from nitrogen, was especially significant. If the fragment from (248) were a dipolar species as opposed to a

[109] 

(248) (255)

radical species, then the addition product should have been the bicyclic compound (256), formed as shown (eq. 110, Path A). However, we isolated the 2-substituted product (257), analogous to the products (255) from other olefins, which must have come from attack of a 2-acetoxy-2-propyl radical fragment (eq. 110, Path B). This result indicates, therefore, that the intermediates in the decomposition of (248) are not polar in nature.

[110] 

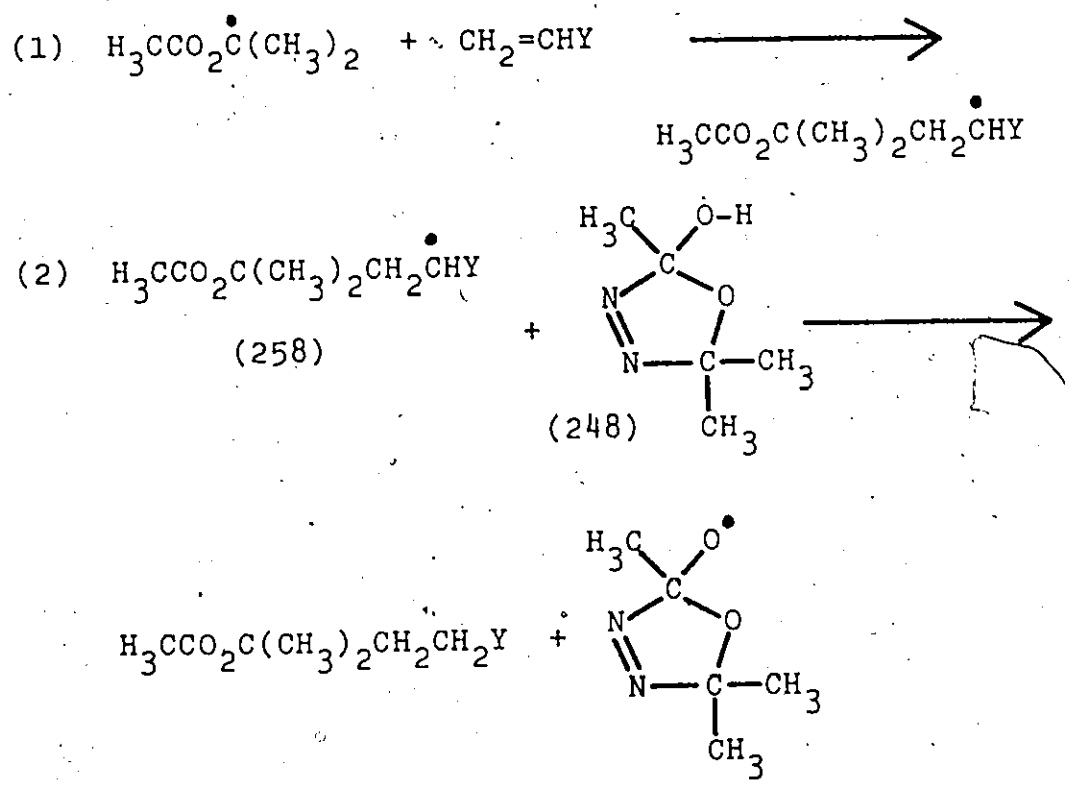
(248) (256) (257)

In order to account for the unusual mode of decomposition of (248) via a radical chain reaction, as well as its ready radical chain addition to olefins, it becomes necessary to assume the cleavage of the H-O bond by radical substitution at H. Although known[198], this is not a favoured process, since the H-O bond dissociation energy of 110.6 kcal/mol[199] is considerably higher than that of well-known substrates for H-abstraction (eg. H-Br = 87.5 kcal/mol, H-SR = 83 kcal/mol, H-C = 98.7 kcal/mol), and is comparable to the H-Cl bond energy of 103.2 kcal/mol[199]. HCl is known for its poor radical chain addition to olefins, which arises from the difficulty of abstracting H from H-Cl. This is a substantially endothermic process. As stated earlier (page 96), both propagation steps in a radical chain reaction must be exothermic or, at worst, slightly endothermic for it to be efficient.

Since (248) decomposes via a radical chain process involving H-abstraction, there must be extenuating circumstances which somehow lower the activation energy of the H-abstraction propagation step. In the case of (248) decomposing in the presence of an olefin, the two propagation steps would be as shown (eq. 111), if no exceptional occurrences took place. The enthalpy change of step (1) comes to about -20 kcal/mol, if one considers the loss of a carbon-carbon double bond and the formation of two carbon-carbon single bonds. However, that of step (2) (eq. 111) comes to about +14 kcal/mol, if one considers only loss of an H-O bond and formation of a

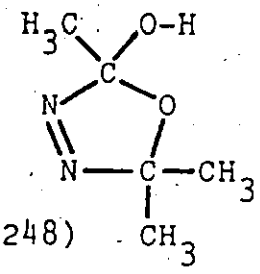
C-H bond. It becomes obvious that a radical chain reaction will not occur, since the relatively stable radical (258) (eq. 111) cannot be expected to abstract hydrogen from the hydroxyl group of (248), any more so than the 2-acetoxy-2-propyl radical can be expected to do so when (248) decomposes without olefins present.

[111]



In view of the fact that a radical chain reaction does occur, there must be concerted formation of a carbonyl group and of nitrogen, together with H-O cleavage in step (2) (eq. 111). Then step (2) becomes as shown (eq. 112), and the resulting enthalpy change becomes approximately -60 kcal/mol (calculated as shown (eq. 112) from values of bond energies

given in reference 199), due to the energy obtained from formation of nitrogen and of a carbonyl group. With this being

(2) $H_3CCO_2C(CH_3)_2CH_2\dot{C}HY$ (258) +  (248) ⟶

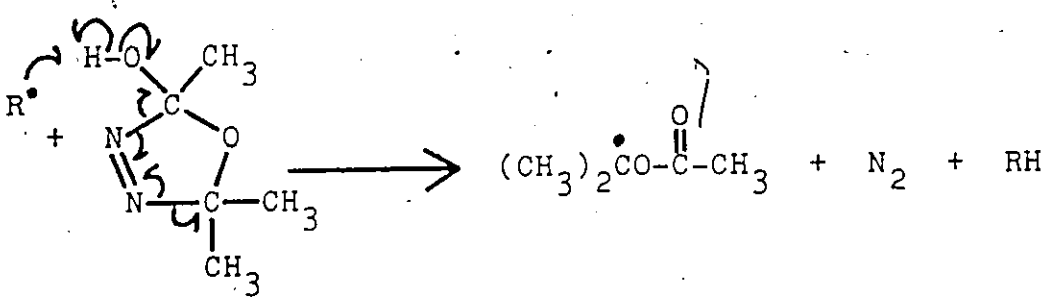
[112] $H_3CCO_2C(CH_3)_2CH_2CH_2Y$ + $H_3C-\overset{O}{\overset{\|}{C}}-O\dot{C}(CH_3)_2$ + $N\equiv N$

lost energy	gained energy	enthalpy change
H-O = 110.6	C-H = 98.7	-503.5
C-O = 85.5	C=O = 179.0	441.7
2xC-N = 145.6	N≡N = 225.8	-61.8
N=N = 100.0	total = 503.5	
total = 441.7		(all values in kcal/mol)

the case, radical chain decomposition of (248) should be a very favourable process, and the efficiency of addition to olefins should be determined to a large extent by step (1) (eq. 111).

Additional support for the concerted decomposition of (248), as shown (eq. 113), came from experiments in which 2,6-di-t-butyl-4-methylphenol, a known inhibitor, was added

to benzene solutions of (248). Inhibition did not take place, but rather initiation and mild acceleration (about twofold) of the conversion of (248) to isopropyl acetate occurred. The initiation was probably due to the aryloxy radicals present

[113] 

(248)

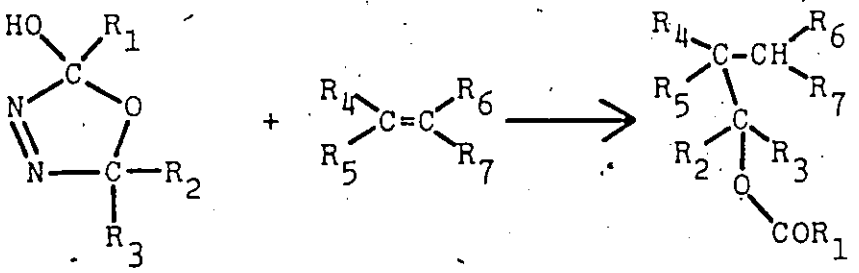
from air oxidation of the phenol. Similarly, di-t-butyl nitroxide initiated decomposition of (248) at room temperature. The observation that so-called stable free radicals will abstract hydroxylic hydrogen from (248) is, therefore, consistent only with a concerted cleavage of the H-O and of the two C-N bonds.

Compound (248) and other members of the family may be of considerable synthetic utility as evidenced by their reaction with alkenes. Normally radical addition of esters to alkenes occurs with bond formation primarily alpha to the acyl carbon of the ester. 2-Hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (248) provides an indirect path for adding an ester cleanly through its ether function (eq. 109). Many unsaturated systems have been treated with (248), and a large number have been functionalized as shown (eq. 109). A list of unsaturated compounds which reacted with (248) to give the

tertiary ester product (255) (eq. 109) is given in Table I. Several other olefins did not react or gave unidentifiable products on reaction with (248). These are listed in Table II. The compounds (255) were prepared by decomposition of (248) in benzene containing an excess of olefin at 50-60°C. The yields ranged from 10 to 85%, and depended primarily on the reactivity of the olefin used. The tertiary ester products (255) were extremely difficult to purify, and only by gas chromatography was purification to analytical quality possible.

The scope of this reaction becomes obvious, should one consider the vast number of variations possible. Theoretically, three functionalities on (248) and four functionalities on the alkene can be altered (eq. 114). This leads to a situation where seven functionalities can be introduced into the product simply by choosing appropriate groups R_1-R_7. Of course, for

[114]



various reasons, not all the theoretical combinations are experimentally possible, but a considerable number should be obtainable.

While the synthetic utility of (248) in functionalizing unsaturated compounds is of considerable importance in

TABLE I

N-phenyl maleimide	Methyl vinyl ketone
Maleic anhydride	Ethyl vinyl ether
Acrylonitrile	Dimethyl fumarate
Acrylic acid	t-Butyl acetylene
Methyl acrylate	Tetrachloroethylene
Crotonaldehyde	Norbornadiene
Norbornene	Cyclohexene
Benzoquinone	1-(Pyrrolidino)-1-cyclohexene
Dimethyl acetylenedicarboxylate	

TABLE II

unidentifiable products	no reaction
α-Methyl styrene	Norbornene-4-carboxylic acid
Styrene	1-Phenylcyclopentene
Ethylazodicarboxylate	Stilbene
Azodicarbonamide	
1,4-Dihydroxy-2-butene	
Benzalacetophenone	
2-Methyl-2-butene	
Mesityl oxide	
1,4-Dichloro-2-butene	
Cyclooctadiene	
Hexachlorocyclopentadiene	5,5-Dimethyl-Δ^3-1,3,4-oxadiazolin-2-one

itself, perhaps more important is a general principle regarding radical pathways in synthesis that emerges from these results. This principle can be stated in the following manner. If the radical chain addition of a reagent X-Y to unsaturated systems is impractical due to adverse thermochemistry of the chain propagating abstraction step, it can be made more favourable and practical by devising and using a new reagent, X-A=B-Y, which delivers the fragments X and Y in a chain reaction by virtue of altered themochemistry from formation of stable co-product A≡B in the propagation step where Y is added. In the case of (248), the fragments X and Y are $H_3CCO_2C(CH_3)_2$ and H , which are delivered by virtue of the combined heats of formation of nitrogen and of a carbonyl group. Normally a reagent, such as $H_3CCO_2C(CH_3)_2$-H, would not deliver the above fragments, but instead would add the fragments $H_2CCO_2C(CH_3)_2H$ and H to olefins. Another advantage of our process is that the two fragments X and Y are added in two discrete operations. This eliminates any complications due to cage reactions, disproportionation or radical combination of X and Y to give XY.

The list of possible fragments X and Y is enormous. Similarly, the stable co-products, other than nitrogen and carbonyl groups, that can be envisioned include CO_2, SO_2, CO, NO_2 and aromatic compounds.

Although the decomposition of a system similar to (248) has been reported[140], the authors did not recognize

that the decomposition might have been due to the same type of altered thermochemistry that we postulated for the decomposition of (248). They also did not attempt to trap any decomposition intermediates with olefins. For a more detailed account of this work see pages 74-76.

E) SUMMARY AND IMPLICATIONS.

The work presented in this thesis represents an examination of some of the chemistry of semicarbazones, of their LTA oxidation products, the 5,5-disubstituted-Δ^3-1,3,4-oxadiazolin-2-ones (228), and of the methyl lithium addition product of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243), 2-hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (248).

We have formulated a general mechanism for the LTA oxidations of carbonyl derivatives that accounts for most of the reported results, as well as our own. The mechanism accounts for the anomalous course of the oxidation of p-dimethylaminobenzaldehyde by invoking an iminooxirane intermediate resulting from decomposition of a first-formed iminooxadiazoline.

Oxidation of ketone semicarbazones led to a series of novel compounds, the 5,5-disubstituted-2-imino-Δ^3-1,3,4-oxadiazolines (227). On hydrolysis these, in turn, gave the highly interesting and synthetically useful 5,5-disubstituted-Δ^3-1,3,4-oxadiazolin-2-ones (228). The reaction of (228) with organometallic compounds opened the door to a new family of α-hydroxy azo compounds, the 2-hydroxy-2,5,5-trisubstituted-Δ^3-1,3,4-oxadiazolines. Some novel and exciting chemistry of one member of this family, the 2-hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (248), was examined. The compound (248) was found to be highly useful for functionalizing unsaturated

compounds, but more importantly the unusual radical decomposition of (248) afforded a new principle regarding radical pathways.

The work presented has thus revealed a new area of heterocyclic chemistry. The synthetic utility of oxadiazolinones (228) has only been tapped, and quite possibly they will be of considerable importance as more of their chemistry is revealed by future workers. Similarly, our study of the chemistry of 2-hydroxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (248) can be considered only the beginning of an exciting avenue of research. The implications of making thermochemistry of addition to unsaturated systems more favourable, by devising reagents that alter the thermochemistry by decomposing to stable co-products as well as radical fragments, are enormous.

Currently in this laboratory, other workers[200] are examining the chemistry of acyclic α-hydroxy azo compounds and α-azo hydroperoxides, as well as their synthetic utility in functionalizing olefins.

EXPERIMENTAL

GENERAL

Infrared spectra were recorded on Perkin-Elmer Models 521 and 337 instruments and on a Beckman IR-5 instrument. The spectra were run in carbon tetrachloride solutions in 0.1 mm sodium chloride cells, and the data are presented in reciprocal centimeters using a polystyrene reference. Ultraviolet spectra were obtained on a Cary Model 14 using quartz cells with hexane as the solvent, and the data are given in nanometers. Proton Magnetic Resonance spectra were recorded on Varian Associates Models HA-100, T-60 and A-60 instruments, using carbon tetrachloride as the solvent (unless otherwise indicated), and the resonances are reported in parts per million (δ) from tetramethylsilane, the internal standard, and are tabulated as chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, se = septet, m = multiplet) and proton integration. Electron Spin Resonance spectra were obtained with a J.E.O.L. Model JES-3BS-X instrument. Gas Chromatographic analyses were done on a Varian Aerograph A90-P3 using a 5' x 1/4", 15% SE 30 column at 150°C, flow rate 60 ml/min. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Elemental analyses were performed by Schwarzkopf

Microanalytical Laboratory in Woodside, New York and by Organic Microanalyses (Dr. C. Daessle) in Montreal, Quebec.

The chemicals used came from Aldrich, Eastman Kodak, J.T. Baker, Matheson or Fisher unless otherwise indicated.

PREPARATION OF SEMICARBAZONES

The method used was similar to that of Vogel[201]. The ketone or aldehyde (0.18 mol) was added to a solution of semicarbazide hydrochloride (20.0 g, 0.18 mol) and sodium acetate (32.0 g, 0.39 mol) in water (200 ml). The mixture was shaken vigorously and then heated for half an hour on a steam bath. Subsequent stirring overnight at room temperature, cooling to 0°C and filtering resulted in the crude semicarbazone. Purification was achieved by recrystallization from ethanol, ethanol-water or water. Identification was accomplished by comparison of melting points, infrared spectra and p.m.r. spectra to those reported in the literature[202,203,204]. The semicarbazones which were prepared are tabulated below.

semicarbazone of	m.p.(°C)	lit. m.p.(°C)	yield(%)
acetone	188	190-91[205]	69
cyclohexanone	164-65	167[205]	70
cyclopentanone	207-08	206[205]	55
diisopropyl ketone	161	160[205]	60
mesityl oxide	162-64	164[205]	71
isopropyl methyl ketone	111	113[205]	52

n-propyl methyl ketone	107-08	106[202]	60
benzyl methyl ketone	196-97	199[205]	67
norboren-7-one	197-98		70
p-dimethylaminoacetophenone	210		69
isobutyraldehyde	126	126[205]	60
furfural	201	203[205]	79
o-chlorobenzaldehyde	225	225[205]	82
cinnamaldehyde	213	211-12[205]	63
p-dimethylaminobenzaldehyde	214-216	216[202]	89
p-methoxybenzaldehyde	210	210[206]	71
o-methoxybenzaldehyde	215	215[205]	76
levulinic acid	187-89	188-89[207]	80

LEAD TETRAACETATE

The method used was similar to that of Fieser[208]. Acetic acid (600 ml) and acetic anhydride (400 ml) were combined in a 3-litre, 3-necked round bottom flask and heated to 55-80°C. While the mixture was stirred vigorously with a mechanical stirrer, lead tetraoxide (red lead) (700 g) was added in 20 g lots. Fresh additions were made only after the orange colour from the previous addition had disappeared. The temperature of the reaction was maintained at 55-80°C at all times. After complete addition of the lead tetraoxide, the brown mixture was cooled to room temperature and the product was filtered, washed with cold acetic acid and recrystallized from hot (not boiling) acetic acid. The yield was 80%.

PREPARATION OF 5,5-DISUBSTITUTED-Δ^3-1,3,4-OXADIAZOLIN-2-ONES (228)

To the semicarbazone (0.03 mol) in well-stirred, ice-cooled methylene chloride (300 ml), with nitrogen bubbling through, was added lead tetraacetate (30.0 g, 0.07 mol). After 30 min, ice water (300 ml) was added followed by 2.4 M hydrochloric acid (20 ml). The mixture, still in the ice bath, was stirred for an additional 20 min. After a heavy brown sludge was removed by filtering the entire mixture through a bed of Celite, the organic layer was separated, washed twice with ice water (200 ml), and dried over magnesium sulfate. Removal of the solvent with a rotary evaporator at room temperature left the crude product as either an oil or a solid. The solid products were purified by sublimation at room temperature and 10^{-2} Torr. The oils were purified by bulb to bulb distillation with a pot temperature of 40°C at 10^{-2} Torr and the receiver in liquid nitrogen. Crude yields were of the order of 55-65% and the yields of purified products were about 40%. The oxadiazolinones which were prepared are listed below, together with melting points or refractive indices, i.r., u.v., and p.m.r. data, as well as analyses.

5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one: m.p. 36-37°C; ν_{max} 1835, 1539 cm^{-1}; λ_{max} 216, 365, 373, 381 nm (ε 3495, 321, 372, 241); δ 1.85 (s).

cyclohexanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one): m.p. 59-60°C; ν_{max} 1826, 1540 cm^{-1}; λ_{max} 215, 362, 375 nm (ε 3501, 286, 320); δ 1.85 (m). λ_{max} (EtOH) 227, 368 nm (ε 3521, 255).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54, H, 6.54, N, 18.17. Found: C, 54.71, H, 6.64, N, 18.18.

cyclopentanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one): n_D^{25} 1.4754; ν_{max} 1840, 1538 cm^{-1}; λ_{max} 223, 360, 364, 377 nm (ε 3608, 287, 318, 369, 246); δ 2.10 (m).

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42, H, 5.75, N, 19.99. Found: C, 51.61, H, 5.84, N, 20.19.

5-isopropyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one: n_D^{25} 1.4345; ν_{max} 1836, 1542 cm^{-1}; λ_{max} 219, 369, 376, 382 nm (ε 3128, 275, 303, 190); δ 0.99 (d, 3), 1.12 (d, 3), 1.64 (s, 3), 2.34 (m, 1).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69, H, 7.09, N, 19.71. Found: C, 50.71, H, 7.04, N, 19.86.

5-methyl-5-n-propyl-Δ^3-1,3,4-oxadiazolin-2-one: n_D^{25} 1.4327; ν_{max} 1835, 1544 cm^{-1}; λ_{max} 216, 367, 374, 381 nm (ε 2940, 247, 276, 167); δ 1.08 (m, 5), 1.73 (s, 3), 2.20 (m, 2).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69, H, 7.09, N, 19.71. Found: C, 50.72, H, 6.83, N, 19.31.

5-benzyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one: m.p. 49-59°C; ν_{max} 1831, 1539 cm^{-1}; λ_{max} 206, 210, 365, 373, 379 nm (ε 9489, 9050, 241, 252, 176); δ 1.66 (s, 3), 3.32 (s, 2), 7.51 (m, 5).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15, H, 5.30, N, 14.73. Found: C, 63.27, H, 5.35, N, 14.97.

5,5-diisopropyl-Δ^3-1,3,4-oxadiazolin-2-one: ν_{max} 1840, 1705, 1545 cm^{-1}; δ 0.92 (d), 1.04 (d) (total integration is 12), 2.70 (m, 2). Sample could not be purified to obtain other data.

bicyclo-[2,2,1]hept-2-ene-7-spiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one): ν_{max} 1835 cm^{-1}; δ 1.50 (m, 2). 2.20 (m, 2), 2.76 (m, 2), 6.32 (t, 2).

PREPARATION OF 5,5-DISUBSTITUTED-2-IMINO-Δ^3-1,3,4-OXADIAZOLINES (227)

The ketone semicarbazone (0.03 mol) was added to ice-cooled methylene chloride (300 ml), with nitrogen bubbling through. Anhydrous potassium carbonate (30 g) was added and the mixture was stirred vigorously. Then, lead tetraacetate (30.0 g, 0.07 mol) was added and the ice-cooled mixture was stirred for a further 30 min, after which time a solution of 50% aqueous potassium carbonate (200 ml) was added. After a heavy brown sludge was removed by vacuum filtration of the entire mixture through a bed of Celite, the organic layer was separated, washed twice with ice-cold potassium carbonate solution (200 ml), and dried over magnesium sulfate. Removal of the solvent with a rotary evaporator at room temperature left the crude product as a clear colourless oil. On standing at 0°C for a short while, this oil solidified to a white crystalline solid in all cases. Purification was achieved by sublimation at room temperature and 10^{-2} Torr. The imino-oxadiazolines prepared, together with spectroscopic data are listed below. An analysis was obtained only in the dimethyl case.

5-isopropyl-5-methyl-2-imino-Δ^3-1,3,4-oxadiazoline: ν_{max} 3415,

3395, 1700, 1555 cm^{-1}; δ 1.10 (d, 6), 1.88 (s, 3), 2.50 (m, 1), 5.99 (broad s, 1).

5-benzyl-5-methyl-2-imino-Δ^3-1,3,4-oxadiazoline: ν_{max} 3310, 1702, 1530 cm^{-1}; δ 1.45 (s, 3), 3.10 (s, 2), 7.08 (m, 5), 7.80 (broad d, 1).

cyclohexanespiro-5'(2'-imino-$\Delta^{3'}$-1',3',4'-oxadiazoline): ν_{max} 3345, 1705, 1540 cm^{-1}; δ 1.88 (m, 10), 7.95 (broad s, 1).

5,5-dimethyl-2-imino-Δ^3-1,3,4-oxadiazoline: m.p. 56-57°C; ν_{max} 3340, 1705, 1530 cm^{-1}; δ 1.60 (s, 6), 7.70 (broad s, 1).

Anal. Calcd. for $C_4H_7N_3O$: C, 42.47, H, 6.19, N, 37.16. Found: C, 42.30, H, 6.27, N, 36.98.

CONVERSION OF IMINOOXADIAZOLINES TO OXADIAZOLIN-2-ONES

The iminooxadiazolines (0.02 mol) were dissolved in methylene chloride (50 ml) and 2.4 M HCl (10 ml) was added. The mixture was stirred vigorously for 20 min; the organic layer was separated, dried over magnesium sulfate and removed on a rotary evaporator at room temperature. The residual oils crystallized on cooling, and the solids were identified as the oxadiazolin-2-ones.

PREPARATION OF 5,5'-DISUBSTITUTED-AZO-1,3,4-OXADIAZOLES (29)

The aldehyde semicarbazone (0.03 mol) was suspended in ice-cooled methylene chloride (300 ml), with nitrogen bubbling through. With vigorous stirring, lead tetraacetate (15 g, 0.035 mol) was added and the mixture was stirred for 40 min, after which time more lead tetraacetate (30 g, 0.07 mol)

was added. The resulting heavy brown sludge was removed by vacuum filtration through a bed of Celite, and the organic layer, which was intensely coloured, was separated, washed with water (200 ml) and dried over magnesium sulfate. Removal of the solvent on the rotary evaporator yielded a highly coloured solid. The products were found to be extremely insoluble in common solvents, and spectra were difficult to obtain. One product was analyzed and the others were identified by analogy. The compounds which were prepared are listed below.

5,5'-di-o-chlorophenyl: m.p. 235-37°C; $\nu_{max}(CHCl_3)$ 1595, 1510 cm^{-1}; δ 6.48 (m, 6), 7.09 (m, 2), (solvent was hexachlorobutadiene); colour, green-yellow. M.W.(Rast) 396.

Anal. Calcd. for $C_{16}H_8Cl_2N_6O_2$: C, 49.61, H, 2.07, N, 21.71, Cl, 18.35. Found: C, 48.94, H, 2.11, N, 20.75, Cl, 19.34.

5,5'-diisopropyl: m.p. 130-31°C; colour, yellow.

5,5'-difurfuryl: m.p. 258-60°C; colour, deep red.

5,5'-di-o-methoxyphenyl: m.p. 270-71°C, colour, orange-red.

5,5'-dicinnamyl: m.p. 231-33°C; colour, brick-red. Second product: m.p. 244-45°C; colour, wine.

5,5'-DISUBSTITUTED-AZO-1,3,4-OXADIAZOLES FROM 2-AMINO-5-SUBSTITUTED-1,3,4-OXADIAZOLES

The 5-substituted-2-amino-1,3,4-oxadiazoles were prepared as described by Gibson[13]. These (0.006 mol) were

dissolved in methylene chloride (100 ml) at 0°C and under nitrogen. Then, lead tetraacetate (15 g, 0.035 mol) was added with vigorous stirring. After 20 min, water (100 ml) was added and the formed heavy brown sludge was removed by vacuum filtration through a bed of Celite. The organic layer, which was highly coloured, was separated, washed with an equal amount of water and dried over magnesium sulfate; the solvent was removed with a rotary evaporator. The result was highly coloured solids, identified as the azo-1,3,4-oxadiazoles by comparison with previously prepared samples. The compounds so prepared were the 5,5'-di-o-chlorophenyl- and the 5,5'-dicinnamyl-azo-1,3,4-oxadiazoles. The cinnamyl derivative was the brick-red, rather than the wine-coloured, solid.

OXIDATION OF p-DIMETHYLAMINOBENZALDEHYDE SEMICARBAZONE

p-Dimethylaminobenzaldehyde semicarbazone (5.0 g, 0.024 mol) was suspended in methylene chloride (300 ml) at 0°C and under nitrogen. The mixture was stirred vigorously and lead tetraacetate (10.0 g, 0.023 mol) was added. Stirring was continued for 2 hr and then more lead tetraacetate (12.0 g, 0.027 mol) was added. After another 2 hr, water (500 ml) was added, the mixture was stirred for 10 min and filtered thrpugh a bed of Celite. The organic layer, which was brown-green in colour, was separated and dried over magnesium sulfate; the solvent was removed on the rotary evaporator. The result was

a green-brown solid which was recrystallized from ethanol and then sublimed (100°C, 10^{-2} Torr) to yield pure p-dimethylaminobenzoyl cyanide (230) as a green-yellow solid (3.0 g, 71%): m.p. 170-71°C (lit[178] 170°C); ν_{max} 2280, 1718, 1640, 1590 cm^{-1}; δ 3.15 (s, 6), 7.30 (q, 4). The product (230) was further identified by alkaline hydrolysis to p-dimethylaminobenzoic acid: m.p. 240-42°C (lit[179] m.p. 242.5-243.5°C); ν_{max} 3300-2500, 1680, 1610, 1530 cm^{-1}; δ 3.13 (s, 6), 7.39 (q, 4). The residual solution from the hydrolysis gave a strong Prussian blue test for cyanide ion.

OXIDATION OF p-DIMETHYLAMINOACETOPHENONE SEMICARBAZONE

p-Dimethylaminoacetophenone semicarbazone was oxidized under identical conditions used for p-dimethylaminobenzaldehyde semicarbazone, and the result was p-dimethylaminoacetophenone (15%) and polymer. The p-dimethylaminoacetophenone was identified by comparison to an authentic sample.

REACTIONS OF 5,5-DIMETHYL-Δ^3-1,3,4-OXADIAZOLIN-2-ONE (243)

A) PREPARATION OF ESTERS AND ETHERS FROM THERMAL DECOMPOSITION

1) 5,5-Dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243) (1.0 g, 0.009 mol) was dissolved in glacial acetic acid (10 ml), and the solution was heated in a sealed tube at 100°C for 1 hr. Then, the solution was poured into water (50 ml) and ethyl ether (100 ml) was added. The mixture was shaken vigorously; the ether layer separated, washed three times with ice water

(100 ml) and dried over magnesium sulfate. Removal of the ether on a rotary evaporator at room temperature yielded an oil (20%), which was identified as isopropyl acetate by comparison of spectra with those reported in the literature[209].

2) Procedure 1) was repeated, substituting m-cresol for acetic acid. The excess m-cresol was removed by extraction of the ether solution with 5% sodium hydroxide solution. The product, m-tolyl isopropyl ether, was obtained in 11% yield and was identified by comparison of spectra to those reported in the literature[210].

3) Procedure 2) was repeated, substituting phenol for m-cresol. The result was phenyl isopropyl ether (10%), identified by comparison of spectra with those in the literature[211].

4) Cyclopentanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one) (1.09 g, 0.008 mol) was dissolved in excess glacial acetic acid and heated at 100°C in a sealed tube for 6 hr. The mixture was poured into water (50 ml) and ethyl ether (100 ml) was added. The mixture was shaken vigorously, the ether separated, dried over magnesium sulfate and removed on a rotary evaporator. The result was a yellow oil (0.025 g, 25%), which was identified as cyclopentyl acetate by comparison of properties to reported values[212].

B) REDUCTION WITH SODIUM BOROHYDRIDE

To a solution of 5,5-dimethyl-Δ^{3}-1,3,4-oxadiazolin-2-

one (243) (1.0 g, 0.009 mol) in 10% methanol-water (25 ml), sodium borohydride was added slowly until the vigorous reaction, observable by frothing, ceased. The methanol was removed on the rotary evaporator and the residual water solution was extracted with ethyl ether. The ether was dried and removed on the rotary evaporator at room temperature to give the product as an oil (0.78 g, 76%): δ 1.50 (s, 3), 1.56 (s, 3), 5.50 (broad s, 1), 6.75 (s, 1). The compound, 5,5-dimethyl-2-hydroxy-Δ^3-1,3,4-oxadiazoline (244), was unstable and decomposed in the p.m.r. probe at 35 C to give isopropyl formate as the only detectable product: δ 1.19 (d, 6), 3.98 (se, 1), 5.32 (s, 1), which was identified by comparison of spectra with those reported in the literature[189].

C) ATTEMPTED KETAL FORMATION

Oxadiazolinone (243) (1.0 g, 0.009 mol) was stirred at room temperature with 10% methanolic HCl for 2 hr. Addition of saturated sodium bicarbonate solution (50 ml) and removal of the methanol on the rotary evaporator, followed by ether extraction, drying of the ether and subsequent removal, yielded only starting material (243) in quantitative yield.

D) ATTEMPTED CYANOHYDRIN FORMATION

Oxadiazolinone (243) (1.0 g, 0.009 mol) was added to water or methanol (20 ml) and sodium cyanide was added with stirring. The result was a vigorous reaction with frothing, and addition of sodium cyanide was stopped when frothing no

longer occurred on addition. The solution was extracted with ether and the ether was dried and removed on the rotary evaporator to give a yellow oil. Crystallization from ethyl acetate-petroleum ether gave white crystals: m.p. 91°C; ν_{max} 3275, 2230 cm^{-1}; δ 1.50 (s, 12), 3.83 (broad s, 2). This product was identified as bishydrazoisobutyronitrile from microanalysis and comparison of spectra with those in the literature[213]. The mother liquors contained a second liquid product, which was not identified.

E) ATTEMPTED SEMICARBAZONE FORMATION

Oxadiazolinone (243) (1.0 g, 0.009 mol) was reacted under the conditions for semicarbazone formation described earlier (page 141). The result was a quantitative yield of acetone semicarbazone.

F) PREPARATION OF 2-HYDROXY-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINE (248)

Compound (248) was prepared by two methods.

1) To excess methyl magnesium iodide in ice-cooled anhydrous ether was added with stirring, 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243) (2.0 g, 0.018 mol) dissolved in ice cold anhydrous ether. After 10 min, an ice cold 20% solution of ammonium sulfate (50 ml) was added slowly, followed by ice cold 3 M sulfuric acid until the solution was neutral to litmus. The ether layer was separated, dried and removed

on the rotary evaporator. The result was an oil (60%), which was identified as the title compound by p.m.r., δ(benzene) 1.41 (s, 3), 1.57 (s, 3), 1.80 (s, 3), 4.83 (broad s, 1); i.r., ν_{max}(benzene) 3580, 3400(broad), 1565 cm^{-1}; and through its further reactions. The product (248) was unstable and decomposed to isopropyl acetate, identified by comparison of spectra with those in the literature[209]. Compound (248) could be stabilized in ether by the addition of two drops of triphenyl stannane.

2) To an ice-cooled solution of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (243) (2.0 g, 0.018 mol) in anhydrous ether (30 ml) was added, gradually and with stirring, a solution of methyl lithium (10 ml, ca. 1.9 M) in ether until the solution in the flask just turned yellow. The addition can be performed like a titration using that colour change as the end point. Stirring was continued for 10 min more at 0°C before ice-cold ammonium sulfate solution (50 ml, 20%) was added slowly. Cold sulfuric acid (3 M) was then added until the aqueous layer was just acidic to litmus. Separation of the ether layer, extraction of the residual aqueous layer twice with ether, drying the combined ether extracts over magnesium sulfate, filtration, addition of two drops of triphenylstannane, and evaporation of the ether with a rotary evaporator at room temperature, until the flask became defrosted and had regained room temperature left (248) as an oil (80%, based on (243). The spectra and properties were identical to

those given in procedure 1) above. The p.m.r. spectrum of the same sample, left for 96 hr at room temperature, showed that 53% of the original (248) was still present due to the effect of the triphenylstannane.

G) ADDITION OF ORGANOLITHIUM COMPOUNDS OTHER THAN CH_3Li

Oxadiazolinone (243) was treated with t-butyl lithium, isopropyl lithium, n-propyl lithium and phenyl lithium under identical conditions to those used for methyl lithium. In the phenyl lithium case, the only isolable product was isopropyl benzoate, identified by comparison of spectra with those in the literature[214]. With the other three lithium compounds, no products were isolated but in each case the appropriately 2-substituted 5,5-dimethyl-2-hydroxy-Δ^3-1,3,4-oxadiazoline was indicated by p.m.r. δ (OH) 4.80 (broad s) Decomposition to an unidentified compound was observed in all cases on standing at room temperature.

REACTIONS OF 2-HYDROXY-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINE (248)

A) EFFECTS OF 2,6-DI-t-BUTYL-4-METHYLPHENOL AND OF DI-t-BUTYL-NITROXIDE

A solution of (248) in benzene, prepared as described above but without added triphenylstannane, was separated into equal portions. One portion was made 0.01 M in the phenol, and aliquots of both portions were scanned by p.m.r. The

initial rate of loss of (248) from the phenol-containing portion was about twice that of the phenol-free portion.

To a solution of (248) in benzene, from which gas was evolving slowly at room temperature, was added a small amount (to make ca. 0.01 M solution) of di-t-butylnitroxide. An immediate substantial increase in the rate of bubbling resulted.

B) SPIN TRAPPING BY NITROSOBENZENE

To a saturated solution of nitrosobenzene in benzene (0.5 ml) was added (248) (20 mg). The e.s.r. spectrum of the resulting solution was obtained, using a Mn^{+2} marker. A strong, triplet signal was recorded, with g = 2.007 and a_N = 11.78 G. A portion of the nitrosobenzene solution without added (248) did not produce an e.s.r. signal at the same instrument settings.

C) TREATMENT WITH NITROSYL CHLORIDE

The procedure used was similar to that of DePuy[197]. To anhydrous ether (25 ml) cooled to -78°C was added (248) (2.0 g, 0.015 mol) and an equivalent of pyridine. Nitrosyl chloride, condensed in a dry ice condenser, was dropped in with vigorous stirring until the solution was just turning brown. The excess nitrosyl chloride was removed under vacuum at -78°C and the slightly green solution was analyzed by p.m.r., after concentration by removal of some of the ether. The

green solution was found to consist of the nitrite (253): δ 1.50, 1.56 (two s, 6), 1.74 (s, 3). Warming to -20°C gave a deep blue solution due to the nitroso compound (254): δ 1.36, (s, 6), 2.20 (s, 3). Warming to room temperature resulted in an unidentifiable yellow decomposition product of the nitroso compound (254).

D) THERMAL DECOMPOSITION

Oxadiazoline (248) was dissolved in benzene and heated to 55°C. Bubbling started immediately and subsided within an hour. Analysis by p.m.r. showed that (248) had decomposed quantitatively to isopropyl acetate, identified by comparison of spectra with those in the literature[209].

E) TRAPPING WITH UNSATURATED COMPOUNDS

A solution of (248) (2.0 g, 0.015 mol) in benzene (30 ml), cooled with ice, was stirred vigorously with a magnetic stirrer. A twofold excess of the unsaturated compound was added all at once, a condenser and a drying tube were fitted to the flask, and the reaction mixture was heated to 50-60°C, with constant stirring, until the p.m.r. spectrum of an aliquot showed that all of (248) was consumed (about 4 hr). The benzene and as much excess unsaturated compound as possible were removed by distillation leaving the crude tertiary ester product (255) (from 10% for cyclohexene to 85% for crotonaldehyde) as an oil. Analytically pure

materials were obtained by g.l.p.c. The unsaturated compounds with which the decomposition product of (248) was successfully trapped are listed below, together with the tertiary ester product formed and its spectral and analytical data.

dimethyl acetylenedicarboxylate: mixture of cis and trans methyl 4-acetoxy-3-carbomethoxy-4-methylpent-2-enoate; δ 1.65 (s), 1.76 (s), 1.91 (s), 1.99 (s), 3.80 (m), 5.88 (s), 6.46 (s).

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.10, H, 6.56. Found: C, 54.29, H, 6.72.

acrylonitrile: 4-acetoxy-4-methylvaleronitrile; ν_{max} 2250, 1740, 1390, 1365, 1255 cm^{-1}; δ 1.55 (s, 6), 2.02 (s, 3), 2.36 (m, 4).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.93, H, 8.38, N, 9.03. Found: C, 60.92, H, 8.35, N, 8.76.

crotonaldehyde: 4-acetoxy-3,4-dimethyl pentanal; ν_{max} 2725, 1735, 1375, 1362, 1255 cm^{-1}; δ 0.95 (d, 3), 1.38 (s, 3), 1.46 (s, 3), 1.92 (s, 3), 1.99-2.75 (m, 3), 9.66 (t, 1).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.79, H, 9.30. Found: C, 61.92, H, 9.32.

methyl vinyl ketone: 5-acetoxy-5-methyl hexan-2-one; ν_{max} 1720, 1735, 1383, 1365, 1250 cm^{-1}; δ 1.43 (s, 6), 1.98 (s, 3), 2.18 (s, 3), 1.80-2.68 (m, 4).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.79, H, 9.30. Found: C, 62.96, H, 9.29.

methyl acrylate: methyl 2-acetoxy-2-methyl pentanoate; ν_{max} 1730, 1380, 1360, 1245 cm^{-1}; δ 1.38 (s, 6), 1.88 (s, 3), 1.90-2.42 (m, 4), 3.61 (s, 3).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.45, H, 8.51. Found: C, 57.17, H, 8.40.

ethyl vinyl ether: ethyl 3-acetoxy-3-methylbutyl ether; ν_{max} 1735, 1380, 1369, 1255 cm^{-1}; δ 1.17 (t, 3), 1.47 (s, 6), 1.94 (s, 3), 2.02 (t, 2), 3.22-3.63 (m, 4).

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.06, H, 10.34. Found: C, 61.89, H, 10.54.

dimethyl fumarate: methyl 4-acetoxy-3-carbomethoxy-4-methyl pentanoate; ν_{max} 1740, 1390, 1369, 1240 cm^{-1}; δ 1.54 (s, 6), 1.98 (s, 3), 2.28-3.18 (m, 3), 3.68 (s, 3), 3.74 (s, 3).

Anal. Calcd. for $C_{11}H_{18}O_6$: C, 53.66, H, 7.32. Found: C, 53.45, H, 7.43.

norbornene: 2-acetoxy-2(2'-norbornyl) propane; ν_{max} 1730, 1388, 1369, 1258 cm^{-1}; δ 1.48 (s, 6), 2.00 (s, 3), 1.00-2.35 (m, 11).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.47, H, 10.20. Found: C, 73.58, H, 10.41.

t-butyl acetylene: 2-acetoxy-2,5,5-trimethyl hex-3-ene; ν_{max} 1738, 1380, 1360, 1248 cm^{-1}; δ 1.01 (s, 9), 1.47 (s, 6), 1.90 (s, 3), 5.54 (s, 2).

tetrachloroethylene: 3-acetoxy-3-methyl-1,1,2,2-tetrachloro butane; ν_{max} 1750, 1661, 1385, 1367, 1240 cm^{-1}; δ 1.72 (s, 6), 1.97 (s, 1), 2.05 (s, 3).

1-(pyrrolidino)-1-cyclohexene: 1-pyrrolidino-2-(2'-acetoxy-2'-propyl) -cyclohexane; ν_{max} 1745, 1640, 1575, 1380, 1355, 1245 cm^{-1}; δ 1.54 (s, 6), 1.40-2.00 (m, 13), 2.08 (s, 3), 2.80-3.30 (m, 5).

N-phenyl maleimide: 3(2'-acetoxy-2'-propyl)-N-phenyl succinimide; ν_{max} 1725, 1398, 1365, 1248 cm^{-1}; δ 1.58 (s, 3), 1.72 (s, 3), 2.02 (s, 3), 2.76-2.92 (m, 2), 3.56-3.80 (m, 1), 7.04-7.60 (m, 5).

maleic anhydride: 3(2'-acetoxy-2'-propyl) succinic anhydride; δ 1.75 (s, 6), 2.11 (s, 3), 3.10 (d, 2), 3.78 (t, 1).

benzoquinone: 2(2'-acetoxy-2'-propyl) hydroquinone; δ 1.50 (s, 3), 1.64 (s, 3), 2.00 (s, 3), 5.38 (broad s, 2), 7.25 (s, 3).

norbornadiene: 3(2'-acetoxy-2'-propyl) tricyclo[2,2,1,$0^{2,6}$]heptane; ν_{max} 1740, 1380, 1365, 1252 cm^{-1}; δ 1.46, 1.50 (two s, 6), 1.94 (s, 3), 1.04-3.00 (m, 9).

acrylic acid: 4-acetoxy-4-methyl pentanoic acid; ν_{max} 3400-2400, 1740, 1720, 1390, 1370, 1250 cm^{-1}; δ 1.50 (s, 6), 2.00 (s, 3), 2.10-2.85 (m, 4), 10.13 (broad s, 1).

cyclohexene: gave three products of which only two were identified; 1) bicyclohexenyl; ν_{max} 3025, 2940, 2865, 2845, 1650 cm^{-1}; δ 1.10-2.30 (m, 14), 5.48-5.88 (m, 4).

Anal. Calcd. for $C_{12}H_{18}$: C, 88.88, H, 11.12. Found: C, 88.71, H, 11.28.

2) 2-acetoxy-2-cyclohexyl propane; ν_{max} 1722, 1379, 1360, 1257 cm^{-1}; δ 1.40 (s, 6), 1.99 (s, 3), 1.06-2.18 (m, 11).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.74, H, 10.87. Found: C, 71.16, H, 11.58.

α-methyl styrene: did not give the expected 2-acetoxy-2-methyl-4-phenyl pentane but rather an unidentified white solid recrystallized from acetone: m.p. 141-42°C; ν_{max} 1735, 1380, 1360,

1250 cm^{-1}; δ 0.81 (s, 3), 1.42 (s, 6), 1.82 (s, 3), 2.28-2.94 (m, 2), 6.76-7.20 (m, 5).

ethyl azodicarboxylate: gave only the reduction product, ethyl hydrazodicarboxylate.

others: the following alkenes reacted with (248) but no identifiable products were isolable; azodicarbonamide, 1,4-dihydroxy-2-butene, benzalacetophenone, 2-methyl-2-butene, mesityl oxide, styrene, 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one, hexachlorocyclopentadiene, cyclooctadiene and 1,4-dichloro-2-butene.

The following three alkenes did not react with (248); stilbene, norbornene 4-carboxylic acid and 1-phenylcyclopentene.

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