THE SYNTHESIS AND THERMAL DECOMPOSITION OF SOME Δ^3-1,3,4-OXADIAZOLINES

THE OXIDATIVE CYCLIZATION OF KETONE CARBOHYDRAZONES AND 4-SUBSTITUTED SEMICARBAZONES. THERMAL DECOMPOSITION OF 5,5-DIARYL-2 PHENYLIMINO-Δ^3-1,3,4-OXADIAZOLINES

by

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TITLE: The Oxidative Cyclization of Ketone Carbohydrazones and 4-Substituted Semicarbazones. Thermal Decomposition of 5,5-Diaryl-2-Phenylimino-Δ^3-1,3,4-Oxadiazolines

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SCOPE AND CONTENTS:

The reaction of lead tetra-acetate with ketone carbohydrazones and 4-substituted semicarbazones gave a series of 2-(substituted imino)-Δ^3-1,3,4-oxadiazolines. Spectroscopic and chemical evidence is presented to establish the proposed structure, and the scope of the reaction is described. The thermolysis of the 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines was studied in chlorobenzene solution. The results of kinetic experiments (gas evolution and infra-red) are reported, and the mechanism of the decomposition is discussed. A survey of the literature pertaining to related lead tetra-acetate oxidations, and to decomposition of cyclic azo compounds is presented.

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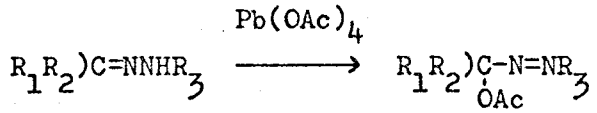
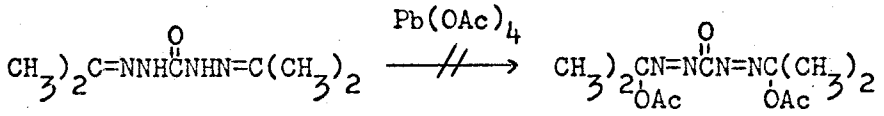
GENERAL INTRODUCTION

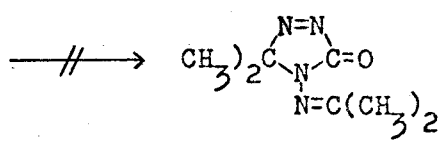
A new synthetic route to azo compounds by the lead tetra-acetate oxidation of ketohydrazones in methylene chloride was reported by Iffland (27) in 1956.



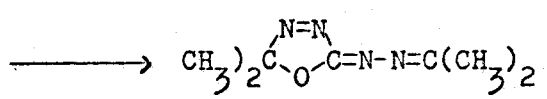
By analogy, the lead tetra-acetate oxidation of acetone carbohydrazone should yield the compound A below, containing two azo acetate functions.



A



B



C

Instead, the reaction in methylene chloride at 0° gave the previously unreported 5,5-dimethyl-2-isopropylazino-Δ^3-1,3,4-oxadiazoline*,C, in high yield.

---

*Further references to these compounds are occasionally abbreviated to "oxadiazoline" in this report. Unless otherwise stated, the 1,3,4-isomer in the same oxidation state as "C" is understood.

The objectives of the further study of this oxidative cyclization have been two fold: (a) to examine the generality of the reaction, and provide evidence for the structure of the products; and (b) to investigate the thermal decomposition of the Δ^3-1,3,4-oxadiazolines.

(a) The Oxidation Reaction: Spectroscopic and chemical evidence was accumulated to conclusively establish the assignment of the lactim structure, C, rather than the isomeric lactam, B. It was possible to extend the oxidative cyclization to the carbohydrazones of diaryl ketones, and to the 4-alkyl and 4-aryl semicarbazones of both alkyl and aryl ketones. In addition, the oxidation of acetone thiocarbohydrazone to the analogous Δ^3-1,3,4-thiadiazoline was accomplished. The spectral data from these compounds, that have a wide range of substituents on the ring, was instrumental in resolving the structural assignment.

(b) Thermal Decomposition: Current interest in the mechanism of decomposition of unsymmetrically-substituted azo compounds prompted a study of the thermolysis of the 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines. In chlorobenzene solution, the oxadiazolines decompose by two parallel first order processes. These are established as a retro-1,3-dipolar-addition producing diaryldiazomethane and phenyl isocyanate; and as a process forming nitrogen directly, as well as phenyl isocyanide and the diarylketone. Both gas evolution and infrared techniques were used in the kinetic experiments.

The variation of para substituents in the 5-phenyl groups has a pronounced effect on the ratio of the two modes of decomposition. The nature of the alternative bond-breaking processes are discussed in the light of correlation of the substituent effects by Hammett and modified Hammett relations.

A survey of the literature bearing on both the oxidation of nitrogenous compounds by lead tetra-acetate, and the thermal decomposition of cyclic azo compounds, is presented in the Historical Introduction.

HISTORICAL INTRODUCTION

General

An investigation of the oxidation of ketone carbohydrazones and 4-substituted ketosemicarbazones with lead tetra-acetate to yield, as cyclized products, Δ^3-1,3,4-oxadiazolines, constitutes the initial phase of the work to be presented in this thesis. In this introduction, a brief survey of the reactions of lead tetra-acetate with nitrogen-containing compounds is first given, in order to illustrate the variety of oxidative attack that is encountered. Reactions of lead tetra-acetate with substituted hydrazine derivatives of ketones and aldehydes, of interest in the present study, are then examined in more detail. In particular the formation of heterocyclic compounds through oxidative ring closure of these hydrazine derivatives with lead tetra-acetate is reviewed.

In studying the properties of Δ^3-1,3,4-oxadiazolines, particular emphasis has been placed on their thermal instability as cyclic azo compounds. The second section of this introduction presents an outline of the thermal decomposition of some cyclic azo compounds and other related nitrogen heterocycles. Previous application of the Hammett equation in the correlation of aromatic substituent effects on homolytic thermal decompositions is also reviewed.

I. Oxidative Cyclization with Lead Tetra-acetate

(i) Reactions of Lead Tetra-acetate with Nitrogen Compounds.

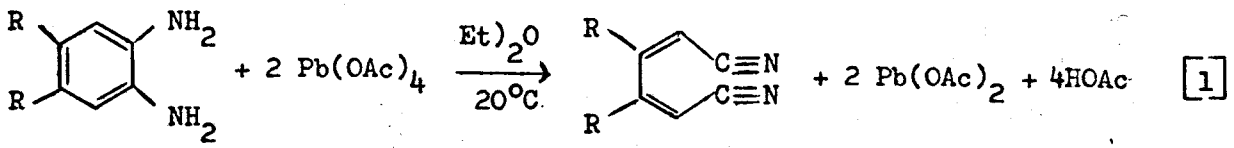
The first applications of lead tetra-acetate in organic chemistry were in the oxidation of hydrocarbons and oxygen-containing compounds. In 1920 Dimroth discovered that lead tetra-acetate readily oxidized the active hydrogens of malonic esters and aryl-substituted methanes to yield the acetoxy derivatives (1). Concurrently, Criegee investigated the conversion of olefins to diacetoxy compounds (2), and the ability of the reagent to cleave 1,2-diols (3). These discoveries have prompted extensive studies of the oxidation of hydrocarbons and oxygen-containing organic substrates, that have been the subjects of comprehensive reviews by Criegee and others (4,5).

However, the oxidation of organic nitrogen compounds with lead tetra-acetate until recently received less attention. Most studies were conducted on nitrogen analogues of previously explored oxygen systems, in order to establish a correlation in reactivity towards the reagent. Accordingly, aromatic amine derivatives, related to phenols; and amino analogues of 1,2-diols have been most extensively investigated.

Para-substituted primary anilines are converted to the corresponding bis-azo compounds in yields of 5-56 percent, in a reaction without analogy in the oxygen case (6,7). In glacial acetic acid at room temperature, the para-nitro and para-chloro substituted compounds gave the highest yields. Under the same conditions, hydrazobenzene was

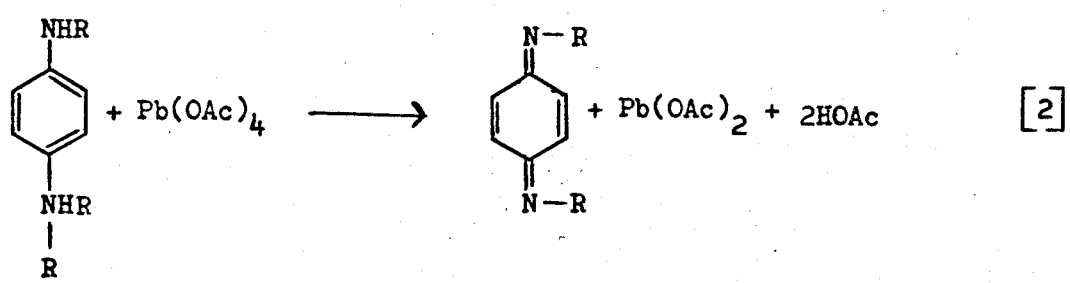
oxidized to azobenzene in 95 percent yield by lead tetra-acetate. The authors suggested a radical mechanism in which the dimerization of intermediate $Ar\dot{N}H$ radicals lead to the formation of hydrazobenzenes.

In the case of other primary aromatic amines, substituted o-phenylenediamines, more extensive dehydrogenation to cis,cis-muconitriles (eq. [1]) was observed with lead tetra-acetate (8). Presumably the reaction proceeded through an intermediate o-quinone di-imine that was



$$R = CH_3,\ Cl \qquad [1]$$

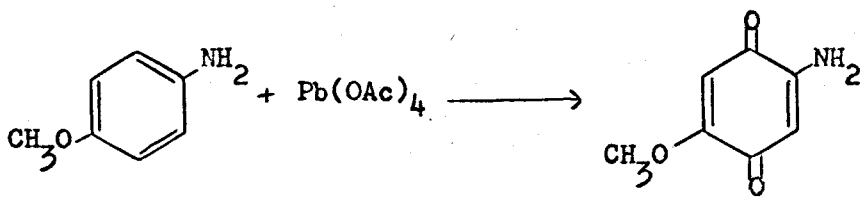
further oxidized to the dinitrile. The conversion of the disulphonyl or dicarboxy derivatives of o- and p-phenylenediamine to the quinone di-imides (eq. [2]) represented a further example of direct amino group oxidation (9-12).



$$R = C_6H_5SO_2 \text{ or } C_6H_5\overset{\overset{O}{\|}}{C}$$

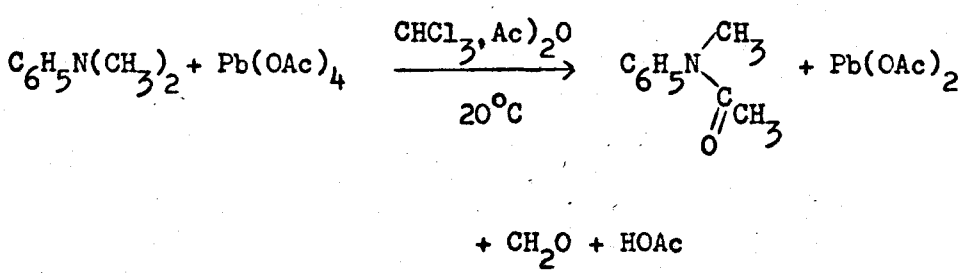
[2]

On the other hand, the oxidation of α-naphthylamine to 1,4-naphthoquinone, and of β-naphthylamine to 2-amino-1,4-naphthoquinone, most likely involved attack by lead tetra-acetate at the aromatic nucleus (6). Protection of the alpha-amino group by a benzenesulphonyl group reduced the oxidation to the α-napthoquinonimine stage, reminiscent of the p-phenylenediamine derivatives (13). Anilines were oxidized to benzoquinones as well (eq. [3]), if further activating groups were present on the ring (6).



[3]

Tertiary aromatic amines have been oxidized (eq. [4]), cleaving an alkyl group to yield the acetylated secondary amine and the corresponding aldehyde (14). With either electron-withdrawing or donating para-substituents, the reaction proceeded in 50-90 percent yield at room temperature.

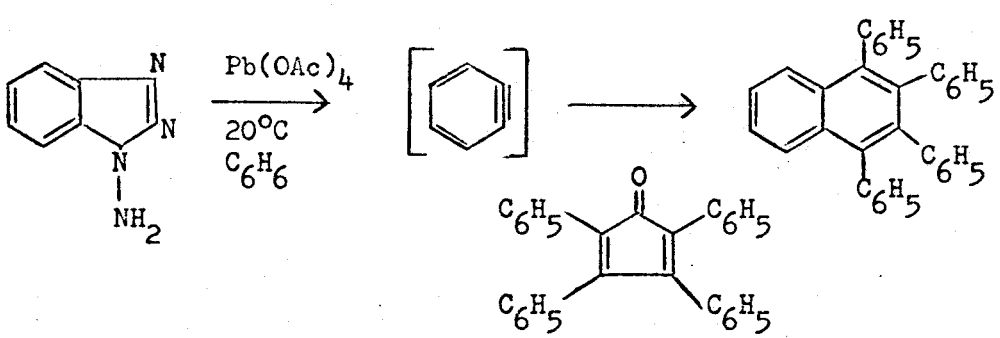


[4]

Still another mode of attack was observed when the acylated aromatic hydroxylamine was oxidized with lead tetra-acetate (eq. [5]). The aromatic nitroso compound formed in less than 10 seconds at -20°C in either propionic acid or ethanol-acetic acid medium (15).

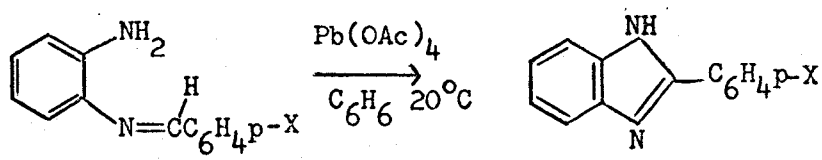
$$C_6H_5N(OH)COC_6H_5 + Pb(OAc)_4 \xrightarrow[-20^\circ C]{EtOH/AcOH} C_6H_5N{=}O + C_6H_5CO_2H + Pb(OAc)_2 + CH_3CO_2H \qquad [5]$$

The lead tetra-acetate oxidation of aromatic amines with unique structural features has been the basis of novel syntheses. The presence of benzyne in the oxidation of 1-aminobenzotriazole (16) has been shown by its capture by tetraphenylcyclopentadienone (eq. [6]). Schiff



[6]

bases of o-phenylenediamine and para-substituted benzaldehydes gave benzimidazoles in 80-90 percent yield (17) on treatment with lead tetra-acetate in either acetic acid or benzene for 2 or 3 minutes (eq. [7]).



[7]

X = Cl, NO_2, CN, $CH_3\overset{\overset{O}{\|}}{C}NH$

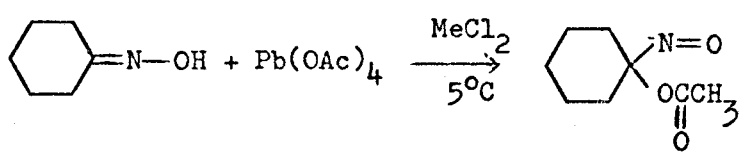
The difficulty encountered in predicting the course of a reaction with lead tetra-acetate is emphasized by the diversity of products obtained in the oxidation of these aromatic amine derivatives. In contrast, the course taken by the reaction in the oxidation of aliphatic primary amines usually lead to nitrile derivatives. In a reaction analogous to the cleavage of 1,2-diols to give carbonyl derivatives, vicinal primary aliphatic amines gave 2 moles of nitrile on treatment with lead tetra-acetate at room temperature in acetic acid (18). Similarly, alpha primary-amino alcohols gave nitrile aldehydes (19,20). Primary aliphatic amines themselves were converted to nitriles in refluxing benzene (21). In addition, alcohols with alpha tertiary-amino groups underwent oxidative cleavage in glacial acetic acid to give the secondary amine and the glycol aldehyde (22).

In a reaction related to the dehydrogenation of amines, Baumgarten (23), and Beckwith (24), have observed that primary amides are converted to the corresponding isocyanates by lead tetra-acetate in benzene solution, or more rapidly in tertiary butanol-triethylamine at 50-60°C. The authors suggested the intermediacy of a nitrene which then rearranged to the isocyanate.

The recent work on the oxidation of ketone derivatives of nitrogen bases is dealt with in succeeding sections. Many of the remaining applications of lead tetra-acetate found in the literature involved either straightforward dehydrogenation of hydrazines, or similar aromatizations of nitrogen heterocycles; and are beyond the scope of this thesis.

(ii) Oxidation of Derivatives of Aldehydes and Ketones.

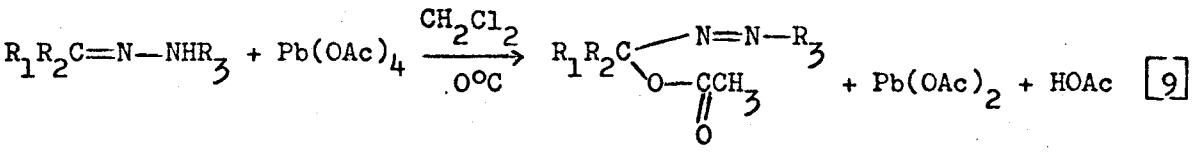
In 1956 Iffland reported a new reaction of lead tetra-acetate with derivatives of ketones and aldehydes (25). Initially, he found that cyclohexanone oxime was oxidized by the reagent in methylene chloride solution at 5°C to produce a blue, unstable oil, 1-nitroso-1-acetoxy-cyclohexane (eq. [8]).



[8]

More recently, Kropf has extended this reaction to the oximes of butyraldehyde, caproaldehyde and 2-phenylacetaldehyde, obtaining as the product under similar conditions, the dimeric form of the corresponding nitrosoacetate (26). In both studies the structures were established by spectral evidence of the nitroso ultra-violet chromophore, by hydrolysis with dilute sulphuric acid to the original ketone, and by oxidation with 30 percent H_2O_2 and solid sodium nitrate to the corresponding 1-nitro-1-acetoxy compound.

Extending the reaction to ketohydrazones, Iffland showed that these compounds are converted to alpha-acetoxy azo compounds on treatment with one mole of lead tetra-acetate in methylene chloride, acetic acid or benzene solution at 0-10°C (27).



$$R_1R_2C{=}N{-}NHR_3 + Pb(OAc)_4 \xrightarrow[0^\circ C]{CH_2Cl_2} R_1R_2C(O{-}C(=O)CH_3)(N{=}N{-}R_3) + Pb(OAc)_2 + HOAc \quad [9]$$

$R_1 = R_2 = CH_3,\ C_6H_5,\ -(CH_2)_5-$

$R_3 = C_6H_5,\ p\text{-}BrC_6H_4,\ p\text{-}NO_2C_6H_5,\ 2,4(NO_2)_2C_6H_3,\ CH_3, t\text{-}C_4H_9.$

The structures of the products, obtained in 65-90 percent yield, were established by analysis, and by relating the ultra-violet spectra to those of known azo compounds. When lead tetrabenzoate was used as the oxidizing agent, the corresponding alpha-benzoyloxyazo compound was formed. Edwards had independently established that benzoyl peroxide reacted with ketohydrazones to produce an identical alpha-benzoyloxy compound (28). As well, Iffland indicated that peracetic acid was capable of converting similar hydrazones to "azoacetates".

Iffland proposed a mechanism for the reaction (eq. [10-12]), based on Cavill's suggestions (29) for the oxidation of enolizable ketones with lead tetra-acetate.

$$R_1R_2C{=}N{-}NHR_3 + Pb(OAc)_4 \longrightarrow R_1R_2C{=}N{-}\dot{N}R_3 + HOAc + \dot{P}b(OAc)_3 \quad [10]$$

$$R_1R_2C{=}N{-}\dot{N}R_3 \longleftrightarrow R_1R_2\dot{C}N{=}NR_3 \quad [11]$$

$$R_1R_2\dot{C}{-}N{=}N{-}R_3 + \dot{P}b(OAc)_3 \longrightarrow R_1R_2\underset{\underset{OAc}{|}}{C}{-}N{=}NR_3 + Pb(OAc)_2 \quad [12]$$

In a reaction related to the cleavage of tertiary aromatic amines (14), N,N-disubstituted ketohydrazones consumed 2 moles of lead tetra-acetate, (eq. [13]) producing an azoacetate, and cleaving a primary or secondary alkyl group to the corresponding carbonyl compound (30). When only one

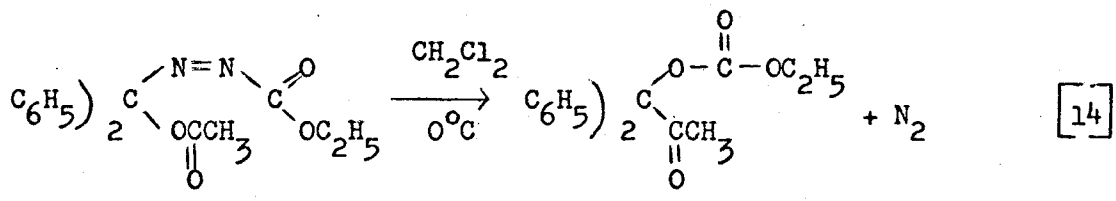
$$R)_2 C{=}N{-}N\begin{matrix}R'\\ \diagdown\\ \diagup\\ CH(R'')_2\end{matrix} + 2Pb(OAc)_4 \xrightarrow[0^\circ C]{CH_2Cl_2} R)_2 C\begin{matrix}N{=}N{-}R'\\ \diagup\\ \diagdown\\ OCCH_3\\ \|\\ O\end{matrix} + R'')_2 C{=}O + 2Pb(OAc)_2 + HOAc \quad [13]$$

$R = C_6H_5,\ CH_3$ R' = alkyl, aryl or t-alkyl

R'' = H, alkyl or aryl.

mole of oxidant was used, the monosubstituted ketohydrazone was isolated. Although the presence of a geminal diacetoxy precursor of the carbonyl compound was excluded, the mechanism has not been investigated further. Iffland found that manganese dioxide in acetic acid, and benzoyl peroxide in methylene chloride, also reacted with N,N-disubstituted hydrazones to produce the acetoxy- and benzoyloxyazo compounds respectively.

Many other workers became interested in the possibilities of synthesis of unsymmetrically-substituted azo compounds through this new reaction. Benzophenone N-carbethoxyhydrazone was reported to give a 28 percent yield of the expected azo compound (31), and 15 percent of a rearranged product, 2-oxo-1,1-diphenylpropylethylcarbonate, formed by loss of nitrogen from the acetoxy-azo compound (eq. [14]). The reaction was carried out at 0°C in the presence of excess $CaCO_3$ to rule out an acid-catalysed decomposition. Attempts to extend the reaction to dialkyl ketones were unsuccessful.



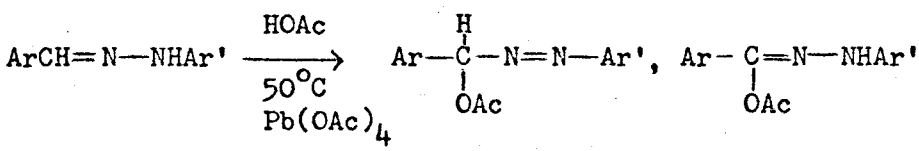
[14]

Iffland reported that benzophenone 4,4-diethylsemicarbazone gave a 63 percent yield of 2-oxo-1,1-diphenylpropyl diethylcarbamate on lead tetra-acetate oxidation (32).

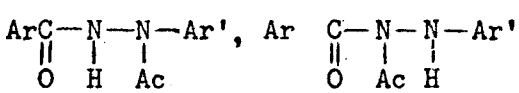
When the benzenesulphonyl- and toluenesulphonylhydrazones of acetone, cyclohexanone and benzophenone were reacted with lead tetra-acetate in acetic acid at 20°C, only the ketones and nitrogen were obtained as identifiable products (33,34). Although the author suggested a direct oxidation to the ketone, work by Norman (35) indicated that an intermediate geminal diacetoxy compound that decomposed to the ketone may have been formed. In the oxidation of benzophenone tosylhydrazone in methylene chloride at lower temperature (-5°C), he was able to isolate

diphenylmethylene diacetate, and in methylene chloride-methanol the dimethyl ketal was recovered.

In contrast, the tosylhydrazone of benzaldehyde was converted to the alpha-acetoxytosylhydrazone by displacement of benzylidene hydrogen, presumably through the rapid isomerization of an intermediate azo-acetate (34). Further work on aldehyde arylhydrazone oxidation by Scott showed that one or more of four substitution products were possible (eq. [15]). The structures of these products were confirmed by independent synthesis by Scott (37).



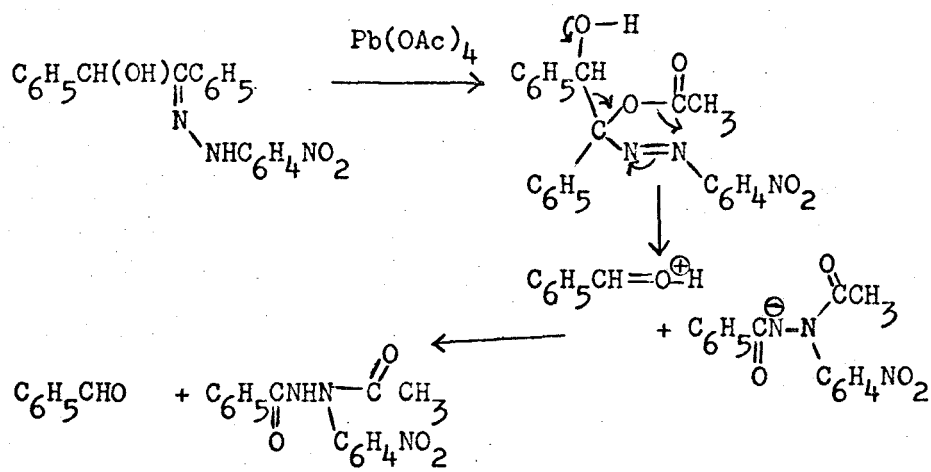
[15]



Ar = p-$CH_3C_6H_4$, C_6H_5, p-ClC_6H_4, p-$NO_2C_6H_4$

Ar' = p-$NO_2C_6H_4$, p-$CH_3C_6H_4SO_2$, 1-methyl-1 H-tetrazol-5-yl.

Norman observed that rearranged products were obtained in some specifically substituted hydrazone systems; increasing the difficulty of predicting the course of reaction with lead tetra-acetate. He observed that benzoin p-nitrophenylhydrazone reacted to yield benzaldehyde and N-acetyl-N'-benzoyl-p-nitrophenylhydrazine (eq. [16]), by way of a rearrangement of the intermediate azoacetate (35). A similar rearrangement was observed on treatment of the azoacetate of benzil mono-p-nitrophenylhydrazone with boron trifluoride-etherate. In the case of



[16]

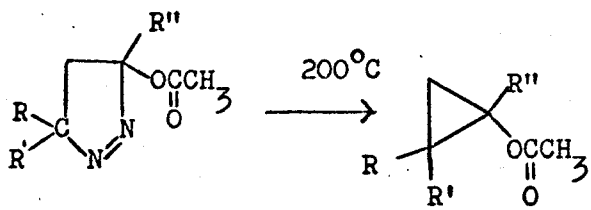
benzophenone benzylhydrazone, reaction with lead tetra-acetate in methylenechloride caused immediate evolution of nitrogen; and led to the isolation of 1,1,2-triphenylethylacetate as the sole product.

As expected, lead tetra-acetate oxidation of unsubstituted keto-hydrazones did not yield azoacetates but gave geminal diacetoxy compounds and nitrogen (38). It seemed, however, that in this case an intermediate diazomethane was involved, since the hydrazone of hexafluoroacetone produced a stable diazomethane with lead tetra-acetate (39). Diazomethane (40), diphenyldiazomethane, and diazofluorene (38) have been oxidized by the reagent to the geminal diacetoxy compounds.

(iii) Synthetic Application of Azoacetate Intermediates.

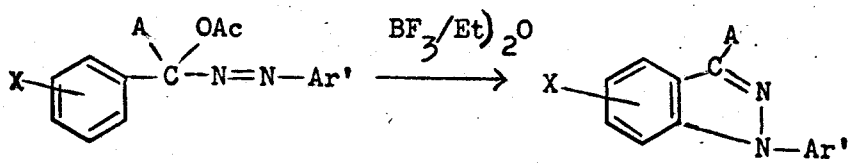
A number of attempts have been made to utilize azoacetates in thermal and acid-catalysed decomposition reactions. The acetyl hydrazone of a steroidal ketone, androstan-17-β-ol-3-one, was apparently converted to the corresponding azoacetate on treatment with lead tetra-acetate in methylene chloride solution. However, attempts to thermally or photolytically decompose the product to the 3-acetyl derivative were unsuccessful (41). The only compounds isolated were the 3-methyl ether, and a

3-enol ether. In another application, thermal decomposition of azoacetates derived from 2-pyrazolines (42) gave 20-60 percent yields of the desired cyclopropanes (eq. [17]). The 3-acetoxy-3-methyl-5-phenyl-1-pyrazoline isomerized on standing, or in the presence of acid, to the corresponding pyrazole and acetic acid.



$R'' = R' = R = CH_3$
$R' = C_6H_5, CH_3$; $R = H$; $R'' = CH_3, H, C_6H_5$ [17]

Norman (43-45) discovered that the azoacetates derived from aryl hydrazones of arylketones gave good yields of the corresponding indazoles on treatment with Lewis acids, such as borontrifluoride etherate or aluminium chloride, in methylene chloride solution at room temperature (eq. [18]). In several cases, direct decomposition of the azoacetate in the lead tetra-acetate oxidation medium was accomplished.



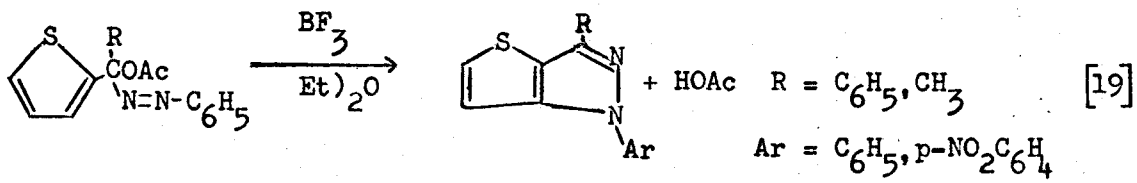
[18]

A = C_6H_5, CH_3

Ar' = C_6H_5, p-$NO_2C_6H_4$

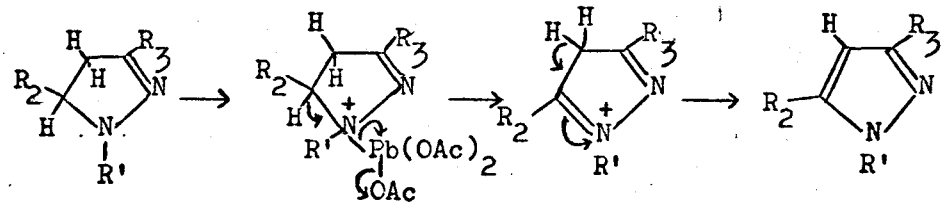
X = H, m-NO_2, p-NO_2, m-CH_3, p-CH_3.

The reaction has been extended to the phenyl hydrazones of ethyl benzoylformate, 2-benzoylpyridine, and 3-benzoylpyridine. Para-nitrophenylhydrazones of ethyl benzoylformate and 4-benzoylpyridine are also cyclized (45). A low yield encountered in the case of the 2-benzoylpyridine was explained in terms of oxidative cyclization of the hydrazone to the pyridine nitrogen to form a water soluble pyrazolopyridinium salt. In the case of the aryl hydrazones of 2-benzoyl- and 2-acetyl-thiophene (45), cyclization into the thiophene ring occurred to form thienopyrazoles (eq. [19]).



[19]

In a further application of lead tetra-acetate oxidation in heterocycle synthesis, Norman showed that 1-substituted-2-pyrazolines, essentially cyclic N,N-disubstituted hydrazones, were converted by lead tetra-acetate to the dehydrogenated product, the one-substituted pyrazole (46). In methylene chloride at room temperature, yields of 80 percent were obtained. The authors suggest a mechanism (eq. [20]) in which the tertiary nitrogen attacks the lead tetra-acetate molecule, followed by a rapid loss of two hydrogens.

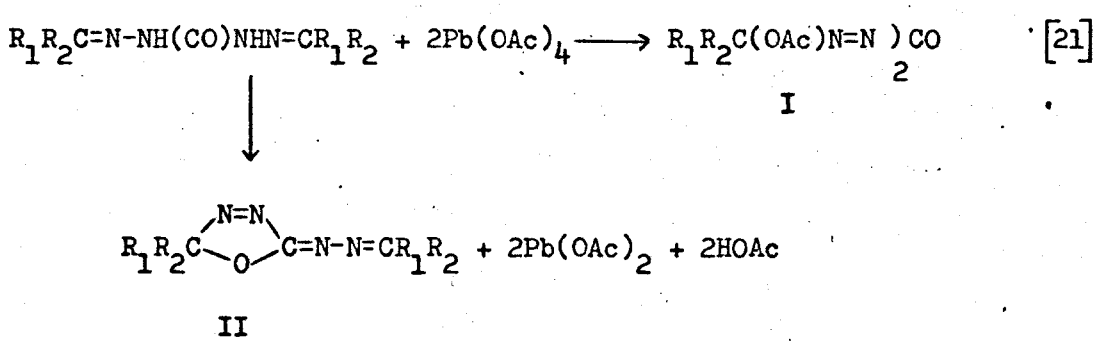


[20]

$R_2 = C_6H_5$ $R_3 = CH_3$, C_6H_5 $R_1 = C_6H_5$, p-$NO_2C_6H_4$.

(iv) Oxidative Cyclization of Nitrogen Compounds.

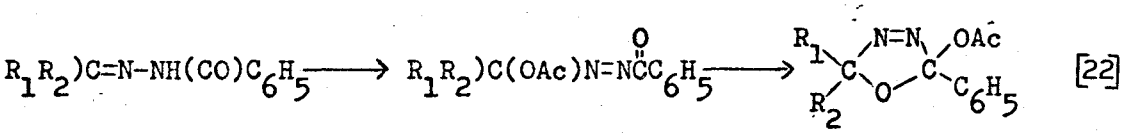
When the investigation of the oxidation of ketone carbohydrazones was initiated, it was anticipated that the product isolable at low temperature would be the di-azoacetate I, in accordance with the previously observed behaviour of ketohydrazones (27). The actual product obtained, however, is shown to be the oxidatively-cyclized 2-alkylazino Δ^3-1,3,4-oxadiazoline II. Precedence for such a ring closure is provided in



[21]

previously reported examples of oxidation of hydrazine derivatives and other nitrogen-containing substrates.

The first cyclization of a substituted dialkyl or diaryl ketohydrazone with lead tetra-acetate was recently reported by Hoffman (47). He found that the oxidation of the benzoyl hydrazones of cyclohexanone, acetophenone and benzophenone lead to the eventual formation of 2-phenyl-2-acetoxy-Δ^3-1,3,4-oxadiazolines III, presumably through an azoacetate intermediate (eq. [22]). Reaction with one mole of lead tetra-acetate at -40°C in methylene chloride produced a deep red-brown solution. The colour was said to be the same as that of substances



[22]

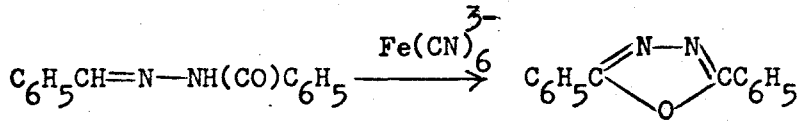
III

$R_1 = R_2 = C_6H_5$

$R_1 = C_6H_5$, $R_2 = CH_3$; R_1-$R_2 = (CH_2)_5$

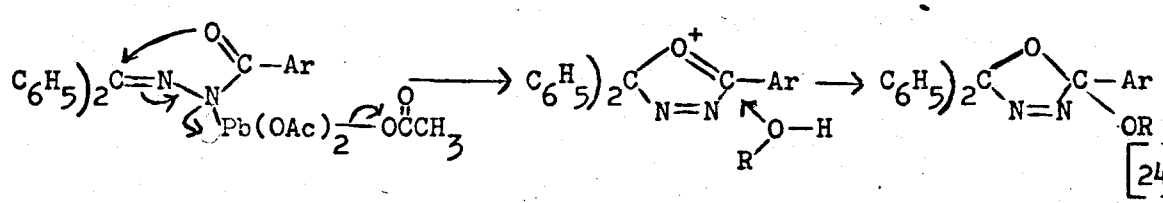
having a phenylcarbonylazo chromophore. On warming to -20°C, the colour of the solution rapidly faded, and work-up gave the nearly colourless 1,3,4-oxadiazoline. The structure of the product was unambiguously assigned by spectral studies and its further reactions. The Δ^3-1,3,4-oxadiazolines lost nitrogen at 50°C to form the epoxides, and were hydrogenated, using a platinum catalyst in ethanol, to the starting hydrazones. On reaction with sodium ethoxide, the cyclohexyl derivative gave ethyl acetate, cyclohexyl benzoate, and nitrogen. The suggestion was made that the acetylazo steroid reported by Pitt (41), and the azoacetate derived from benzophenone N-carbethoxyhydrazone (31), may in

reality have the Δ^3-1,3,4-oxadiazoline structure. This cyclization seems to be related to that of benzaldehyde benzoylhydrazone. Stolle (48) reported its oxidation to 1,5-diphenyl-1,3,4-oxadiazole IV with aqueous alkaline potassium ferricyanide (eq. [23]). Treatment of the silver salt of the hydrazone with iodine also gave the oxadiazole.



[23]

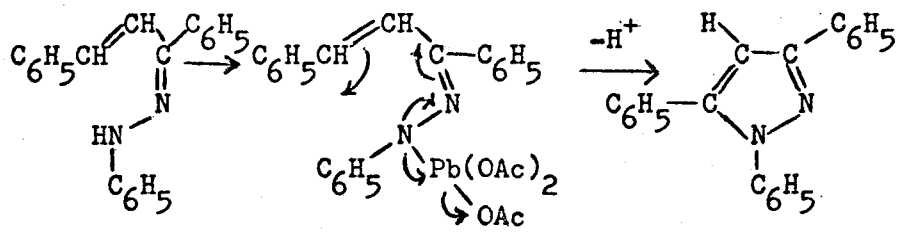
Norman reported the lead tetra-acetate oxidation of both benzophenone benzoyl- and para-nitrobenzoylhydrazones in methylene chloride at room temperature over a period of 12 hours (35). Under these more severe conditions, only the 1-acetoxy-1,1-diphenyl-2-arylethylene oxides were recovered. The observation that the 1-methoxyethylene oxide was obtained when methylene chloride - methanol was used as the solvent, prompted Norman to suggest a polar mechanism (eq. [24]) that does not involve an azoacetate intermediate.



[24]

The conversion of chalcone phenylhydrazone V to 1,3,5-triphenylpyrazole VII by lead tetra-acetate in glacial acetic acid under reflux was observed by Norman as well (45). Employing a similar mechanism in this case, he envisaged intra-molecular nucleophilic attack by the olefinic double

bond in an initial intermediate VI.

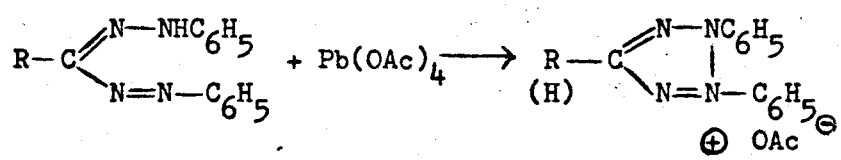


[25]

V VI VII

An analogous mechanism was favored by Norman in the oxidation of the o-phenylenediamine benzaldehyde Schiff bases to benzimidazole (eq. [7]); for which earlier authors had written free radical alternatives (17).

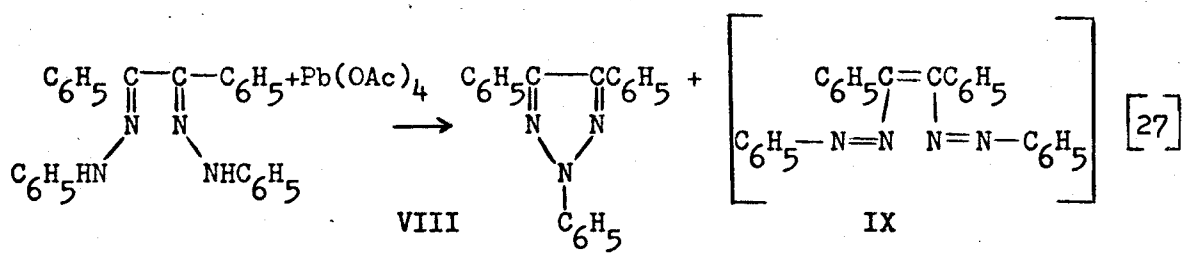
Oxidation of formazans to tetrazolium salts by lead tetra-acetate in dry chloroform (eq. [26]) occurred at room temperature (49). A mercuric oxide-amylnitrite reagent was also employed. Formazans in which R = $CH_3C{=}O$ or $CO_2C_2H_5$, and in which the N-aryl groups did not contain complex-forming groups, were converted into tetrazoluim salts under the same conditions by lead tetra-acetate; but with replacement of the group on the middle carbon by hydrogen (50). The mechanism of this reaction, in which $Cu(NO_3)_2$ could also be used as the oxidant, has not been investigated.



[26]

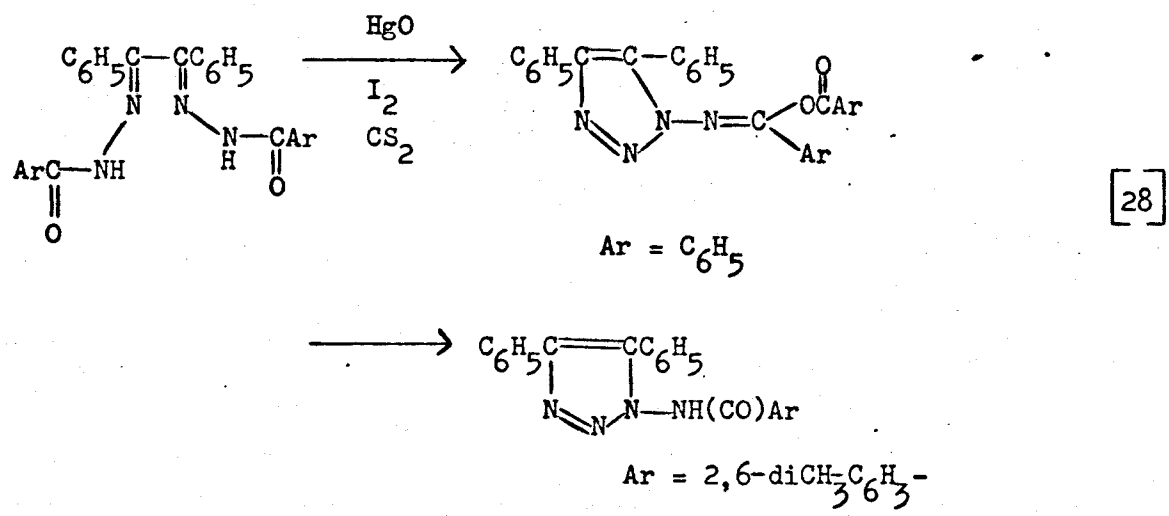
Another cyclization reaction in which other oxidants such as mercuric oxide-iodine (51), silver oxide (51), and copper sulphate (52) as well as lead tetra-acetate were active, was the conversion of osazones

to 2H-1,2,3-triazoles. Norman observed that the phenyl osazone of benzil was converted to the 2,4,5-triphenyl-2H-1,2,3-triazole VIII in 33 percent yield by lead tetra-acetate (35).



[27]

None of the anticipated di-azoacetate could be detected. An unidentified, highly coloured product, obtained in low yield, could be the 1,2-diphenyl-1,2-di(phenylazo)ethylene IX that was isolated by Alexandrou (51) in the silver oxide oxidation of benzil arylosazones. Osazones produced from 1,2-diketones and aroylhydrazines (51) gave 1-amino-1H-1,2,3-triazoles (eq.[28]). In this case, migration or cleavage of the 2-aroyl group was favoured over cleavage of the 3-aryl group that occurred with phenyl osazones.

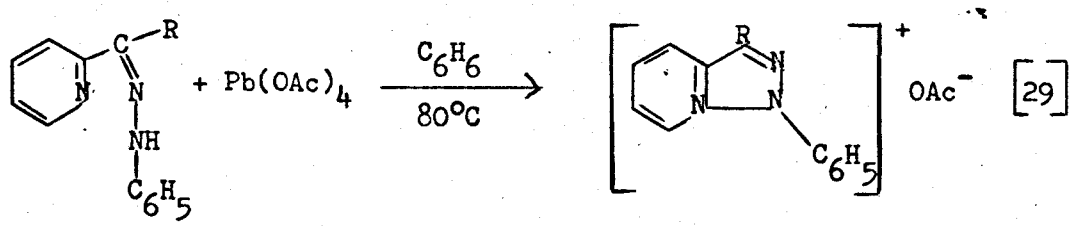


[28]

Oxidative cyclization by lead tetra-acetate has not been restricted to nitrogen containing systems. Mihailovic et al. (53,54) discovered that heating acyclic alcohols for one hour in refluxing benzene with an equivalent of lead tetra-acetate gave tetrahydrofurans in 50 percent yield. Hydroxy ethers reacted similarly, with closure to the carbon alpha to the ether linkage being favoured (55-57). Tabushi and Oda have observed that the hydrocarbon biallyl can be cyclized by lead tetra-acetate in acetic acid at 70°C to give, as the major products, 1,4-diacetoxy-cyclohexane and 4-acetoxy-1-cyclohexene (58).

(v) Fused Heterocyclic Ring Synthesis.

The possibilities of preparation of fused heterocyclic ring systems through lead tetra-acetate oxidative ring closure have been investigated more intensively. In 1952 Kuhn (59) employed lead tetra-acetate in glacial acetic acid solution at 90°C to cyclize 2-acetyl- and 2-benzoyl-pyridine phenylhydrazones to the corresponding 1H-v-triazolo[1,5-a] pyridin-8-ium salts (eq.[29]). In the 2-benzoyl case, where the syn- and anti-phenylhydrazones

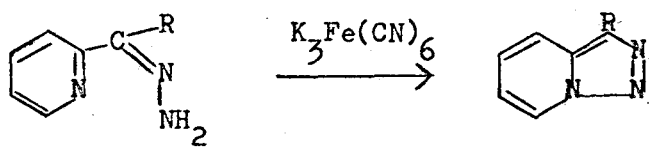


[29]

R = CH_3, C_6H_5

were separated, only the syn isomer reacted to give the triazolopyridinium salt. The reaction was extended to the 2-acetylquinoline phenylhydrazone as well.

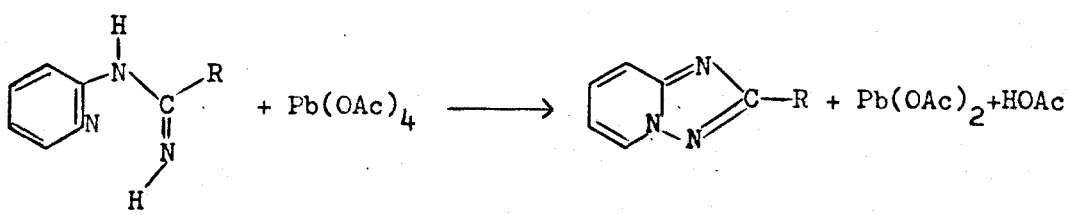
Bower (60) was able to effect a similar closure in the 2-acetylpyridine hydrazone, and 2-pyridinecarboxaldehyde hydrazone cases (eq. [30]); using aqueous alkaline potassium ferricyanide as the oxidant to give good yields of v-triazolo[1,5-a] pyridines. In a reaction



[30]

R = H, CH_3

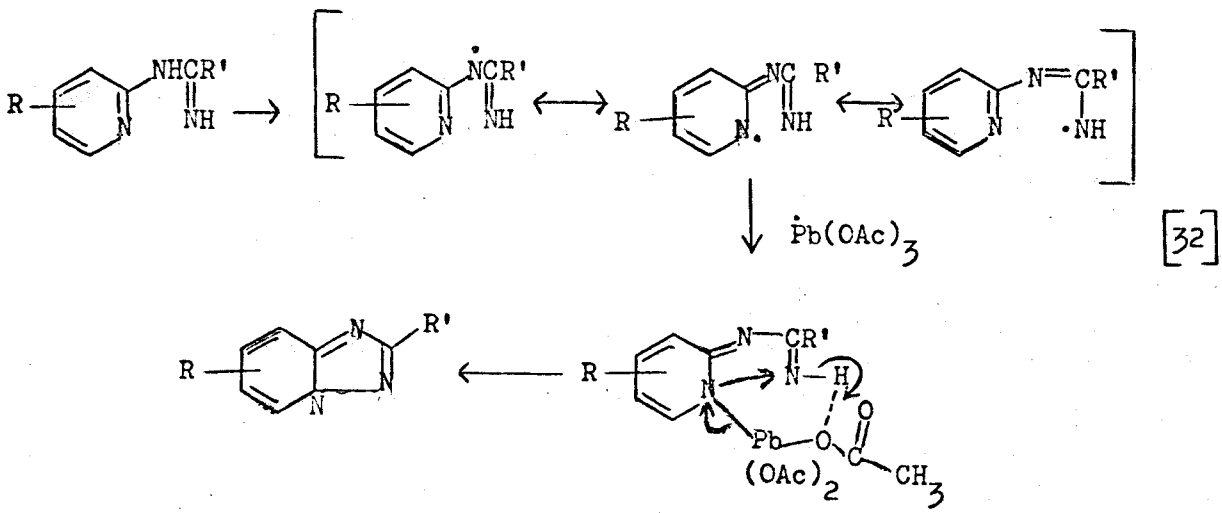
necessitating the removal of 4 hydrogens, he was able to convert the 2-[2-aminoethyl] pyridine to the corresponding pyrazolo[1,5-a]pyridine with potassium ferricyanide. Lead tetra-acetate oxidation of the N-(2-pyridyl)amidines, isomeric with the 2-pyridylketone hydrazones, provided a route to the s-triazolo(1,5-a)pyridines, as shown in equation [31].



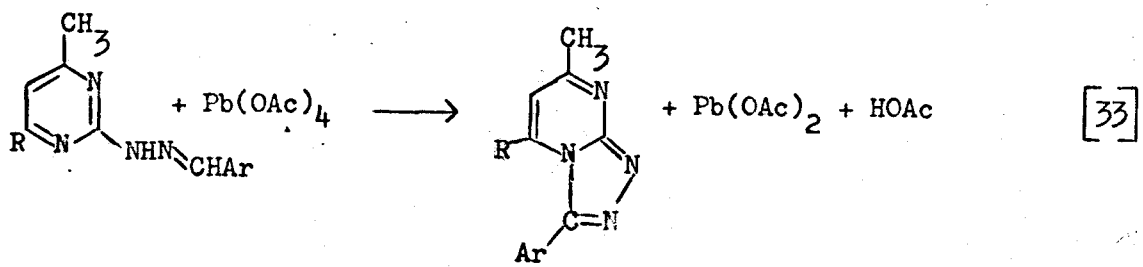
[31]

R = CH_3, C_6H_5

An analogous closure was investigated by Potts in the preparation of 2-phenyl-s-triazolo [2,3-a] pyrazines by the cyclization of the corresponding pyrazinyl amidines (61). The necessary amidines are readily prepared by the condensation of the desired pyrazinylamine and the substituted nitrile. Refluxing the amidines in dry benzene with an equivalent of dry lead tetra-acetate gave 60 percent yields. In an extension of Bower's work, Potts has cyclized a series of N-(2-pyridyl)-amidines to yield s-triazolo [1,5-a] pyridine ring systems (62). Pyridines methylated in the 3, 4, and 5 positions, and bearing alkyl or aryl amidine groups in the 2 positions, were successfully dehydrogenated with lead tetra-acetate in refluxing benzene. Attempts to prepare the parent unsubstituted N-(2-pyridyl)formamidine were unsuccessful. The author described the reaction mechanism on a free radical basis, as shown in equation [32], speculating that high boiling residues obtained contain dimeric products.



The substituted hydrazone systems discussed above show examples of cyclization toward the alkylidene substituents. Alternatively, if the hydrazine employed has a heterocyclic ring substituent on nitrogen, closure can take place into this ring with loss of an alkylidene hydrogen. For instance, Bower (63) oxidized the N-(2-pyrimidyl)hydrazones of substituted benzaldehydes to the corresponding s-triazolo-[4,3-a] pyrimidines (eq. [33]). The reactions were carried out by warming the

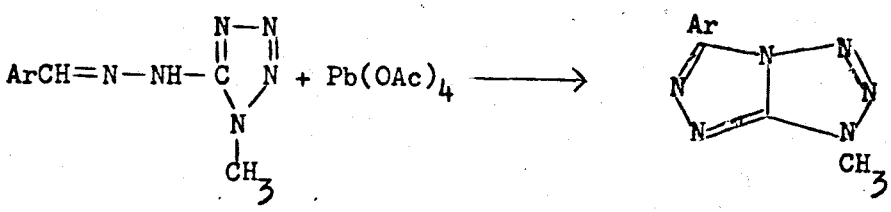


[33]

Ar = p-BrC_6H_4, m-$NO_2C_6H_4$, C_6H_5

R = OH, CH_3

hydrazones with lead tetra-acetate in acetic acid or benzene. A similar closure has been noted by Scott (37) in the reaction of 1-methyl-1H-tetrazol-5-ylhydrazones of benzaldehydes at 60°C in glacial acetic acid (eq. [34]). Other products resulting from acetylation reactions mentioned

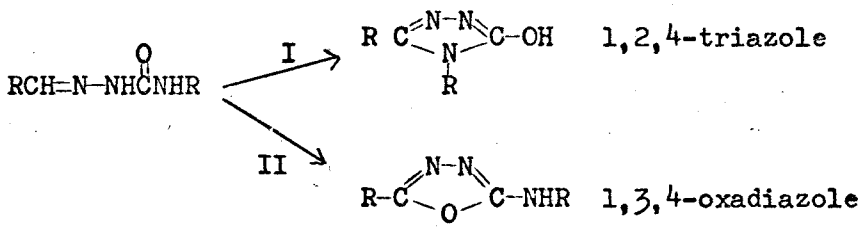


[34]

by Scott, are apparently not isolated from the pyrimidylhydrazones.

(vi) Cyclization of Semicarbazide Derivatives.

In the preceeding sections, examples of oxidative cyclization have all involved the unambiguous formation of one bond in the ring-closure reaction. However, the synthesis of 5-membered ring compounds from substituted semicarbazides introduces the possibility of either carbon-oxygen or carbon-nitrogen bond formation. The alternatives are shown schematically in equation [35] for an aldehyde semicarbazone. The lead



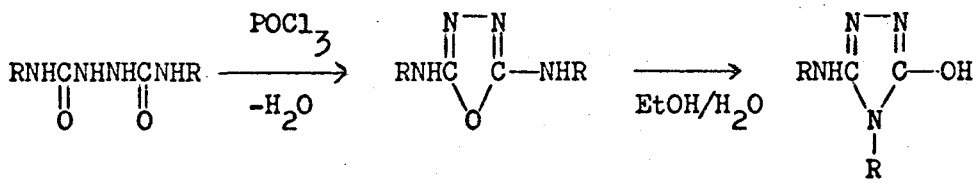
[35]

tetra-acetate oxidation of ketone semicarbazones and carbohydrazones reported in this thesis involves carbon-oxygen closure to give Δ^3-1,3,4-oxadiazolines.

Varied conditions have been used to effect closure of substituted semicarbazides to form the alternative 1,2,4-triazoles. These include pyrolytic and base-catalysed eliminations, as well as oxidative cyclization. Review articles (64,65) have considered these reactions as a general method of synthesis of s-triazoles.

Recent studies by Gehlen raise the possibility that 1,3,4-oxadiazoles are actually favoured kinetically, but are isomerized to 1,2,4-triazoles under the usual reaction conditions. Neat phosphorous

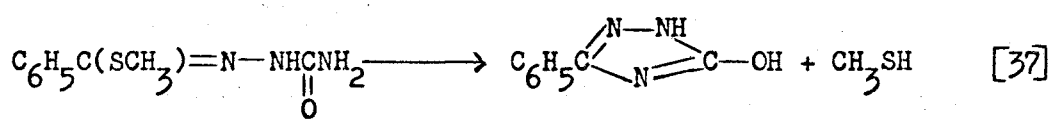
oxychloride dehydrates some hydrazine derivatives to the oxadiazoles, as shown in equation [36] . The product is converted to the isomeric



[36]

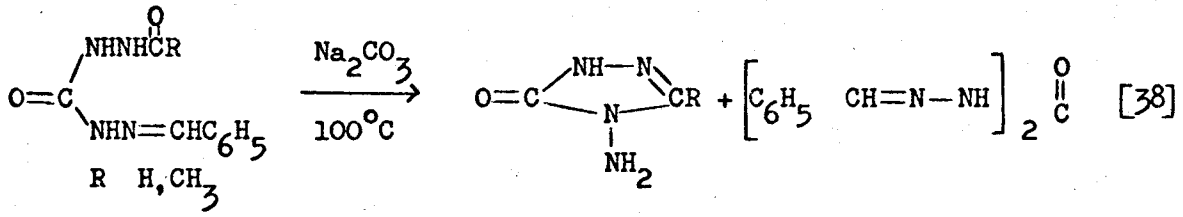
triazole by 10 percent aqueous ethanol, or more rapidly by aqueous potassium hydroxide (66).

Examination of the reaction conditions in triazole syntheses reveals a general use of aqueous conditions and elevated temperatures. Pyrolytic elimination of methylthiol from 1-(∝ -methylthio)benzylidene semicarbazone to yield 3-hydroxy-5-phenyl-2H-1,2,4-triazole (eq. [37]), required a temperature of 210°C (67).



[37]

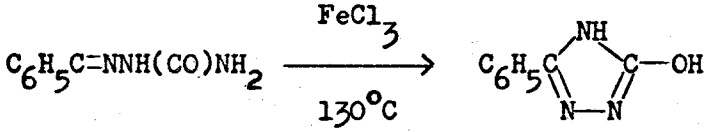
Dehydration procedures for the preparation of 1,2,4-triazoles and the related urazoles call for aqueous KOH at 100°C (64,65). Gehlen has recently broadened the scope of these reactions through comprehensive studies of the cyclization of alkylated 1-acyl-semicarbazides (68), and 3-hydrazino derivatives of 1-acyl-semicarbazides (69). The reaction conditions specified are again aqueous base at 100°C. Kroeger (70) has successfully cyclized carbohydrazide derivatives in an aqueous sodium carbonate medium (eq. [38]).



[38]

The benzylidene imino group exchange emphasizes the possibility of further reaction under these conditions.

The synthesis of s-triazoles by oxidative closure is more closely related to the reaction of lead tetra-acetate with keto-carbohydrazones and keto-semicarbazones. Young and Witham (71) first investigated the preparation of 1,2,4-triazoles by oxidative closure of benzaldehyde semicarbazone, using alcoholic ferric chloride at 130°C (eq. [39]). The use of alcoholic media at high temperatures was continued in the extension of



[39]

this ferric chloride oxidation to N-substituted semicarbazones (72-74). In all cases, ring-formation took place with closure to nitrogen to form 1,2,4-triazoles.

Oxidation of benzaldehyde thiosemicarbazone with alcoholic ferric chloride gave contrasting results. Carbon-sulphur bond closure led to the isolation of the 1,3,4-thiadiazole (75). It may be that the semicarbazone oxidations also involve initial carbon-oxygen bond closure to form oxadiazoles. The facile isomerization of oxadiazoles to triazoles, observed by Gehlen, should occur rapidly at 130° in the hydroxylic ethanol solvent which is

employed in the ferric chloride reactions. No mechanistic studies on these oxidation reactions have been reported. It seems that direct comparison with the low temperature, anhydrous, lead tetra-acetate oxidation of semicarbazone derivatives would not be meaningful.

(vii) The Mechanism of Lead Tetra-Acetate Oxidations.

Considerable uncertainty exists as to whether oxidation of nitrogen-containing substrates by lead tetra-acetate involves a free radical mechanism, or nucleophilic displacement on an organo-lead intermediate. Free radical mechanisms have been employed to explain azoacetate formation from keto-hydrazones (eq. [10-12]; page 12), azobenzene formation from anilines (6,7), and benzimidazole formation from o-phenylenediamine Schiff bases (eq. [7]); page 9). Such mechanisms have been refuted by Norman (35,48). He was able to consistently apply a polar mechanism to the oxidations of pyrazolines (eq. [20]; page 18), benzophenone benzoylhydrazones (eq. [24]; page 20), and chalcone phenylhydrazones (eq. [25]; page 21).

Electron spin resonance spectroscopy may prove valuable in deciding if intermediates with unpaired spin are actually involved in the oxidation reactions. Although the formazan to tetrazolium salt oxidation by lead tetra-acetate was assigned a polar mechanism by Norman (35), Russell recently obtained the E.S.R. spectrum of an oxygen-stable free radical intermediate present in the interconversion of the two species (76). Several workers have also studied the formation of an iminoxy radical by the reaction of lead tetra-acetate with ketoximes (77-79). In particular, Lown has carried

out a detailed investigation on cyclopentanone, cyclohexanone and acetone oximes (80,81). He identified the spectrum of the intial iminoxy radical X (eq. [40]), as well as the nitrosoacetate radical anion that is derived

$$R)_2C{=}NOH + Pb(OAc)_4 \longrightarrow 2R)_2C{=}N{-}\dot{O} + Pb(OAc)_2 + 2HOAc \qquad [40]$$

X

$$R_2)C{=}NOH + Pb(OAc)_4 \longrightarrow R)_2\underset{\underset{OAc}{|}}{C}{-}\underset{\underset{OAc}{|}}{N}{-}OH + Pb(OAc)_2 \qquad [41]$$

$$R)_2\underset{\underset{OAc}{|}}{C}{-}\underset{\underset{OAc}{|}}{N}{-}OH \rightleftharpoons R)_2\underset{\underset{OAc}{|}}{C}{-}N{=}O + HOAc \qquad [42]$$

XI

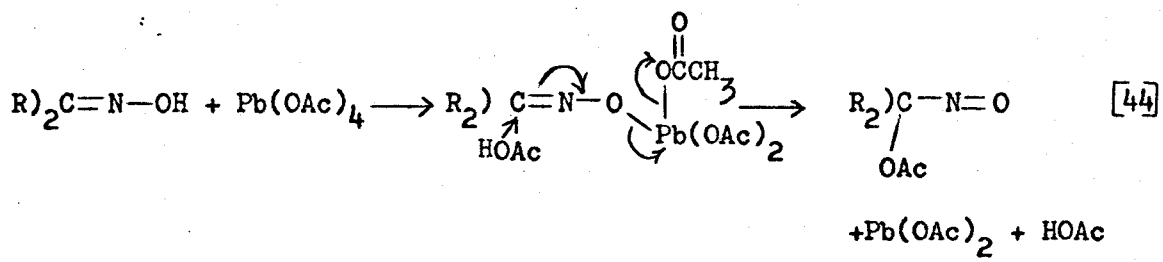
$$2R)_2\underset{\underset{OAc}{|}}{C}{-}\underset{\underset{OAc}{|}}{N}{-}OH + Pb(OAc)_4 \longrightarrow R)_2\underset{\underset{OAc}{|}}{C}{-}\underset{\underset{OAc}{|}}{N}{-}\dot{O} + Pb(OAc)_2 + 2HOAc \qquad [43]$$

XII

from the nitrosoacetate XI (eq. [42]). In addition, the spectrum of an intermediate nitroxide radical XII (eq. [43]) was observed. Since the iminoxy radical X was stable in the presence of excess lead tetra-acetate, Iown felt that the evidence was consistent with the concurrent reactions that are shown above in equations [40-43]. The addition to the carbon-nitrogen double bond, rather than oxidation of the hydroxyl group, lead to the azoacetate in this scheme.

Although Lown's mechanistic proposals are speculative, they emphasize the complexity of the oxidation reaction. The alternative scheme for oxime oxidation (5), involving acid exchange and two electron transfer

(eq. [44]), does not take into account the radical species detected by

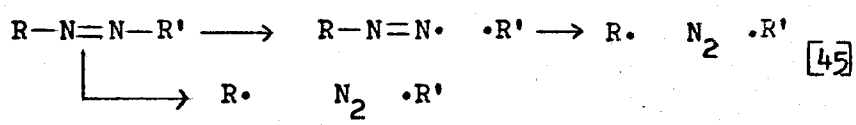


[44]

E.S.R. spectroscopy. It is clear that further studies are necessary to resolve the mechanism of oxidation of these carbonyl derivatives

II. The Thermal Decomposition of Cyclic Azo Compounds

Until recently, the investigations of the decompositions of azo compounds were mainly concerned with open-chain azo alkanes. Thermal and photolytic decomposition of these compounds yields alkyl radicals and nitrogen, as shown in equation [45] . Interest in the fragmentation as a



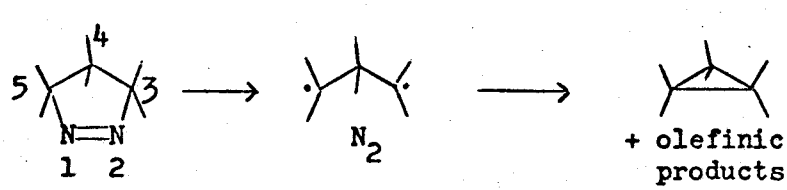
[45]

source of radicals has led to extensive exploration of both the effect of alpha substitution on the rates of decomposition, and the fate of the radicals produced. Alkyl, aryl and cyano substituents, that are known to stabilize radical centers, enchance the rates of thermolysis of azo compounds. The radicals formed either combine immediately in the so-called "cage effect", or undergo typical abstraction and addition reactions. Recent reports by Overberger (82), Cohen (83), and Bartlett (84), contain comprehensive summaries of work to date on these two aspects of open-chain azoalkane decomposition.

Azoalkane thermolysis has been written as either a concerted or step-wise process in equation [45]. The concerted cleavage of two bonds in the rate-determining first step is considered likely in cases where the two incipient radicals are the same, or have similar energies. Seltzer has applied kinetic hydrogen-deuterium isotope effect measurements to the problem of concerted cleavage. He finds that the decomposition of the symmetrical azo-bis(1-phenyl)ethane involves simultaneous cleavage of both C—N bonds (85). Isotope effects obtained in studies on (1-phenyl)ethylazo-2-propane predict more stretching of the C—N bond to the $C_6H_5(CH_3)CH$ group, in an unsymmetrical, concerted transition state (86). In (1-phenyl)ethylazomethane decomposition, Seltzer finds that only the benzyl azo bond cleaves to form a short-lived diazomethyl radical (87). Azoalkane decomposition is therefore best described as a concerted bond cleavage, unless a large difference in the stability of the radicals is expected.

(i) Decomposition of 1-pyrazolines.

The decomposition of Δ^3-1,3,4-oxadiazolines, reported in this thesis, can be considered as a specific example of the thermolysis of 5-membered cyclic azo compounds (1-pyrazolines). Recent studies of 1-pyrazoline decomposition have been sparked by interest in their utility in cyclopropane synthesis, as shown in equation [46]. Overberger (88,89)

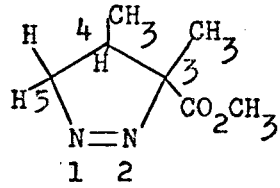


[46]

has investigated the decomposition of symmetrical 3,5-diaryl-1-pyrazolines having para-chloro, para-methoxy and para-hydrogen substituents. These 1-pyrazolines decompose more rapidly than the corresponding open-chain azoalkanes. The rate-enhancement is attributed to a weakening of the C—N bonds, caused by the ring constraint. Increased steric interaction in the cis-3,5-disubstituted compounds causes them to decompose faster than the trans isomers. It was observed that the rate was independent of the para-substituents, and that the reaction gave nearly stereo-selective closure to cyclopropanes of the same geometry. Accordingly, Overberger postulated a concerted, homolytic decomposition followed by rapid closure of a biradical intermediate.

Crawford (90) has studied the thermal decomposition of a series of alkylated pyrazolines in order to compare the products of the intermediate biradical with those products resulting from cyclopropane pyrolysis. Increases in the rate of 1-pyrazoline decomposition are obtained from successive methyl substitution at positions three and five. Since stabilization of both radical centers is important, a concerted decomposition is likely. Kinetic isotope effect studies indicate the small amount of olefinic products result from the same intermediate biradical which gives cyclopropane. In agreement with Overberger, Crawford also observes both geometrical isomers in the cyclopropane products. He postulates the formation of a singlet "π_u" biradical, that would require rotation of the C_3-C_4 bond before overlap of the p-orbitals would be possible.

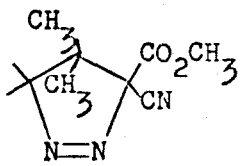
Other 1-pyrazolines that have been studied have electronegative substituents at the three position. Van Auken (91) studied the neat



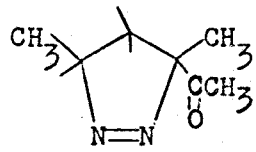
XIII

pyrolysis of the 1-pyrazoline XIII, obtaining cis- and trans-cyclopropanes in 1:1 ratio, as well as minor amounts of olefins. Heterolysis of the 2-3 bond to form a zwitterionic intermediate, having a negative charge at carbon three, was proposed as the first step in the decomposition. The photolysis of pyrazoline XIII led to stereospecific cyclopropane formation in 76 percent yield. The isolation of the unsaturated ester, methyl tiglate, indicated that the retro-addition of diazomethane was also occurring in the photolysis.

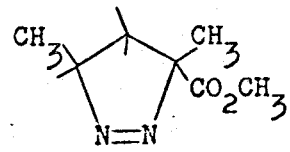
In a series of publications (92-94), McGreer has reported the products of thermal decomposition of 1-pyrazolines that have electronegative substituents at position three. Pyrazoline XIV decomposes more rapidly in polar than in non polar solvents, and yields olefinic products



XIV



XV

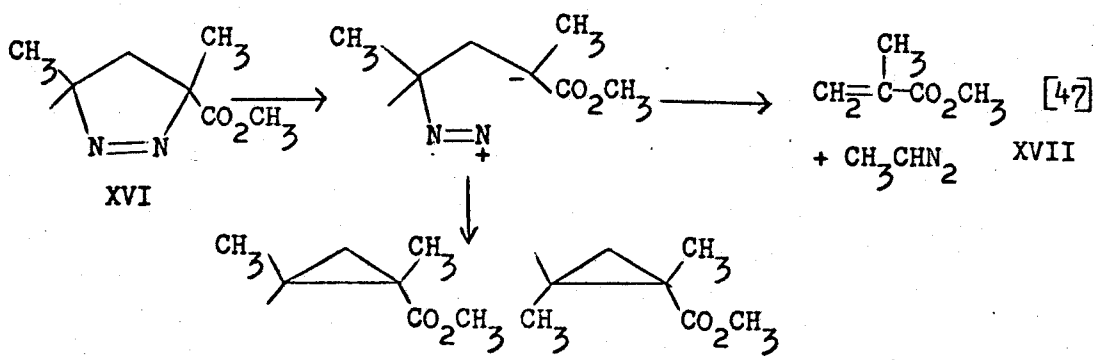


XVI

that arise from the migration of methyl groups from carbon four to carbon five. Since equal quantities of each of the two possible olefins are not obtained, McGreer postulates an ionic transition state in which methyl migration and nitrogen loss occur simultaneously.

The 3-acetyl-1-pyrazoline XV gives some closure to oxygen to yield dihydrofurans as products of the thermolysis. The isomeric 3-acetyl-1-pyrazoline, in which the methyl groups are trans, gives very little ether product. Therefore, the same free zwitterionic intermediate is not formed from the two compounds. McGreer postulates a dipolar transition state in which negative charge is delocalized over the carbonyl function, but partial bonding is retained between carbon three and nitrogen. Ring closure is then either concerted with nitrogen loss, or occurs in a subsequent fast step.

The decompositions of the 3-carbomethoxy-3,5-dimethyl-1-pyrazoline XVI and its trans isomer are not enhanced by polar solvents. If a free ionic intermediate was formed during the thermal decomposition of XVI, an acceleration of the rate by polar solvents would be expected. Methyl methacrylate, XVII, should also be formed by the low energy, retro-addition

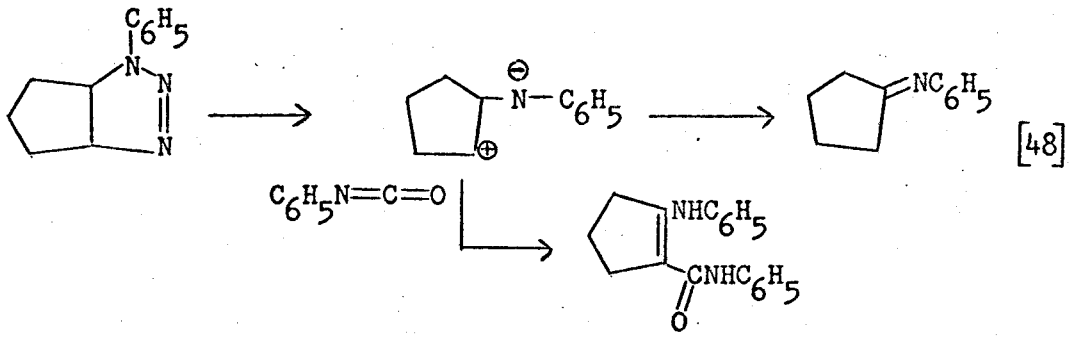


process shown in equation [47]. However, pyrazoline XVI shows the loss of geometry in cyclopropane formation that is observed in all reported decompositions of 1-pyrazolines. Such isomerism cannot be readily explained in terms of the concerted loss of nitrogen, and subsequent closure of reactive biradical or ionic intermediates. McGreer favours a spectrum of transition states similar to those proposed for open-chain azo-compounds by Seltzer (page 33). Depending on the ring substituents, 1-pyrazoline decomposition could involve a range from fully-concerted nitrogen loss to a single, heterolytic, bond cleavage. McGreer speculates that cis- and trans-cyclopropanes can arise in a concerted transition state through steric distortion, that produces a favourable geometry for inversion to occur during the ring closure.

A comprehensive mechanism covering all of the 1-pyrazoline thermal decompositions investigated to date is not available. The application of mechanistic proposals for azo-decomposition to a new example must be approached with caution.

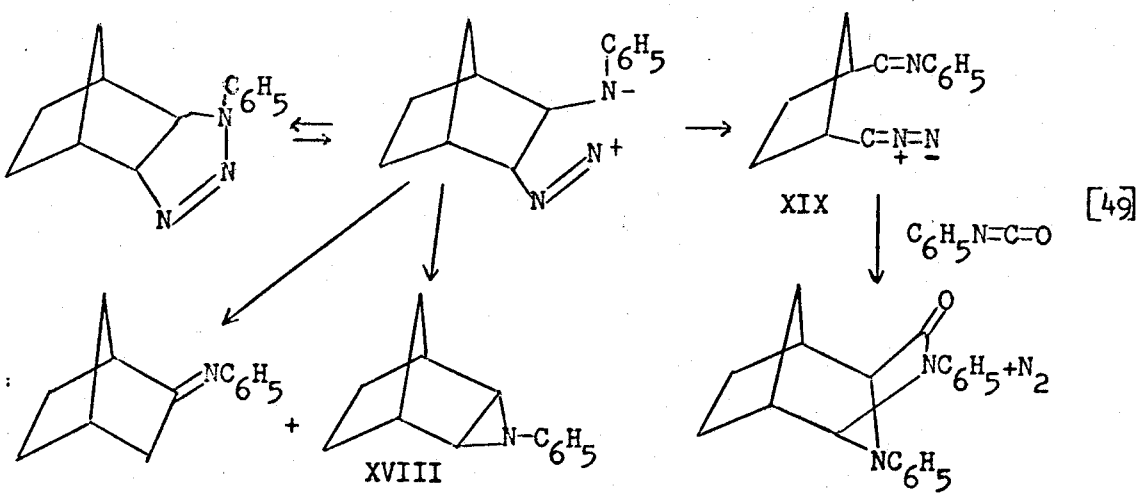
(ii) Pyrolysis of Triazoles and Oxadiazolines.

The pyrolysis of heterocycles containing azo functions bonded to one carbon, and to one other hetero atom, would be expected to be polar processes. The thermal decompositions of 1,2,3-triazoles have been explained by postulating 1,3-dipolar intermediates. For example, the adduct of phenylazide and cyclopentene decomposes to give the corresponding imine, as shown in equation [48]. Phenyl isocyanate can be used to intercept the



[48]

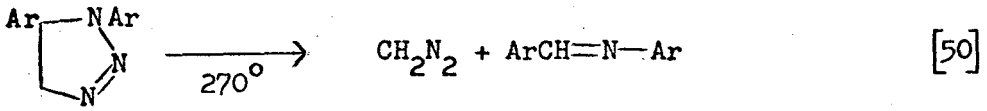
intermediate zwitterion (95). The 1,2,3-triazole derived from phenyl azide and norbornylene(96) decomposes to give the imine, and also the aziridine XVIII (eq. [49]). Decomposition in the presence of phenyl isocyanate gives a product in which the norbornyl ring system has been opened. The mechanism is thought to involve initial N-N single bond cleavage in



[49]

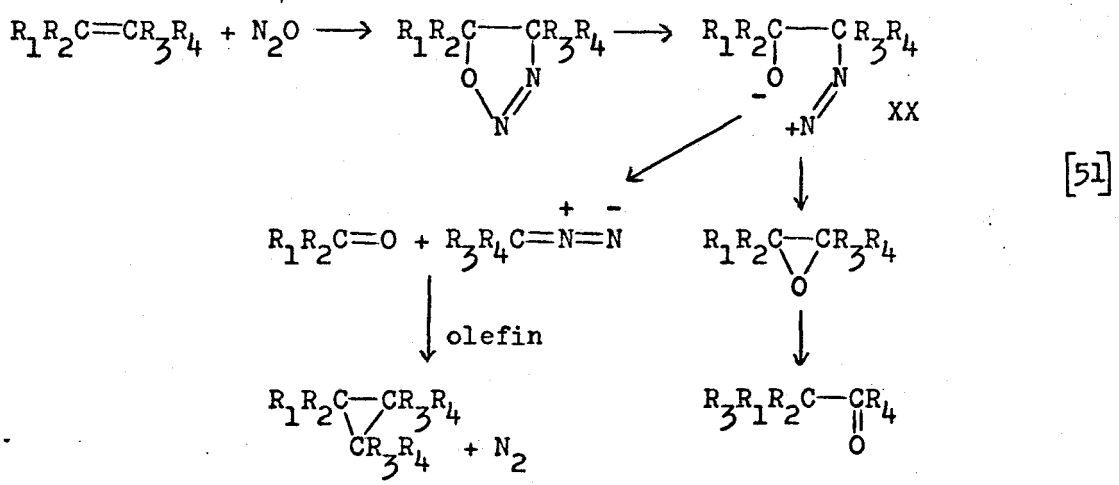
the triazole, followed by ring opening to the diazo compound XIX. Attack by phenyl isocyanate then leads to the observed product. In this system, an ionic intermediate derived from cleavage of only one bond to the azo group is postulated.

Thermal decomposition to diazocompounds has also been postulated for 3,4-diaryl-1,2,3-triazoles, (97) as shown in equation [50]. In view of the severity of the reaction conditions and lack of experimental detail, further work on this pyrolysis seems to be indicated.



[50]

Buckley (98) reports that the reaction of N_2O with olefins at 250° proceeds via a 1,2,3-oxadiazole intermediate (eq. [51]). He postulates heterolysis of the O-N bond to form the zwitterion XX.

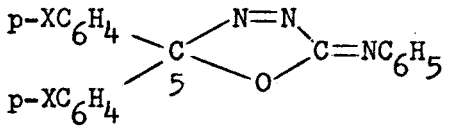


[51]

Subsequent cleavage of the C-C bond yields ketone and the substituted diazomethane. Alternatively, loss of nitrogen leads to an epoxide. The mechanism again must be considered tentative in view of the high temperature, and reliance on product studies alone.

(iii) Application of the Hammett Equation to Thermal Decompositions.

The thermal decomposition of the Δ^3-1,3,4-oxadiazolines XXI, reported in this work, involves the cleavage of the bonds to oxygen and



XXI

nitrogen at carbon five. Therefore, the influence of para substituents in the 5-phenyl groups on the reactivity of the molecule towards thermolysis has been studied. In this section, the quantitative correlation of reactivity with structure by linear free energy relationships, such as the Hammett equation, will be introduced. In particular, the applicability of such treatments to unimolecular decompositions will be assessed.

In 1937, L. P. Hammett (99) proposed an empirical relation correlating reactivity in the side chain of benzene derivatives with the nature of the meta and para substituents. In the Hammett equation [52], k is

$$\log k/k_o = \rho\sigma \qquad [52]$$

the rate or equilibrium constant for a meta or para substituted benzene derivative, and k_o is that for the unsubstituted compound. The σ parameter is a characteristic of the substituent alone, and ideally is independent of the reaction being studied. For a given reaction in a substituted series,

ρ is a constant depending only on the conditions. The Hammett σ was defined by equation [53], where log K and K_o are the dissociation constants

$$\sigma_m = \log K_m - \log K_o; \quad \sigma_p = \log K_p - \log K_o \qquad [53]$$

for the substituted and unsubstituted benzoic acids at 25.0°C respectively. Since ρ for this equilibrium process was defined as +1.0, then electron-withdrawing groups (that increase benzoic acid strength) have positive sigma values. Conversely, electron-releasing groups have negative sigma values. Reactions aided by electron withdrawal have positive ρ values, while those accelerated by electron donation have negative ρ values. It follows that if the absolute value of ρ is greater than 1.0, then the reaction is more susceptible to substituent effects than the ionization of benzoic acid.

Comprehensive reviews have been published by Jaffé (100), and by Wells (101) on the application of the Hammett equation in organic chemistry. In particular, Wells examined the validity of the Hammett equation as a linear free energy relationship, and the theoretical basis of the σ and ρ parameters. It is important to note the inverse dependence of ρ on temperature (to a first approximation), that must be taken into account especially in reactions where the absolute magnitude of ρ is small. A detailed examination of the above aspects of the Hammett equation is beyond the scope of the present discussion.

Hammett assumed that substituent effects were solely electrostatic in nature (99). However, the success of theoretical interpretation of the sign and magnitude of substituent constants has been dependent on the premise that both resonance and inductive effects are important. Investigations of these correlations are summarized by Wells (101), and later by Ehrenson (102). Experimentally, the importance of resonance effects is reflected in the poor fit of the Hammett equation to data from reactions in which the carbon alpha to the benzene ring develops carbonium ion character in the transition state.

Several attempts have been made to establish new sets of substituent constants, based on standard electrophilic reactions in which resonance stabilization of positive charge is important. H. C. Brown (103) established the σ^+ parameter based on the solvolysis of para-substituted cumyl chlorides. The resulting modified Hammett equation, $\log k/k_o = \rho\sigma^+$, does correlate a number of side-chain reactions where positive charge is developed at the transition state. Deno (104) obtained a similar σ^+ constant from arylcarbonium ion equilibrium constants in sulphuric acid solution.

Yukawa and Tsuno (105-107) have been able to show that these revised substituent parameters are linearly related (eq. [54]). They argue

$$(\sigma_A^+ - \sigma) = r(\sigma_B^+ - \sigma) \qquad [54]$$

that the degree of resonance delocalization should depend on the amount of charge generated at the transition state. Therefore, the substituent constant should also vary with the reaction, depending on the relative importance of the resonance contribution. This principle is embodied in the modified Hammett relation;

$$\log k/k_o = \rho(\sigma - r\Delta\sigma_r^+)$$

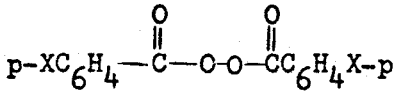
in which r is a constant for a given reaction and $\Delta\sigma_R^+$ is the difference between the Brown σ^+ and Hammett σ constants.

This modified equation has been found to correlate data from over 30 reactions in which neither the Hammett σ, or σ^+ gave satisfactory fits. Although theoretical interpretation of three parameter equations is difficult, it seems that the r value relates the fraction of positive charge at the transition state of the reaction under study to that in the standard cumyl chloride solvolysis.

The relationship of Tsuno and Yukawa has been used to correlate the retro-addition reaction of diphenyldiazomethane and phenylisocyanate encountered in the thermolysis of the Δ^3-1,3,4-oxadiazolines. It has therefore been discussed in some detail. However, comprehensive modified Hammett treatments involving a separation of polar and resonance effects have been developed by Wepster (108), and by Taft (109). The reviews cited earlier, by Wells (101), and by Ehrenson (102), provide detailed information on these approaches.

The correlation of free radical processes by the Hammett equation has had only limited success. Hammett did not include any examples of free radical reactions in his original proposal (99). Tabulations of ρ values for free radical processes by Jaffé (100) indicate that the correlation is generally less exact than in polar reactions. Good agreement is usually found in the reactions of radicals with other molecules, where the electrophilic character of the radical is an important factor. These reactions proceed through a polar transition state that has some charge-transfer character. Therefore, the substituent effect is similar to that in heterolytic reactions, and Ingold (110) has shown that many such reactions are better correlated by σ^+ values.

All para substituents that can stabilize an odd electron should accelerate homolytic reactions that generate free radicals by unimolecular decomposition. It is not surprising that the formation of triphenylmethyl radicals from hexaphenylethane (111) is enhanced by groups with either positive or negative sigma values. Blomquist (112), and Swain (113), have studied the unimolecular decomposition of benzoylperoxide, XXII. Although Swain obtained a linear Hammett plot with $\rho = -0.38$ at 80°C, Blomquist found rate enhancement by both electron-withdrawing and donating substituents. The authors suggested that changes in the electron repulsion in the oxygen-



XXII

oxygen bond in the ground state were the cause of the rate differences. Recent studies by O'Driscoll (114) indicate no further decrease in the rate of decomposition of substituted benzoylperoxides for total positive sigma values greater than 0.6. He assigns this effect to a balance of increasing transition state stabilization with concurrent decreasing ground state energy.

Few studies on the Hammett correlation of the decomposition of azo compounds have been reported. The rate of decomposition of 3,5-diaryl-1-pyrazolines (page 34 ; this Thesis) studied by Overberger, show no significant variation with para substituents. Yamamoto (115) has studied the decomposition of m- and p-substituted phenylazotriphenylmethanes (eq. [55]). He reports that the modified equation of Tsuno and Yukawa gives a good linear relation

$$p\text{-}XC_6H_4\text{—}N{=}N\text{—}C(C_6H_5)_3 \longrightarrow p\text{-}XC_6H_4\cdot + N_2 + \cdot C(C_6H_5)_3 \qquad [55]$$

with $\rho = -0.92$ and $r = 0.9$ at 59°C. However, a plot of log k/k_o versus the Hammett σ employing Yamamotos' data (116) shows a maximum value for the unsubstituted compound. It seems likely that the modified equation obscures the fact that a linear free energy relationship does not apply in this case. Wilmarth (117) found that the decomposition of substituted tetrazenes, XXIII, to hydrazyl radicals (eq. [56]) was correlated by the Hammett equation.

$$\left[(p\text{-}XC_6H_4)_2N\text{—}\underset{\displaystyle O{=}C\,CH_3}{\overset{|}{N}}\text{—}\right]_2 \longrightarrow 2\ (p\text{-}XC_6H_4)_2N\text{—}\underset{\displaystyle O{=}C\,CH_3}{\overset{|}{N}}\cdot \qquad [56]$$

XXIII

However, he notes that interaction of the para substituent with the odd electron is not observed in the E.S.R. spectrum; and that a polar transition state can be written. Wilmarth concludes, by reference to the studies on benzoylperoxide decomposition, that the above conditions are necessary for correlation of homolytic decompositions by the Hammett equation. Conversely, it seems likely that in cases where stabilization of the odd electron by the substituents is possible, only small differences in transition state energy will be encountered. Ground state energy differences should then be important. In these cases, then, the substituent effects will have to be assessed in terms of the molecular structure of the compound being studied.

EXPERIMENTAL

General

(i) Outline of Experimental Section.

The syntheses of a series of substituted Δ^3-1,3,4-oxadiazolines by the lead tetra-acetate oxidation of ketone carbohydrazones is first described. The alteration in the reaction conditions on proceeding from alkyl to aryl ketone derivatives should be noted. Modifications of established procedures for the preparation of acetophenone and benzophenone carbohydrazones are given.

The extension of the oxidation reaction to the 4-substituted semicarbazones of acetone and a series of p,p'-disubstituted benzophenones is then presented, including the synthesis of the requisite substrates. Procedures employed in the catalytic and lithium aluminium hydride reductions, and in the hydrolysis of some of the Δ^3-1,3,4-oxadiazolines are outlined.

The latter portion of the experimental section describes the kinetic procedures used in the study of the thermal decomposition of the 5,5-diaryl-2- phenylimino -Δ^3-1,3,4-oxadiazolines. Gas evolution and infra-red spectroscopic techniques are outlined. The calculation of the reaction rate constants from the observed data concludes the section.

(ii) General Spectroscopic and Analytical Techniques.

The infra-red spectrum of each compound prepared was routinely recorded on a Beckman I.R. 5 instrument, employing thin film, KBr wafer, or carbon tetrachloride solution samples. Whenever the proton substitution

pattern aided in confirmation of structure and purity, the N.M.R. spectrum was recorded on a Varian A-60 spectrometer in $CDCl_3$ or CCl_4 solution (tetramethylsilane, internal reference). The expected absorptions in the N.M.R. and I.R. spectra were observed for all the previously reported compounds that have been prepared. These spectral data are not reproduced in detail in this Thesis for reasons of space. However, it can be assumed that products of preparations have spectra compatible with the assigned structures.

The infra-red, N.M.R., ultra-violet, and mass spectrometric data on the Δ^3-1,3,4-oxadiazolines is presented in tabular form, and fully discussed in the section on Results and Discussion. This information will not be repeated in conjunction with the individual preparations. The ultra-violet and visible spectra of the new heterocycles were recorded on a Carey Model 21 instrument, in either 95% ethanol or n-hexane (Fisher Spectrograde) solutions. The mass spectra were recorded on an Hitachi-Perkin Elmer Model RMU-6A spectrometer. The indices of refraction of the liquid oxadiazolines were determined with an Abbe Model 3L refractometer. The molecular weights reported for the oxadiazolines were obtained in chloroform using a Mechrolab Model 301A Vapour Pressure Osmometer.

The adsorbants used in column chromatographic separations were Fisher 80-200 mesh activated or neutral alumina, 1:1 Fisher animal charcoal (powder) and celite (Johns-Manville, 535), or Florisil brand

magnesia-silica gel as supplied by Fisher. Thin layer chromatography was done with Camag DSO aluminum oxide, and iodine vapour development. Stock solvents (Mallinkrodt or Shawinigan Chemicals), were fractionated through a three foot Vigreux column prior to use in chromatography, or in recrystallization.

Melting points were determined using a Thomas "Unimelt" capillary melting point apparatus. As expected, the decomposition points of the thermally unstable oxadiazolines were dependent on the rate of heating. The values recorded in the preparations that follow were obtained by rapid heating (10 degrees/minute) to within a few degrees of the expected temperature. The critical range was then traversed over the following minute.

(iii) Preparation of Analytical Samples.

The elemental analyses of the new Δ^3-1,3,4-oxadiazolines have generally not shown the precision desired in such measurements, in spite of repeated attempts to secure pure samples. Some care was taken in the sample preparation. The oxadiazolines derived from the carbohydrazones were sealed in vacuo; and on one occasion, freshly prepared samples were packed in "dry ice" prior to shipment. However, no improvement in the analyses was noted. All solid derivatives were repeatedly recrystallized, and then evacuated to remove traces of solvent. Sample purity was monitored by both thin layer chromatography, and the decomposition point of the material.

It should be noted that the more thermally stable oxadiazolines derived from the acetone semicarbazone derivatives did give satisfactory analyses. As well, duplicate samples of the same homogeneous material sent to different analysts often gave conflicting results, randomly scattered about the calculated values. It seemed likely that the difficulty lay in the thermal instability of the materials, and not in the structural assignment. This is borne out by the mass spectrometric and osmometric investigations, and by the stoichiometry of the thermolyses.

Microanalyses were done by Alfred Bernhardt, Max-Planck Institut, Mulheim, Germany; and by C. Daessle, 5757 Decelles Ave., Montreal, P. Q.

(iv) Common Reagents used in Syntheses.

In this section, the sources of supply of the reagents that have been repeatedly employed in synthetic series are given.

Oxidation Reactions

(1) Methylene chloride - Matheson-Coleman-Bell, used as supplied.

(2) Lead Tetra-acetate - Matheson-Coleman-Bell (moist with acetic acid). Washed with 30-60 petroleum ether prior to use.

Carbohydrazone and Semicarbazone Preparations

(1) Ethanol - 95 percent stock used as supplied, unless otherwise specified.

(2) Semicarbazide Hydrochloride - Fisher Certified Reagent.

(3) Sodium Acetate - British Drug Houses, Lab. Chemical.

(4) Aniline - Eastern Chemical, Laboratory grade. Distilled, b.p. 183-185°, stored under nitrogen.

I. Preparation of Substituted Δ^3-1,3,4-Oxadiazolines

(i) Oxidation of Ketone Carbohydrazones.

(a) Preparation of Carbohydrazide

Carbohydrazide was prepared by the method of Kesting (118), except that a two-fold excess of readily available 85 percent hydrazine hydrate was employed in lieu of the 99 percent hydrate specified.

A mixture of 309 g (2.58 mole) of diethylcarbonate (Matheson-Coleman-Bell, reagent) and 520 g (8.85 mole) of hydrazine hydrate (85%, Matheson Chemicals, Technical) was heated under reflux on a steam bath for 48 hours. The flask was then fitted for distillation, and 200 ml of aqueous ethanol was distilled off at atmospheric pressure. On cooling, carbohydrazide separated from the residue in large, colourless, monoclinic crystals. After one recrystallization from ethanol, the yield was 203.6 g (86.5%), m.p. 151-153° (lit. (118) m.p. 156°). Material recrystallized again prior to use had m.p. 155-156°.

Attempts to prepare carbohydrazide using anhydrous hydrazine gave lower yields. The reaction of diethylcarbonate (100 g, 0.833 mole) and anhydrous hydrazine (87 g, 2.58 mole) produced only 42.8 g (57%) of carbohydrazide. An ethanol-insoluble residue in this experiment was recrystallized from water-alcohol to give 24.2 g of a white powder, m.p. 195-198°. Hydrazidocarbohydrazide, $[NH_2NH(CO)NH-]_2$, has a melting point of 197° (119).

(b) Preparation of 5,5-Dimethyl-2-Isopropylazino-Δ^3-1,3,4-Oxadiazoline

Acetone Carbohydrazone

Acetone carbohydrazone was prepared by the method of Pickering et al (119). Gentle heating of a mixture of carbohydrazide (10.0 g, 0.11 mole) and 75 ml of acetone initiated an exothermic reaction that kept the mixture at reflux until all the solid had disappeared. After cooling, filtering and recrystallizing from ethanol, acetone carbohydrazone (18.3 g, 97%) was obtained as white needles m.p. 158-160° (lit. (119) m.p. 160°).

Oxidation of Acetone Carbohydrazone

The experimental conditions employed in the lead tetra-acetate oxidations were based on the procedure outlined by Iffland (27), for the preparation of azo-acetates from ketone phenylhydrazones.

A slightly yellow solution of lead tetra-acetate (57.5 g, 0.129 mole) in 250 ml of methylene chloride was cooled to 0° in a one liter, 3-necked flask equipped with mechanical stirrer and dropping funnel. Purified-grade nitrogen was bubbled through the solution to remove oxygen. Dropwise addition of acetone carbohydrazone (18.3 g, 0.11 mole) in 75 ml of methylene chloride over fifteen minutes was accompanied by the precipitation of a white solid (lead diacetate), and a gradual deepening of the initial faint-yellow colour. The reaction mixture was allowed to stir for an additional 15 minutes at 0°, and then 100 ml of ice-water was added. After stirring for 10 minutes, the dark-brown slurry was filtered by suction

through a bed of celite. The pale-yellow methylene chloride layer was separated, and washed with three 100 ml portions of water, one 100 ml portion of saturated sodium bicarbonate, and finally with three 100 ml portions of water. After drying with anhydrous sodium sulphate, and rotary evaporation of the solvent at room temperature, the oxadiazoline was obtained as a yellow-orange oil. The crude yield was 14.1 g (77%). Rapid distillation gave 11.3 g (62%) of a bright yellow liquid, b.p. 89-90° (5 mm), $n_D^{25} = 1.5124$. The molecular weight found by osmometry was 168 (M.W. calc. 168).

Column chromatography on activated or neutral alumina, or on 1:1 celite/charcoal using petroleum ether/chloroform mixtures as eluants led to the recovery of less pure material in low yield. On standing at room temperature in the presence of light and oxygen, solutions of this oxadiazoline in non-polar solvents gradually deposit an unidentified, insoluble, white solid.

A number of freshly-distilled samples, sealed in vacuo, were sent for analysis.

Calc. for $C_7H_{12}N_4O$:	C, 49.98	H, 7.19	N, 33.31
Found:	C, 50.17	H, 7.07	N, 34.03
	49.22	7.32	33.11
	49.03	7.12	33.14
	49.14	6.91	32.97

(c) Preparation of 5-Ethyl-5-Methyl-2-(2-Butylazino)-Δ^3-1,3,4-Oxadiazoline

2-Butanone Carbohydrazone

This compound was prepared by the method of Pickering (119), employed in the synthesis of acetone carbohydrazone. The reaction of 17.6 g (0.24 mole) of 2-butanone (Matheson-Coleman-Bell, reagent) with 10.0 g (0.11 mole) of carbohydrazide gave 14.5 g (66%) of 2-butanone carbohydrazone, as white needles from diethylether, m.p. 113° (lit. (119) m.p. 113°).

Oxidation of 2-Butanone Carbohydrazone

An experimental procedure identical to that previously described for the oxidation of acetone carbohydrazone was used.

The oxidation of 2-butanone carbohydrazone (7.0 g, 0.35 mole) with 20.0 g (0.45 mole, 1.25 equiv.) of lead tetra-acetate gave 5.64 g (81%) of an orange-yellow oil. Rapid, vacuum distillation, employing an oil bath at 120°C, gave 4.7 g (67%) of bright-yellow liquid, b.p. 95° (5 mm), $n_D^{25} = 1.5062$.

An analytical sample of freshly distilled material was again sealed in vacuo for shipment.

Calc. for $C_9H_{16}N_4O$:	C, 55.08	H, 8.22	N, 28.55
Found:	C, 53.79	H, 8.14	N, 28.92.

(d) Preparation of 5-Methyl-5-Phenyl-2-(1-Phenylethylazino)-Δ^3-1,3,4-Oxadiazoline

Preparation of Acetophenone Carbohydrazone

The preparation of acetophenone carbohydrazone from the ketone and carbohydrazide was attempted in both ethanol and dimethylsulphoxide solvents. Yields were disappointing in both instances. Although a higher conversion to the desired product apparently occurs in dimethylsulphoxide, the actual yield is kept low by an acceleration of the accompanying thermal decomposition of the carbohydrazone.

Method I - Ethanol Solvent

The method of Pickering (119) was used. Carbohydrazide (6.12 g, 0.07 mole) was heated gently for one hour with 24.5 g (0.22 mole) of acetophenone (M.C.B, practical, distilled, b.p. 101-102°/15 mm) in 100 ml of absolute alcohol. On cooling, the clear yellow solution deposited 8.1 g of yellow-white crystals, m.p. 185-193°. Two recrystallizations from ethanol gave 4.7 g (23.5%) of white needles, m.p. 201-204°. The reported melting point of acetophenone carbohydrazone is 204° (119).

However, this material was found to rapidly consume 1.5 equiv. of lead tetra-acetate in methylene chloride solution at 0° to yield a tacky, white solid with a strong odour of acetophenone. The rapid consumption of lead tetra-acetate indicated that the carbohydrazone was contaminated with readily oxidizable material, probably the acetophenone 4-aminosemicarbazone.

Method II - Dimethylsulphoxide Solvent

A solution of acetophenone (24.5 g, 0.22 mole) and carbohydrazide (6.12 g, 0.07 mole) was heated in 100 ml of dimethylsulphoxide on a steam bath for one hour. The solution gradually turned a deep-yellow colour. After cooling, it was poured into 250 ml of a crushed ice-water mixture to produce a yellow gum. Extraction of this material with hot alcohol, and cooling, gave 2.89 g (14.4%) of acetophenone carbohydrazone, m.p. 204-206°. Concentration of the filtrate gave 2.8 g of yellow needles, m.p. 121-122°C (lit. (120) m.p. of acetophenone azine, 121°C). The residue that was insoluble in ethanol weighed 5.8 g (m.p. > 230°). It was thought to be the hydrazidocarbohydrazone, $[C_6H_5(CH_3)C=N-NH(C=O)NH-]_2$, m.p. 240, but was not further investigated.

At room temperature, reaction for an hour gave a 45% yield of acetophenone 4-aminosemicarbazone, and an 11% yield of acetophenone carbohydrazone. The crude product was partitioned with chloroform, in which the 4-aminosemicarbazone is insoluble.

Oxidation of Acetophenone Carbohydrazone

The lead tetra-acetate oxidation procedure previously given for dialkyl ketone carbohydrazones was employed. It was necessary to raise the temperature to 25° for fifteen minutes after addition of the carbohydrazone to obtain reaction.

The oxidation of 2.0 g of acetophenone carbohydrazone with 7.5 g (2.2 equiv.) of lead tetra-acetate gave 1.64 g of a yellow oil. On addition of petroleum ether, a white precipitate of 0.2 g of the starting material was obtained. Thin layer chromatography showed that the petroleum

ether solution contained three major components. The infra-red spectrum of the mixture had absorptions at 5.75 μ (broad) and at 5.95 μ, in addition to the oxadiazoline C=N at 6.01 μ. Similar absorptions in the I.R. of the crude oxidation product of benzophenone carbohydrazone (Experimental, page 60) have been assigned to the methylene diacetate (here $CH_3(C_6H_5)C(OAc)_2$), and a monoacetylated material. Intensive investigation of the other components of the product mixture were not undertaken in this case.

Chromatography of 0.2 g of the petroleum ether - soluble material on neutral alumina (50/50 chloroform-petroleum ether elution) gave 0.14 g of slightly impure oxadiazoline, representing a 41% yield based on carbohydrazone. Chromatography on 1:1 celite/charcoal using petroleum ether elution, monitored by infra-red and N.M.R. spectroscopy, gave a pure sample of the oxadiazoline, n_D^{25} = 1.6260; but in very low yield. The rapid deterioration of this material under laboratory conditions prevented the preparation of a sufficiently pure sample for satisfactory elemental analysis.

(e) Preparation of 5,5-Diphenyl-2-Diphenylmethylazino-Δ^3-1,3,4-Oxadiazoline

Preparation of Benzophenone Carbohydrazone

An attempt to prepare this compound by the method of Pickering (119), by heating carbohydrazide with an excess of benzophenone (3 moles), gave only benzophenone 4-aminosemicarbazone, m.p. 221-223° (lit. (119) m.p. 223-224) in 50% yield.

Alternative syntheses used were the condensation of benzophenone with carbohydrazide in dimethyl sulphoxide, and the reaction of benzophenone hydrazone with phosgene in dry pyridine.

Method I - Dimethylsulphoxide

A solution of 5.0 g (0.06 mole) of carbohydrazide, and 25.0 g (0.14 mole) of benzophenone in 150 ml of dimethyl sulphoxide was heated on a steam bath for 48 hours. During this time the solution gradually became deep, brilliant-yellow. After cooling, the solution was poured into 500 ml of an ice-water mixture. The supernatant liquid was decanted from the oily, yellow solid produced. Trituration with 25 ml of cold ethanol and filtration gave 6.0 g (26%) of crude benzophenone carbohydrazone. Two recrystallizations from ethanol gave 4.1 g of white needles, m.p. 224-225° (lit. (119) m.p. 222-223°).

Other preparations by this method gave yields of 20-30 percent. Extension of the heating period gave increased decomposition of the product to diphenyl ketazine. This impurity is difficult to remove, and contaminates the oxadiazoline in the subsequent oxidation. It was for this reason that a low temperature synthetic route to the carbohydrazone through the phosgene reaction was developed

Method II - Reaction of Phosgene with Benzophenone Hydrazone

Benzophenone hydrazone was prepared by the method of Cohen (121). Benzophenone (100 g, 0.55 mole) and 37.0 g (0.62 mole) of 85% hydrazine hydrate heated for 5 hours in 100 ml of absolute alcohol gave 61.0 g (56%) of benzophenone hydrazone m.p. 97-98° (lit. (121) m.p. 97-98°), after two recrystallizations from ethanol-water. The hydrazone is

appreciably soluble in dilute alcohol-water solutions even at 0°.

A solution of benzophenone hydrazone (61.0 g, 0.311 mole) in 300 ml of pyridine (Fisher Certified Reagent; distilled from barium oxide, b.p. 113-114°) was cooled to 0° in a 1 liter 3-necked flask equipped with a mechanical stirrer and a condenser with $CaCl_2$ drying tube. Phosgene gas (Matheson) was condensed from a cylinder using a dry ice-acetone condenser. The liquid phosgene (16.9 g, 0.17 mole) was allowed to distill at room temperature into the reaction vessel above the surface of the stirring pyridine. The solution gradually became a deep orange-brown. The solution was stirred for an additional 30 minutes with continued cooling. It was then poured into 1.5 liters of 10% acetic acid solution, containing crushed ice. The voluminous, white precipitate was filtered to give 61.0 g (94%) of crude benzophenone carbohydrazone having an infra-red spectrum that was nearly superimposable with that of an authentic sample. Two recrystallizations from ethanol-water, employing decolourizing carbon in each case, gave 28.8 g (47% recovery) of white needles, m.p. 224-225°. The poor recovery is attributed to adsorption of the carbohydrazone on the charcoal.

In a further experiment, it was shown that the treatment of benzophenone carbohydrazone with phosgene in pyridine at 0° converts it to a water-soluble material. Therefore, this reaction requires a slow addition of no more than one equivalent of phosgene.

Oxidation of Benzophenone Carbohydrazone

The previously outlined oxidation procedure was used, except that upon completion of the addition of the carbohydrazone, the solution was warmed to 30° for 15 minutes.

Benzophenone carbohydrazone (28.8 g, 0.07 mole) was oxidized with 67.2 g (0.15 mole) of lead tetra-acetate to give a reddish-orange oil. Recrystallization from petroleum ether-chloroform gave 10.5 g (36.5%) of shiny, yellow plates, m.p. 113-114° (decomp.). The molecular weight by osmometry was 411 (M.W. calc. 416).

Analytical samples were recrystallized a further three times, and indicated only one component by thin layer chromatography using several chloroform-petroleum ether eluant mixtures.

Calc. for $C_{27}H_{20}N_4O$:	C, 77.86	H, 4.84	N, 13.45
Found:	C, 78.37	H, 4.85	N, 13.93
	77.71	4.38	12.83
	76.74	5.01	13.49

Other Oxidation Products

In one experiment, the oxidation products remaining in the filtrate following the crystallization of the Δ^3-1,3,4-oxadiazoline were examined.

The filtrate remaining from the oxidation of 0.615 g of benzophenone carbohydrazone, after 0.283 g (46%) of oxadiazoline had been removed, gave 0.280 g of pale-red oil. Thin layer chromatography showed two major components of roughly equal concentration in the mixture. Recrystallization of the oil from petroleum ether gave 0.1 g (25%) of diphenylmethylenediacetate as white needles, m.p. 120-122°C (lit. (38) m.p. 121°).

The N.M.R. spectrum ($CDCl_3$) of diphenylmethylenediacetate showed a singlet at 8.04 τ (6H), and a multiplet centered at 2.66 τ (10H), while its infra-red spectrum showed a single carbonyl region absorption at 5.75 μ, and no NH or OH absorptions. Treatment of a sample of diphenylmethylenediacetate with a 2,4-dinitrophenyl hydrazine-ethanol-phosphoric acid reagent, gave a red, crystalline solid identical with an authentic sample of benzophenone 2,4-dinitrophenylhydrazone.

The residual red oil in $CDCl_3$ gave an N.M.R. spectrum having a singlet at 8.16 τ (3H), and a multiplet centered at 2.86 τ (20H). Its infra-red spectrum had two carbonyl-region absorptions at 5.70 μ, and at 5.99 μ, but no NH absorption. The spectroscopic evidence indicates that this compound is an acetyl derivative of benzophenone carbohydrazone in which an amide carbonyl group and both diphenylmethyl residues are retained. The structure has not been investigated further.

(f) Preparation of 5,5-Dimethyl-2-Diphenylmethylazino-Δ^3-1,3,4-Oxadiazoline

Preparation of 1-Diphenylmethylene-5-Isopropylidene Carbohydrazide

Benzophenone 4-aminosemicarbazone (1.0 g, 3.9 m mole; prepared by the method of Pickering (119), m.p. 221-223°) was added to 80 ml of acetone in a 100 ml flask fitted for reflux, and heated on a steam bath for three hours. During this time, the 4-aminosemicarbazone slowly entered solution. On cooling, a mass of white needles separated from the solution. After filtration and drying 1.0 g (86%) of 1-diphenylmethylene-5-isopropylidene carbohydrazide, m.p. 200-202°, was obtained.

The compound was characterized by its N.M.R. spectrum ($CDCl_3$) showing two singlets at 8.12 τ and 8.15 τ(6H), and a multiplet at 2.5-2.8 (10H). The infra-red spectrum ($CHCl_3$) showed a typical carbohydrazone carbonyl absorption at 5.86 μ, and NH absorption at 2.98 μ.

Oxidation of 1-Diphenylmethylene-5-Isopropylidene Carbohydrazide

The experimental procedure for the lead tetra-acetate oxidation of dialkylketone carbohydrazones was used.

Treatment of 0.440 g (1.51 m mole) of 1-diphenylmethylene-5-isopropylidene carbohydrazide with 1.0 g (2.25 m mole) of lead tetra-acetate gave 0.361 g (82%) of a yellow oil. Recrystallization from petroleum ether gave 0.2 g, m.p. 110-111° (no decomp.).

The N.M.R. spectrum of the crude product (CCl_4) showed a singlet at 8.38 τ(6H) and a multiplet at 2.2-2.8 τ(10H) and no other absorptions. It was concluded that only one of the possible isomers was produced.

(g) Preparation of 5,5-Dimethyl-2-Isopropylazino-Δ^3-1,3,4-Thiadiazoline

Preparation of Acetone Thiocarbohydrazone

This compound was prepared by the method of Stephen and Wilson (122). Thiosemicarbazide (Eastman Rgt.; 12.0 g, 0.117 mole) was added to 150 ml of dry acetone and heated under reflux for 12 hours. The mixture was still opaque after two hours, and a small amount of white solid remained at the end of the reflux period.

The excess acetone was distilled, and the residual white solid extracted with 50% petroleum ether/chloroform. Concentration of the

extracts gave acetone thiocarbohydrazone. After two recrystallizations from petroleum ether/chloroform, 7.3 g (33.5%) of white needles that softened and resolidified at 144-145°, and then melted again sharply at 185° were obtained (lit. (122) m.p. 192°d - from alcohol/petroleum ether).

Oxidation of Acetone Thiocarbohydrazone

The general procedure used for the lead tetra-acetate oxidation of acetone carbohydrazone was used, except that exactly one equivalent of oxidant was employed. In this experiment, the addition of the thiocarbohydrazone to the stirred, cooled lead tetra-acetate solution resulted in rapid precipitation of lead diacetate, and a deep red-brown colouration. The reverse addition of the oxidant solution to the thiocarbohydrazone in methylene chloride gave the same result.

In one experiment, the oxidation of 6.8 g of acetone thiosemicarbazone gave 6.0 g of a red-brown oil after work up. Extraction with petroleum ether (b.p. 30-60°) gave 1.3 g of red oil whose N.M.R. spectrum had a complex (10 absorptions) spectrum in the 7.5-8.5 τ region. The oil was chromatographed on Florisil (5x10 cm column), using rapid elution with large volumes of petroleum ether. The orange oil (0.2 g) obtained on evaporation of the bright-yellow eluant had an N.M.R. spectrum that indicated it contained approximately 50% of the desired product. Repeated recrystallization of this material from petroleum ether (b.p. 30-60°) gave yellow, rhombic crystals m.p. 65.0-65.5°.

Analysis for this compound only were performed by Schwarzkopf Microanalytical Lab., 56 37th Ave., Woodside 77, New York.

Calc. for $C_7H_{12}N_4S$: C, 45.65 H, 6.46 N, 30.44

Obtained: C, 45.95 H, 6.55 N, 30.51

(ii) Oxidation of Ketone 4-Substituted Semicarbazones.

The 4-phenyl- and 4-benzylsemicarbazones employed as substrates in the lead tetra-acetate oxidations were prepared by the general method of Borsche and Merkwitz (123,124) in which the semicarbazones are heated with the appropriate amine:

$$R_1R_2)C{=}N{-}NHC(=O)NH_2 \xrightarrow{R_3NH_2} R_1R_2)C{=}N{-}NHC(=O)NHR_3$$

In an alternative synthesis, 4-phenylsemicarbazide hydrochloride can be reacted with the desired ketone in one step. Such an approach was attempted in the synthesis of benzophenone and p,p'-dimethylbenzophenone 4-phenylsemicarbazones. It was abandoned as a general method in view of the disappointing yields, and contamination of the product with the corresponding ketazine.

(a) Preparation of 5,5-Dimethyl-2- Benzylimino - Δ^3-1,3,4-Oxadiazoline

Acetone 4-Benzylsemicarbazone

Acetone semicarbazone was prepared by the standard method of Cheronis and Entrikin (125). The reaction of 32 g of acetone with 1.1 equivalents of semicarbazide hydrochloride and sodium acetate in aqueous

medium gave, after filtering and drying, 56.3 g (89%) of acetone semicarbazone as a chalky, white solid, m.p. 183-185° (lit. (124) m.p. 187°). In the amine displacements, acetone semicarbazone prepared in this way was used without further purification. Wilson's modification (126) of the method of Borsche was used for the benzylamine reaction. Acetone semicarbazone (20.0 g, 0.17 mole) was added in one portion to 37.2 g (0.35 mole) of benzylamine (Eastern, reagent) that had been heated to reflux in a 500 ml, 3-necked flask equipped with magnetic stirrer and condenser. The large flask accommodated the vigorous evolution of ammonia that ensued. After continued reflux for five minutes, the flask was cooled, 40 ml of alcohol was added, and the dark-brown solution was poured into one liter of a 10% acetic acid-ice mixture. The resulting white precipitate was filtered by suction, washed until free of amine with 10% acetic acid, and then with water until the washings were no longer acidic. Recrystallization from ethanol gave, as a first crop, 13.3 g (32%) of N,N'-dibenzylurea, m.p. 166-167° (lit. (126) m.p. 167°). Concentration of the filtrate gave white needles of acetone 4-benzylsemicarbazone, 6.0 g (17%), m.p. 111-112° (lit. (126) m.p. 113°).

5,5-Dimethyl-2- Benzylimino - Δ^3-1,3,4-Oxadiazoline

The procedure followed in the oxidation of the carbohydrazones of dialkyl ketones was used. During the addition of 4-benzylsemicarbazone (6.0 g, 0.029 mole) to a solution of 20.0 g (0.045 mole) of lead tetra-acetate, a precipitate of white lead diacetate was observed, but no

yellow colour developed. The colourless methylene chloride solution obtained on work up gave a faintly-yellow oil with a characteristic odour. Recrystallization from petroleum ether gave 1.5 g (25%) of 5,5-dimethyl-2- benzylimino -Δ^3-1,3,4-oxadiazoline as white needles m.p. 38-39°. The yield was lowered by the belated discovery that the solid sublimes readily at room temperature. The molecular weight found by vapour pressure osmometry was 204 (M.W. calc. 203).

Analysis. Calc. for $C_{11}H_{13}N_3O$: C, 65.00 H, 6.45 N, 20.68

Obtained: C, 65.14 H, 6.28 N, 20.54

(b) Preparation of 5,5-Dimethyl-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

Acetone 4-Phenylsemicarbazone

This compound was prepared by the same procedure as that for 4-benzylsemicarbazone, except that a large excess of aniline was used. The reaction of 20.0 g of acetone semicarbazone with 100 ml of refluxing aniline gave 10.0 g (30%) of acetone 4-phenylsemicarbazone, m.p. 154-155.5 (lit (123) m.p. 155-156°). In this case, the crude product was dried, and extracted with chloroform. Evaporation of the chloroform, and recrystallization from ethanol gave the desired compound. The insoluble residue was N,N'-diphenylurea.

5,5-Dimethyl-2- Phenylimino -Δ^3-1,3,4-Oxadiazoline

Acetone 4-phenylsemicarbazone (10.0 g, 0.052 mole) was oxidized with lead tetra-acetate (34.8 g, 0.078 mole) at 0° in methylene chloride by the usual procedure.

The precipitation of lead diacetate was rapid at 0°, and the solution gradually became lemon-yellow in colour. After work up, the evaporation of the brilliant-yellow methylene chloride solution gave a light orange oil. One recrystallization from petroleum ether-chloroform gave yellow needles of the Δ^3-1,3,4-oxadiazoline, m.p. 72-73°, that weighed 9.6 g (95%). The molecular weight found by vapour pressure osmometry was 183 (M.W. calc. 189).

An analytical sample was prepared by two further recrystallizations from petroleum ether-chloroform.

Calc. for $C_{10}H_{11}N_3O$: C, 63.47 H, 5.86 N, 22.21

Obtained: C, 63.69 H, 5.82 N, 22.20

(c) Preparation of 5,5-Diphenyl-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

Benzophenone 4-Phenylsemicarbazone

The condensation of 4-phenylsemicarbazide hydrochloride with benzophenone in aqueous ethanol solution was used to synthesize this compound.

4-Phenylsemicarbazide hydrochloride was prepared by the method of Borsche and Merkwitz (123). The chalky, white, acetone 4-phenylsemicarbazone, obtained from the reaction of 20.0 g (0.17 mole) of acetone semicarbazone with aniline, was heated on a steam bath for one hour

with 200 ml of dilute HCl (15 ml conc. acid in 100 ml of solution). After filtration of the insoluble diphenylurea, the dark-brown solution was reduced in volume by rotary evaporation on a steam bath, and allowed to crystallize. 4-Phenylsemicarbazide hydrochloride separated in glistening, white plates, m.p. 213-214° (lit. (123) m.p. 214°). Concentration of the filtrate gave two further crops, for a combined yield of 16.8 g (52.8%). In a larger scale preparation, the reaction of 80.0 g of acetone semicarbazone gave a total of 69.9 g (55%).

To a solution of benzophenone (Eastman; 20.0 g, 0.11 mole) in 300 ml of ethanol was added a solution of 4-phenylsemicarbazide hydrochloride (20.6 g, 0.11 mole), and sodium acetate (16.0 g, 0.20 mole) in 50 ml of water. On heating under reflux for 12 hours, the solution gradually became deep-yellow in colour, and a fine, white precipitate formed. Filtering while hot, and then cooling, gave a first crop of 7.0 g of white needles at this point. The filtrate was heated an additional 12 hours to give a further crop of 5.5 g of the semicarbazone on cooling. The combined yield was 12.5 g (36%).

Purification of the benzophenone 4-phenylsemicarbazone was made difficult by the co-crystallization of benzophenone azine produced by the thermal decomposition of the product in solution. Repeated recrystallization from ethanol-water gave material melting at 161-163° (lit. (124) m.p. 163°). However, solutions of this material in either ethanol or methylene chloride remained pale-yellow, indicating that ketazine was still present.

5,5-Diphenyl-2- Phenylimino -Δ^3-1,3,4-Oxadiazolines

The lead tetra-acetate oxidation procedure for the diaryl-ketone 4-phenylsemicarbazones was based on that used for the carbohydrazones of arylketones.

Benzophenone 4-phenylsemicarbazone (5.0 g, 0.016 mole), in 50 ml of methylene chloride, was added dropwise to a stirred solution of lead tetra-acetate (10.6 g, 0.024 mole) in 250 ml of methylene chloride maintained at 0°. No precipitate, or change in colour of the solution was noted, so the temperature was raised to 30°. The solution gradually became yellow-orange in colour, and a white precipitate slowly formed over fifteen minutes. After 40 minutes the reaction was halted by the addition of 100 ml of distilled water. During the standard work up, it was noted that the aqueous and base washings had a light-violet colour. The methylene chloride extracts were reddish-orange in colour, and on evaporation gave a deep red oil.

The dark oil was dissolved in a minimum amount of chloroform, and diluted with 250 ml of petroleum ether (b.p. 30-60°). The resulting voluminous precipitate of brown, amorphous solid was filtered off, and the orange solution concentrated on a rotary evaporator until the yellow crystals of oxadiazoline separated. In this experiment, co-precipitation of benzophenone azine, derived from the starting material, necessitated extensive fractional recrystallization to obtain pure material.

Repeated recrystallization from petroleum-ether chloroform gave bright-yellow prisms (1.0 g, 20%) of 5,5-diphenyl-2- phenylimino -Δ^3-1,3,4-oxadiazoline, m.p. 125-128° (decomp).

Calc. for:	$C_{20}H_{15}N_3O$	C, 76.66	H, 4.83	N, 13.41
Obtained:		C, 76.60	H, 5.11	N, 13.40

The dark-red oil, obtained by evaporation of the filtrate after removal of the oxadiazoline, had a sharp, penetrating odour, and a lachrymatory effect. Its N.M.R. spectrum ($CDCl_3$) had two singlet absorptions at 8.13 τ, and at 8.11 τ, (total rel. area 3) in addition to a multiplet centred at 2.82 τ. (rel. area 13). This suggested incorporation of at least one acetyl function per remaining semicarbazone residue. The infrared spectrum of the residue had peaks at 5.64 μ and at 5.73 μ, but showed no NH absorption.

(d) Preparation of 5,5-Di-(p-tolyl)-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

Preparation of p,p'-Dimethylbenzophenone 4-Phenylsemicarbazone

The reaction of aniline with the semicarbazone prepared from p,p'-dimethylbenzophenone was used to prepare this compound.

p,p'-Dimethylbenzophenone (Eastman Rgt., 20.0 g, 0.094 mole) was reacted with 21.0 g (0.189 mole) of semicarbazide hydrochloride and 15.5 g (0.189 mole) of sodium acetate in 200 ml of ethanol, and sufficient water to dissolve all the reactants at reflux. After heating on a steam bath for 15 hours, the solution was filtered to remove a fine, white precipitate, cooled and diluted with 200 ml of water. The yellow oil produced was recrystallized from ethanol-water once to give 22.3 g (90%) of p,p'-dimethylbenzophenone semicarbazone, m.p. 135-140° (lit. (127) m.p. 143-144°).

Once-recrystallized material had an infra-red spectrum indistinguishable from that of a purified sample, m.p. 140-142°; and was therefore employed directly in the aniline displacement reaction.

p,p'-Dimethylbenzophenone semicarbazone (22.3 g, 0.083 mole) added to 125 ml of refluxing aniline by the usual procedure, gave a light-yellow chalky solid, that was récrystallized twice from ethanol-water to give 24.9 g of p,p'-dimethylbenzophenone 4-phenylsemicarbazone as white needles, m.p. 175-178°. A sample recrystallized once more had m.p. 177-178°. The compound was characterized by its infra-red absorptions (CCl_4) at 2.93 μ and 5.92 μ, and by its N.M.R. absorptions. It shows singlet methyl absorptions at 7.65 τ and at 7.70 τ (total 6H) and a multiplet centred at 2.83 τ (13H, aromatic protons). In these derivatives the NH protons do not seem to give sharp absorptions and have not been identified.

5,5-Di-p-tolyl-2- Phenylimino -Δ^3-1,3,4-Oxadiazoline

The oxidation of 20.3 g of p,p'-dimethylbenzophenone 4-phenyl-semicarbazone, by the same method as that described for the unsubstituted benzophenone derivative, gave 9.83 g (49%) of large, yellow prisms from petroleum ether/chloroform.

After four recrystallizations, an analytical sample had a decomposition point of 103-105°C (red melt, gas evolved). Analyses were obtained on the sample from two analysts: (a) Daessle (b) Bernhardt.

Calc. for $C_{22}H_{19}N_3O$:		C, 77.39	H, 5.61	N, 12.31
Obtained:	(a)	C, 77.42	H, 5.09	N, 12.83
	(b)	76.39	5.54	12.41

(e) Preparation of 5,5-Di-(p-chlorophenyl)-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

Preparation of p,p'-Dichlorobenzophenone

At the time of these investigations, p,p'-dichlorobenzophenone was not available in economical quantities from commercial suppliers. It was therefore synthesized by the Friedel-Crafts reaction of chlorobenzene and carbon tetrachloride, and subsequent hydrolysis of the diaryldichloromethane produced (128).

A two liter, 3-necked flask was equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a dropping funnel. Carbon tetrachloride (Mallinkrodt Rgt; 77.7 g, 0.5 mole), aluminium chloride (Baker, Rgt; 135.0 g, 1.0 mole), and 400 ml of carbon disulphide (Fisher Cert. Rgt.) were placed in the flask, and chlorobenzene (Fisher Cert. Rgt., 111.5 g, 1.0 mole) was added dropwise with stirring at room temperature. A deep-red complex formed immediately. After stirring for 12 hours at room temperature, the mixture was refluxed gently on a steam bath for three hours.

Attempted hydrolysis by a slow, dropwise addition of water to the cooled mixture resulted in a vigorous, delayed evolution of HCl that expelled part of the contents of the flask. It is advised that the mixture be poured over crushed ice with vigorous stirring.

The remaining solvent was allowed to evaporate, and 200 ml of water was added to hydrolyse the aluminium chloride. After the addition of 250 ml of chloroform, the mixture was filtered; the chloroform layer was separated, dried, evaporated , and the resultant red oil slowly poured into 50 ml of conc. sulphuric acid.

After the vigorous evolution of gas ceased, the dark-brown solution was poured into one liter of an ice-water mixture. The white precipitate was filtered, washed with water by decantation until free of acid, and dried to give 187 g (74.5%) of a mixture of 2,4'-dichlorobenzophenone and p,p'-dichlorobenzophenone. Extraction with petroleum ether (b.p. 30-60°) removes the 2,4'-dichlorobenzophenone. The residue was recrystallized from ethanol-water to give 64.9 g (25.2%) of p,p'-dichlorobenzophenone, m.p. 145° (lit. (128) m.p. 145°).

Preparation of p,p'-Dichlorobenzophenone 4-Phenylsemicarbazone

A solution of 25.0 g (0.098 mole) of p,p'-dichlorobenzophenone, and 22.3 g (0.20 mole) of sodium acetate in 500 ml of ethanol was heated under reflux for 15 hours. After cooling and diluting with an equal volume of water, 4,4-dichlorobenzophenone semicarbazone was obtained as fine, light-brown crystals, m.p. 190-192 (lit. (127) m.p. 191.5-192.5). The yield was 29.5 g (93%). This material was used in the aniline displacement without further purification.

The reaction of 29.5 g of p,p'-dichlorobenzophenone semicarbazone with 150 ml of refluxing aniline gave 34.0 g (98.4%) of yellow-brown crystalline material that was insoluble in ethanol. Recrystallization from 300 ml of boiling $CHCl_3$ gave dense, colourless, rhombic crystals, m.p. 230-231° (73.5% recovered). The material turns yellow on exposure to light.

Preparation of 5,5-Di-(p-chlorophenyl)-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

The standard oxidation procedure previously described for benzophenone-4-phenylsemicarbazone was modified to accommodate the sparing solubility of the dichloro compound in methylene chloride.

A solution of 20.0 g (0.052 mole) of p,p'-dichlorobenzophenone 4-phenylsemicarbazone in 350 ml of methylene chloride was added over 10 minutes to a solution of 34.6 g (0.078 mole) of lead tetra-acetate in 200 ml of methylene chloride that had been cooled to 0°. The mixture was allowed to react at 30° for one hour, and then worked up in the usual fashion.

Since the red oil obtained as the crude product could not be induced to crystallize, it was chromatographed on Florisil (5x10 cm column). Rapid elution with large volumes of petroleum ether was necessary, as the material slowly decomposed on the column.

Concentration of the brilliant-yellow eluant gave a light yellow solid that was an approximately 1:1 mixture of p,p'-dichlorobenzophenone, and the desired product (I.R. spectrum). Fractional crystallization from petroleum ether gave 4.0 g (20%) of fine pale-yellow needles, m.p. 105-110° (decomp.).

Analysis Calc. for $C_{20}H_{13}N_3OCl_2$:	C, 62.85	H, 3.40	N, 11.00
Obtained:	C, 62.35	H, 3.54	N, 10.57

(f) Preparation of 5,5-Di-(p-anisyl)-2- Phenylimino - Δ^3-1,3,4-Oxadiazoline

Preparation of p,p'-Dimethoxylbenzophenone

This compound was prepared by the condensation of anisic acid and anisole catalysed by chloroacetic anhydride, using a modification of the method of Unger (129). When the reaction of 0.1 equivalent quantities was carried out in a bomb reactor at 170° as prescribed by Unger, the apparently exothermic reaction caused the interior temperature to rise rapidly to 210°. Only charred material was recovered from this attempt. However, the reaction proved to be more manageable at 150° and 1 atm.

Anisic acid (M.C.B. Pract; 15.2 g, 0.10 mole), anisole (Eastern Pract; 10.8 g, 0.10 mole), and chloroacetic anhydride (Baker Pract; 34.2 g, 0.2 mole) were placed in a 125 ml, 2-necked flask that was equipped with a thermometer, and a reflux condenser with calcium chloride drying tube. On heating to 150° in an oil bath, the slurry liquified to a light-brown melt that slowly darkened as the reaction proceeded. The temperature of the flask contents rose to 154°, and then subsided to the bath temperature over a period of 15 minutes. Heating was continued for three hours. After cooling, the dark-brown oil was poured slowly with stirring into 250 ml of saturated sodium carbonate solution. After the evolution of gas ceased, the solution was extracted with ether. The ether extracts were dried, evaporated, and the brown, crystalline residue recrystallized from ethanol to give 14.2 g (66.7%) of

p,p'-dimethoxybenzophenone, m.p. 140-142 (lit. (130) m.p. 143-144°) with an infra-red spectrum (K Br wafer) identical with that in the literature (131). The yield in a duplicate run was 53%.

Preparation of p,p'-Dimethoxybenzophenone 4-Phenylsemicarbazone

The reaction of 25.5 g of p,p'-dimethoxybenzophenone with two equivalents of semicarbazide hydrochloride and two equivalents of sodium acetate in 300 ml of 80% ethanol at reflux for 48 hours gave a reddish-yellow oil on dilution with water. The extended reaction time was shown to be necessary by examining 5 ml aliquot samples at 12 hour intervals. The semicarbazone of this unreactive ketone has not been described in the literature.

In the present study, the crude product was dissolved in chloroform, and the solution was washed with water, dried and evaporated to give 23.0 g of a reddish oil that could not be induced to crystallize. Strong infra-red absorptions at 2.98 μ and 5.95 μ indicated that it probably contained a high concentration of the desired product. Therefore, it was reacted directly with 125 ml of refluxing aniline in the usual manner. After two recrystallizations, from petroleum ether-chloroform in this case, 16.3 g (41.2% based on ketone) of p,p'-dimethoxybenzophenone 4-phenylsemicarbazone was obtained as white needles m.p. 195-195.5°.

This compound was characterized by its infra-red absorptions ($CHCl_3$) at 2.97 μ and 5.95 μ, and by its N.M.R. spectrum ($CDCl_3$) which showed two singlets at 6.20 and at 6.26 τ (6H, CH_3O) and a complex multiplet centred at 2.75 τ (13H).

Preparation of 5,5-Di-(p-anisyl)-2- Phenylimino -Δ^3-1,3,4-Oxadiazoline

The oxidation of p,p'-dimethoxybenzophenone 4-phenylsemicarbazone (7.2 g, 0.02 mole) with 12.9 g (0.03 mole) of lead tetra-acetate at 30° followed the procedure established for benzophenone 4-phenylsemicarbazone.

The light-yellow crystalline material obtained from the petroleum ether extraction of the crude product was shown to be approximately a 1:1 mixture of the desired oxadiazoline, and p,p'-dimethoxybenzophenone. Fractional crystallization from petroleum ether, in which the ketone is more soluble, gave 1.05 g (14.5%) of yellow prisms, m.p. 91-93° (decomp., red melt).

The unsatisfactory elemental analyses obtained on this derivative are attributed in large measure to its thermal instability. Kinetic studies (this work) have shown that it decomposes with a half-life of 14.5 min. at 49°. However, since the results bracket the calculated value, they do not suggest a change in molecular formula.

Calc. for $C_{22}H_{19}N_3O_3$:	C, 70.76	H, 5.13	N, 11.25
Obtained:	C, 71.61	H, 4.87	N, 10.96
	68.94	5.24	10.93

(iii) Chemical Reactions of Δ^3-1,3,4-Oxadiazoline Derivatives.

(a) Catalytic Reduction

The hydrogenation of the Δ^3-1,3,4-oxadiazolines derived from several of the ketone carbohydrazones, and from acetone 4-benzylsemicarbazone followed the same experimental procedure. Accordingly, only

the reduction of the compound obtained from acetone carbohydrazone will be discussed in detail.

Reduction of 5,5-Dimethyl-2-Isopropylazino-Δ^3-1,3,4-Oxadiazoline

To a light-yellow solution of 0.980 g of the title compound in 200 ml of ethanol in a 500 ml pressure hydrogenation bottle was added 0.588 g of 5% palladium/charcoal catalyst (M.C.B.). The solution was shaken under a pressure of 48 p.s.i. of hydrogen at room temperature for three hours.

The mixture was filtered twice, and the colourless filtrate was evaporated to give 0.733 g (74.8%) of light-grey powder, whose infra-red spectrum in chloroform was identical to that of acetone carbohydrazone. After one recrystallization from ethanol the material had m.p. 160° (lit. (119) m.p. 160°).

Reduction of 5-Ethyl-5-Methyl-2-(2-Butylazino)-Δ^3-1,3,4-Oxadiazoline

Reduction of 0.786 g of this compound gave 0.680 g (81.5%) of a white powder whose N.M.R. and I.R. spectra were identical with those of 2-butanone carbohydrazone. A recrystallized sample (0.2 g) had m.p. 110-113° (lit. (119) m.p. 110-113°).

Reduction of 5,5-Diphenyl-2-Diphenylmethylazino-Δ^3-1,3,4-Oxadiazoline

Reduction of 0.206 g of this compound gave 0.156 g (75.7%) of crude benzophenone carbohydrazone as a clear oil, with an infra-red

spectrum (CCl_4) identical with that of an authentic sample. Recrystallization from CCl_4 gave white needles (93 mg) of benzophenone carbohydrazone, m.p. 224-225°.

Reduction of 5,5-Dimethyl-2- Benzylimino - Δ^3-1,3,4-Oxadiazoline

Reduction of 0.300 g of this oxadiazoline gave 0.275 g (91.4%) of white, powdery acetone 4-benzylsemicarbazone having an infra-red spectrum superimposable with that of an authentic sample.

(b) Reduction with Lithium Aluminium Hydride

Reduction of 5,5-Dimethyl-2-Isopropylazino- Δ^3-1,3,4-Oxadiazoline

Lithium aluminium hydride (0.33 g, 8.8 m mole) was dissolved in 200 ml of absolute ether (sodium-dried) in a 500 ml, 3-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser with attached $CaCl_2$ drying tube. The dropwise addition of the oxadiazoline derivative (1.442 g, 8.6 m mole) in 75 ml of absolute ether at room temperature caused the immediate formation of a yellow complex.

The mixture was refluxed for 12 hours, cooled to room temperature, and saturated sodium sulphate solution added dropwise with stirring until gas evolution ceased, and the grey solid separated cleanly from solution.

Evaporation of the dried ether layer gave only a minor amount (0.100 g) of a white solid that was not identified.

Acetone carbohydrazone was recovered by drying the solid residue in the reaction flask, and extracting it 3 times with boiling chloroform. Evaporation of the extracts gave a total of 0.979 g (61.1%) of a clear, colourless oil whose infra-red spectrum was the same as that of authentic acetone carbohydrazone. After recrystallization from ethanol-water, the yield was 0.423 g (30%).

Reduction of 5-Ethyl-5-Methyl-2-(2-Butylazino)-Δ^3-1,3,4-Oxadiazoline

The reduction of this compound (1.244 g, 6.4 m mole) with a large excess of lithium aluminium hydride (0.48 g, 12.8 m mole), gave, after evaporation of the dried ether layers , 0.997 g (80%) of slightly yellow oil.

The complex N.M.R. spectrum of this material in CCl_4 indicated it was a mixture. A white solid that separated from the N.M.R. sample was identified by its own infra-red and N.M.R. spectrum as the 1.5-di-(2-butyl)carbohydrazide, $[CH_3(C_2H_5)CHNHNH]_2C{=}O$. With this information, it was possible to resolve the N.M.R. spectrum of the crude product in terms of a 30:70 mixture of 2-butanone carbohydrazone, and the further reduced 1,5-di-(2-butyl)-carbohydrazide.

Attempts to crystallize further quantities of the carbohydrazide from the reduction product were unsuccessful. It was suspected that the material was being air oxidized during the attempted recrystallizations from CCl_4 - petroleum ether.

Reduction of 5,5-Diphenyl-2-Diphenylmethylazino-Δ^3-1,3,4-Oxadiazoline

A solution of 0.400 g (0.96 m mole) of this derivative was heated at reflux in ether for 12 hours with a large excess of lithium aluminium hydride (0.095 g, 2.53 m mole). Extraction of the crude product with petroleum-ether gave 0.192 g of recovered starting material. The residue gave 98 mg of benzophenone carbohydrazone, m.p. 223-225°, having an I.R. spectrum superimposable with that of an authentic sample. This represents a yield of 52%, based on the material actually reduced.

(c) Hydrolysis Attempts

Hydrolysis of 5,5-Dimethyl-2-Isopropylazino-Δ^3-1,3,4-Oxadiazoline

A qualitative examination of the hydrolysis of this oxadiazoline derivative was made in both acidic and basic methanolic solution. The approximately 0.5 N solutions were prepared by dissolving the calculated amount of conc. HCl, or KOH in 200 ml of stock methanol.

A solution of 0.3 g of the derivative in the methanolic base was light yellow. On heating under reflux, the colour slowly faded over a one hour period. The solution was cooled, neutralized with dilute sulphuric acid (phenolphthalein indicator) and evaporated to dryness at room temperature. The totally water-soluble, faint-pink solid had an infra-red spectrum (KBr wafer) that showed broad absorptions at 6.1 μ and at 2.9-3.1 μ that were similar to those in the spectrum of carbohydrazide. No further investigation of this material was undertaken.

An initially light-yellow solution of 1.0 g of the oxadiazoline derivative in methanolic acid solution also slowly became colourless when heated under reflux for one hour. After cooling and rotary evaporation of the solvent, the residual solid was dried under vacuum. Soxhlet extraction with absolute ether for 12 hours gave only small amounts (90 mg) of unidentified oily residue.

The infra-red spectrum (KBr) of the solid had broad ammonium salt absorption at 2.9-4.2 μ, but no strong carbonyl absorption near 6.0 μ. Its N.M.R. spectrum in D_2O showed only one broad absorption (5.8τ), and was unchanged on addition of water.

The primary purpose of these studies had been to elucidate the structure of the lead tetra-acetate product of acetone carbohydrazone. Since these hydrolytic reactions seemed to lead to extensive degradation of the molecule, they were not further investigated.

Hydrolysis of 5,5-Diphenyl-2-Diphenylmethylazino-Δ^3-1,3,4-Oxadiazoline

A qualitative study of the acid hydrolysis of this derivative was undertaken.

A brilliant-yellow solution of 0.1 g of the compound in 15 ml of ether that had been saturated with p-toluenesulphonic acid monohydrate, was allowed to stand at room temperature for two hours. During this time, the colour gradually faded and a white precipitate formed in the solution. After filtration, the ether extracts were washed with saturated sodium bicarbonate and water; dried, and evaporated to give a

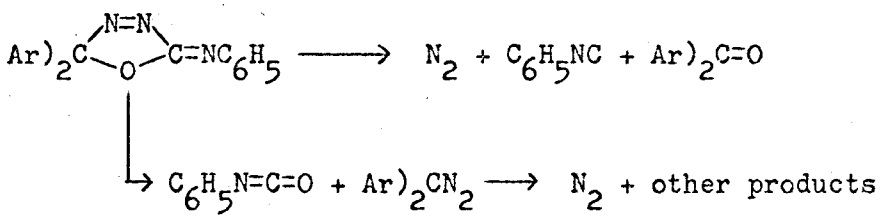
clear, colourless oil. Its I.R. spectrum ($CHCl_3$) had the same absorptions as a reference spectrum of benzophenone. The separated white solid showed a broad salt-like absorption in the infra-red (KBr wafer) at 2.9-4.0 μ. When it was dissolved in saturated sodium acetate solution, a white precipitate formed that was identified (I.R.-KBr) as benzophenone hydrazone. Identical treatment of benzophenone carbohydrazone led to the formation of a white precipitate in the acidic ether solution that also gave benzophenone hydrazone on neutralization. The ether solution was again shown to contain benzophenone by infra-red examination.

II. Thermal Decomposition of 5,5-Diaryl-2-Phenylimino-Δ^3-1,3,4-Oxadiazolines

(i) Kinetic Studies

(a) General

The thermal decomposition of the Δ^3-1,3,4-oxadiazolines, described in this work, leads to the production of one mole of nitrogen gas through two competing processes. One of these processes yields nitrogen directly, at least without the intervention of a long-lived intermediate. The other process involves the formation of a diaryldiazomethane which then decomposes at a measurable rate. These reactions are summarized below:



The kinetic methods employed in the study of the thermal decomposition reactions have been chosen in the light of the proposed mechanism above. Accordingly, both the rate of gas evolution, and the change in diaryldiazomethane concentration with time, have been investigated. In this general section, the experimental conditions which have remained constant throughout the two studies are considered.

In each set of experiments, the reaction vessel containing the bulk of the solvent was thermally equilibrated, prior to introduction of the sample, in a stirred thermostatted bath (Fisher Inhibited Bath Oil).

The temperature of the oil was controlled by means of a 150 watt light bulb that was connected through a relay to a thermoregulator (Magna-Set T260; Precision Thermometer and Instrument Co.). The temperature of the bath did not vary from day to day at a given regulator setting within the limits ($\pm 0.1^{\circ}$) of the thermometer used. An Anschutz thermometer that had been calibrated by the Physical Chemistry Laboratory of the National Research Council of Canada was employed.

The light bulb was wrapped with 2 layers of aluminium foil before immersion, to prevent irradiation of the reaction vessel. A wooden bath covering with suitable apertures cut for introduction of the necessary apparatus excluded the greatest proportion of light from the laboratory.

In both kinetic methods, chlorobenzene (Fisher Certified Reagent, Eastern Reagent) was used as the solvent.

At the outset of the work, the solvent was further purified by shaking with several portions of conc. sulphuric acid until the initially faint-yellow discolouration was no longer observed. After washing with several portions of water, bicarbonate solution, and then water again; the solvent was dried over anhyd. calcium chloride and distilled. Distillation from P_2O_5 gave a center cut that was strongly acidic (extract with an equal volume of water had pH 2). Therefore, material actually used was the middle fraction, b.p. 131.5-132.5°, obtained by distillation after drying with $CaCl_2$ alone, and rejecting the initial azeotrope. A strong tendency towards emulsification at all stages of the extraction procedure results in poor recovery by this method.

No systematic variation was noted among the results from individual gas evolution experiments that had employed solvent: (i) purified by acid-wash, (ii) purified by one passage through a 1 x 20 cm activated alumina column, or (iii) taken directly from the bulk supply. It was concluded that the reaction was not measurably sensitive to remaining solvent impurities. Hence, chlorobenzene chromatographed once on activated alumina was employed in the latter stages of the work on the 5,5-di-p-substituted compounds.

Material taken from the same sample of each Δ^3-1,3,4-oxadiazoline was used in both the gas evolution and infra-red spectrometric experiments. In each case kinetic samples were stored at freezer temperatures until required.

(b) Gas Evolution Techniques

The gas evolved in the thermolysis reaction was measured in a conventional gas burette at a constant pressure of one atmosphere, maintained by a manually adjusted mercury reservoir (Fig. 1). Thermostatted water from a constant temperature bath (Labline Inc., Chicago Ill., cat. No. 3052) was circulated through the burette jacket. The vacuum line manifold, and connecting sections to the reaction flask and burette were fashioned from capillary tubing to reduce the non-thermostatted volume, and were wrapped with glass wool to minimize temperature fluctations.

The design of the reaction vessel has been described and illustrated in a report by J. Warkentin (132). Basically, it consisted of a 50 ml flask (effective volume) fitted with a top-driven magnetic stirrer, and a

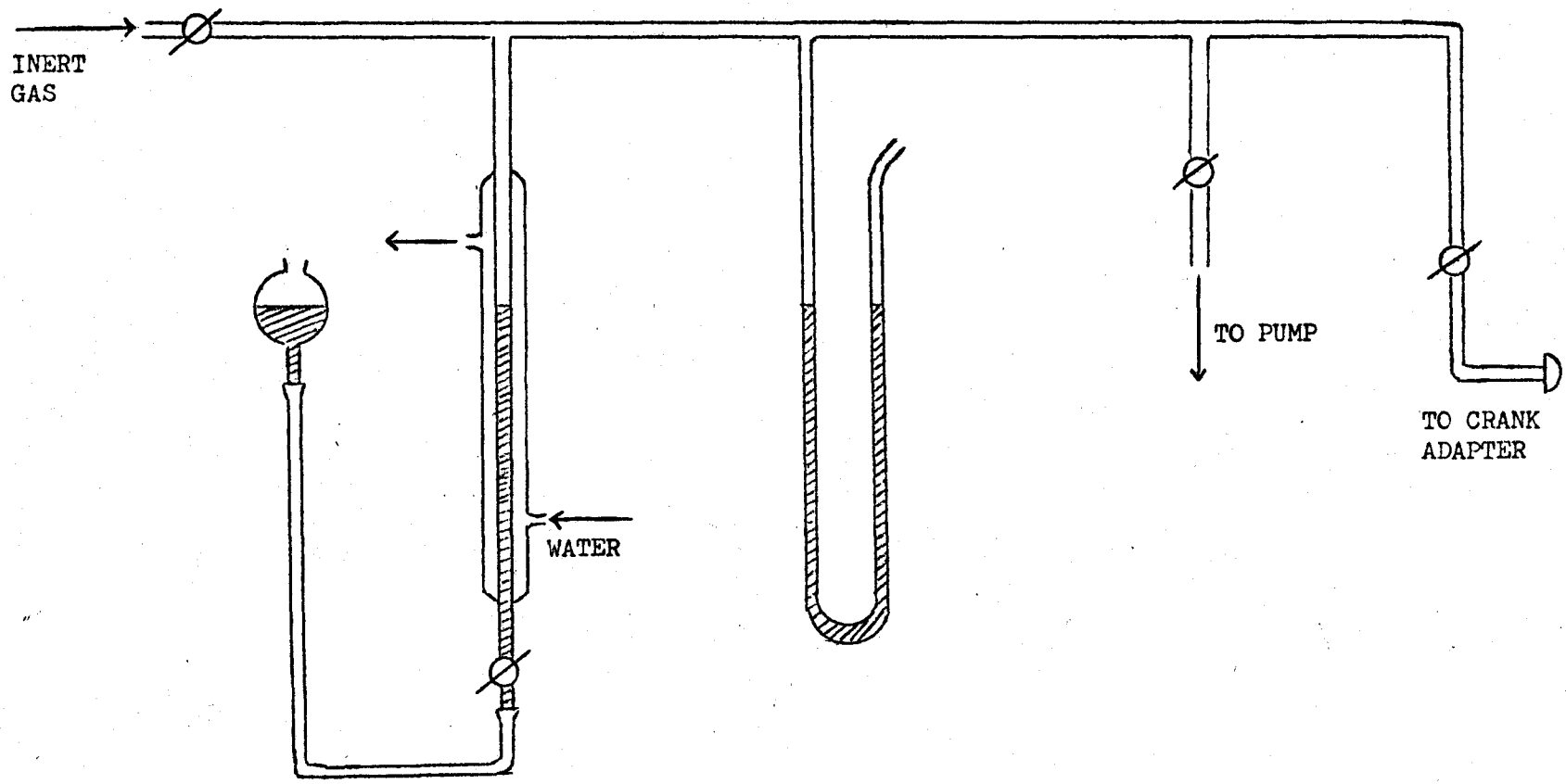


Fig. 1. Apparatus for Kinetic Measurements by Gas Evolution

capillary inlet that had a rubber septum for sample injection. A capillary outlet was attached to the measurement line by means of a crank-type adapter fitted with ball-joint connections. The desired volume of solvent (50 ml) was introduced into the flask, and the sealed unit connected to the vacuum line. The solvent is degassed by conventional freeze-thaw cycles while outside the bath, filled to near one atmosphere with an inert gas, and then conveniently introduced into the heating bath by rotation of the crank.

After thermal equilibration, the pressure of the system was adjusted to one atmosphere. The oxadiazoline sample was dissolved in the minimum amount of chlorobenzene, and injected directly into the rapidly stirred solution using a syringe with 6 inch needle. Readings were taken by slightly reducing the pressure in the system using the leveling bulb, and noting the time and volume when the manometer again indicated one atmosphere.

Careful recovery and weighing of the residue in the syringe and sample preparation flask allowed calculation of the amount of material injected, and hence the theoretical V^{∞} value. The evolution of gas was usually followed to greater than 90% of reaction.

In initial experiments, the inert gas introduced into the line was purified grade nitrogen that had been passed through a gas purification train of the Fieser type (133). When it became apparent that oxygen had no gross effect on the thermolyses (as shown by the infra-red studies performed with air present), a purified grade of argon (Canada Liquid Air; O_2 spec. 10 ppm) was used without further treatment.

The solutions in all the experiments were stirred at 2000 r.p.m. to prevent supersaturation of the chlorobenzene with nitrogen. The stirrer speed was calibrated by marking the shaft, and viewing it in the light from a stroboscopic frequency measuring device (Strobotac).

(c) Infra-red Spectroscopic Studies

The rate of formation and disappearance of the diaryldiazomethane intermediate in the thermolysis of the Δ^3-1,3,4-oxadiazolines was obtained by recording the change in the intensity of the characteristic, isolated diazo absorption near 2040 cm^{-1} in the infra-red spectrum.

In outline, the experimental approach consisted of the removal and dry-ice cooling of aliquots of a thermolysis reaction mixture at known times. The infra-red spectra of these samples were then recorded directly in solution, using chlorobenzene as the reference solvent. The decomposition reaction was carried out in the presence of the atmosphere to allow convenient, frequent sampling, and rapid quenching. Since a relatively high concentration of the intermediate is necessary for infra-red analysis, the limited amounts of highly purified starting materials available legislated the use of a small volume of solution. The use of visible spectroscopy is complicated by the formation of other unidentified coloured products absorbing in the same region as diphenyldiazomethane.

In detail the kinetic procedure was as follows: The chlorobenzene solvent (5-10 ml) was transferred by pipette into a tightly-stoppered, 20 x 200 mm test tube that was partially immersed in the heating bath, and allowed to thermally equilibrate. The oxadiazoline was dissolved in the minimum quantity of solvent and injected by syringe directly into the

equilibrated liquid. In order to calculate the initial concentration, the volume injected was noted, and the residue in the syringe and sample flask was recovered and weighed. The solution was vigorously shaken to ensure thorough mixing and rapid thermal equilibration, all the while being kept in the heating fluid. Aliquots of the reaction mixture (0.1 ml) were transferred by dropper pipette into test tubes that were at dry ice temperature. The time (±0.03 min., estimated) of the sampling operation was noted. The reaction was monitored until the concentration of diazomethane had fallen to about 10% of its maximum value, (20 to 30 points).

The infra-red diazo absorption of each sample was traced at least twice on a Perkin Elmer 521 instrument using sodium chloride solution cells (chlorobenzene reference). The molarity of the sample was obtained by comparing the average height of the peak traces with a calibration curve established from the absorpions of standard solutions of the diaryldiazomethane.

Such a simplified procedure introduces a number of possible errors in the measurements. A gradual concentration change resulting from solvent loss in the system could occur. However, at a point in the reaction when the primary decomposition processes are complete, the infra-red absorption of phenyl isocyanate at 2270 cm^{-1} should reach a constant, maximum value. In the latter stages of the reaction the phenyl isocyanate absorbtion does remain constant, indicating concentration changes are negligible.

Thermal equilibrium might not be expected to be reached as quickly or maintained as well in this simple system as in the gas evolution experiments. In a control experiment in which the temperature of the equilibrated solvent in the test tube was measured, it was shown that the temperature dropped less than two degrees when the amount of solvent used for a sample was injected. The temperature rose to within 0.5° of the bath temperature in less than a minute.

However, the best assessment of the possible errors in this study lies in the degree of success obtained in comparing results from the two methods of measurement. The total of the gas evolved and the diazomethane in solution was found to approach a constant value near 100 mole per cent (Results and Discussion, page 151). If gross errors in temperature or concentration are involved in either experiment, this correlation would not be observed.

Preparation of Diaryldiazomethanes

The diaryldiazomethanes used to establish the concentration calibration curves were synthesized by the oxidation of the corresponding ketone hydrazones with mercuric oxide (134).

Preparation of Diphenyldiazomethane

Benzophenone hydrazone was prepared by the method of Cohen (121), described on page 58 of this thesis.

A mixture of 10.0 g (0.051 mole) of benzophenone hydrazone, 27.0 g (0.123 mole) of yellow mercuric oxide (Baker Rgt.), 5 ml of

ethanol saturated with potassium hydroxide, and 11.5 g of anhydrous sodium sulphate, in 200 ml of anhydrous ether, was placed in a 500 ml pressure bottle. The bottle was stoppered, and shaken for one hour. The reaction mixture was filtered, and then evaporated at room temperature to give a dark-red oil. The oil was dissolved in petroleum ether (b.p. 30-60°), filtered again, and induced to crystallize by dry-ice cooling. Two subsequent recrystallizations from petroleum ether were accomplished by cooling at ice temperature. Diphenyldiazomethane (6.5 g, 65.7%) was obtained as red needles, m.p. 30-31° (lit. (135) m.p. 29°).

Preparation of 4,4'-Dimethyldiphenyldiazomethane

The hydrazones of substituted benzophenones were prepared by the method of Szmant et al (136), except that absolute alcohol was substituted for 95% alcohol.

A solution of 4,4'-dimethylbenzophenone (27.4 g, 0.13 mole) in 150 ml of absolute alcohol was heated under reflux for 12 hours in a 500 ml flask. The flask was equipped with a soxhlet extractor containing 20 g of freshly crushed calcium oxide. The reflux condenser on the extractor was protected with a calcium chloride drying tube.

After half of the solvent had been distilled, the residue was filtered while hot, and allowed to crystallize. One recrystallization from alcohol/water gave 23.4 g (80%) of fluffy, white needles, m.p. 104-107° (lit. (137) m.p. 108-110°) that yellowed on exposure to light.

The oxidation of 14.9 g (0.066 mole) of this hydrazone with 40.1 g (0.184 mole) of yellow mercuric oxide for 4 hours gave 4.1 g

(28%) of 4,4'-dimethyldiphenyldiazomethane as dense, violet, rhombic crystals. After three recrystallizations from petroleum ether, material used in the infra-red measurements softened at 98-100°, and melted at 100-101.5° (lit. (135) m.p. 100-101°).

Preparation of 4,4'-Dichlorodiphenyldiazomethane

4,4'-Dichlorobenzophenone hydrazone was again prepared by the method of Szmant (136). The reaction of 25.1 g of 4,4'-dichlorobenzophenone gave 22.3 g (84%) of fine, rhombic crystals, m.p. 86-89° (lit. (136) m.p. 91-93°) after one recrystallization from alcohol/water. This hydrazone also yellows in light.

Oxidation of 9.3 g of 4,4-dichlorobenzophenone hydrazone with mercuric oxide for 5 hours at room temperature gave 4.6 g (50%) of 4,4'-dichlorodiphenyldiazomethane as fine red needles which softened at 90-97° and melted at 97-98.5° (lit. (135) m.p. 70°). Under these conditions unreacted dichlorobenzophenone hydrazone is also recovered.

This material had a molar extinction coefficient (infra-red 2040 cm^{-1}) nearly the same as the other derivatives, and showed no NH absorption. It is believed that the literature melting point is in error.

(ii) Product Studies

In investigating the thermal decomposition of the Δ^3-1,3,4-oxadiazolines, the main emphasis has been on the products of the two primary processes. The end products of the thermolysis, that arise by further reaction of the initially formed species in solution were not of immediate interest; and their quantitative isolation has not been pursued. Instead, investigation of the components of the reaction mixture after 50% gas evolution has been given more attention.

Investigation of Products after Partial Reaction

In a typical reaction designed for product study, a weighed amount (0.2 g) of 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline was decomposed in 50 ml of chlorobenzene under the usual gas evolution conditions. When 50% of one equivalent of gas had been evolved, the reaction flask was cooled rapidly in a dry-ice/acetone mixture, and the dark, orange-red solution transferred to a distillation apparatus. After removal of the solvent at room temperature (1 mm), a pasty, red solid was obtained. Its infra-red spectrum (CCl_4), had sharp single absorptions at 2270 cm^{-1} (phenyl isocyanate), 2125 cm^{-1} (phenyl isonitrile), 2042 cm^{-1} (diphenyldiazomethane), 1655 cm^{-1} (benzophenone), as well as at 1706 cm^{-1} (undecomposed Δ^3-1,3,4-oxadiazoline). The products, tentatively assigned in this way, were further identified as follows.

(i) Phenyl isocyanate. The addition of a drop of aniline to the infra-red sample solution resulted in the disappearance of the absorption at 2270 cm^{-1}. When a petroleum ether solution of the residue that no

longer contained unreacted oxadiazoline, was heated with a drop of aniline; and then cooled, white needles of N,N'-diphenylurea were formed. The diphenylurea, formed by the reaction of aniline and phenyl isocyanate was identified by comparison with an authentic sample obtained from the displacement reaction of aniline on acetone semicarbazone (page 66, this Thesis). In a quantitative experiment, the decomposition of 184 mg of 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline in 50 ml of chlorobenzene containing 1 ml of added aniline, led to the recovery of 77 mg (124%) of diphenylurea after complete reaction. The predicted yield (60.2 mg) is based on the rate constant obtained for the retro-addition process, $1.45 \times 10^{-3} sec^{-1}$. Since the recovery is based on unrecrystallized material identified by infra-red, the high value is attributed in part to impurity.

(ii) Phenyl Isocyanide. A sample of this material was prepared by the hydrolysis of excess chloroform with alcoholic potassium hydroxide in the presence of aniline (138). The yellow reaction mixture, containing precipitated salt, was washed with water, saturated oxalic acid solution (to remove aniline), and then with water again. The dried chloroform layer was evaporated to give phenyl isocyanide as a yellow oil. Its infra-red spectrum (CCl_4) had an intense single peak at the same frequency (2125 cm^{-1}) as the absorption observed in the thermolysis mixture. Particularly convincing evidence for the assignment was the same penetrating, malevolent odour of the decomposition residue and the synthetic sample.

(iii) Diphenyldiazomethane. The dark red oil, obtained by evaporating the petroleum ether-soluble portion of the residue was dissolved in the minimum amount of chloroform, and placed on a short 2 x 4 cm column of neutral alumina. When rapidly eluted with 100 ml of petroleum ether under air pressure, a violet band was quickly discharged from the column to give a violet solution of diphenyldiazomethane. Decomposition was minimized by the short contact time possible with such a non-equilibrium approach. After two such chromatographies, the yield of diphenyldiazomethane having an infra-red spectrum (CCl_4) indentical with that of an authentic sample was 71% (based on concentration expected at 11.0 minutes in light of later kinetic studies).

At the time these exploratory experiments were done, the diazomethane was further characterized by its visible absorption at 530 mu (lit. (135) 526 mu), and by its thermal decomposition in dilute CCl_4 solution to give benzophenone (in the presence of air).

(iv) Benzophenone. After the removal of the coloured diphenyldiazomethane band from the neutral alumina chromatographic column, described in section (iii) above, elution with an additional 200 ml of petroleum ether gave a clear oil on evaporation, with an infra-red spectrum (CCl_4) superimposable with that of authentic benzophenone. In one experiment, the crude yield was 140 mg from the decomposition of 339 mg for 11.0 minutes, or 83%. The calculation is based on a rate constant of $1.48 \times 10^{-3}_{sec}{}^{-1}$ for the direct decomposition reaction.

(v) Recovery of Starting Material. When the residue obtained after distillation of the chlorobenzene was dissolved in petroleum ether, yellow crystals separated from the solution. Before recrystallization, the material from the reaction of 339 mg for 11.0 minutes weighed 56 mg (117%) and had an infra-red spectrum the same as 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline in all but minor detail. The yield is based on a rate constant for disappearance of starting material of $2.93 \times 10^{-3} sec^{-1}$.

Infra-red spectra of the residues obtained from the decomposition of the 5,5-di-p-chlorophenyl- and 5,5-di-p-totyl derivatives to 50% gas evolution also showed the presence of diarylketone, phenyl isocyanide, phenyl isocyanate and diaryldiazomethane. The relative magnitudes of the observed absorptions varied as predicted by the later kinetic studies on the effect of the para substituents.

A qualitative study of the reactivity of these two derivatives was carried out by recording the infra-red spectra of samples from carbon tetrachloride solutions maintained at 60°. The spectra showed the expected absorptions for the two processes. The height of the isocyanate and isocyanide peaks were in a 2.6:1.0 ratio for the methyl-substituted compound, while the same ratio was 0.34:1.0 for the di-p-chloro compound, after 4 hours. These observations were in accord with the trends predicted by the kinetic studies.

Products After Complete Reaction

In experiments employing the 5,5-di-p-chlorophenyl-,5,5-di-p-tolyl-, and 5,5-diphenyl compounds, the dark-red solutions remaining after gas evolution had ceased were cooled, and the solvent distilled at room temperature. Infra-red spectra ($CHCl_3$) of the dark-red, pasty residues were recorded in each case.

The spectra of all three residues had their most prominent infra-red absorptions at positions corresponding to peaks in the related benzophenone spectrum. In particular, the carbonyl absorptions near 1666 cm^{-1} were identified. A peak at 2270 cm^{-1} (phenyl isocyanate) was observed in all cases but was strongest in the spectrum of the di-p-tolyl-compound. The diaryldiazomethane absorption near 2040 cm^{-1} was no longer observed. The characteristic odour of phenyl isocyanide was apparent, although only a small absorption at 2125 cm^{-1} was observed. The odour of this compound permeates the recovered chlorobenzene, indicating that the isocyanide is at least partially lost in the distillation.

An absorption at 2008 cm^{-1} was observed in the spectra of the 5,5-di-p-tolyl-, and 5,5-diphenyl derivative residues. Attempts to isolate the materials exhibiting this absorption were unsuccessful.

In the case of the residue from the unsubstituted compound, chromatography on 1:1 celite/charcoal, or on neutral alumina proved unsuccessful. On handling solutions of the residue in non polar solvents in air, the peak at 2008 cm^{-1} gradually disappeared from the spectrum.

A petroleum ether solution of the residue was washed with cold, dilute HCl, water, and then dried and evaporated. After this treatment, the material aborbing at 2008 cm^{-1} in the I.R. was no longer present in the residue, indicating that it is readily hydrolysed.

It was suspected that the material was the ketenimine produced by the reaction of phenyl isocyanide with the diarylcarbene arising from the diaryldiazomethane.

(iii) Methods of Calculation

A preliminary investigation of the data derived from infra-red spectroscopic experiments, and gas evolution studies is described in the Results and Discussion, pages 144-155.

In determining the rate constants of the reactions, a conventional first order rate law (139) has been applied in one of the following forms:

(i) $\log_e \frac{a}{a-x} = kt$

where x = conversion at time t

a = initial concentration

k = first order rate constant

(ii) $\log_e \frac{C_\infty}{C_\infty - C_t} = kt$

where C_∞ = concentration of product at complete reaction

C_t = concentration of product at time t.

Form (ii), valid when the product is proportional to the starting material consumed, has been employed in the trial plot of the gas evolution data (Fig. 2, page 146). In the determination of the total

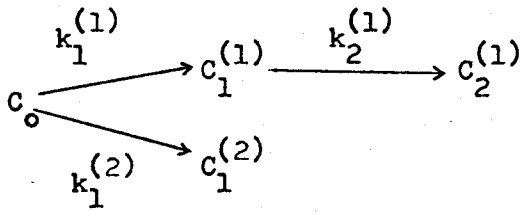
first-order rate constant for disappearance of starting material, (Fig. 4, page 153), form (ii) is also employed using $V_{\infty}^{N_2} = C_{\infty}$. The assumption was made that all the diazomethane decomposes to give nitrogen.

Form (i) of the rate law was employed in determining the rate of diazomethane decomposition in the latter stages of experiments followed by infra-red spectroscopy. In this case, the initial concentration was taken as the diazomethane still present after effective disappearance of the starting material.

In the special case of the 5,5-di-p-methoxy-Δ^3-1,3,4-oxadiazoline, where only retro-1,3-dipolar addition is observed, form (ii) of the rate law was also used. C_{∞} was taken as the theoretical maximum concentration of p,p'-dimethoxydiphenyldiazomethane, and C_t as the concentration at time t by infra-red measurement.

However, in the other decompositions where both parallel first order reactions are significant, an expression for the maximum concentration of diaryldiazomethane was obtained that allowed isolation of the two rate constants.

Rodigiun et al (140) have obtained the general solutions of such parallel and consecutive reactions. Using their notation the processes involved in the thermolysis of the oxadiazolines can be described as follows.



where C_o^o = Initial concentration of oxadiazoline

C_o = Oxadiazoline concentration at time t

$C_1^{(1)}$ = Diazomethane concentration at time t

$C_2^{(1)}$ = Nitrogen evolved from diazomethane

$C_1^{(2)}$ = Nitrogen evolved directly.

The rate equations for the diazomethane producing process are as follows:

$$\frac{d\,C_o}{dt} = -k_1^{(1)}C_o - k_1^{(2)}C_o \qquad [57]$$

$$\frac{d\,C_1^{(1)}}{dt} = -k_2^{(1)}C_1^{(1)} + k_1^{(1)}\,C_o \qquad [58]$$

$$\frac{d\,C_2^{(1)}}{dt} = k_2^{(1)}C_1^{(1)} \qquad [59]$$

The solutions obtained by Rodguin are given in equations [60-62].

$$C_o = C_o^o\, e^{-a_1 t} \qquad a_1 = k_1^{(1)} + k_1^{(2)} \qquad [60]$$

$$C_1^{(1)} = C_o^o \frac{k_1^{(1)}}{k_2^{(1)} - a_1} \left[e^{-a_1 t} - e^{-k_2^{(1)} t} \right] \qquad [61]$$

$$C_2^{(1)} = C_o^o \frac{k_1^{(1)}}{a_1} \left[1 + \frac{1}{-a_1 + k_2^{(1)}} \left(k_2^{(1)} e^{-a_1 t} - a_1 e^{-k_2 t}, \right) \right] \qquad [62]$$

If the expression for the diazomethane concentration (equation [61]) is written in a reduced form by substituting:

$$\beta = \frac{C_1^{(1)}}{C_o^o} = \frac{[\text{Diazomethane}]}{[\text{Oxadiazoline}]}_{\text{Initial}} t$$

and $K = \frac{k_2^{(1)}}{k_1^{(1)} + k_1^{(2)}}$, $\mathcal{E} = \frac{k_1^{(1)}}{a_1}$, and $\tau = a_1 t$.

Then equation [61] becomes:

$$\beta = \frac{\mathcal{E}}{K-1} \left[e^{-\tau} - e^{-K\tau} \right] \qquad [63]$$

The maximum concentration of diazomethane is given by:

$$\beta_{max} = \frac{\mathcal{E}}{K-1} \left[e^{-\tau_{max}} - e^{-K\tau_{max}} \right] \qquad [64]$$

By differentiating equation [63] with respect to τ one obtains:

$$\tau_{max} = \frac{1}{K-1} \log_e K \qquad [65]$$

By substitution:

$$\beta_{max} = \mathcal{E} \times K \left[\frac{K}{1-K}\right] \left[\frac{k_2^{(1)}/a_1}{1-k_2^{(1)}/a_1}\right] \qquad [66]$$

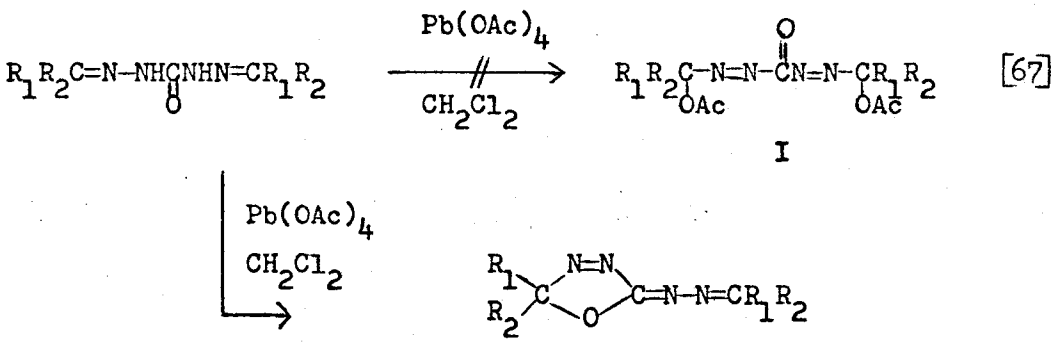
$$= \frac{k_1^{(1)}}{a_1} \left[\frac{k_2^{(1)}}{a_1}\right]$$

The application of this relation to the determination of the rate constants is examined in the Results and Discussion section, pages 155-162.

RESULTS AND DISCUSSION

General

In undertaking the lead tetra-acetate oxidation of ketone carbohydrazones, the original expectation was that an azoacetate, I, shown in equation [67], might be isolated at low temperature. Precedant for the formation of such products stems from the discovery of azoacetates as either intermediates or final products in oxidations of substituted hydrazones of ketones, as reviewed in the Historical Introduction of this thesis. The major products recovered in the



I

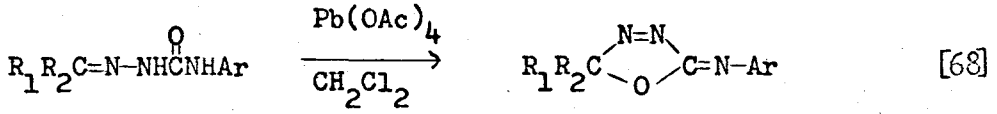
II

[67]

$R_1 = R_2 = CH_3$
$R_1 = CH_3$ $R_2 = C_2H_5$
$R_1 = CH_3$ $R_2 = C_6H_5$
$R_1 = C_6H_5$ $R_2 = C_6H_5$

oxidation of the ketone carbohydrazones, however, have been shown to be the Δ^3-1,3,4-oxadiazolines II. An extension of the reaction to the

semicarbazones shown in equation [68], has provided the series of 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines, IIA, whose thermal decomposition is the basis of the second portion of this discussion.



$$R_1R_2C{=}N{-}NHCNHAr \xrightarrow[CH_2Cl_2]{Pb(OAc)_4} R_1R_2C\begin{matrix}N{=}N\\ \diagdown\ \diagup\\ O\end{matrix}C{=}N{-}Ar \qquad [68]$$

IIA

Prior to the examination of these results, it is objective of this discussion to rigorously establish the structural assignments II and IIA. Evidence for the cyclic nature of the products is cited first, followed by detailed argument excluding cyclic isomers.

I. Cyclization of Ketone Carbohydrazones and Semicarbazones

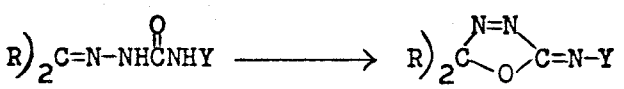
(i) Heterocyclic Nature of Oxidation Products.

An examination of spectroscopic and analytical evidence leads to the conclusion that the products are monomeric, oxidatively-cyclized materials differing in molecular formula from the substrates by only two hydrogens. Elemental analyses, particularly in the case of the more thermally stable derivatives, are in close agreement with the calculated values. Similarly molecular weight measurements obtained by vapour pressure osmometry agree with the proposed molecular formulae. Mass spectrometric examination of the oxidation product of acetone 4-phenylsemicarbazone (M.W. 191), employing a low ionizing voltage (11 e.v.), shows a molecular ion at the predicted m/e value, 189.

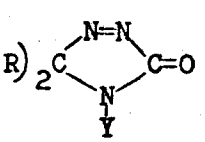
The infra-red spectra of the derivatives show no absorption in the region 3200-3500 cm^{-1}, where the starting materials have an N-H band. In addition, absorptions at 1740 and 1225 cm^{-1}, characteristic of an acetoxy group, are not observed. Absence of acetyl or acetoxy substitution is definitely shown by the N.M.R. spectra. In the alkyl derivatives the high field signals are readily interpreted in terms of ring and side-chain substituents, while the oxidation products of the aryl-substituted semicarbazones of diaryl ketones show no protons above 2.8 τ.

Facile reduction of the oxidation products to the original semicarbazone or carbohydrazone, in high yield under mild conditions, seems compatible only with structures in which no fragmentation or rearrangement has occurred in the oxidation step. The stoichiometry of the thermal decomposition reactions is likewise readily accommodated only by a monomeric, cyclic structure.

It is evident that ring closure could involve the formation of either a carbon-oxygen or a carbon-nitrogen bond. The two resultant



IIB

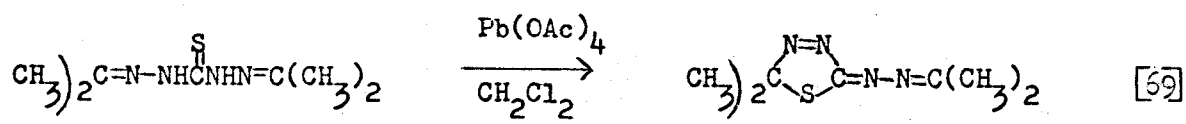


III

R = alkyl, aryl

Y = C_6H_5, $C_6H_5CH_2$, -N=C(R_2

heterocycles, the Δ^{1}-1,2,4-triazolin-3-one, III, and the Δ^{3}-1,3,4-oxadiazoline, IIB, are related as lactam and lactim isomers, respectively. Correct assignment of structure then depends on careful analysis of the spectroscopic evidence and chemical behaviour of the oxidation products. As will be noted in the subsequent discussion the spectroscopic differences expected between the lactim and lactam functional groups are not striking, and a fine choice of model compounds is necessitated. The corresponding open-chain compounds, the amide-imide isomers are rapidly interconverted in a tautomeric equilibrium well known to favour the amide form. Indeed a preliminary assignment of structure favoured the Δ^{1}-1,2,4-triazolin-3-one alternative (141). However, subsequent oxidation of acetone thio carbohydrazone (eq. [69]) gave a sulphur analogue in which easier distinction between C=S and C=N in the infra-red, along with other evidence, allows assignment of structure IIC. In the light of this result, re-examination of the literature for more exact spectral models led to conclusive assignment of the Δ^{3}-1,3,4-oxadiazoline structure for the oxygen systems. In the subsequent discussion, the infra-red, ultra-violet, N.M.R., mass spectrometric, and chemical evidence substantiating

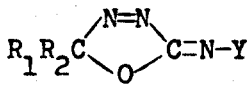


IIC [69]

these structures will be reviewed in turn.

TABLE I

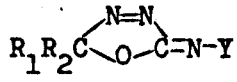
Infra-Red Absorptions of 2-Imino-Δ^3-1,3,4-Oxadiazolines



				Assignment				
				Stretching Modes		Skeletonal		
	R_1	R_2	Y	C-H $\mu(cm^{-1})$	C=N- $\mu(cm^{-1})$	(i) $\mu(cm^{-1})$	(ii) $\mu(cm^{-1})$	(iii) $\mu(cm^{-1})$
1	CH_3	CH_3	$(CH_3)_2C=N-$	3.32 (3012) 3.40 (2941)	5.99 (1669)	8.17 (1224)	8.83 (1133)	10.14 (986) 10.39 (962)
2	CH_3	C_2H_5	$CH_3(C_2H_5)C=N-$	3.35 (2985) 3.40 (2941)	5.99 (1669)	8.29 (1206)	8.79 (1138)	10.42 (960) 10.72 (942)
3	CH_3	C_6H_5	$CH_3(C_6H_5)C=N-$	3.26 (3067) 3.40 (2941)	6.01 (1664)	8.32 (1202)	9.71 (1030) 10.44 (952)	13.11 (763) 14.44 (692)
4	C_6H_5	C_6H_5	$(C_6H_5)_2C=N-$	3.28 (3046)	6.02 (1661)	8.33 (1200)	9.57 (1045) 9.78 (1022)	13.31 (751) 14.44 (692)
5	CH_3	CH_3	$(C_6H_5)_2C=N-$	3.28 (3046)	5.97 (1675)	8.12 (1232)	8.82 (1134)	10.34 (970) 10.51 (952)
6	CH_3	CH_3	$CH_2C_6H_5$	3.31 (3018) 3.47 (2879)	5.83 (1715)	8.14 (1229)	8.82 (1134)	10.14 (986) 10.56 (943)
7	CH_3	CH_3	C_6H_5	3.32 (3009) 3.23 (3093)	5.89 (1698)	8.17 (1224)	8.96 (1116)	10.19 (981) 10.51 (952)
8	C_6H_5	C_6H_5	C_6H_5	3.26 (3067)	5.86 (1706)	8.65 (1156)	9.59 (1043) 9.81 (1021)	11.08 (901)
9	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	3.31 (3024) 3.43 (2918)	5.91 (1698)	8.69 (1151)	9.64 (1037) 9.84 (1016)	10.89 (917)

TABLE I CONT'D.

Infra-Red Absorptions of 2-Imino-$\Delta^3$1,3,4-Oxadiazolines



				Assignment				
				Stretching Modes		Skeletonal		
	R_1	R_2	Y	C-H $\mu(cm^{-1})$	C=N- $\mu(cm^{-1})$	(i) $\mu(cm^{-1})$	(ii) $\mu(cm^{-1})$	(iii) $\mu(cm^{-1})$
10	p-ClC_6H_4	p-ClC_6H_4	C_6H_5	3.28 (3066)	5.90 (1701)	8.80 (1136)	9.57 (1047) 9.84 (1017)	10.99 (909)
11	p-$MeOC_6H_4$	p-$MeOC_6H_4$	C_6H_5	3.41 (2936) 3.51 (2851)	5.90 (1701)	8.68 (1152)	9.72 (1029) 9.92 (1008)	10.91 (916)
12	CH_3	CH_3	CH_3 (a)		5.81 (1721)			
13	$(CH_3)_2C$ (N=N) S C=N-N=$C(CH_3)_2$			3.34 (2982)	6.17 (1621)		10.41 (961) 14.91 (671)	

(a) Value obtained by A. M. Cameron.

(ii) Spectral Properties of Δ^3-1,3,4-oxadiazolines.

Infra-red.

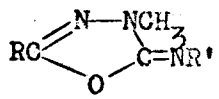
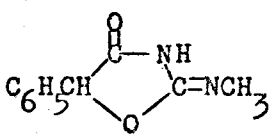
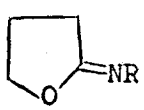
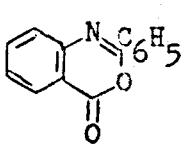
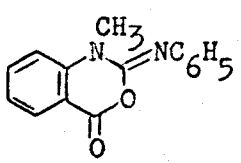
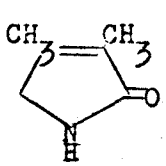
Characteristic infra-red absorptions observed in the spectra of the Δ^3-1,3,4-oxadiazolines derived from both carbohydrazones and semicarbazones are given in Table I. As noted previously, a common feature of the spectra is a lack of absorption in the carbonyl region above 1715 cm^{-1}, or in the carbon-oxygen stretching region at 1225-1250 cm^{-1}. Acetoxy substitution is thus excluded. No absorption above 3075 cm^{-1} is indicative of the absence of either NH or OH groups in the compounds as well.

The assignment of the intense absorptions observed in the 1660-1715 cm^{-1} range is of particular importance in distinguishing the possible lactam (triazolinone), and lactim (oxadiazoline) isomers. In the oxadiazoline structure, these bands are assigned to the C=N stretching frequency.

A certain ambiguity in assignment of these absorptions is introduced by the fact that α,β-unsaturated lactams, such as example 9, Table II, exhibit a carbonyl band near 1680 cm^{-1}. However, it is well known that exocyclic C=N gives intense absorption in the same region, as shown by the other examples in Table II. Najer and co-workers have studied the infra-red spectra of oxazolones. N-alkylimino groups in such compounds (examples 1,4) absorb at 1700-1710 cm^{-1}, and N-arylimino groups (examples 2,3) at somewhat lower frequency. Other workers have reported exocyclic C=N absorptions of N-phenyl and N-cyclohexylimino butyrolactone (examples 5,6) in the same region. Kurihara and Yoda have

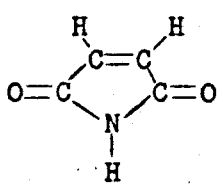
TABLE II

Infra-Red Model Compounds For Exocyclic C=N

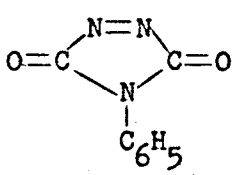
Example	Structure	C=N Frequency (cm^{-1})	Reference
			
1	R = C_6H_5, R' = CH_3	1710	(142)
2	R = C_6H_5, R' = C_6H_5	1660-1680	(143)
3	R = H, R' = C_6H_5	1675	(144)
4		1700	(145)
			
5	R = C_6H_{11}	1705	(146)
6	R = C_6H_5	1700	(147)
7		$\frac{C=N}{C=O}$ = 0.45	(148)
8		$\frac{C=N}{C=O}$ = 1.34	(148)
9		1680 (C=O)	(149)

observed that the imino stretching frequency becomes more intense relative to carbonyl when made exocyclic in the benzoxazines, examples (7,8). It is evident that the intense band near 1670 cm^{-1} in the infra-red spectra would be expected for a 2-imino-Δ^{3}-1,3,4-oxadiazoline structure.

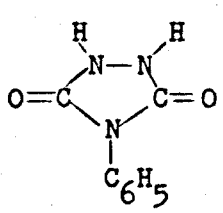
The alternative triazolinone isomer can be considered as the diaza analogue of an unsaturated lactam, and might also be expected to have carbonyl absorption near 1670 cm^{-1}. However, there is evidence that the presence of an alpha azo function raises the carbonyl stretching frequency in the same manner as the halo substituent in acid chlorides. For instance, although maleimide IV shows absorption at 1675 cm^{-1} (150), the Δ'-1,2,4-triazolin-3,5-dione V absorbs at 1780-1760 cm^{-1} (151). In contrast, the unoxidized precursor, 4-phenylurazole VI has a carbonyl band at 1687 cm^{-1} (152). Similarly cinnamamide, $C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}NH_2$ (ν CO 1666),



IV



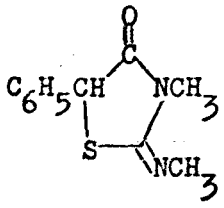
V



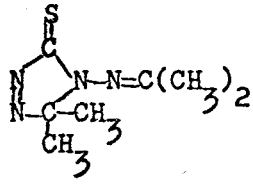
VI

absorbs at higher frequency than the nitrogen analogue phenylazocarboxamide (153), $C_6H_5N{=}N\overset{O}{\overset{\|}{C}}NH_2$ (ν C=O 1702). One would expect the "carbonyl" region absorption of the products to be at higher frequency than is observed, if they were Δ'-1,2,4-triazolinones rather than Δ^{3}-1,3,4-oxadiazolines.

More conclusive assignment is made possible by examination of the infra-red spectrum of the thio analogue prepared from acetone thiocarbohydrazone (Table I, 13). The strongest band in the infra-red spectrum of this compound occurs at 1621 cm^{-1}. Najer and co-workers (154) have also studied iminothiazalones such as VII, reporting the alpha-thio-N-alkylimino stretching frequency at 1621 cm^{-1}. An alternative triazolin-thione structure, VIII, for the oxidation product can be excluded in this



VII



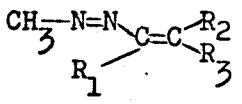
VIII

case on the basis of the absence of both a broad thioureide ($-\overset{S}{\overset{\|}{C}}-N<$) band at 1550-1475 cm^{-1}, and an intense C=S peak at 1025-1225 cm^{-1} that have been assigned in the thioamide spectrum (155). Indeed, the starting material in the oxidation, acetone thiocarbohydrazone, has strong absorption at 1470 and at 1235 cm^{-1}.

In examining other characteristic recurring bands in Table I, it is apparent that the absorption at 1130-1200 cm^{-1} is observed in all the compounds studied. Although assignment of absorptions in this region of the spectrum is difficult, persistence of this band in spite of varied ring substitution makes it likely that it is a characteristic ring vibration associated with the C-O-C linkage.

Electronic Absorption Spectra.

Discussion of the ultra-violet spectra of the oxadiazolines contained in Table III should be prefaced by a consideration of the difficulty encountered in the selection of model compounds. A survey of the literature reveals that no specific data are available on the spectra of representative Δ^3-1,3,4-oxadiazolines or Δ'-1,2,4-triazolin-3-ones, the two isomeric possibilities. Models, then, are restricted to carbon analogues of these heterocycles. Comparison of the ultra-violet spectra of dienes with their azo analogues is found in the studies of Hagarty (156) on diazabutadienes. He found that the absorption maxima of these compounds could be successfully correlated using Woodward's rules for diene substitution, at least for alkyl or hydrogen substituents. Hagarty



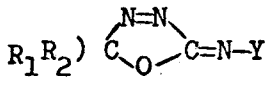
IX

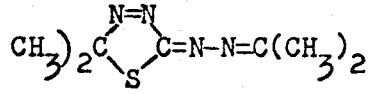
observed that the broad π-π^* absorption obscured the weaker n-π^* transition expected at higher wavelength for the azo linkage, in all but the mono-substituted case, (R_1=R_2=H_1 R_3=CH_3), where the π-π^* band occurs at lowest wavelength.

Good model systems for the Δ'-1,2,4-triazolin-3-one structure become available if the substitution of carbon for nitrogen is accepted. The α,β-unsaturated pyrrolidinones 1(a), (b), (c), 2, in Table IV show no absorption maxima above 240 mu. Comparison of models 1(c) and 3 shows that the delocalization through the lactam group is negligible compared to

TABLE III

Ultra-Violet Absorption Maxima of Δ^3-1,3,4-Oxadiazolines



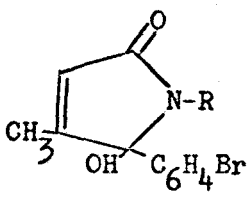
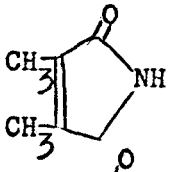
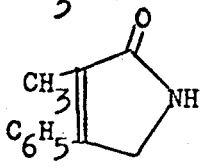
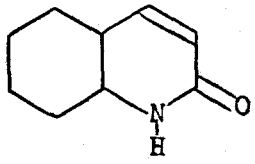
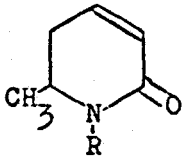
	R_1	R_2	Y	λmax (mu)	log ε	λmax (mu)	log ε	Solvent
1	CH_3	CH_3	$(CH_3)_2C=N-$	-	-	291	3.74	EtOH
2	CH_3	C_2H_5	$CH_3(C_2H_5)C=N-$	-	-	295	3.73	EtOH
3	CH_3	C_6H_5	$CH_3(C_6H_5)C=N-$	245	3.88	314	3.91	EtOH
4	C_6H_5	C_6H_5	$(C_6H_5)_2C=N-$	252	4.08	322	3.96	EtOH
5	CH_3	CH_3	$(C_6H_5)_2C=N-$	251	3.98	322	4.03	Hexane
6	CH_3	CH_3	$CH_2C_6H_5$	247	3.83	335	2.57	EtOH
7	CH_3	CH_3	C_6H_5	221	3.90	322	3.82	EtOH
8	C_6H_5	C_6H_5	C_6H_5	220	4.14	326 (357sh)	3.79	Hexane
9	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	224	4.30	325 (360sh)	3.82	Hexane
10	p-ClC_6H_4	p-ClC_6H_4	C_6H_5	226	4.54	329 (357sh)	3.85	Hexane
11	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	C_6H_5	230	4.38	324 (357sh)	3.81	Hexane
12	CH_3	CH_3	CH_3 (a)	248	3.99	345.0 336.8 332.5	1.60 1.52 1.52	Pentane " "
13				<210	3.97 (at 210)	335	3.67	Hexane

(a) Values recorded by A. M. Cameron.

TABLE IV

Ultra-Violet Absorptions of Model Compounds For

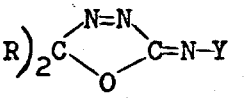
Δ'1,2,4-Triazolin-3-ones

	Model Compound	Absorption Maximum (mu)	Extinction Coefficient	Conditions	Reference
					
1	(a) R=H	(220-250) No Maximum	10,700-3,600	EtOH	157
	(b) $R=CH_3$	230	12,700	EtOH	157
	(c) $R=C_6H_5$	(230-280) No Maximum	16,800-3,000	EtOH	157
2		215-216	14,000	EtOH	158
3		258	15,000	EtOH	159
4		210	11,000	EtOH	160
					
5	(a) $R=C_2H_5$	250	1570	EtOH	161
	(b) $R=CH_3$		1000	EtOH	162

direct conjugation of a phenyl group with the double bond. Most authors report that α,β -unsaturated, six-membered lactams such as model 4 also have absorption maxima only at short wavelengths; but attention should be drawn to some contradictory values quoted for pyridones (model 5(a), (b)).

There is no doubt that the absorptions at markedly longer wavelength, 247-329 mu, exhibited by the oxidation products in this work render the Δ'-1,2,4-triazolin-3-one structure extremely unlikely. As well, the distinct bathochromic shift encountered on substituting further unsaturated groups on what would be a lactam nitrogen is in disagreement with the observations in the pyrrolidinone models.

On the other hand, the generalized oxadiazolinone structure, II, can be considered as a semicyclic diene in which the substituent Y



II

introduces further conjugation, and in which a beta alkoxy group may have an auxochromic effect. However, in view of the radical differences in the effect of substituents on shifting from butadiene to unsaturated carbonyl derivatives, calculation of an exact maximum in a system where three carbons have been replaced by more electronegative atoms can only be approximate. The bathochromic shift on substituting the beta alkoxy group in oxadiazoline 1, , Table III, with an R-S group in the thio analogue 13, is 44 mu. This represents a value intermediate to the difference in effect between beta OR and SR in enones (55 mu); and in

dienes (24 mu), quoted by Scott (163). If one accepts the auxochromic effect of the heteroatom substituents, the observed absorptions can be qualitatively accounted for in terms of the oxadiazoline structure employing a substituted diene model.

As an example consider the 2-phenylimino-Δ^3-1,3,4-oxadiazolines in Table III (Y= C_6H_5). Noting that trans-1-phenylbutadiene has λ max 280, (ε = 28,000) and allowing increments of 15 mu for constraint of the double bonds in the ring, and 25 mu for the auxochromic effect of the OR group, one arrives at a value of 320 mu. The observed π-π^* transition is in the range 322-329 mu for the 2-phenylimino compounds. It should also be noted that comparison of $C_6H_5N{=}NC_6H_5$ (trans; λ max = 319 mu) and $C_6H_5CH{=}CHC_6H_5$ (trans; λ max = 295 mu) indicates that substitution of an azo group for an ethylene group may result in a slight bathochromic shift (164).

Examination of the spectra in Table III indicates that the weak n-π^* absorption expected at longer wavelength for an azo-linkage is obscured by the more intense π-π^* band, in all but compounds 6 and 12. In these cases, the π-π^* transition is at sufficiently short wavelength to allow observation of the lower intensity peak. A shoulder at about 360 mu in the compounds 8-11 may also be caused by an n-π^* transition.

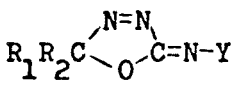
Nuclear Magnetic Resonance.

The position and relative area of the signals observed in the N.M.R. spectra of the oxadiazolines are recorded in Table V. Those values assigned to side-chain substituents in the carbohydrazone-derived compounds ($Y=R_1R_2C=N-$) correspond closely to the position of resonance in the starting materials. For instance, 5,5-dimethyl-2-isopropylazino $-\Delta^3$-1,3,4-oxadiazoline (compound 1, Table V) shows two singlets at 7.99-8.05 τ (6H), while the acetone carbohydrazone precursor has two singlets at 7.97-8.09 τ.

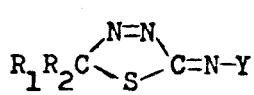
Oxadiazolines having methyl substituents on the ring in Table V absorb near 8.4 τ. A good model compound, 2-phenylazo-2-acetoxypropane (165) $CH_3)_2C(OAc)N=NC_6H_5$, shows a singlet corresponding to the isopropyl methyl groups at 8.38 τ. This correlation legislates against the alternative triazolinone structure in which a higher τ value might be expected; since the shielding constant for a beta OR group is greater than that for a beta NHR group(166). As well, the thiadiazoline analogue (compound 13, Table V) shows ring methyl absorption at 8.17 τ. This change in chemical shift is in good agreement with the difference in shielding constants for beta OR and SR groups established by Shoolery (166). On the other hand, little change in the chemical shift of the ring methyl signal on going from a Δ'-1,2,4-triazolinone to a Δ'-1,2,4-triazolinthione would be expected.

TABLE V

N.M.R. Proton Frequencies of Δ^3-1,3,4-Oxadiazolines



Compound	R_1	R_2	Y	Chemical Shift τ[a] Ring Substituents	Chemical Shift τ[a] Side-Chain Substituents
1	CH_3	CH_3	$(CH_3)_2C=N-$	8.38 s (6H)	7.99 (3H) 8.05 (3H)
2	CH_3	C_2H_5	$CH_3(C_2H_5)C=N-$	8.47 s (3H) 9.27 t (3H)	8.09 q - 8.10 s, 7.72 q (7H)
3	CH_3	CH_3	$(C_6H_5)_2C=N-$	8.38 s (6H)	2.2-2.8 m (10H)
4	CH_3	C_6H_5	$CH_3(C_6H_5)C=N-$	8.05 s (3H)	7.52 s (3H) 2.0-2.7 m (10H)
5	C_6H_5	C_6H_5	$(C_6H_5)_2C=N-$		2.2-2.9 m
6	CH_3	CH_3	$CH_2C_6H_5$	8.46 s (6H)	5.44 s (2H) 2.6 m (5H)
7	CH_3	CH_3	C_6H_5	8.38 s (6H)	2.2-2.8 m (5H)
8	CH_3	CH_3	CH_3	8.38 s (6H)[b]	6.81 s (3H)[b]
9	C_6H_5	C_6H_5	C_6H_5		2.5-3.0 m
10	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	7.68 s (6H)	2.2-3.1 (13H)
11	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$	C_6H_5	6.22 s (6H)	2.9 q/2.66 m (13H)
12	p-ClC_6H_4	p-ClC_6H_4	C_6H_5		2.6-3.0 m



13	CH_3	CH_3	$(CH_3)_2C=N-$	8.17 s (6H)	7.83 s (3H) 7.88 s (3H)

[a]Spectra recorded in $CDCl_3$ or CCl_4, tetramethylsilane internal reference.
[b]Values obtained from A. M. Cameron. (s=singlet, t=triplet, q=quartet, m=multiplet)

It has not been possible to analyse the complex N.M.R. spectra of the oxadiazolines bearing only aryl substituents. However, these spectra do confirm the absence of acetoxy groups as alluded to in the preliminary arguments for a cyclic structure. As well, the lack splitting of the N alkyl protons in compounds 6 and 8, Table V, supports the infra-red evidence that the hydrogens are lost from nitrogen in the oxidation step.

Mass Spectroscopy.

The results of mass spectrometric examination of the Δ^3-1,3,4-oxadiazolines are recorded in Table VI. The data for each compound is divided in terms of two possible modes of decomposition that can be represented in general form as follows:

Mode I

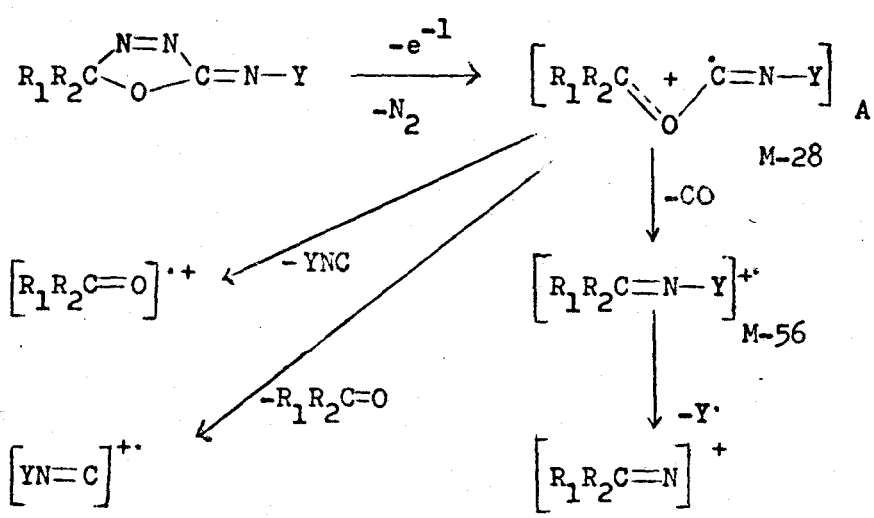


TABLE VI

Mass Spectra of Δ^3-1,3,4-Oxadiazolines

Δ^3-1,3,4-Oxadiazoline	Mode I[a] m/e Values				Mode II[a] m/e Values		
	$R_1R_2C{=}N{-}Y$	$R_1R_2C{=}O$	$YN{=}C$	Y	$R_1R_2CN_2$	R_1R_2C	$YN{=}C{=}O$
1. 5,5-Dimethyl-2-Isopropylazino	112	58(43)[b]	82(67)[b]	56(41)	70	42	98
2. 5,5-Diphenyl-2-Diphenylmethylazino	360(322) (283) (180)	182	206(205)	180	194	166(165) (152)	222(180)
3. 5,5-Dimethyl-2-Phenylimino	133(118)	58(43)	103	77	70	42	119(91)
4. 5,5-Dimethyl-2-Benzylimino	-	58(43)	117(116)	91	-	42	133(91)
5. 5,5-Diphenyl-2-Phenylimino	257(180)	182	103	77	-	166(165) (152)	119(91)
6. 5,5-Di-p-Chlorophenyl-2-Phenylimino[c]	325,327	250,252	103	77	264	232,236	119(91)
7. 5,5-Di-p-Methyl-2-Phenylimino[c]	285	210	103	77	222	194(179) (165)	119(91)

Spectra Recorded with Ionizing Voltage = 11 ev

8. 5,5-Dimethyl-2-Phenylimino — Molecular Ion (189), M-28(161), M-43(146) in addition to m/e values observed in 70 ev spectrum.

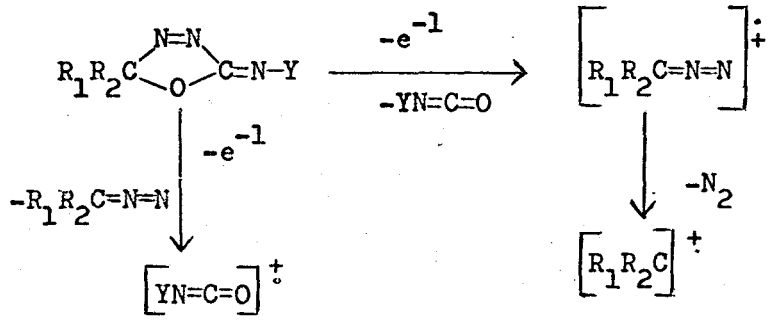
9. 5,5-Dimethyl-2-Benzylimino — M-28(175), M-43(160) in addition to m/e values observed in the 70 ev spectrum.

[a] Intense m/e values in the 70 ev spectra are assigned according to the two fragmentation schemes outlined on on page 121, and page 123.

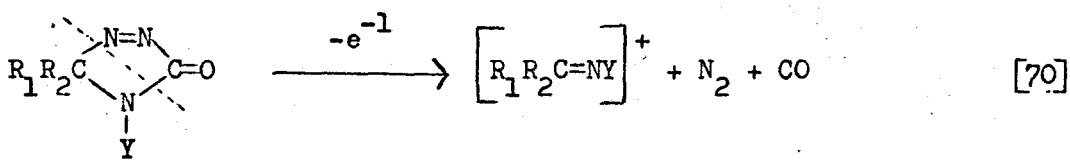
[b] Values in brackets refer to peaks assigned to further decomposition of the indicated fragment ion.

[c] "Mode I" peaks are much more intense than "Mode II" for oxadiazoline (6). The reverse is true for oxadiazoline (7).

Mode II

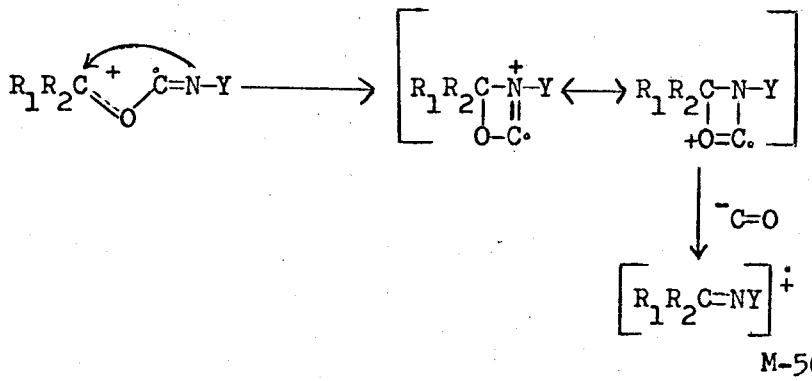


In the 70 e.v. spectrum of the oxadiazolines, the first peak in the high-mass region is the fragment ion resulting from the loss of 56 mass units. Initially, only the Δ'-1,2,4-triazolin-3-one structure was thought to be compatible with such a decomposition. Direct loss of nitrogen and carbon monoxide molecules yields an M-56 ion, as shown in equation [70] .



[70]

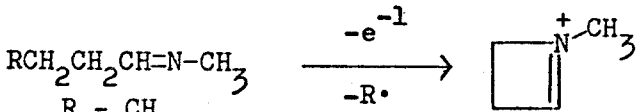
However, the decomposition of the initial M-28 ion in the proposed fragmentation of the oxadiazolines to yield an M-56 ion, as shown in equation [71], seems equally probable. A similar four-membered transition state has previously been invoked in both mass spectrometric and ground state processes. Studies by Djerassi and co-workers (167) of the mass spectra of azomethines prompt them to propose a four-membered



[71]

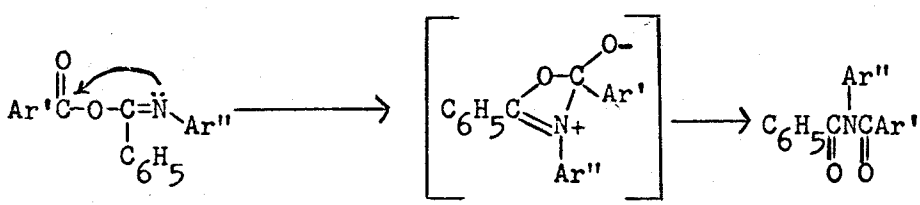
M-56

ion to explain the observed alkyl-group cleavage as shown in equation [72] .



[72]

A good ground state analogy for the intermediate ion and its subsequent reactions is found in the thermal rearrangements of arylisoimides in benzene or acetonitrile solution at 42°C (168), as shown in equation [73] .

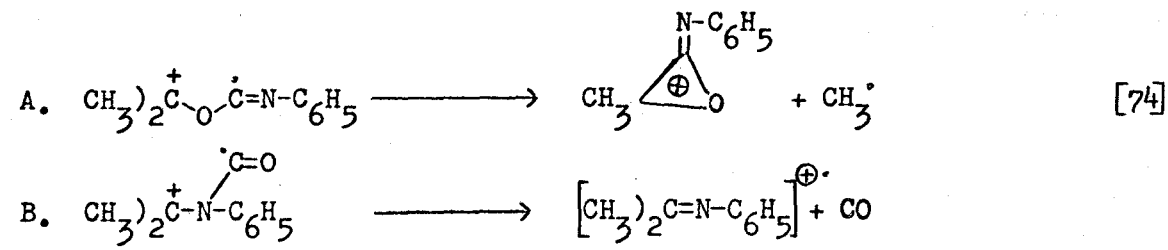


[73]

Indeed, in the absence of electron-withdrawing groups on Ar", the isoimides are too unstable to be isolated.

The 11 e.v. spectrum of 5,5-dimethyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline (compound 8 , Table VI) shows, in addition to a molecular ion, an M-28 peak as might be expected. Furthermore, the M-43 peak can be accommodated by loss of a methyl group from the fragment ion A in

equation [74] , whereas the alternative M-28 ion, B, from a Δ'-1,2,4-triazolin-3-one would be expected to lose carbon monoxide so readily as to exclude any competing methyl group fission.



[74]

Further comment on the interesting correlation between thermal and electron-impact induced fragmentation of the Δ^3-1,3,4-oxadiazolines will be made in connection with the discussion of the mechanism of the thermolysis.

(iii) Chemical Reactivity.

The thermal decompositions, catalytic and lithium aluminum hydride reductions, and hydrolysis of the oxidation products have been studied in relation to the structure assignment. As mentioned previously, these reactions have indicated a monomeric, cyclic structure. Both the reductions are ring-opening reactions that regenerate the starting semicarbazone or carbohydrazone. Such transformations make it unlikely that rearrangements or cleavage of other than N-H bonds has occurred during the oxidation; and support a simple, reversible cyclization.

However, any ring-opening reaction leading to the starting materials could go through an imide intermediate that would be rapidly converted to the observed amide in a tautomeric equilibrium. Conclusive application of the data to the triazolinone-oxadiazoline isomerism problem is hence

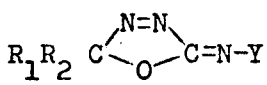
precluded. However, the reactivity displayed by the compounds in relation to that of analogous systems, leads to conclusion that the reactions are readily accommodated only in terms of an oxadiazoline structure.

Reduction

Data on the reduction of the oxidation products is contained in Table VII. Attention is drawn to the mild conditions employed in the

TABLE VII

Yields in Reduction Reactions of Δ^3-1,3,4-Oxadiazolines



	R_1	R_2	Y	Percentage Yield of Reduction Product [a]	
				Catalytic Hydrogenation [b]	$LiAlH_4$ [c]
1	CH_3	CH_3	$(CH_3)_2C=N-$	74	61
2	CH_3	C_2H_5	$CH_3(C_2H_5)C=N-$	81	80 [d]
3	C_6H_5	C_6H_5	$(C_6H_5)_2C=N-$	76	52
4	CH_3	CH_3	$CH_2C_6H_5$	91	-
5	CH_3	CH_3	CH_3 [e]	63	-

a Where Y = $R_1R_2)C=N$ reduced material is carbohydrazone $[R_1R_2C=N-NH]_2C{=}O$.

Where Y = R reduced material is semicarbazone $R_1R_2C{=}NHCNHR$ (O).

b Catalytic hydrogenations carried out in ethanol solution at 25°C; 50 psi hydrogen.

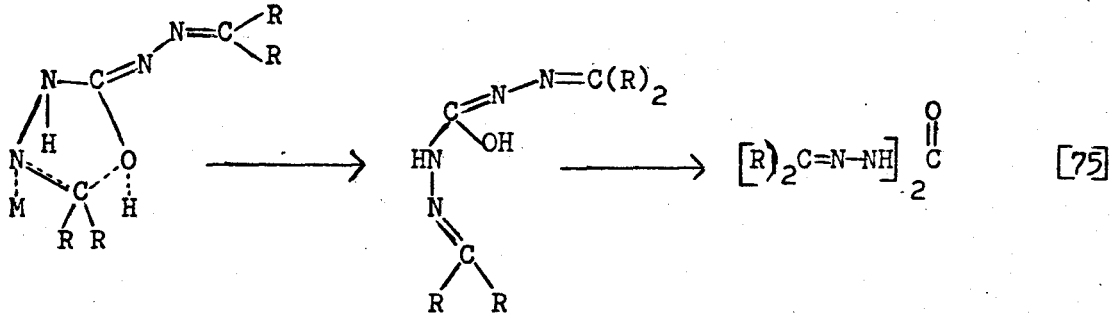
c $LiAlH_4$ reductions used excess of hydride in refluxing ether for 12 hours.

d Yield includes 56% of $CH_3(C_2H_5)CHNHNHCNHNHCH(C_2H_5)CH_3$ (O) by N.M.R.

e Values obtained by A. M. Cameron.

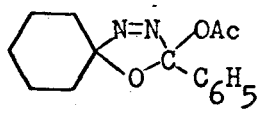
catalytic hydrogenations (25°C; 50 p.s.i. hydrogen) that make it unlikely that any molecular rearrangements occur in this reaction. The crude product isolated contained only the corresponding carbohydrazone or semicarbazone, as shown by infra-red spectroscopy. However, a near quantitative yield of reduction product is obtained only in the case of acetone 4-benzyl semicarbazone (example 4). It is suspected that losses are due to adsorption on the charcoal catalyst. Indeed, attempted purification of benzophenone carbohydrazone by treatment with decolourizing carbon in hot ethanol gave disappointing yields as described in the Experimental section, page 59.

A possible mechanism for these catalytic reductions under mild conditions is based on proposals (169) for allylic rearrangement during the reaction. The carbon-oxygen ring bond in the oxadiazoline structure bears an allylic relationship to the azo linkage. Cleavage of the C-O band followed by a proton transfer in the resultant imide leads to products, as shown in equation [75] . Precedent for such reductive ring opening is

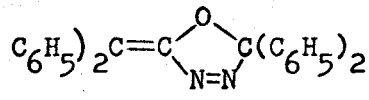


[75]

found in other studies on the few known Δ^3-1,3,4-oxadiazolines. For instance, Hoffman (47) has demonstrated the catalytic reduction of oxadiazoline X to cyclohexanone benzoylhydrazone, and Kirmse (170) has



X

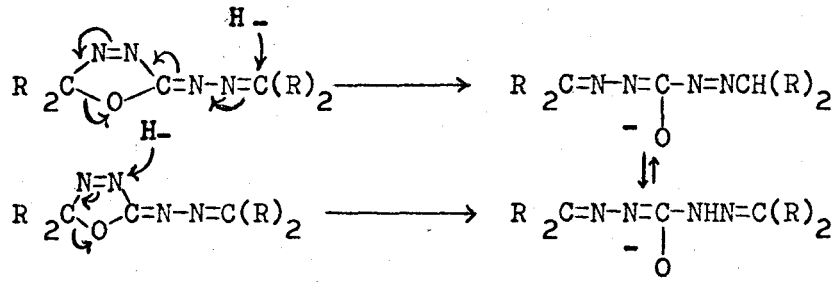


XI

shown that oxadiazoline XI is reduced on platinum/charcoal to the corresponding hydrazone. The similarity of the preceding examples and the reductions reported here, in both conditions and products, lends strong support to the oxadiazoline structure.

Reductions with lithium aluminium hydride have been restricted to the compounds derived from carbohydrazones, as shown in Table VII. Again all of the examples studied gave the starting carbohydrazone, and in the case of the methyl ethyl ketone derivative the corresponding 1,5-di(2-butyl)-carbazide, $CH_3(C_2H_5)CHNHNH(CO)NHNHCH(C_2H_5)CH_3$, was also identified in the reaction mixture. The temperature of refluxing ether medium employed in the hydride reductions again would not be expected to promote any thermal rearrangement.

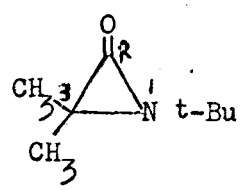
In the absence of more complete studies involving the derivatives of semicarbazones, the mechanism of the reaction can be formulated as either an attack by hydride ion at the imino group in the side chain; or as nucleophilic attack on the azo linkage in the ring. The two possibilities are shown in equation [76] for the oxadiazoline case. If one postulates a rapid azo-hydrazone interconversion, either position of initial attack leads to the same intermediate aluminate. Attack at the imino group should



[76]

be favoured, since it involves the preferred addition at a terminus of the conjugated system. The reactivity of the imino linkage under these conditions is demonstrated by the isolation of the 1,5-dialkyl carbohydrazide.

On the other hand, attack at a lactam carbonyl function might be expected to compete favourably with ring opening in a Δ^1-1,2,4-triazolinone.



XII

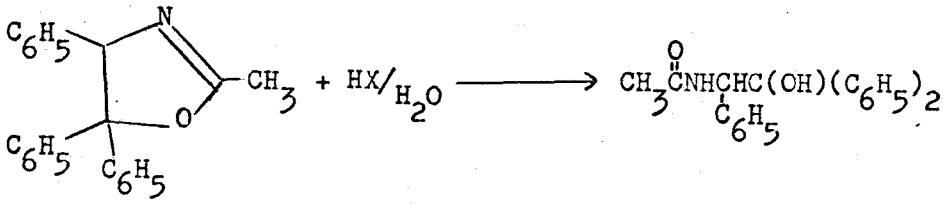
For instance, Sheehan (171) has observed ring fission in the hydride reduction of aziridinone XII, but at the 1,2 rather than the 1,3 bond, to yield the amino aldehyde and alcohol. Several examples of cleavage of the carbonyl-nitrogen bond in other tertiary amides such as $n\text{-}C_3H_7\overset{O}{\overset{\|}{C}}N(CH_3)C_6H_5$ (172), and N-acyl carbazoles (173), are also cited. Therefore, in light of the chemistry of model systems, the hydride reductions also support the oxadiazoline assignment.

Hydrolysis

The structural information to be derived from the hydrolysis of the oxidation products has been minimized by the tendency of initially formed products to hydrolyse further. As outlined in the Experimental section, the hydrolysis of the acetone carbohydrazone oxidation product

with either mineral acid or base in hot methanolic solution gave water soluble materials no longer containing methyl substituents (N.M.R.), as the only isolated products. Milder treatment of the benzophenone carbohydrazone derivative with p-toluene sulphonic acid hydrate in ether at room temperature led to the isolation of benzophenone and benzophenone hydrazone. Under the same conditions, benzophenone carbohydrazone is also hydrolysed to benzophenone and the benzophenone hydrazone salt. Heating the oxidation product in dry chlorobenzene containing acid did actually give a low yield of the benzophenone carbohydrazone itself.

In view of the limited evidence, one can only speculate on the mechanism of the hydrolysis. However, it is clear that the heterocyclic ring is readily opened by acid; and that an intermediate carbohydrazone is likely formed. Such reactivity supports the assignment of the oxadiazoline structure. Other imidic esters, such as XIII, shown in equation [77]



[77]

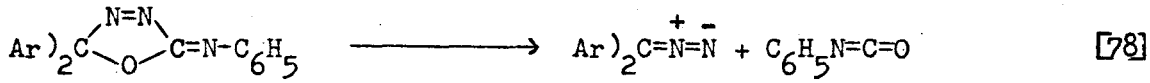
XIII

are hydrolysed to the corresponding open-chain amides by mineral acid (174). Similar acid hydrolysis of a lactam such as a Δ'-1,2,4-triazolin-3-one would seem unlikely under such mild conditions.

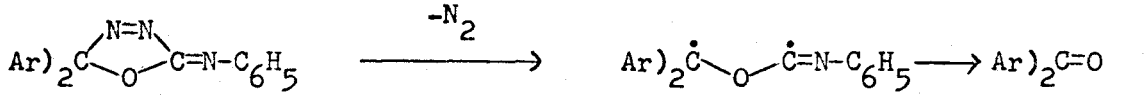
Thermal Decomposition

Later sections of the discussion will deal in some detail with the thermolysis of the heterocycles prepared from diaryl ketone semicarbazones. However, aspects of these decompositions bearing on the question of the lactam-lactim isomerism will be included here in support of the structural assignment.

In terms of an oxadiazoline structure, the decomposition reactions can be formulated as two parallel processes shown in equations [78] and [79] . In the process involving direct loss of nitrogen, a simple single-

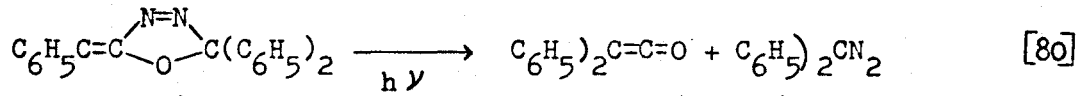


[78]



[79]

bond cleavage in the diradical intermediate gives rise to the ketone and isocyanide species. The formation of diaryl diazomethane and phenyl isocyanate finds analogy in the photolysis of oxadiazoline XI, to diphenylketene and diphenyldiazomethane (eq. [80]), observed by Kirmse (170).

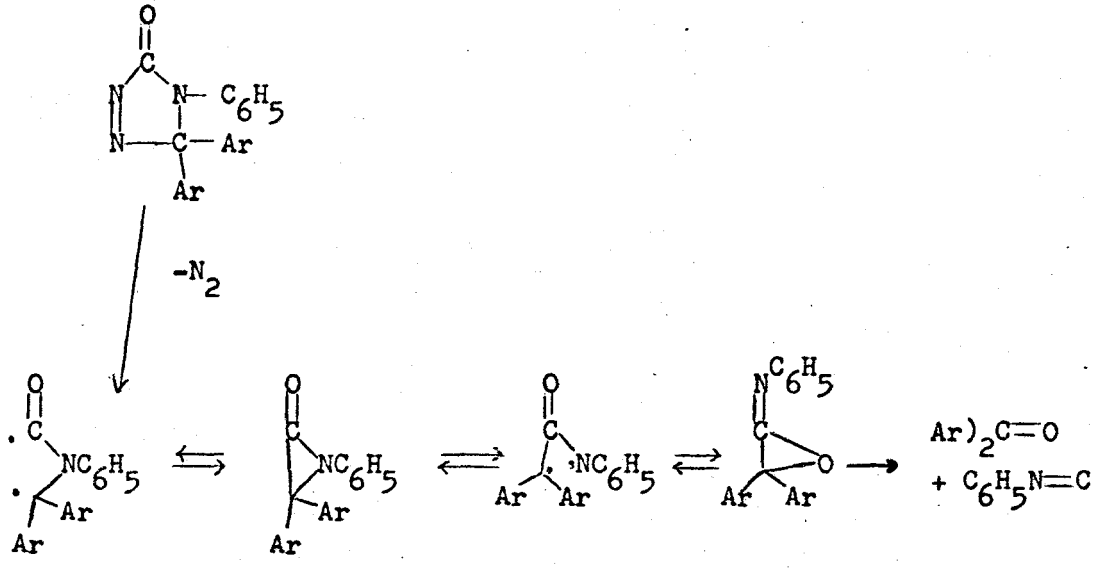


[80]

XI

The comparison is not exact since possible differences between photolytic and thermal reactions are neglected.

The retro-dipolar addition yielding diaryl-diazomethane and phenyl isocyanate is likewise readily understood in terms of the alternative Δ^1-1,2,4-triazoline structure. However isocyanide and ketone could only arise by thermal decomposition of the diradical A, presumably through an α-lactam B, as shown in equation [81]. Sheehan (175), has reported that some α-lactams (aziridinones) do yield isocyanide and ketone on heating. Rearrangements to imino oxiranes, such as intermediate C below, are postulated.

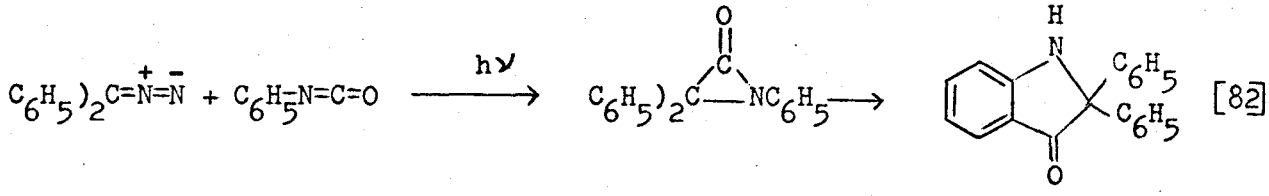


[81]

A B C

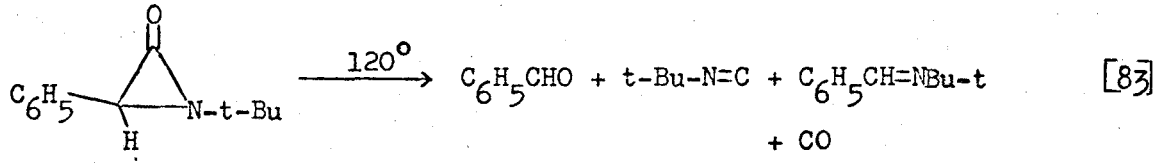
However, other evidence arising from studies of the chemistry of α-lactams makes it unlikely that they are intermediates in the decompositions reported here. First, Sheehan (176,177), and Sarel (178), have isolated

only ring-expanded products from reactions in which the ∝-lactam B is postulated as on intermediate. For instance, the photo-addition of diphenyl diazomethane and phenyl isocyanate (176) yields 2,2-diphenyl-indoxyl as shown in equation [82]. The infra-red spectrum of the thermal



[82]

decomposition products in the present study has no absorption in the region 1700-1715 cm^{-1} expected for possible indoxyl products (176). Secondly, Baumgarten and Fuerholzer (179) have shown that the thermal decomposition of aziridinone XIV (eq. [83]), although yielding aldehyde and isocyanide, gives some azo methine and carbon monoxide as well. In the work in this



[83]

thesis, gas yields indicate that such decarbonylation, expected in Δ'-1,2,4-triazolin-3-one decomposition, is not significant. In addition, Fuerholzer indicates that some aziridinone continues to exist even after heating to 120°C. The infra-red spectrum of partially decomposed material in the thermolysis of the oxidation products of the diaryl ketone semi-carbazones, however, shows no absorption in the ∝-lactam carbonyl region (1835 cm^{-1}).

A Δ'-1,2,4-triazolin-3-one structure necessitates the intervention of an ∝-lactam intermediate to satisfactorily explain the thermal

decomposition products. However since the experimental observations are not in agreement with the known chemistry of ∝-lactams, it is clear that the results of the thermolyses are also compatible only with a Δ^3-1,3,4-oxadiazoline structure.

(iv) Summary of Evidence for the Structure of the Oxidation Products.

The spectra and chemical evidence that has been presented conclusively establishes the 5,5-disubstituted-2-imino- Δ^3-1,3,4-oxadiazoline structure for the compounds prepared by lead tetra-acetate oxidation of ketone carbohydrazones and semicarbazones. A summary of this evidence is presented below.

(a) Analytical data, in conjunction with molecular weight measurements, indicate a monomeric species differing from starting materials by two hydrogens. Infra-red and N.M.R. spectra indicate the loss of N-H without acetoxyl incorporation. A heterocyclic structure is therefore indicated.

(b) Recourse to model systems shows that characteristic infra-red absorptions in the 1620-1720 cm^{-1} region are best assigned to an exo-cyclic >C=N- grouping.

(c) Ultra-violet absorptions in the 250-325 mu range are expected for the conjugated system present in the Δ^3-1,3,4-oxadiazoline structure. Models indicate that the possible isomer, a Δ'-1,2,4-triazolin-3-one would absorb only at shorter wavelength.

(d) In the N.M.R. spectra, the chemical shift of protons in ring methyl groups agree with values in model systems also having protons situated beta to azo and to oxygen functions.

(e) The m/e values observed in mass spectra recorded at both high and low ionizing voltages are most readily explained in terms of an oxadiazoline structure.

(f) Facile reduction of the compounds to the starting materials, by both catalytic and $LiAlH_4$ methods, finds analogy in the documented behaviour of Δ^3-1,3,4-oxadiazolines. Reactivity towards acid hydrolysis is similarly in agreement with observations in other imidic ester systems.

(g) The products of thermal decomposition can only be satisfactorily explained in terms of a Δ^3-1,3,4-oxadiazoline structure. Intermediates that might arise from the isomeric possibility would be expected to yield products that are not, in fact, observed.

(v) Reactivity of Ketone Carbohydrazones and Semicarbazones Towards Lead Tetra-Acetate.

Considerable variation in the conditions necessary to effect oxidation are encountered in going from alkyl to aryl ketone derivatives, in both the carbohydrazone and semicarbazone series. For reference, data bearing on the efficiency and reaction conditions have been assembled in Table VIII.

It is noted that the yields of 5,5-dialkyl oxadiazolines are markedly higher than those of the 5,5-diaryl compounds. The dialkyl ketone derivatives are oxidized rapidly at $0^{\circ}C$ in methylene chloride to give crude

TABLE VIII

Reaction Conditions and Yields in the Oxidation of Ketone Carbohydrazones and 4-Substituted Semicarbazones

	Substrate	Temperature[a] (°C)	Reaction Time[a] (min)	Yield (percent)	Melting Point (°C)
A.	Carbohydrazones				
1.	Acetone	0°	15	77	bp 88-90/5 mm
2.	2-Butanone	0°	"	81	bp 95/5 mm
3.	Acetophenone	25°	"	41[b]	
4.	Benzophenone	30°	"	36.5[b]	113-114 d
5.	Benzophenone Acetone	0°	"	82	110-111
B.	4-Phenyl Semicarbazones				
6.	Acetone	0°	15	95	72-73
7.	Benzophenone	30°	40	20	125-128 d
8.	4,4-Dimethylbenzophenone	30°	40	49	103-105 d
9.	4,4Dichlorobenzophenone	30°	60	20[c]	105-110 d
10.	4,4-Dimethoxybenzophenone	30°	40	14.5[c]	91-93 d
	4 Benzyl Semicarbazone				
11.	Acetone	0°	15	25	38-39

[a]Temperature and reaction time refer to the period following addition.

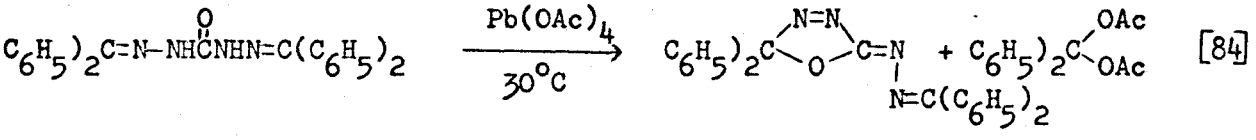
[b]A methylene diacetate is also a product.

[c]An approximately equal amount of the ketone is recovered.

products whose N.M.R. spectra indicate the absence of products of side-reactions. In addition, the other substituents on the carbohydrazone or semicarbazone do not seem to affect this efficiency.

On the other hand, the diaryl ketone derivatives were unreactive towards lead tetra-acetate at 0°C. When the temperature was raised to 30°, and the reaction time increased, oxadiazolines were obtained. However, competition from side reactions lowered yields, and resulted in a complex mixture of products.

Positive identification of all other reaction products was considered to be beyond the scope of this investigation. However, in the case of dibenzophenone carbohydrazone oxidation (eq. [84]), the reaction residues yield diphenylmethylenediacetate in 25% yield. In addition,



[84]

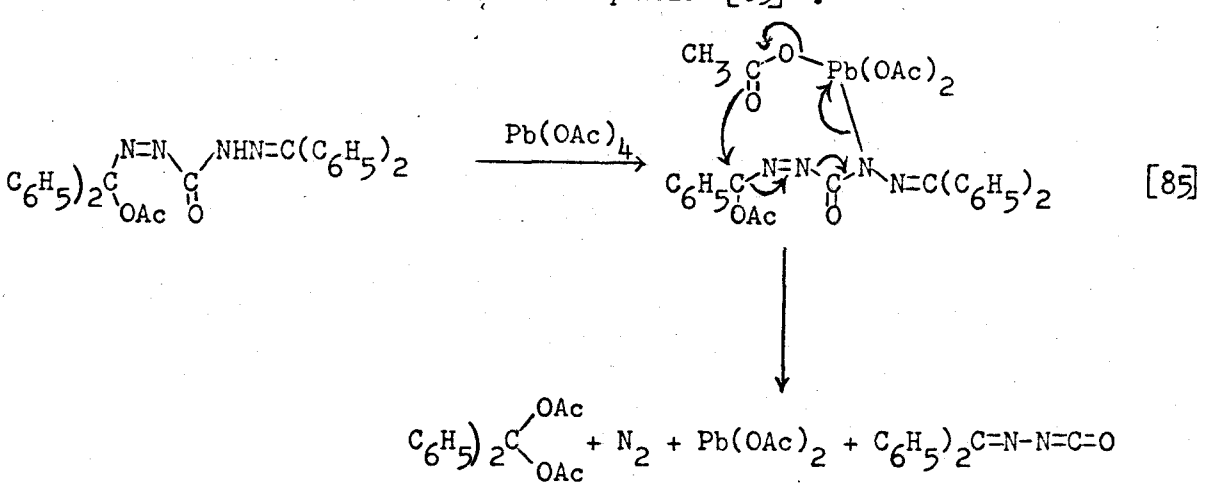
+ monoacetylation products

a mono-acetylated compound retaining both benzhydryl groups, and showing an amide carbonyl but no N-H absorption in the infra-red, was isolated. No positive identification of this material was made. The infra-red spectrum of the acetophenone carbohydrazone oxidation residue indicated the presence of analogous methylene diacetate and mono-acetylated compounds.

It is well known that methylene diacetates are readily hydrolysed to the corresponding ketones and acetic acid (35). Therefore, benzophenones isolated from the oxidation of the 4-phenylsemicarbazones of diaryl ketones may also be derived from intermediate diaryl

methylene diacetates. In cases where solubilities of the ketone and oxadiazoline are comparable, at least an equal amount of ketone is inevitably isolated from the oxidation (examples 9 and 10, Table VIII). No attempt to quantitatively recover ketone was made in these preparative experiments. Qualitative infra-red and N.M.R. examination of the remaining residues from the 4-phenylsemicarbazone oxidations indicate incorporation of at least one acetyl function per ketone group.

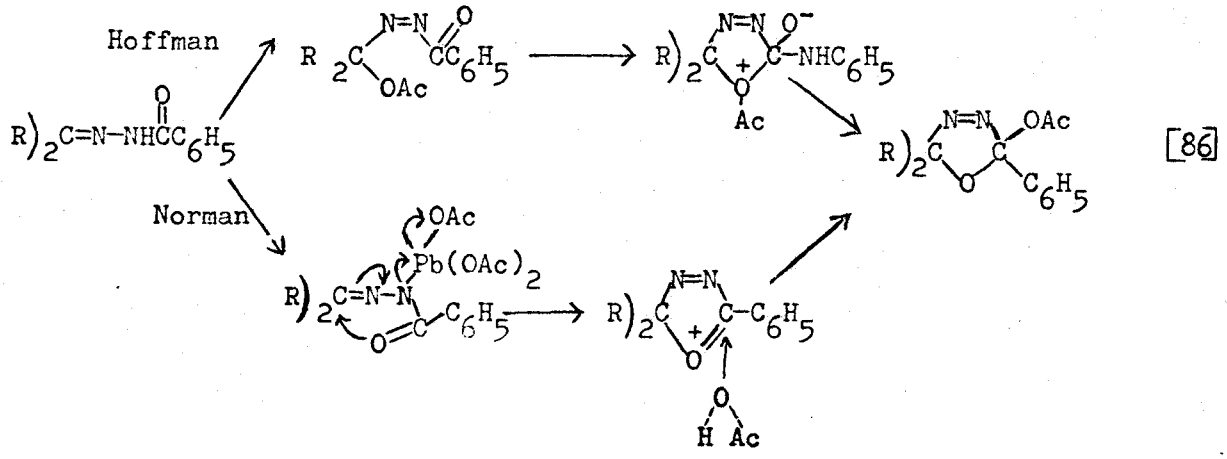
The production of methylene diacetates in the lead tetra-acetate oxidation of p-toluenesulphonylhydrazones of ketones has been explained by Norman (35) in terms of attack by acetic acid on an intermediate azo-acetate. The formation of nitrogen and a stable p-toluene sulphonate ion are said to provide the driving force for the reaction. Application of a similar mechanism in the present case does not lead to formation of a stable anionic species. It is considered more likely that the diphenylmethylene diacetate arises by attack of a second lead tetra-acetate molecule on an intermediate azoacetate as shown in equation [85] .



[85]

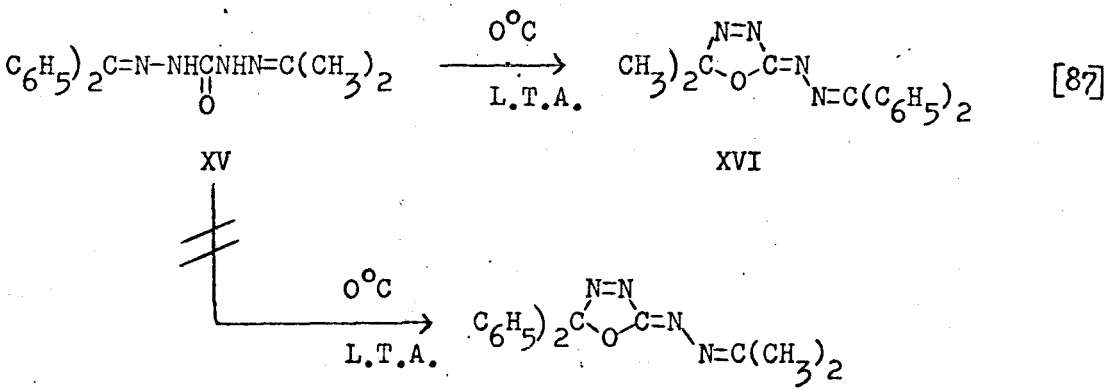
Mechanism of Oxadiazoline Formation

A mechanism for the observed oxadiazoline formation must take into account studies by other workers on the lead tetra-acetate oxidation of N-substituted hydrazones. As outlined in the Historical Introduction, Criegee (4), and Norman (35) have successfully explained many such oxidations in terms of polar decompositions of intermediate lead triacetate complexes. Moreover, Norman (35), and Iffland (27) have observed that electron-withdrawing para substituents in phenyl hydrazones of ketones retard azoacetate formation. Displacement by the electron pair of the hydrazone NH group on $Pb(OAc)_4$ is postulated as the rate-determining step in these oxidations. The oxidation of benzoyl hydrazones to 2-acetoxy-Δ^3-1,3,4-oxadiazolines, recently reported by Norman (35), and by Hoffman (47), is more closely related to the reactions reported here. Differing polar mechanisms have been proposed by each author, as shown in equation [86] .



[86]

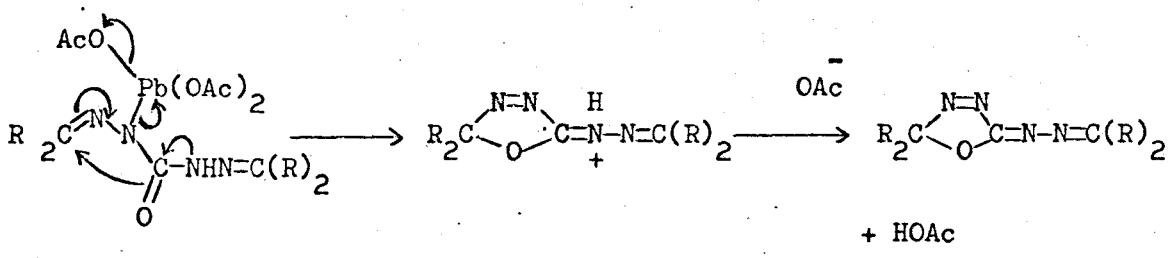
In the present study, some evidence concerning the mechanism of the reaction is available from the oxidation of acetone benzophenone carbohydrazone XV, as shown in equation [87]. The oxidation of this unsymmetrical carbohydrazone proceeds in high yield at 0°C to give only one of the possible oxadiazolines, XVI, at least as indicated by the N.M.R.



[87]

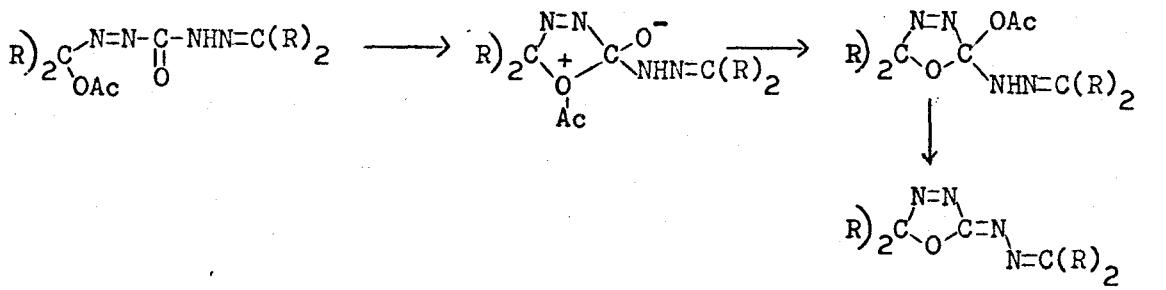
spectrum of the crude product. Of the two related symmetrical carbohydrazones, only acetone carbohydrazone reacts rapidly under these conditions. Therefore, it appears that the initial attack by $Pb(OAc)_4$ is at the hydrazone linkage that is eventually oxidized to the azo group. Furthermore, this attack would also be the rate-determining step; if the results of kinetic studies on the oxidation of phenyl hydrazones are applicable.

The mechanism advanced for benzoyl hydrazone oxidation by Norman (35) seems most attractive for the cyclization step in the carbohydrazone reactions. Following intramolecularly promoted decomposition of the lead intermediate, deprotonation of the resultant cation by acetate ion leads directly to the oxadiazoline (eq. [88]). The alternative mechanism



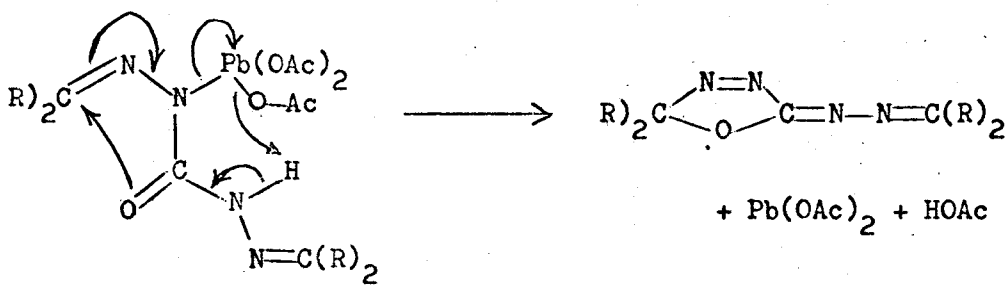
[88]

proposed by Hoffman would require elimination of acetic acid from an initially formed acetate (eq. [89]). Such an uncatalysed elimination would not be expected to be rapid at low temperature.



[89]

It should be noted that Norman assigns the oxonium ion mechanism on the evidence that in methanolic solution, a methoxy rather than acetate group is incorporated into the Δ^3-1,3,4-oxadiazoline. He ignores the fact that alcohols rapidly react with $Pb(OAc)_4$ to form alcoholates. Hence it is still possible that the methanol group has been transferred to the substrate from a lead species. Therefore, an alternative mechanism involving concerted removal of the second proton from nitrogen by another lead acetate ligand cannot be ruled out. Such a mechanism, shown in equation [90] , has the advantage of avoiding the charge development postulated in the other reaction schemes.



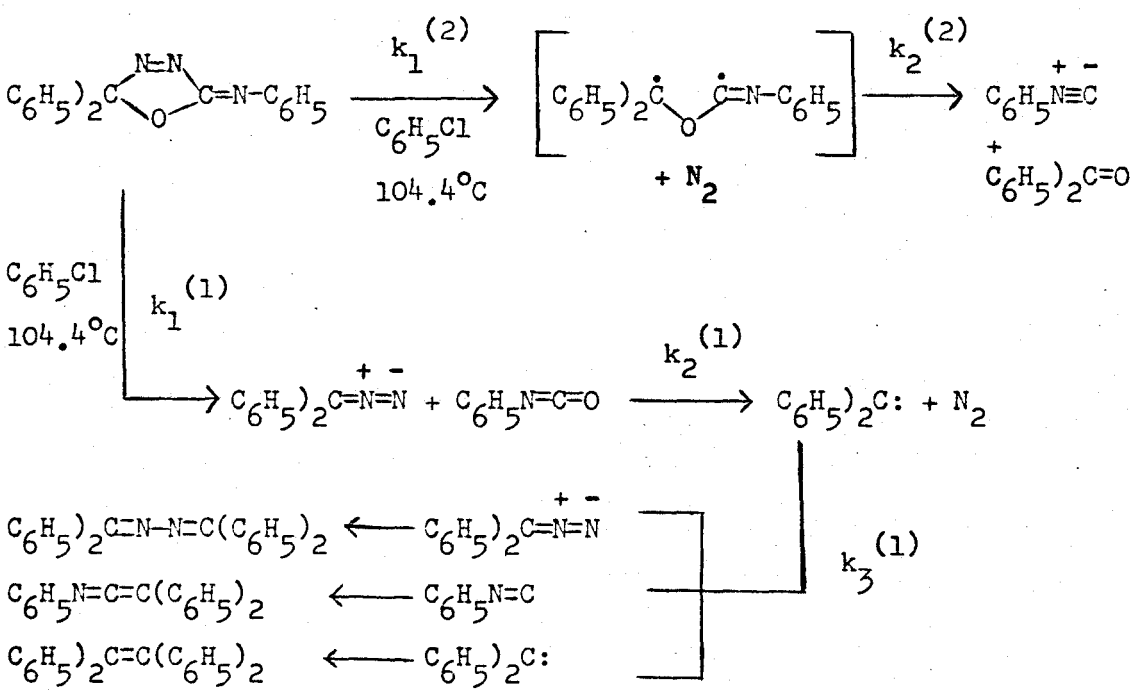
[90]

Since the alkylidene-imino functions in the oxadiazoline products from carbohydrazones have not entered into the mechanisms described, it is clear that exactly analogous schemes can be written for the 4-substituted semicarbazone reactions.

II. The Thermal Decomposition of 5,5-Diaryl-2-Phenylimino-Δ^3-1,3,4,-Oxadiazolines.

The thermal decomposition of cyclic azo compounds has been the subject of recent investigations by Overberger (88), Crawford (90) and others. These studies have been reviewed in the Historical Introduction. The 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines are examples of cyclic azo compounds showing a marked difference in the polarity of the terminal substituents of the azo linkage. An examination of the thermolysis of the oxadiazolines was prompted by interest in the effect of such unsymmetrical substitution on bond rupture processes in azo compounds.

Decomposition of the oxadiazolines in solution actually involves two parallel first-order processes which are outlined below for 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline. Direct loss of a nitrogen molecule, leading eventually to the formation of phenylisocyanide and benzophenone, is assigned



a rate constant $k_1^{(2)}$. The competing process, a retro-1,3-dipolar addition yields phenylisocyanate and diphenyldiazomethane (rate constant = $k_1^{(1)}$). Under the reaction conditions, the diazo compound decomposes to nitrogen and a reactive diphenylcarbene species (rate constant = $k_2^{(1)}$). Some of the further possible coupling reactions of the carbene with the diazomethane, isocyanide and itself are summed under rate constant $k_3^{(1)}$.

Data substantiating this reaction scheme has been obtained from product studies and kinetic experiments. The discussion will proceed from the preliminary observations to the more detailed kinetic studies, to establish first the nature, and then the relative importance of the proposed reactions.

(i) Identification of Primary Decomposition Processes.

Gas evolution studies, employing 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline, revealed the existence of two decomposition reactions producing nitrogen gas. As outlined in the Experimental, approximately 1.0×10^{-2} molar solutions of the oxadiazoline were decomposed in oxygen-free chlorobenzene solution at $104.4^{\circ}C$. The evolution of nitrogen began immediately and proceeded smoothly to yield the theoretical amount for one mole of gas. However, a plot of $\log (V_\infty - V)/V_\infty$ versus time, expected to be linear for unimolecular first-order decomposition, showed a decrease in slope with time. Data for a typical gas evolution experiment is recorded in Table IX, and plotted in Figure 2 (page 146). The rate of gas evolution, as reflected by the slope of the curve in Figure 2, falls to a lower but constant value.

TABLE IX

Data For A Typical Gas Evolution Experiment With 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline In Chlorobenzene At 104.4°C

Run II

Initial Concentration: 8.91×10^{-3} molar.

V_∞ observed = 14.90 V_∞ calculated = 14.33 % Yield = 103.9

Time (min.)	Volume Evolved (ml)	$V_\infty - V$	$\log_{10} V_\infty - V$	$\log_{10} V_\infty (V_\infty - V)$
0.8	0.80	14.10	1.14922	0.02397
1.3	1.55	13.35	1.12549	0.04770
1.8	2.40	12.50	1.09691	0.07628
2.8	3.30	11.60	1.06446	0.10873
3.9	4.30	10.60	1.02531	0.14788
4.8	4.95	9.95	0.99782	0.17537
6.2	5.90	9.00	0.95424	0.21895
7.6	6.70	8.20	0.91381	0.25938
9.3	7.60	7.30	0.86332	0.30987
11.1	8.40	6.50	0.81291	0.36028
13.1	9.10	5.80	0.76343	0.40976
15.6	9.95	4.95	0.69461	0.47858
17.7	10.50	4.40	0.64345	0.52974
21.0	11.20	3.70	0.56820	0.60599
24.9	11.85	3.05	0.48430	0.68889
27.9	12.30	2.60	0.41497	0.75822
31.5	12.70	2.20	0.34242	0.83077
34.8	13.05	1.85	0.26717	0.90602
40.0	13.50	1.40	0.14613	1.02706
46.2	14.00	0.90	$\bar{1}$.95424	1.21875
53.2	14.30	0.60	$\bar{1}$.77815	1.39504

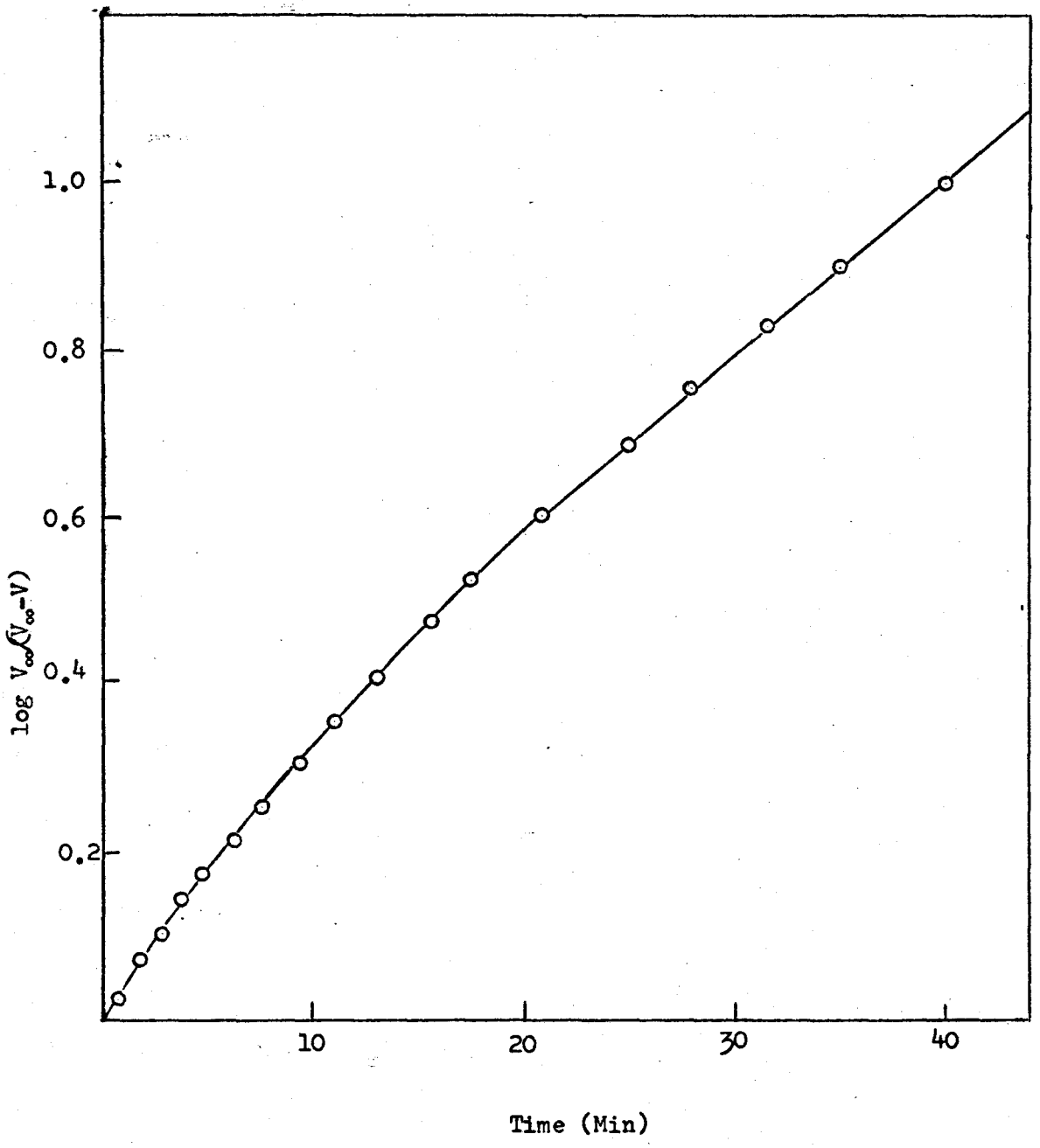


Fig. 2. Rate of Gas Evolution in the Decomposition of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline

In view of this apparent intercession of a second gas producing process, experiments were undertaken in which the decomposition was quenched at dry-ice temperatures after one half-life of gas evolution. Qualitative analysis of the complex reaction mixture at this point revealed the presence of phenyl isocyanate and diphenyldiazomethane, corresponding to one possible decomposition pathway. Phenyl isocyanide, benzophenone, and unchanged starting material were also observed. The infra-red absorptions of the diazomethane, isonitrile and isocyanate in the comparatively open region of the spectrum between 2000-2500 cm^{-1} aid in their identification. Characterization of the compounds in most cases was effected by isolation of the pure materials or their derivatives and comparison with authentic samples. Further details of the product studies are reported in the Experimental section.

In gas evolution experiments carried to completion, the residue showed that benzophenone and phenyl isocyanate were still present as major components. Diphenyldiazomethane and starting material were no longer observed, and only a low concentration of phenyl isocyanide remained (infra-red analysis). The infra-red spectrum, however, now showed an absorption at 2000 cm^{-1} that is characteristic of ketenimines, $R)_2C=C=N-R$ (182). The coupling reaction of phenyl isocyanide with diphenylcarbene could give rise to the ketenimine $C_6H_5)_2C=C=NC_6H_5$. However, efforts to isolate the material absorbing at 2000 cm^{-1} by chromatography were unsuccessful. Ketenimines are known to be hydrolysed by traces of moisture, and would be difficult to isolate.

The identification of diphenyldiazomethane as an intermediate led to the hypothesis of a reaction scheme involving two parallel decompositions. In order to resolve the gas evolution data, the variation of the diazomethane

TABLE X

A Comparison of Kinetic Data From Decompositions of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline Followed by Gas Evolution and Infra-Red Methods

I. Gas Evolution

Weight of Oxadiazoline 0.179 gm — V_∞ (calculated)[a] 14.33 ml

Concentration 8.91×10^{-3} molar — V_∞ (experimental) 14.90 ml

Time (min.)	Volume (ml)	Mole Percent[b]	Time (min.)	Volume (ml)	Mole Percent[b]
0.8	0.80	5.58	13.1	9.10	63.49
1.3	1.55	10.81	15.6	9.95	69.44
1.8	2.40	16.75	17.7	10.50	73.27
2.8	3.30	23.02	21.0	11.20	78.16
3.9	4.30	30.00	24.9	11.85	82.34
4.8	4.95	34.54	27.9	12.30	85.84
6.2	5.90	41.18	31.5	12.70	88.43
7.6	6.70	46.75	34.8	13.05	91.05
9.3	7.60	53.04	40.0	13.50	94.20
11.1	8.40	58.61	46.2	14.00	97.68

[a] Temperature of gas collected was 32.4°C

[b] Mole percent = Volume/V_∞ (calc.) x 100

TABLE X (CONT'D)

A Comparison of Kinetic Data From Decompositions of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline Followed by Gas Evolution and Infra-Red Methods

II. Infra-red Measurement of Diphenyldiazomethane

Weight of oxadiazoline 0.150 gm Concentration 8.04×10^{-2} molar

Time (min.)	Molarity[a] of Diazomethane	Mole Percent[b]	Time (min.)	Molarity[a] of Diazomethane	Mole Percent[b]
1.2	0.45	5.59	16.1	2.10	26.10
2.1	0.91	11.32	19.0	1.97	24.50
3.2	1.33	16.57	22.1	1.79	22.25
4.1	1.68	20.90	24.9	1.58	19.65
5.1	1.91	23.75	27.3	1.47	18.38
6.0	2.04	25.35	29.3	1.33	16.55
7.0	2.20	27.35	32.2	1.16	14.45
8.2	2.27	28.20	35.1	1.06	13.20
9.0	2.36	29.35	38.7	0.87	10.82
10.2	2.44	30.35	43.1	0.72	8.96
11.2	2.47	30.70	48.0	0.53	6.59
13.0	2.33	29.00			

[a] Molarity was obtained by interpolation on a calibration cure established for 2042 cm^{-1} absorption of diphenyldiazomethane in chlorobenzene.

[b] Mole percent = $\frac{\text{Molarity of Diphenyldiazomethane}}{\text{Initial Molarity of Oxadiazoline}} \times 100$

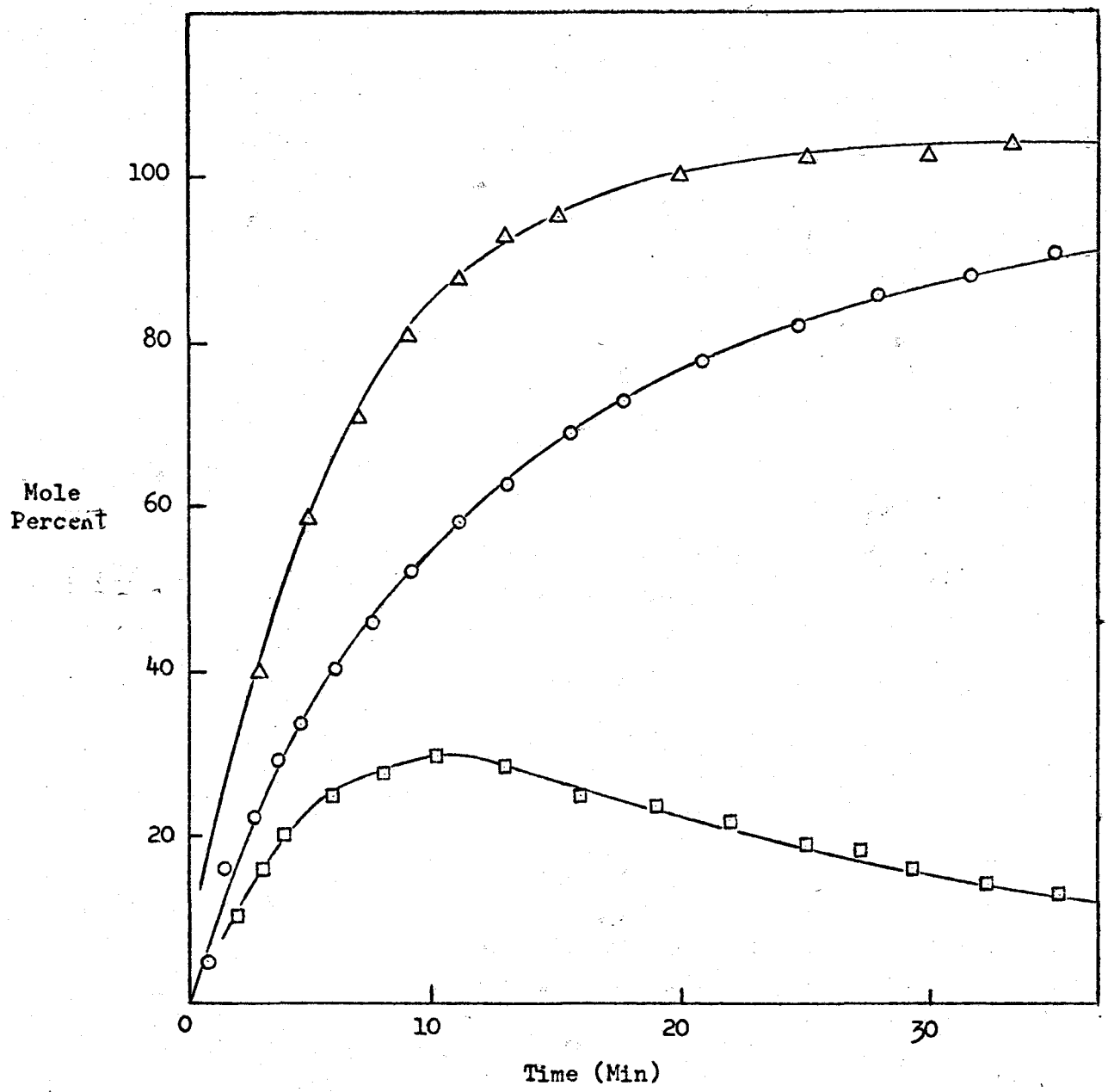


Fig. 3. Diphenyldiazomethane in Solution, and Nitrogen Evolved during Decomposition of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline

KEY —○—○— Gas Evolved
—□—□— Diazomethane in Solution
—△—△— Gas + Diazomethane

concentration throughout the reaction was followed by infra-red spectroscopy. Comparison of results from gas evolution and infra-red kinetic experiments was achieved by reducing the data in both cases to absolute concentration units (mole percent). The change in concentration of diazomethane with time for a typical experiment is recorded in Table X. Gas evolution data in mole percent units for another experiment under the same conditions is also included for comparison. When the two sets of results are displayed graphically (Figure 3, page 150), it is evident that the diazomethane concentration rises to a maximum and then decays; while the amount of nitrogen evolved approaches one mole. The change in the sum of gas evolved plus diazomethane remaining in solution is also plotted in Figure 3. The sum of these two quantities should approach a constant value of 100 mole percent if starting material is consumed by only two reactions. Of course this condition will be strictly obeyed only if negligible amounts of diazomethane react by other than gas evolution processes. In practice, the total mole percent of gas evolved and remaining diazomethane did achieve a nearly constant value at a point where calculations showed that starting material had effectively disappeared.

It has been further postulated that the two competing primary processes are both unimolecular decompositions. Accordingly, the approach of the combined concentrations (C) of nitrogen and diazomethane in the system towards one mole (C_∞) should obey a first-order kinetic relationship. A plot of $\log C_\infty/(C_\infty - C)$ against time employing data obtained from the experiments recorded in Table XI, page 152, for the 5,5-diphenyl-Δ^3-1,3,4-oxadiazoline is indeed linear (Figure 4, page 153). The successful comparison of data from the two different kinetic experiments also sheds light on any possible concentration

TABLE XI

Determination of Total Rate[a] of Decomposition of

5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline

Time[b] (min)	Mole Percent Gas	Mole Percent Diazomethane	Combined Concentration (C)	$C_\infty - C$[c]	log $C_\infty/(C_\infty - C)$
1.0	8.3	5.5	13.8	90.1	0.09619
3.0	24.3	16.3	40.6	63.3	0.2153
5.0	36.0	23.4	59.4	44.5	0.3683
7.0	44.5	27.0	71.5	32.4	0.4961
9.0	51.6	29.5	81.1	22.8	0.6587
11.0	57.4	30.6	88.0	15.9	0.81525
13.0	63.4	29.6	93.0	10.9	0.97922
15.0	67.8	27.7	95.5	8.4	1.0903
20.0	77.0	23.3	100.3	3.6	1.5309
25.0	83.1	19.5	102.6	1.3	
30.0	86.5	16.0	102.5	1.4	
35.0	91.1	13.0	104.1	-	
∞	103.9	0	103.9	-	

[a] The total rate of decomposition is assumed to be equal to the rate of appearance of diphenyldiazomethane and nitrogen gas.

[b] Data is interpolated from the respective concentration - time graphs (cf. Figure 3, Page 150).

[c] The mole percent of nitrogen evolved after complete reaction is taken as C_∞.

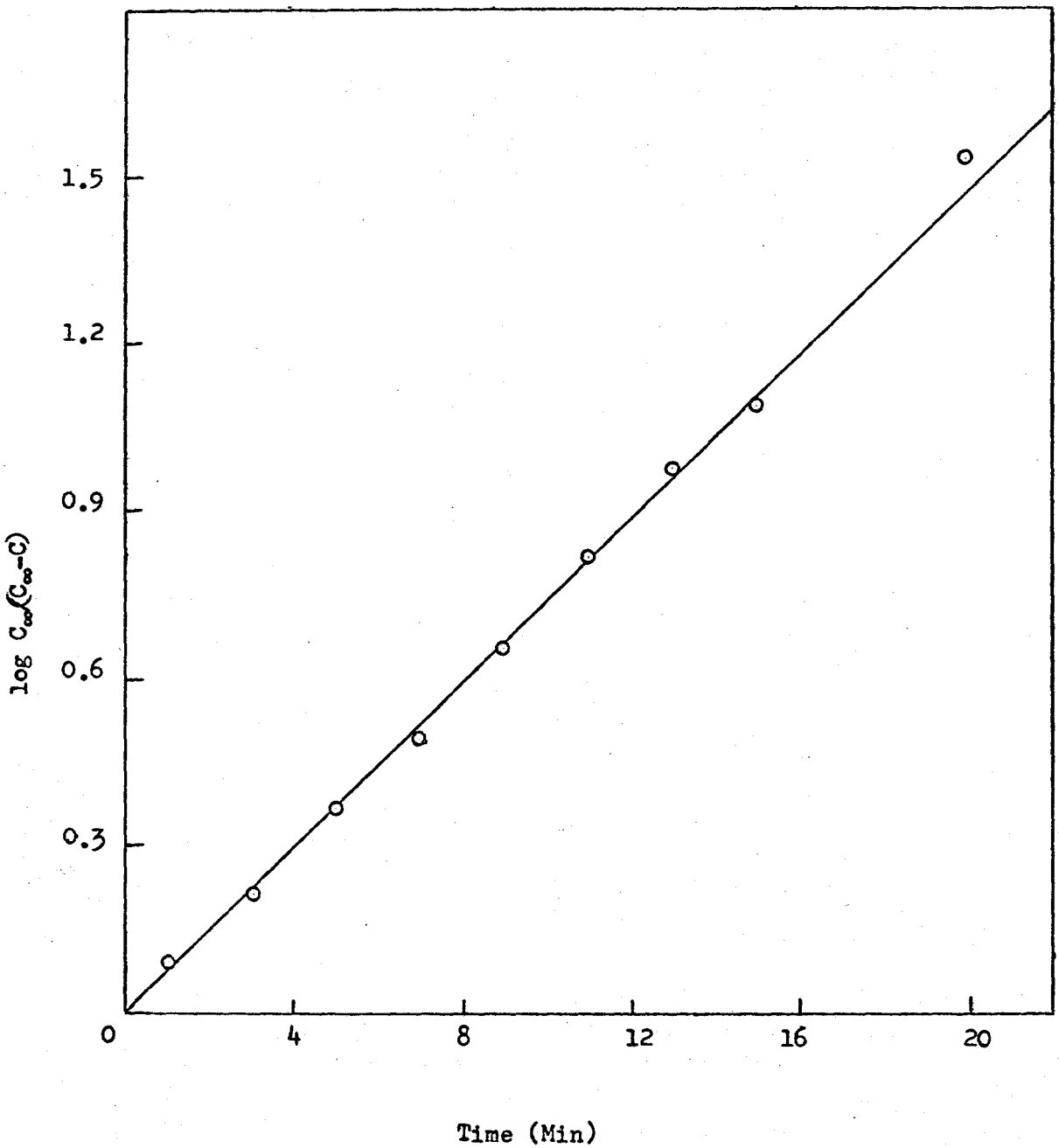


Fig. 4. Total Rate of Decomposition of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in Chlorobenzene at 104.4°

dependence of the decomposition. Gas evolution experiments were conducted at 1.0×10^{-2} molar concentrations of oxadiazoline. The infra-red studies employed initial concentrations of 9.0×10^{-2} molar to obtain sufficiently high concentrations of diphenyldiazomethane for spectroscopic measurement. Therefore, it can be concluded that the primary decomposition processes are not affected by a 10 fold change in concentration. This is in agreement with the proposal that both reactions are unimolecular.

The correlation of data from the two kinetic approaches also indicates that the effect of oxygen on the primary processes is minimal. Nitrogen evolution experiments were done under oxygen-free conditions, while experiments followed by infra-red methods were done in equilibrium with the atmosphere. Gas evolution experiments in which oxygen is present are difficult to interpret, since the consumption of oxygen by diphenylcarbene lowers the effective gas yield.

When two parallel unimolecular processes are postulated in a system, there is some concern that a bimolecular catalysis is responsible for one process. The results of several experiments tend to make this possibility unlikely in the present work.

In an experiment designed to trap phenyl isocyanate as diphenylurea, the 5,5-diphenyl oxadiazoline was decomposed in 50 ml of chlorobenzene containing one millilitre of added aniline. Not only was the calculated amount of the urea recovered, but the gas evolution data from the experiment showed the same rate profile as in other runs (cf. Figure 2, page 146). Basic catalysis therefore seems unlikely.

The decompositions of several 5,5-diaryl derivatives bearing different para substituents were examined qualitatively in reagent carbon tetrachloride at 60.0°C. Infra-red spectra showed that the relative concentrations of the products varied throughout the course of the reaction in the same way as they did in experiments conducted in chlorobenzene. Therefore, spurious catalysis of one of the reactions by a chlorobenzene impurity seems unlikely. Furthermore, gas evolution experiments employing chlorobenzene used directly as received could not be distinguished from experiments using chlorobenzene that had been extensively purified.

In summary, the following conclusion can be drawn from inspection of the experimental data without resorting to an exact kinetic calculation. Two first-order processes, one a retro-dipolar addition and the other a direct gas-forming reaction, are both necessary and sufficient to describe the thermal decomposition. In addition, the rates of these reactions are independent of initial concentration, and the presence of oxygen. Catalysis of either reaction by impurities is also unlikely. Under these conditions, the diphenyldiazomethane intermediate subsequently decomposes to yield nitrogen. The two pathways lead to the overall evolution of one equivalent of nitrogen based on the initial amount of oxadiazoline.

(ii) Calculation of the Rate Constants of the Thermal Decomposition Reactions.

The proposed reaction scheme can be described in general terms as a combination of two parallel first-order processes, one of which is composed of two consecutive first-order reactions. The solutions obtained by Rodiguin (140) for the rate equations in such systems are presented in the

Experimental, page 101. These solutions do not yield a simple manageable relationship between the experimentally measured concentrations and the rate constants of the three reactions. However an expression relating the three

$$\left[\text{Diazomethane}\right]_{max} = \frac{k_1^{(1)}}{a_1} \left[\frac{k_2^{(1)}}{a_1}\right] \left[\frac{k_2^{(1)}/a_1}{1 - k_2^{(1)}/a_1}\right] \qquad [66]$$

where $k_1^{(1)}$ = rate of diazomethane formation

$k_1^{(2)}$ = rate of direct gas evolution

$a_1 = k_1^{(1)} + k_1^{(2)}$

$k_2^{(1)}$ = rate of decomposition of diazomethane

rate constants at the point of maximum diazomethane concentration has been derived (eq. [66]). The disadvantage of employing such an expression for calculation of the rate constants is the error introduced by the emphasis on the one maximum point. More precise values of the rate constants for the kinetic data that are available might be obtained by computer analysis. However any method of calculation must rely on at least two experiments (gas evolution and infra-red analysis) performed under different conditions. As subsequent discussion will show, the importance of bimolecular reactions in the complex reaction mixture can only be approximately predicted. In light of the complexity of the system, it was apparent that no additional information would be gained by an exact computer analysis. Therefore, calculation of the rate constants was undertaken employing the maximum relationship of equation [66] .

Examination of the maximum expression indicates that three quantities are necessary to isolate the primary rate constants $k_1^{(1)}$ and $k_1^{(2)}$. The maximum value of the diphenyldiazomethane concentration can be obtained by inspection of a concentration vs. time plot (cf. Figure 3, page 150). The total first-order rate constant ($k_1^{(1)} + k_1^{(2)}$) can also be obtained graphically from the rate of appearance of gas and diazomethane, as shown in Figure 4, page 153.

The rate of disappearance of diazomethane, $k_2^{(1)}$, can be taken from two sources. After effective disappearance of the oxadiazoline, the rate of gas evolution can be assigned to diphenyldiazomethane decomposition alone. The decay in the concentration of diazomethane, measured by infra-red, similarly yields $k_2^{(1)}$. In calculations of rate constants for the 5,5-diaryl oxadiazolines, the value obtained from infra-red kinetic studies has been applied (Table XII). In the case of the 5,5-di-p-tolyl oxadiazoline, values of diazomethane decomposition from both sources are nearly the same. However, in the 5,5-diphenyl oxadiazoline where a comparison is also possible, the value of $k_2^{(1)}$ derived from the gas evolution studies is somewhat higher.

There is some justification for choosing the rate constant derived from the infra-red measurements. In these experiments, the diphenylcarbene produced should be rapidly oxidized to benzophenone by the oxygen present. Induced decomposition of the diphenyldiazomethane by either the carbene, or another reactive species derived from it (i.e., ketenimine) will therefore be unlikely. In fact, the rate constant in Table XII for disappearance of diphenyldiazomethane agrees quite well with

TABLE XII

Decomposition of Diaryldiazomethanes in Chlorobenzene at 104.4°

Diaryldiazomethane	$kx10^3 sec^{-1}$ [a] (Infra-red)	$kx10^3 sec^{-1}$ [a] (Gas Evolution)
Diphenyldiazomethane	0.76 ± 0.08	0.91 ± 0.03
4,4-Dimethyldiphenyldiazomethane	1.36 [b]	1.39 ± 0.03
4,4-Dichlorodiphenyldiazomethane	0.83 ± 0.11	- [c]

[a] Deviations quoted are standard deviations.

[b] Single determination.

[c] The low gas yield from diazomethane decomposition does not allow calculation in this case.

the value of $7.50 \times 10^{-4} sec^{-1}$ obtained by Murgulescu (181) for decomposition in xylene at this temperature.

The apparently faster rate of decomposition in the gas evolution case may be due to an induced reaction. However, such processes should be unimportant in the initial stages of the reaction where the concentrations of products are low. Since the comparison of the gas evolution and diazomethane data are made at the outset of the reaction, the use of the value of $k_2^{(1)}$ from the infra-red should introduce little error at this point.

The rates of the two primary processes in the decomposition of the 5,5-diphenyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline are shown in Table XIII. The direct formation of nitrogen and the retro addition compete almost equally for the starting material under these conditions. The activation energies for these two dissimilar processes, involving the cleavage of two different bonds at the same benzhydryl carbon, must be nearly equal. The oxadiazolines are examples of azo compounds that do not exclusively yield nitrogen in the primary decomposition process. Apparently, the nature of the substituents on the azo linkage can determine alternative thermal reactions which do not involve cleavage of both C-N bonds. In the present case, such a reaction is equal in importance to the elimination of nitrogen.

The complexity of the reaction mixture in the thermal decompositions introduces the possibility of other interfering reactions. The importance of these must be assessed before accepting the proposed reaction scheme.

One approximation that has been made is that diphenyldiazomethane is consumed only by unimolecular decomposition. However, induced decomposition by phenyl isocyanide, by a possible ketenimine, or by diphenyl carbene must be considered. Successful correlation of the gas evolution and infra-red experiments indicate that these induced reactions are not of great importance. Diphenylcarbene is removed from the reaction by oxygen only in the infra-red experiments. The effect of phenyl isocyanide must also be small since it is at a ten-fold higher concentration in the infra-red experiments.

TABLE XIII

Decomposition of 5,5-Diphenyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in Chlorobenzene at 104.4°

A. Parameters Employed in Calculation			
(i)	Total rate constant for oxadiazoline decomposition	$(k_1^{(1)} + k_1^{(2)})$	$2.93 \pm 0.15 \times 10^{-3}$ sec^{-1} [a]
(ii)	Maximum concentration of diphenyldiazomethane		31.1 ± 0.5 mole percent [a]
(iii)	Rate constant for diphenyldiazomethane decomposition	$(k_2^{(1)})$	$0.76 \pm 0.08 \times 10^{-3}$ sec^{-1} [a]
B. Rate Constants for Primary Decomposition Processes [b]			
(i)	Diphenyldiazomethane Production (Retro-1,3-dipolar addition)	$(k_1^{(1)})$	$1.45 \pm 0.12 \times 10^{-3}$ sec^{-1} [c]
(ii)	Direct gas evolution	$(k_1^{(2)})$	$1.48 \pm 0.12 \times 10^{-3}$ sec^{-1} [c]

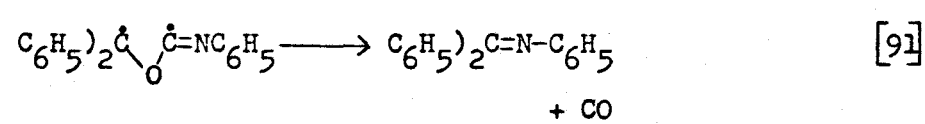
[a] Deviations quoted are standard deviations.

[b] Calculated by the maximum expression of eq. [66], page 156.

[c] Deviations quoted for $k_1^{(1)}$ are maximum limits, obtained by an analysis with appropriate bias to maximize diazomethane production (i.e., largest value of diazomethane max, coupled with the largest values of $(k_1^{(1)} + k_1^{(2)})$ and $k_2^{(1)}$; and vice versa). The deviation for $k_1^{(2)}$ is obtained by difference from the value of $(k_1^{(1)} + k_1^{(2)})$ used in each calculation.

Diphenylcarbene can also react with diazomethane to form ketazine without the evolution of nitrogen. Studies of ketazine formation in the decomposition of diphenyldiazomethane in benzene have been made by Bethell (182). If similar reactivities apply in chlorobenzene, then the yield of ketazine would be only five percent at the concentrations found in the gas evolution experiments. However, since the carbene formed can react with other species in the present experiments, ketazine formation should be even less important. Detailed analysis of the product mixtures, not undertaken here, would be necessary to accurately establish the fate of the carbene species.

Side reactions producing gaseous products other than nitrogen must be considered. Gas evolution studies on a series of 5,5-diaryl oxadiazolines, showing wide variation in the ratio of the two first-order processes, gave good agreement between calculated and experimental V_∞ values. Hence, evolution of gas from other processes must be of minor importance. In particular, there is no loss of carbon monoxide from a possible intermediate diradical in the direct decomposition reaction (eq. [91]). Such a process has been postulated to explain the fragmentation



[91]

pattern in the mass spectra of the oxadiazolines (eq. [71], page 124).

It is known that phenylisocyanate undergoes a bimolecular thermal decomposition at 200°C to give diphenylcarbodiimide and CO_2 (183). This reaction is shown in equation [92] . In the oxadiazoline

$$C_6H_5N=C=O \longrightarrow C_6H_5N=C=CC_6H_5 + CO_2 \qquad [92]$$

decomposition the isocyanate absorption in the infra-red spectrum did not decrease after reaching its maximum value. Dimerization of phenylisocyanate under the conditions of the thermal decompositions is therefore not a significant reaction.

The reversibility of the retro-dipolar addition under the conditions of the experiment was ruled out by a control reaction. A solution of phenyl isocyanate and diphenyldiazomethane in chlorobenzene showed no consumption of isocyanate or production of phenylisocyanide. Since the reactions were carried out in vessels immersed in covered constant temperature baths, there was a minimum exposure of the reaction mixture to light. Diphenyldiazomethane and phenyl isocyanate do undergo a photoreaction which is presumed to involve an α-lactam intermediate (equation [82] , page 133).

The disappearance of phenyl isocyanide as the reaction proceeds is attributed to its reaction with diphenylcarbene.

The unimolecular thermal isomerization of phenyl isocyanide to benzonitrile has a rate constant of only 27.6×10^{-5} at 200°C, and should not be significant at 104.4°C (184).

(iii) The Effect of Substitution on the Rates of Decomposition of 5,5-Diaryl-Δ^3-1,3,4-oxadiazolines

In both of the proposed thermal decomposition reactions, bonds to the carbon at the five-position of the oxadiazolines are broken in the first step. Accordingly, a Hammett treatment of the effect of varying the para substituents in both of the 5-phenyl groups was undertaken in order to shed light on the polarity of these bond cleavages. Rate constants calculated for the two primary reactions are shown in Table XIV.

Qualitative examination of the results reveals that changing the substituents has a pronounced effect on the ratio of the two reactions. There is a shift from predominantly direct loss of nitrogen with electron-withdrawing para-chloro groups, to almost exclusively retro-addition with electron-donating para-methoxy substituents.

The study of the thermal decomposition of the 5,5-di-p-methoxyphenyl oxadiazoline actually required a change in experimental conditions. Since the rate of production of diazomethane was too rapid for measurement at 104°C, an extrapolation of the rate of the reaction at lower temperatures was necessary. Under these conditions, the maximum concentration of di-p-methoxydiphenyldiazomethane was close to 100 percent. This observation indicates that the gas evolution from the competing parallel reaction constitutes only a few mole percent of the total decomposition, and is no longer readily detected. The experiments also showed that the rate of decomposition of the diazomethane at these lower temperatures was very much slower than its rate of formation. Accordingly, the reaction was treated as the simple first-order process shown in equation [93].

TABLE XIV

Decomposition of 5,5-Diaryl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in Chlorobenzene at 104.4°

Oxadiazoline	Maximum Concentration[a] of Diaryldiazomethane	$a_1 \times 10^3 sec^{-1}$[b]	$k_1^{(1)} \times 10^3 sec^{-1}$[b]	$k_1^{(2)} \times 10^3 sec^{-1}$[b]
5,5-Di-p-Chlorophenyl-	10.2 ± 1.5	4.00 ± 0.01	0.61 ± 0.13[c]	3.39 ± 0.13[c]
5,5-Diphenyl-	31.1 ± 0.5	2.93 ± 0.15	1.45 ± 0.12	1.48 ± 0.12
5,5-Di-p-tolyl	62.0 ± 0.9	9.01 ± 0.35	7.81 ± 0.31	1.20 ± 0.20
5,5-Di-p-anisyl	95.1 ± 3.3	(34.7)	34.7 ± 6.5	—

[a]Concentration expressed in mole percent. Deviations quoted are standard deviations.

[b]$k_1^{(1)}$ = rate of production of diaryldiazomethane

$k_1^{(2)}$ = rate of disappearance of oxadiazoline; $(k_1^{(1)} + k_1^{(2)}) = a_1$

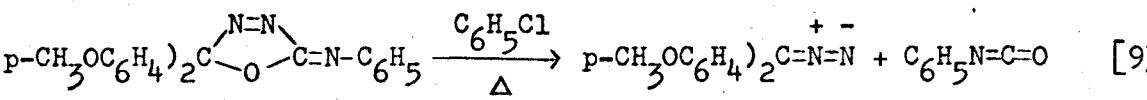
[c]Deviations calculated as described for 5,5-diphenyl compound in Table XIII.

TABLE XV

Rate of Di-p-methoxydiphenyldiazomethane Formation from 5,5-Di-p-anisyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline

Temperature °C	$k_1^{(1)} \times 10^3 sec^{-1}$[a]
73.4	2.71 ± 0.25
58.8	0.67 ± 0.01
49.3	0.0242

[a]Deviations quoted are standard deviations, for average values of several runs. A single determination was made at 49.3°.



[93]

Rate constants obtained by treating the change in diazomethane concentration as a first-order process are shown in Table XV. The extrapolation necessary to obtain the rate constant for the methoxy compound at 104.4° also allowed calculation of the activation parameters for the retro addition. Values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, shown in Table XVI, were obtained from a plot of log k/T versus 1/T (Fig. 5, p. 166).

TABLE XVI

Activation Parameters for 5,5-Di-p-anisyl-2-Phenylimino-Δ^{3}-1,3,4-Oxadiazoline

$\Delta H^{\neq}$ k.cal. mole^{-1} [a]	$\Delta S^{\neq}$ e.u [a]
20.0 ± 1.3 [b]	-13.1 ± 4.0 [b]

[a] Calculated from slope of log k/T vs. 1/T (Fig. 5), using the relation from transition state theory:

$$k = KT/h \exp. (-\Delta H^{\neq}/RT + \Delta S^{\neq}/T)$$

$$(R \log_e k/T - R \log_e K/h) = \Delta S^{\neq} + \Delta H^{\neq}(-1/T)$$

[b] Deviations quoted are calculated from the maximum and minimum slopes of Figure 5.

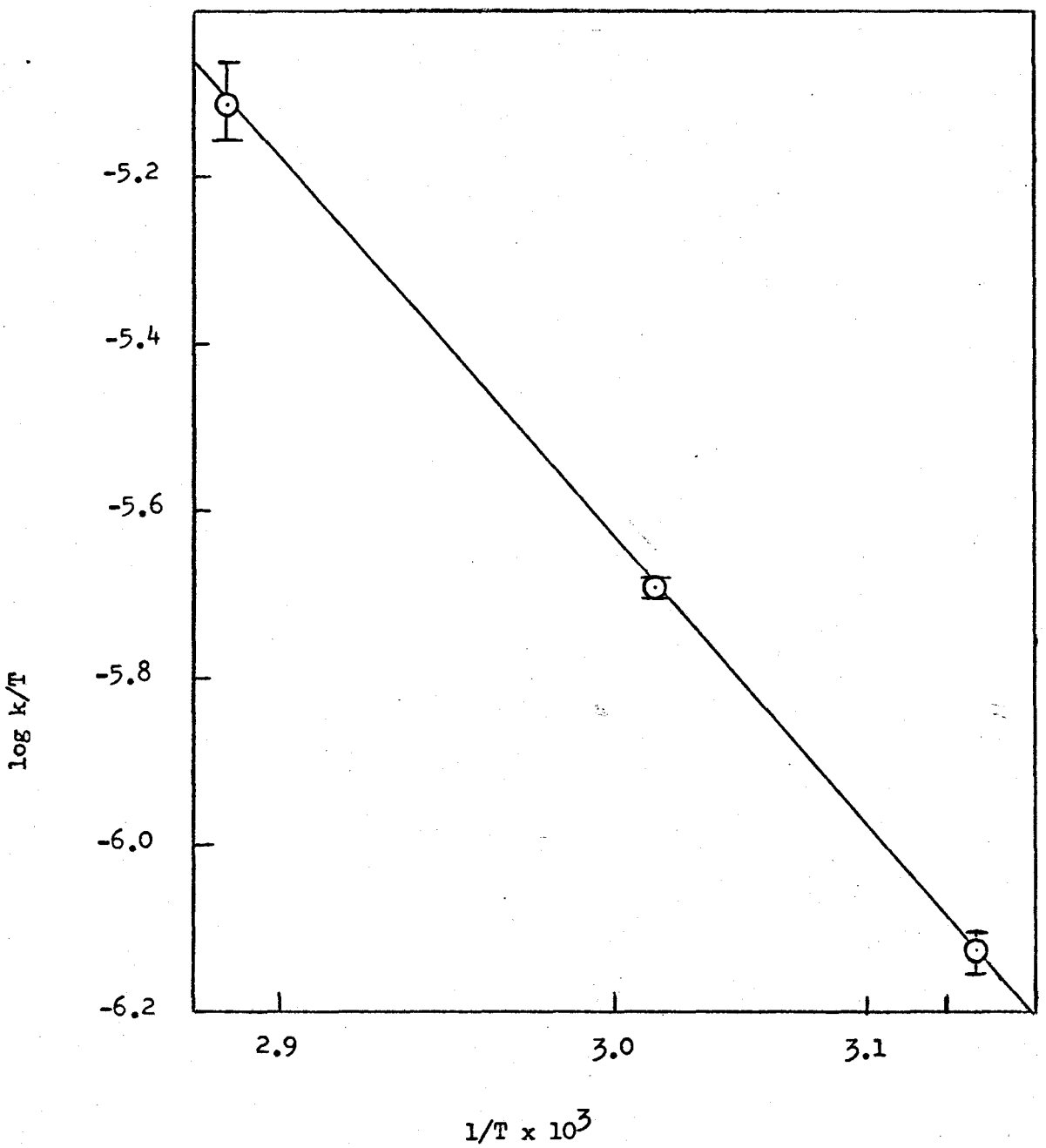


Fig. 5. Plot of log k/T vs. 1/T for the Decomposition of 5,5-Di-p-Anisyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in Chlorobenzene

TABLE XVII

Correlation of Rates of Diazomethane Formation from 5,5-Diaryl-Δ^3-1,3,4-Oxadiazolines by the Hammett Relation

5-Substituents of Oxadiazolines	$k_1^{(1)} \times 10^3$ sec^{-1}	$\log_{10} k/k_o$ [a]	2σ [b]	$2\sigma^+$	$2(\sigma + r\Delta\sigma_R^+)$ [c]
Diphenyl	1.45±0.12	0.000±0.036	0.00	0.00	0.00
Di-p-chlorophenyl	0.61±0.13	-0.378±0.080	0.45	0.23	0.34
Di-p-tolyl	7.81±0.31	0.732±0.017	-0.34	-0.62	-0.48
Di-p-anisyl	34.7±6.5	1.379±0.075	-0.54	-1.56	-1.05

[a] The deviation quoted in each $\log_{10} k/k_o$ was obtained through use of the corresponding extreme values of k.

[b] The Hammett and modified Hammett relations were used, assuming that the effect of para substituents in geminal phenyl groups was additive.

[c] A value of r = 0.5 in conjunction with $\Delta\sigma^+_r = (\sigma^+ - \sigma)$ was used. Brown's σ^+ values are employed.

Activation parameters for a strictly analogous retro-addition are not available. However, unimolecular decompositions, such as the reverse Diels-Alder of cyclopentadiene (185), have entropies of activation near zero. The rather high value obtained here, indicates a need for confirmation through further studies on the other derivatives. A possible explanation is that the transition state here may be sufficiently polar to increase solvent ordering with respect to the ground state. Ionization

reactions in non-polar solvents do have large negative entropies of activation.

Attempted correlation of the rates of the retro-1,3-addition reaction with the substituent constants σ and σ^+ are shown in Figure 6 (Table XVII). A linear relationship with log k/k_o is not obtained in either case. However, the modified Hammett relation of Tsuno and Yukawa (107), shown below, gives a linear fit with $r = 0.5$. The slope yields $\rho = -1.31$ with a standard deviation of the

$$\log k/k_o = \rho(\sigma + r\Delta\sigma_R^+)$$

points from the line of 0.06. An approximate uncertainly in ρ of $\pm$ 0.12 is obtained from the maximum and minimum slopes of lines drawn through the ends of the error tie-lines.

The modified relation is based on the assumption that the degree of resonance delocalization depends on the amount of charge developed at the transition state. The values of the substituent constants therefore vary with the electron demand at the transition state. In the oxadiazoline retro-addition, a negative ρ value, with $r = 0.5$ indicates that only a partial positive charge is developed at the transition state. Comparison with a model reaction allows a better interpretation of the meaning of the calculated parameters. Tsuno and Yukawa have shown that the Diels-Alder reaction of para-substituted 1-phenylbutadienes with maleic anhydride, studied by Dewitt (186), is correlated by the modified relation when

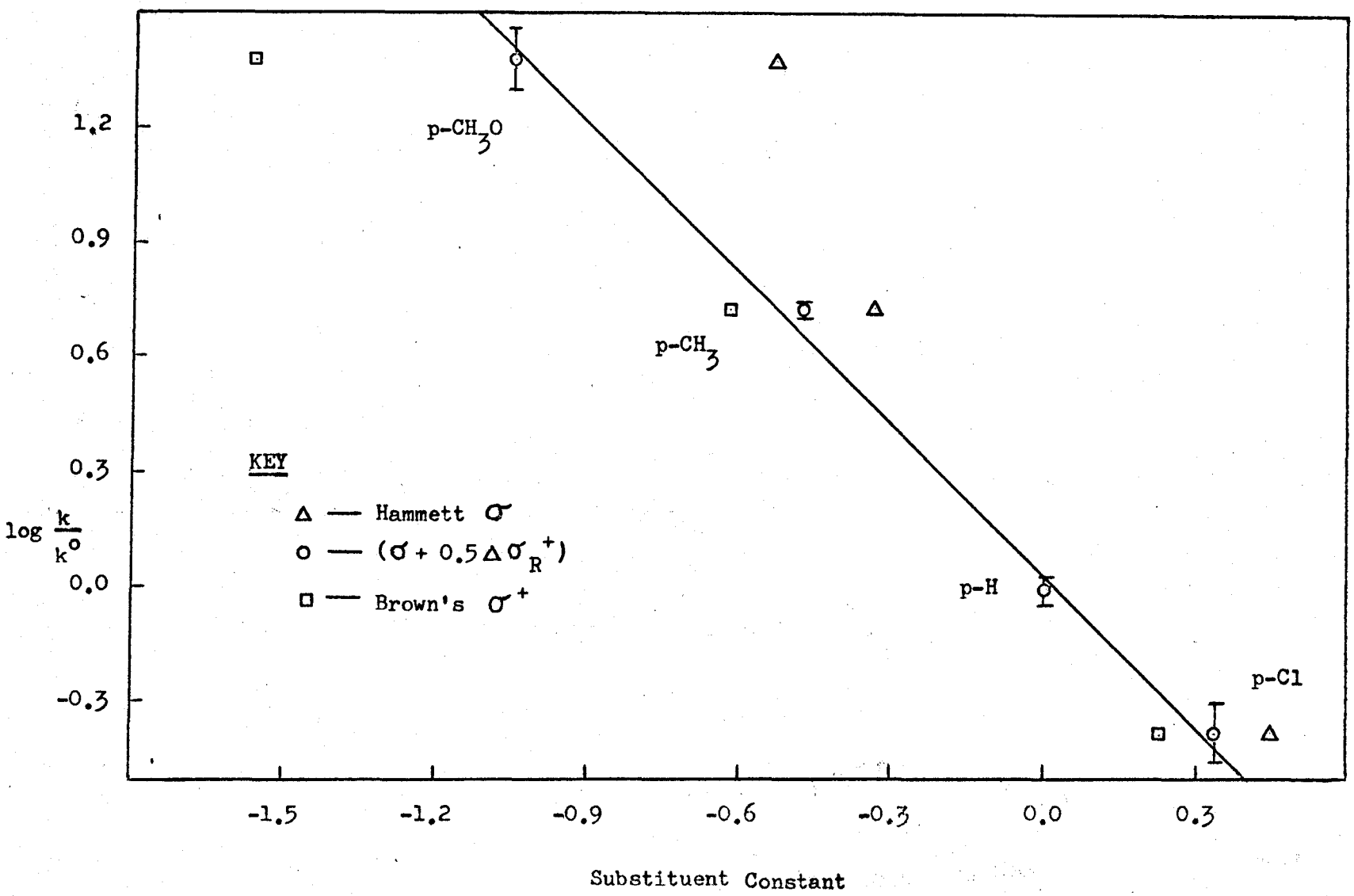
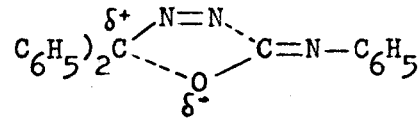
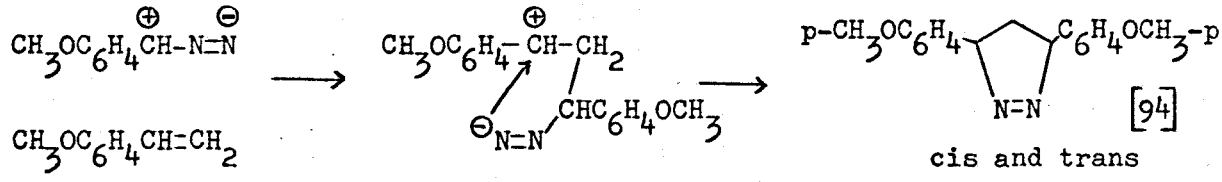


Fig. 6. Correlation of the Rates of Diazomethane Formation at 104.4° by Hammett and Modified Hammett Relations

r = 0.475 with a ρ value of -0.711 at 45°C. The tentative conclusion is that the electron deficiency at the transition state for diazomethane formation is of the same order of magnitude as that in the model Diels-Alder reaction. A possible transition state for the retro-addition is shown below. The extent of the indicated C-N bond stretching cannot be assigned on the basis of the evidence on hand.



Indeed, controversy continues over the mechanism of the forward reaction, the 1,3-dipolar addition of diazo methanes. Huisgen (187) has written the dipolar addition of diazomethanes to olefins as a concerted process. However, Overberger (89) finds that the addition of aryl-diazomethanes to styrenes gives both cis- and trans-1-pyrazolines (eq. [94]). These products are accounted for in terms of free rotation



cis and trans

in an intermediate that results from only a single bond formation in the first step of the addition.

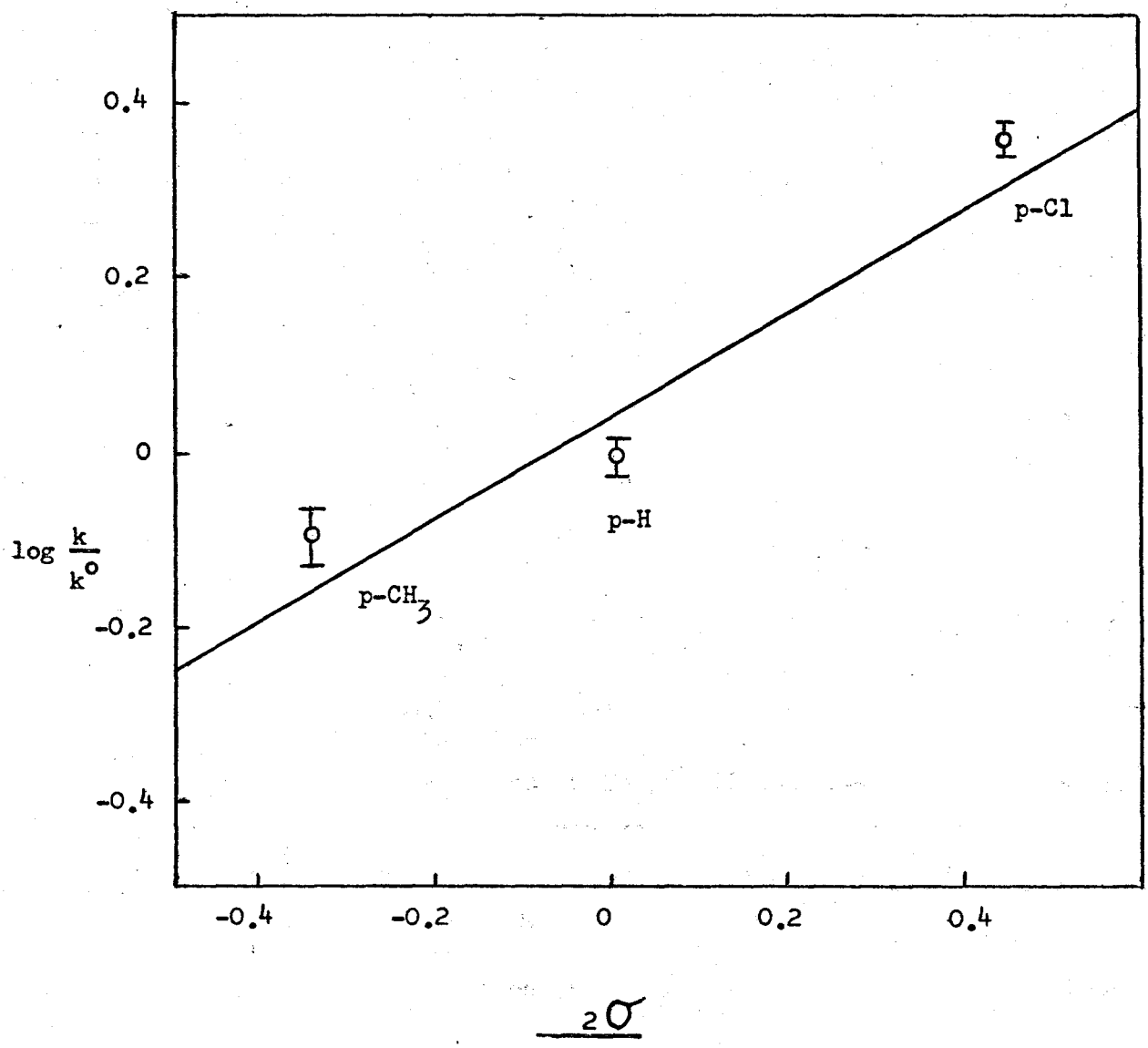


Fig. 7. Correlation of the Rates of Direct Evolution of Nitrogen by the Hammett equation at 104.4° (Hammett σ substituent constants)

The Hammett relation has also been applied to the reaction leading to the direct evolution of nitrogen (Table XVIII; Fig. 7, page 171).

TABLE XVIII

Correlation of Rates of Direct Evolution of Nitrogen from 5,5-Diaryl-Δ^3-1,3,4-Oxadiazolines

5-Substituents of Oxadiazoline	$k_1^{(2)} \times 10^3$ sec^{-1}	$\log_{10} k/k_o$ [a]	2σ
Diphenyl	1.48±0.12	0.000±0.023	0.00
Di-p-chlorophenyl	3.39±0.13	0.360±0.014	0.45
Di-p-tolyl	1.20±0.20	-0.092±0.033	-0.34

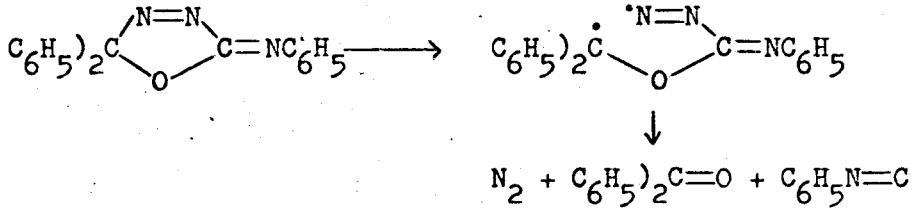
[a] Deviations quoted for $\log_{10} k/k_o$ were obtained through use of the corresponding extreme values of k.

A ρ value of +0.62 is obtained when σ is employed as the substituent constant, indicating a small acceleration of the rate of reaction by electron-withdrawing substituents.

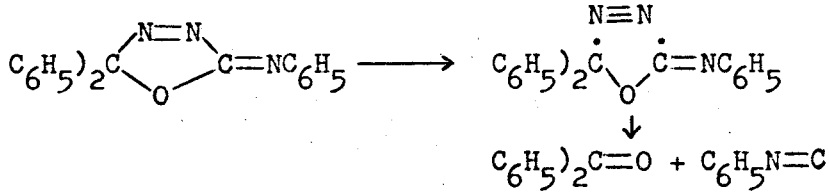
The substituent dependence of the reaction suggests that the C-N bond at the five position is being broken in the transition state of the rate determining step. The production of ketone, isocyanide and nitrogen in the overall process raises the possibility of one or two additional bonds being broken in a concerted process. The mechanisms that can be considered are outlined on the following page. Initially formed

HOMOLYTIC CLEAVAGE

A One Bond

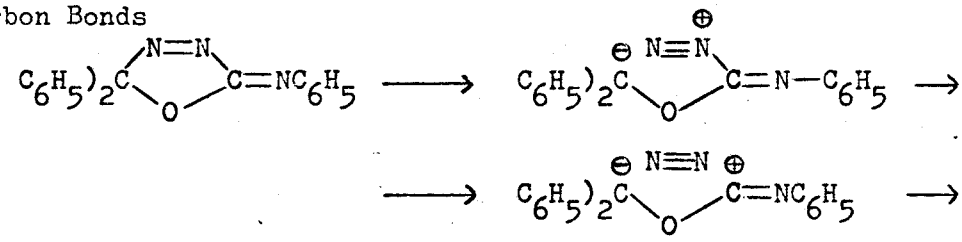


B Two Bond (Concerted)

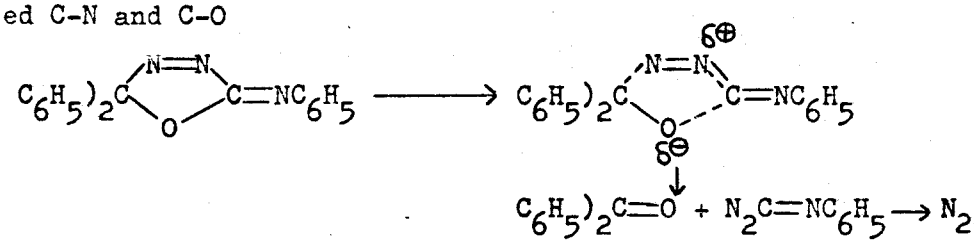


HETEROLYTIC CLEAVAGE

C Azo Carbon Bonds

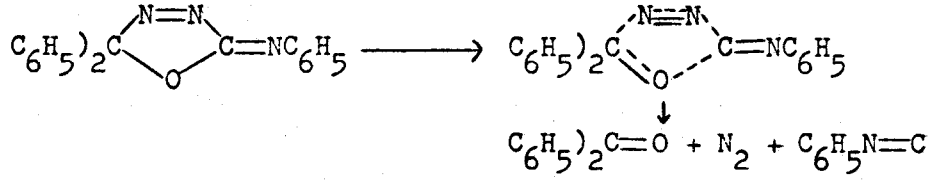


D Concerted C-N and C-O



FULLY CONCERTED

E



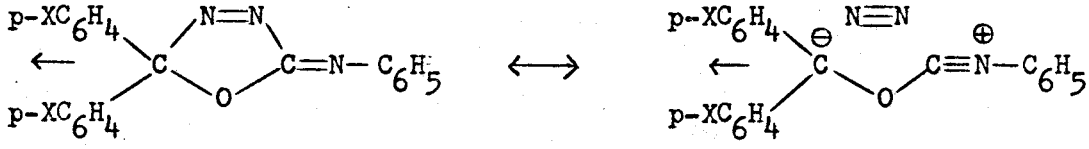
intermediates are considered to decompose rapidly to products.

If the reaction involves formation of a radical center at carbon five (homolytic mechanisms A and B), one would expect stabilization of the transition state by electron donating and withdrawing substituents. In the Historical Introduction (page 45), it is noted that in homolytic decompositions where delocalization of the odd electron is possible, the transition state energy should not vary greatly with substitution. The effect of para substituents could then be more important in the ground state. It has been shown that the decomposition of p,p'-disubstituted benzoyldimides (188) is accelerated by electron withdrawing substituents (eq. [95]). The reactivity order is attributed to weakening of the C-N

$$p\text{-}XC_6H_4\overset{O}{\overset{\|}{C}}\text{-}N{=}N\text{-}\overset{O}{\overset{\|}{C}}C_6H_4\text{-}Xp \longrightarrow p\text{-}XC_6H_4\overset{O}{\overset{\|}{C}}\cdot + N_2 + \cdot\overset{O}{\overset{\|}{C}}C_6H_4X\text{-}p \qquad [95]$$

Rate: X = Cl > CH_3 > CH_3O

bonds in the ground state by inductive electron withdrawl. A similar effect on the azo carbon bonds in the oxadiazolines can be illustrated by the resonance contributors to the ground state depicted below.



Since the magnitude of ρ is small the substituent effect can plausibly be assigned to the ground state.

The negative charge development at the transition state, implicit in the heterolytic mechanisms C, should result in a much larger positive ρ value. The zwitterionic intermediates postulated should be relatively unfavourable in the non-polar chlorobenzene solvent. Development of negative charge on oxygen in the concerted mechanism D also suggests that C-O bond cleavage is more advanced than that of C-N at the transition state. However, a benzhydryl-like carbon-azo bond is expected to be much weaker than a bond between oxygen and the sp^2 imino carbon. Mechanisms involving extensive negative charge development at carbon five or at oxygen seem unlikely on the basis of present evidence.

The fully concerted mechanism E can accommodate the observed substituent effects in terms of ground state energy differences. Clearly, the available evidence only allows the definite conclusion that the C_5-N bond is being broken in a rate-determining step. Attempts to capture a possible diradical intermediate with an olefinic solvent were not successful. Therefore, the mechanism involving the cleavage of 2 azo-carbon bonds and the fully concerted decomposition cannot be distinguished on the basis of present knowledge.

Since the rate of diphenyldiazomethane formation is nearly equal to that for the direct loss of nitrogen, the processes have comparable activation energies. Hence, demonstration of the concerted nature of the former reaction would aid in a more definitive assignment of mechanism for the direct loss of nitrogen.

(iv) Correlation of Decomposition in the Mass Spectrometer and in Pyrolysis Reactions

The use of thermal decomposition studies to confirm mass spectral assignments has interested several authors. The decomposition of pyrazine 2,3-dicarboxylic anhydride (189), phthalic anhydride (190), and 2,5-diphenyl-1,3,4-oxadiazole (191) have been studied in this regard.

The mass spectra of several of the oxadiazolines have been analysed in terms of 2 modes of decomposition, as shown in Table VI, page 122. Peaks are observed that correspond to fragmentation of the molecular ion to give diazomethane and phenyl isocyanate species in one process, and phenyl isocyanide and ketone by another pathway. As might be expected, the former process predominates in the spectrum of the 5,5-di-p-tolyl oxadiazoline, while the latter is more important in the 5,5-di-p-chlorophenyl case.

However, the fragmentation corresponding to loss of carbon monoxide from an M-28 species to give an M-56 ion that is observed in the mass spectrum, does not occur to any great extent in the pyrolysis. According to a proposed mechanism (page 124), the loss of CO would be more likely to occur from a charged fragment in the mass spectrometer, than from the corresponding diradical in a strictly thermal process.

The correlation of electron-impact induced reaction and thermal decomposition must take into account the difference in charge on the two species being compared.

SUMMARY

The reaction of lead tetra-acetate with carbohydrazones and 4-substituted semicarbazones of alkyl and aryl ketones has been investigated. In methylene chloride solution, oxidative cyclization occurred to give 5,5-disubstituted-2-(N substituted)imino-Δ^3,1,3,4-oxadiazolines. These new compounds have been characterized by spectroscopic and chemical evidence that eliminates isomeric structures.

Although the dialkyl ketone derivatives reacted rapidly at 0° to give high yields of the cyclic product, aryl ketone derivatives required longer reaction at 30° and gave lower yields. However, varying the substituents on the nitrogen that is incorporated into the imino group did not have a marked effect on the efficiency of the oxidation.

The extension of the reaction to acetone thiocarbohydrazone gave the corresponding Δ^3-1,3,4-thiadiazoline; but in lower yield than the oxygen analogue.

An improved synthesis of benzophenone carbohydrazone from the ketone hydrazone and phosgene is described. The use of dimethylsulphoxide as a solvent in aryl ketone carbohydrazide condensations has also been investigated.

The thermal decomposition of 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines has been studied in chlorobenzene solution at 104°C. Product analysis, and kinetic experiments employing both infra-red and gas evolution techniques, have shown that two parallel first order reactions are operative in the thermolysis. In one reaction, the oxadiazoline undergoes a retro-1,3-addition to give the corresponding diaryldiazomethane and phenyl isocyanate. The other process yields nitrogen directly, and leads to the formation of phenyl isocyanide and the diaryl ketone.

A study of the effect of para substituents in the 5-phenyl groups of the oxadiazolines showed that the production of diaryldiazomethane was enhanced by electron-donating groups. The rate data was correlated by the modified Hammett relation of Tsuno ($r=0.5$, $\rho = -1.3$), indicating that the breaking of the C-O bond in the transition state involves the formation of partial positive charge at carbon five.

In contrast, the reaction that produces nitrogen, phenyl isocyanide and ketone is accelerated by electron-withdrawing groups. This substituent effect is attributed to a weakening of the bond from carbon five to the azo group in the ground state. On the basis of the evidence, the reaction can be formulated as a fully concerted process producing the three molecular species directly; or as homolytic decomposition producing nitrogen and a diradical that rapidly decomposes to ketone and phenyl isocyanide.

The mass spectra of the Δ^3-1,3,4-oxadiazolines show fragment ions corresponding to both of the thermal decomposition pathways.

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