THE REACTION OF DIAZOALKANES WITH HETEROCUMULENES

MECHANISM AND SYNTHETIC UTILITY

By

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REACTION OF DIAZOALKANES WITH HETEROCUMULENES

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ABSTRACT

A new approach to the synthesis of 3,3-dialkyloxindole systems which involves reaction of a dialkyldiazomethane, generated (in situ) by the thermolysis of a 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one, with an aryl isocyanate, has been developed. Minor products of the reaction are a 2-imino-5,5-dialkyl-4-oxazolidone and a 5,5-dialkylhydantoin. The synthesis of both a 2-imino-5,5-dialkyl-4-thiazolinethione and a 5,5-dialkyl-2,4-dithiohydantoin has been achieved in a similar manner, using phenyl isothiocyanate in place of phenylisocyanate. Spectroscopic data, in particular ^{13}C chemical shifts, and chemical transformations are cited in support of the structural assignments. Possible mechanisms for the formation of the heterocyclic compounds are considered.

ACKNOWLEDGEMENTS

I am grateful to Professor J. Warkentin for his encouragement and continued interest throughout the course of this work. The assistance of Mr. Brian Sayer in obtaining the ^{13}C nmr spectra is most appreciated. Thanks are also due to Mr. A. J. Paine who synthesised two of the compounds used in the thermolysis studies. Finally, I wish to acknowledge the support of the National Research Council of Canada in the form of a postgraduate scholarship during the years 1971-1973.

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CHAPTER I

INTRODUCTION

General

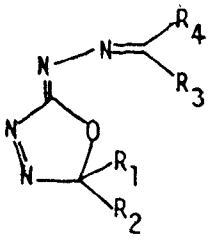
This introduction will illustrate how the mechanism of thermal decomposition of both 2-imino-Δ^3-1,3,4-oxadiazolines and Δ^3-1,3,4-oxadiazolin-2-ones is such that the compounds have some potential as a source of diazoalkanes in synthesis.

Then those reactions of diazoalkanes with cumulative systems which have been reported in the literature, will be examined; particular attention being paid to both the nature of the products formed and the mechanism of their formation.

Finally the known methods of synthesis of the various heterocyclic compounds formed from the reactions of Δ^3-1,3,4-oxadiazolines with aryl isocyanates and phenyl isothiocyanate will be reviewed.

Synthesis and Thermal Decomposition of Δ^3-1,3,4-Oxadiazolines

Synthesis of the Δ^3-1,3,4-oxadiazoline ring system is accomplished by the oxidative cyclisation of ketone semicarbazones and carbohydrazones. In the case of carbohydrazones the products are 2-alkylidene-hydrazono - Δ^3-1,3,4-oxadiazolines (1),[1,2] while in the case of 4-substituted andunsubstituted semicarbazones the products are 2-imino-Δ^3-1,3,4-oxadiazolines (2).[3,4] Acid-catalysed hydrolysis of the latter affords the corresponding Δ^3-1,3,4-oxadiazolin-2-ones (3).[5]



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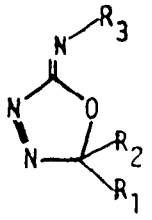

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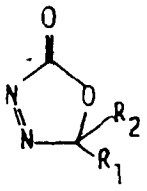

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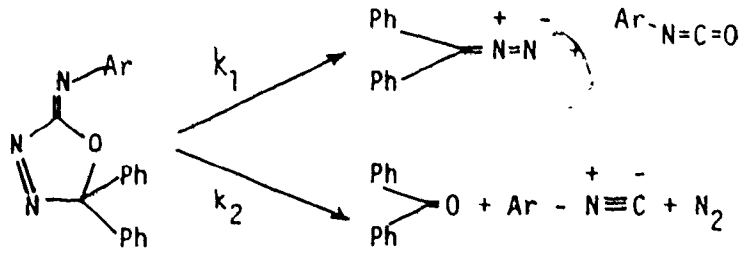
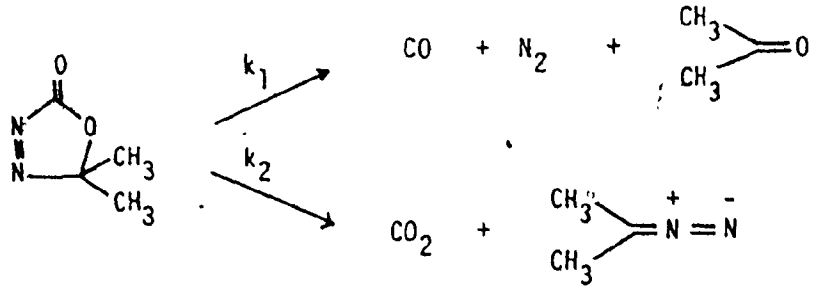
Several people have examined the thermal decomposition of both the iminooxadiazolines and the oxadiazolinones. Warkentin and West,[6] in 1969, reported that 5,5-diaryl-2-phenylimino-Δ^3-1,3,4-oxadiazolines thermally decomposed by a duality of pathways. In one first order process, the oxadiazoline underwent a retro-1,3-addition to yield the corresponding diaryldiazomethane and phenyl isocyanate while in the other nitrogen, phenyl isocyanide and the diaryl ketone were formed. Similarly, it was found that thermolysis of 5,5-diphenyl-2-(arylimino)-Δ^3-1,3,4-oxadiazolines[7] occurred by two parallel first order processes.

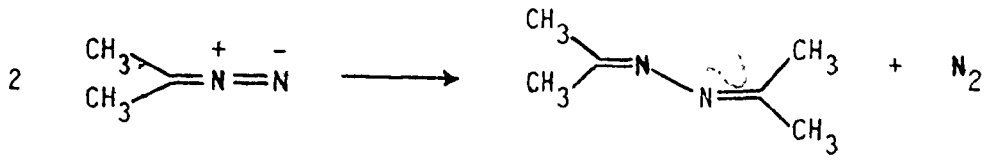


However, Cameron and Warkentin did note that when the two phenyl groups were replaced by methyl groups, there was one significant difference in

the mode of decomposition. For while the expected thermolysis products were formed; that is acetone, aryl isocyanide, and nitrogen from the one pathway and dimethyldiazomethane and an aryl isocyanate from the other, the concentration of the aryl isocyanate rose to 23% of the theoretical maximum and then slowly decreased, long after decomposition of the iminooxadiazoline was complete. This fact, together with the results of several control experiments, indicated that there was a reaction between the dimethyldiazomethane and aryl isocyanate formed initially in the decomposition and that the addition product thus formed, then reacted further with the aryl isocyanate. However the identity of the product was open to speculation since there was no information pertaining to its structure.

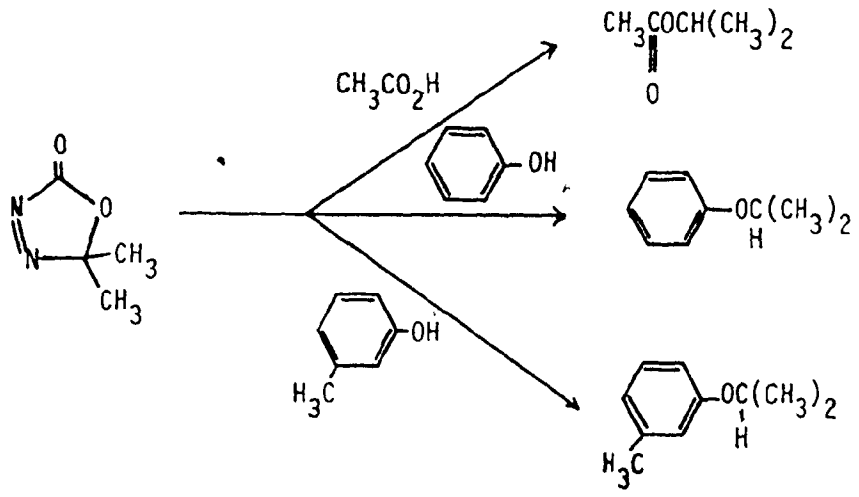
In 1972, Lee, Cameron and Warkentin[8] published a paper describing the thermolysis of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one. They found that this molecule also fragmented by a duality of pathways. In nonpolar solvents such as carbon tetrachloride, the decomposition led primarily to carbon monoxide, nitrogen and acetone. However, in polar solvents such as methanol, decomposition led mainly to carbon dioxide and dimethyldiazomethane which, if no reactive trap was present, went on to acetone azine.





Since thermolysis of the oxadiazoline system in a polar solvent affords predominantly the diazoalkane it seemed reasonable that if a suitable reagent was present during the decomposition, the diazoalkane could be trapped. Should this prove to be the case, thermal decomposition of oxadiazolines promises a simple route to usable complex diazoalkanes. For, fairly complex diazoalkanes are, in general, difficult to prepare due to three factors: firstly, the usual route involving base-catalysed oxidation of hydrazones with mercuric oxide or silver oxide results in traces of metallic impurities which strongly catalyse decomposition of the product diazoalkanes; secondly, hydrazones tend to disproportionate to azines and hydrazones; thirdly, some diazoalkanes react rapidly with themselves to form azines.

Utilising 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one as the source of dimethyldiazomethane, Knittel[4] was able to isolate isopropyl acetate, phenyl isopropyl ether and m-tolyl isopropyl ether when the oxadiazolinone was decomposed in glacial acetic acid, phenol, and m-cresol, respectively. Although the yields were very low, 20% in the case of the ester and only 11% in the case of the ethers, the fact that the anticipated products of reaction between the diazoalkane and the carboxylic acid or the phenol were formed, does indicate that thermolysis of oxadiazolin-ones could prove to be a viable source of diazoalkanes in synthesis.



The Reactions of Diazoalkanes with Heterocumulenes

Cumulenes are, by definition, compounds with double bonds adjacent to each other. The parent compound is allene in which the centre as well as the terminal atoms are carbon. However, if one or more of the atoms of the cumulative systems are hetero atoms, such as oxygen, nitrogen or sulphur, they are known as heterocumulenes. The heterocumulenes can be divided into two groups: (I) heterocumulenes having one or two hetero atoms in the cumulative arrangement (by this definition one or two carbon atoms are part of the cumulative system); and (II) heterocumulenes in which all three atoms in the cumulative arrangement are hetero atoms. Group I can be subdivided into three groups, namely (i) systems with two carbons and one hetero atom; (ii) systems with one carbon and two like hetero atoms; and (iii) systems with one carbon and two different hetero atoms. Examples of group I heterocumulenes are ketene (4), carbon dioxide (5), and carbonyl sulphide (6).

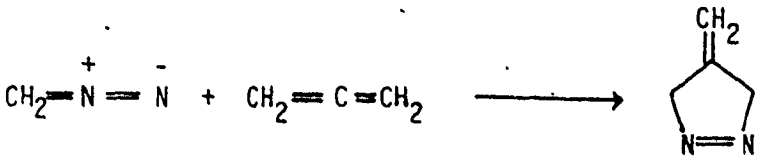
$H_2C=C=O$ (4) $O=C=O$ (5) $O=C=S$ (6)

Group II can be subdivided into two groups, namely (i) systems with two like hetero atoms; and, (ii) systems with three different hetero atoms. Typical examples of these two groups are sulphur dioxide and N-sulphinylamines

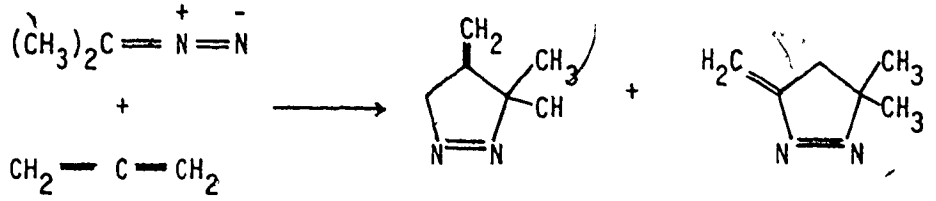
$O=S=O$ $R-N=S=O$

In order to limit the extent of the material presented and to ensure better correlation, only reactions between diazoalkanes and cumulative systems which approximate four-electron double bond systems, will be discussed. Reactions between diazoalkanes and those compounds with typical dipolar character or adjacent single and triple bond systems such as nitrones, nitrile oxides, azomethine imines, nitrile imines, cyanates, thiocyanates, nitrous oxide, azoxy compounds, azosulphides, azides and S-nitroso compounds will not be considered. Included in this category are, of course, dimerization reactions of diazoalkanes.

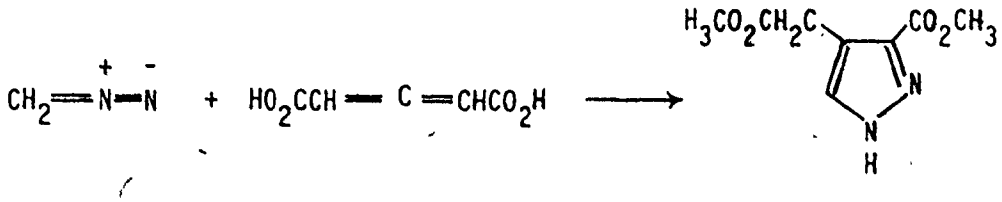
The earliest reported work on the reaction of a diazoalkane with a cumulene appears to be that of I.A. D'Yakanov[9] in 1945. He claimed that the product of reaction between diazomethane and allene in ethereal solution at 15° was 4-methylene-Δ^1-pyrazoline. Twenty years later Dowd,[10] and Crawford and Cameron[11] independently confirmed D'Yakanov's observations and established by nmr spectroscopy that the structure of the 1:1 adduct of diazomethane and allene was, in fact, 4-methylene-Δ^1-pyrazoline.



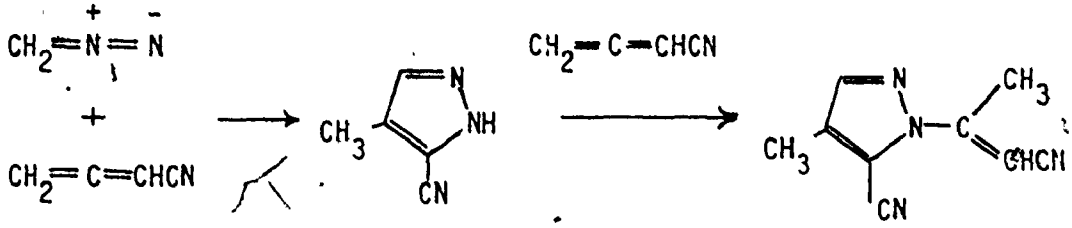
When 2-diazopropane was used in place of diazomethane, Crawford, Cameron and Tokunaga[12] found that two isomeric cycloaddition products were formed, namely 3,3-dimethyl-4-methylene-Δ^1-pyrazoline and 3,3-dimethyl-5-methylene-Δ^1-pyrazoline.



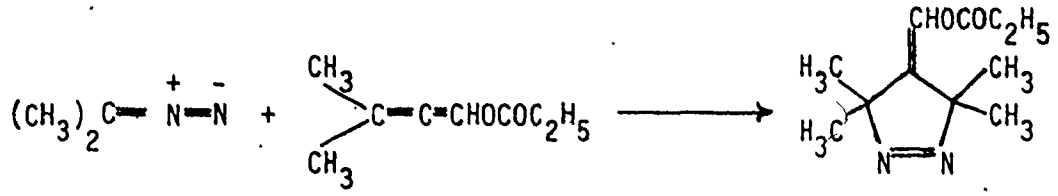
In 1958, Corsano, Capito and Bonamico[13] isolated methyl 3-carbomethoxypyrazole-4-acetate upon treatment of an ethereal solution of the allenic acid, glutinic acid, with diazomethane.



Six years later, Ried and Mengler[14] undertook an extensive investigation of the reaction of diazoketones and diazoalkanes with cyanoallene. Equimolar quantities of diazomethane and cyanoallene were found to yield the 1:1 adduct, 4-methyl-5-cyanopyrazole, but in the presence of an excess of cyanoallene further attack occurred at the unsubstituted nitrogen, resulting in the formation of the 2:1 adduct.

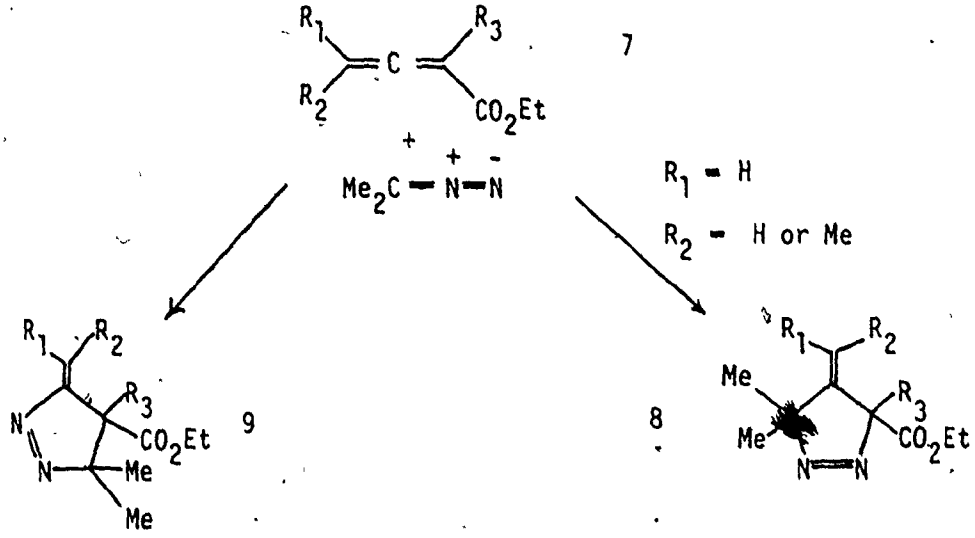


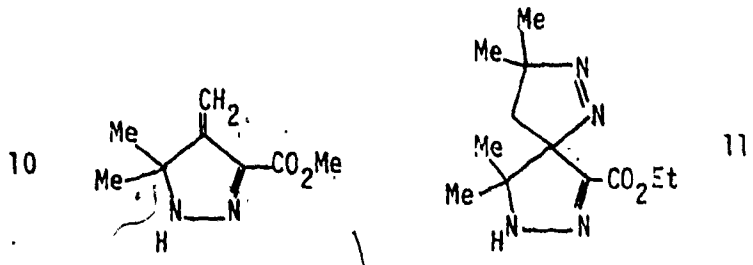
Day and Whiting[15] found that dimethyldiazomethane and 3-methylbuta-1,2-dienylpropionate reacted slowly at 0-20° to afford a crystalline adduct in low yield. From spectroscopic data and photolytic decomposition products, the compound was determined to be 3,3,5,5-tetramethyl-4-(propionyloxymethylene)-pyrazoline.



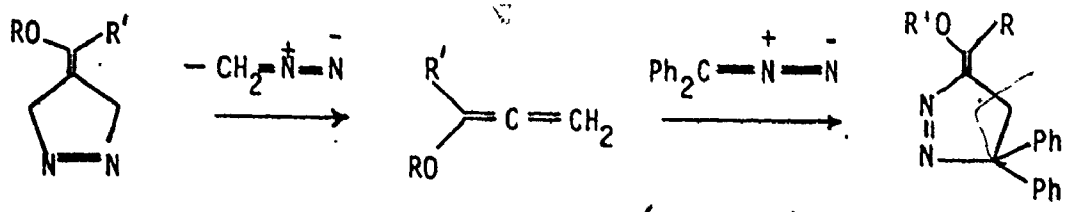
On extending the study to reactions between dimethyldiazomethane and a series of conjugated allenic esters (7 R=H, Me) Andrews and Day[16] found that, although in all cases cycloaddition occurred at the more electrophilic (αβ) double bond, the orientation was dependent in a very clear-cut way on the substitution at the γ-carbon atom. Thus, adducts of the type (8) were found to be the sole products formed from allenic esters (7, R_3=Me) in which at least one of the groups R^1 and R^2 is hydrogen. However, while esters (7, R^1=R^3=H) which lacked the α-methyl group behaved similarly, the reaction was complicated somewhat by the very ready tautomerisation of the initial adduct (8, R^3=H). Thus, methyl butadienoate rapidly formed 4-methylene-Δ^2-pyrazoline (10) with dimethyldiazomethane. In the presence of an excess of the diazo compound

further attack occurred at the exo-double bond and the spiro system (11) was obtained. The γ,γ-disubstituted allenes (7, R^1=R^2=Me, R^3=H and Me) in contrast, yielded the isomeric 3-alkylidene pyrazolines (9, R^1=R^2=Me) in which dimethyldiazomethane had added to the α,β-double bond in the opposite sense.

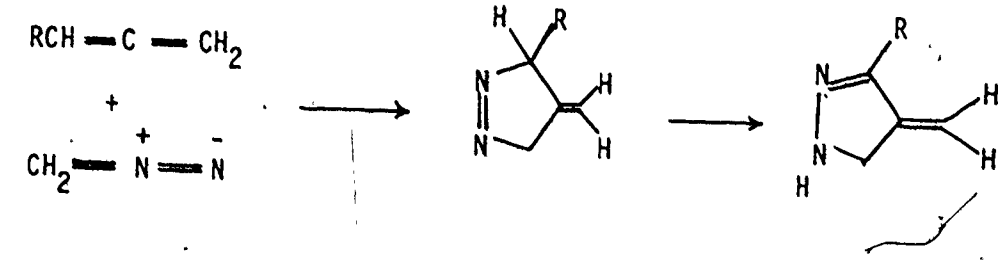


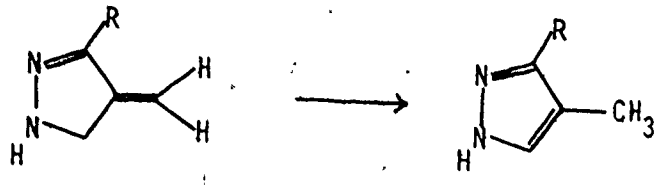


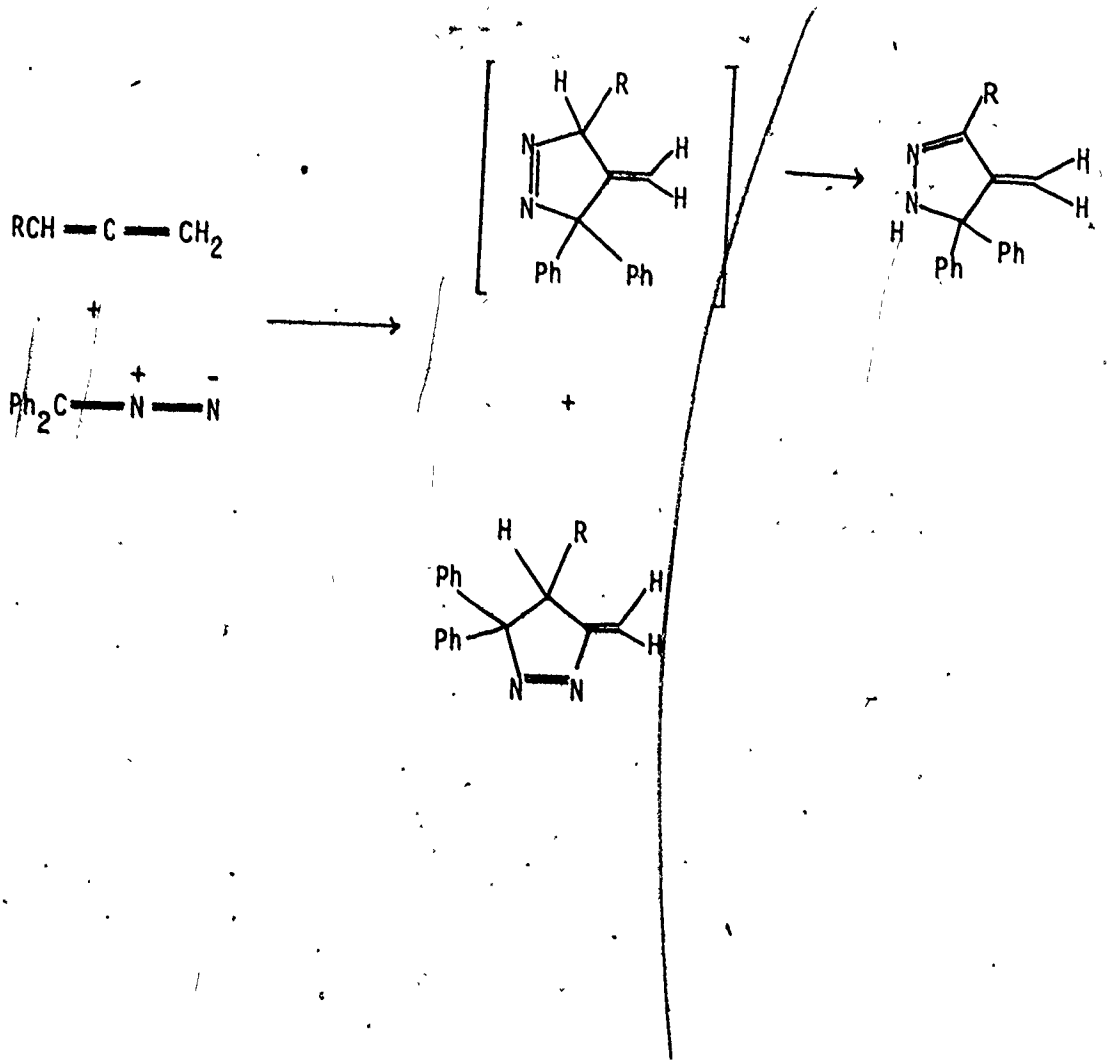
Battioni and Vo-Quang[17] investigated the reaction of diazomethane and diphenyldiazomethane with several alkoxyallenes and discovered, as had Day and Whiting, that cycloaddition occurred at the double bond β to the substituent rather than at the double bond bearing the electron-donating substituent. Furthermore, they found that the direction of addition to the double bond was determined by the nature of the substituents on the diazo compound.



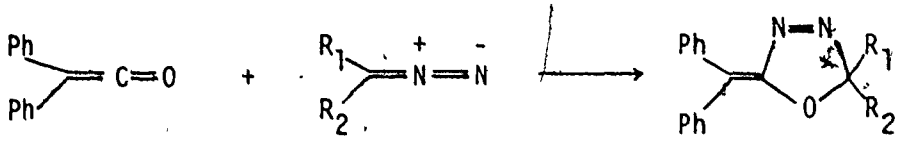
A subsequent study[18] of the reactions of both diazomethane and diphenyldiazomethane with allene ketones and esters revealed that cycloaddition occurred at the double bond α to the electron-withdrawing substituent. The direction of addition of diazomethane to the allenic systems was found to be unique, the nitrogen of the diazoalkane always being attached to the carbon atom bearing the substituent, but such was not the case with diphenyldiazomethane as compounds arising from two different modes of cycloaddition were isolated. Thus, a mixture of 3-substituted-4-methylene-Δ^2-pyrazolines and 3-substituted-4-methylpyrazoles was formed from reaction of diazomethane with the allenic ketones and esters while a mixture of the 3-substituted-4-methylene-5,5-diphenyl-Δ^1-pyrazolines and 3,3-diphenyl-4-substituted-5-methyl-Δ^1-pyrazolines was obtained from reaction of diphenyl diazomethane with the allenic systems.





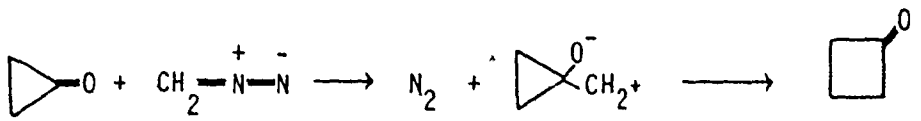


One of the earliest accounts of the reaction of a diazoalkane with a heterocumulene in the literature is that of Staudinger and co-workers[19,20] in 1916. On reacting diphenylketene with diphenyldiazomethane they obtained a stable addition compound to which they initially assigned the diazolinone structure. However, on further examination of the product they[21] discovered that thermal decomposition at 160-170° did not afford crystalline tetraphenylethylene and, furthermore, no carbon monoxide was evolved and thus the addition compound was reassigned the Δ^3-1,3,4-oxadiazoline structure. Similar addition compounds were obtained when 4-methoxy-diphenyldiazomethane and diazomethane were used but when benzylphenyldiazomethane was used, an addition compound containing two molecules of ketene and one molecule of diazo compound was isolated. Its structure, however, was not determined.

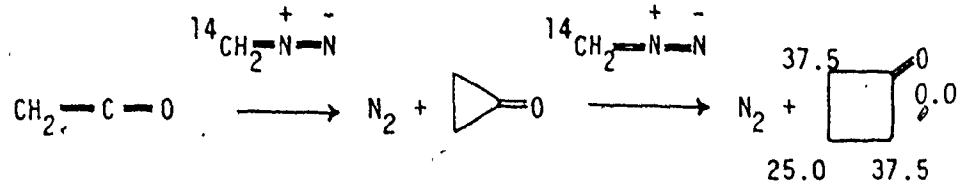


The next mention of a diazoalkane-ketene reaction in the literature was in 1931. Lipp and Köster,[22] in the course of research into possible syntheses of cyclopropanone, passed ketene into an ethereal solution of diazomethane at room temperature and after treating the reaction mixture with an aqueous semicarbazide solution, were able to isolate cyclobutanone semicarbazone. They suggested that the reaction proceeded via cyclopropanone as an intermediate and in support of this mechanism, cited the fact that the second step was similar

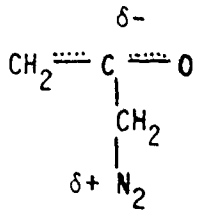
to the path proposed for the formation of methyl ethyl ketone from acetone and diazomethane.



Proof that an intermediate possessing the symmetry properties of cyclopropanone was involved in the formation of cyclobutanone from ketene and diazomethane came from the work of Semenow, Cox and Roberts.[23] Using C^{14}-labelled diazomethane, they were able to show that the C^{14} distribution was consistent with initial formation of cyclopropanone and subsequent introduction of a methylene group on either side of the carbonyl group.

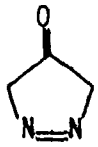


In 1966, Hammond and Turro[24,25,26] reported the synthesis of cyclopropanone, methyl-cyclopropanone and 2,2-dimethyl-cyclopropanone by the slow addition of a methylene chloride solution of the diazoalkane to the ketene at -78°. Characterisation of the cyclopropanones was accomplished by spectroscopy and chemical reactions. The authors considered that the addition of the diazoalkane to the ketene probably involved a zwitterion intermediate such as (A).



A

For, although the addition of diazoalkanes to ketenes is formally a simple methylene transfer, the decomposition of azo compounds to yield carbenes generally requires either a high temperature, or a catalyst. However, while 1,3-cycloadditions of diazomethane and ketene to yield (12), (13) or (14) may occur, none of these compounds is known to evolve nitrogen spontaneously.



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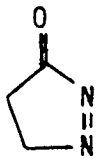

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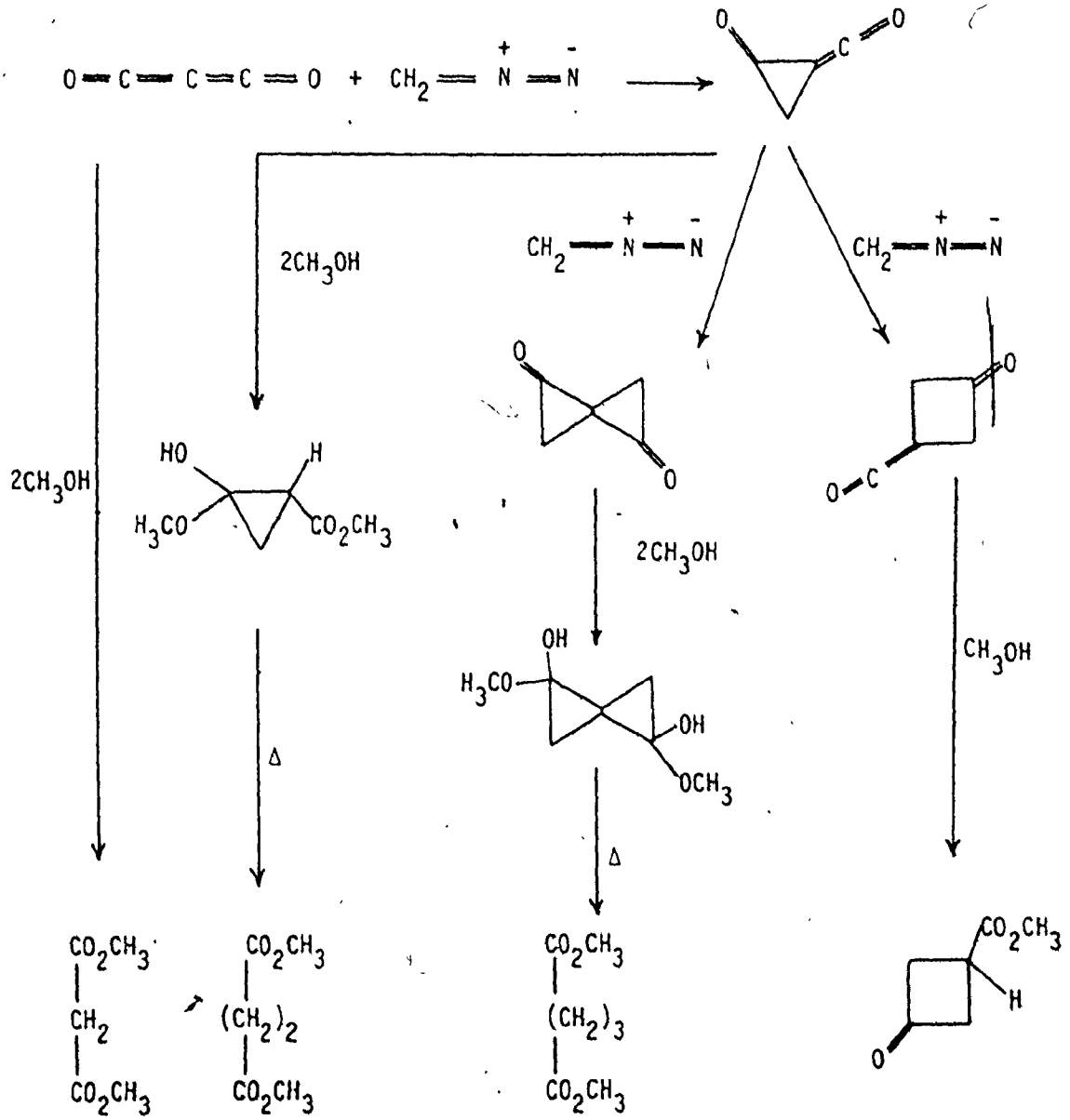
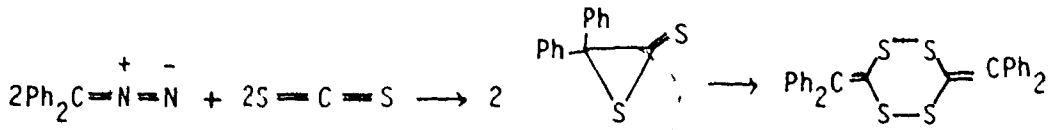
The only account of the reaction of a diazoalkane with carbon suboxide is that of Schaafsma, Steinberg and De Boer.[27] On adding a methanolic solution of diazomethane to an ethereal solution of the heterocumulene, they were able to isolate eight compounds, four of which were identified as methyl malonate, methyl succinate, methyl glutarate and methyl 3-oxocyclobutanecarboxylate. Mechanistically, it was thought that the reaction involved the formation first of an unsaturated oxocyclopropanone from one molecule of diazomethane and one molecule of carbon suboxide, analogous to the formation of cyclopropanone from a molecule of diazomethane and a molecule of ketene. This intermediate could then react in several different ways: it could add two molecules of methanol yielding 1-hydroxy-1-methoxy-2-carbomethoxy

cyclopropane or it could react with a second molecule of diazomethane and subsequently with methanol, affording methyl 3-oxocyclobutanecarboxylate and probably 1,5-dihydroxy-1,5-dimethoxy spiropentane as well, since cyclopropanone semiacetals are known to isomerise to propionic esters. Methyl malonate undoubtedly was formed through reaction of one molecule of carbon suboxide with two molecules of methanol.

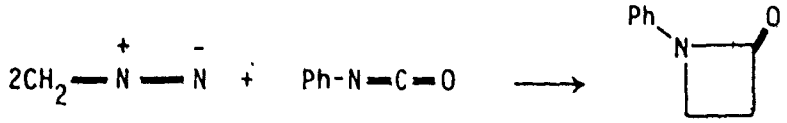


Schönberg, Frese and Brosowski[28] found that reaction of diphenyldiazomethane with carbon disulphide in refluxing toluene and trituration of the resultant oil with hot ethanol afforded crystalline 3,6-diphenylmethylene-1,2,4,5-tetrathiacyclohexane. Formation of the heterocycle was believed to occur via a three-membered ring intermediate.

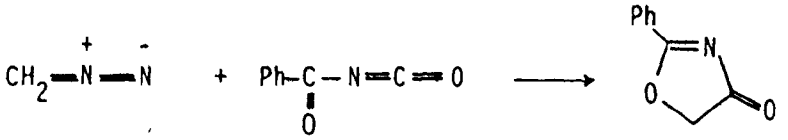


The first mention of the reaction of a diazoalkane with a heterocumulene in the literature appears to be that of von Pechmann[29] in 1895. On reacting diazomethane with phenyl isocyanate he obtained an oily product which was not further characterised.

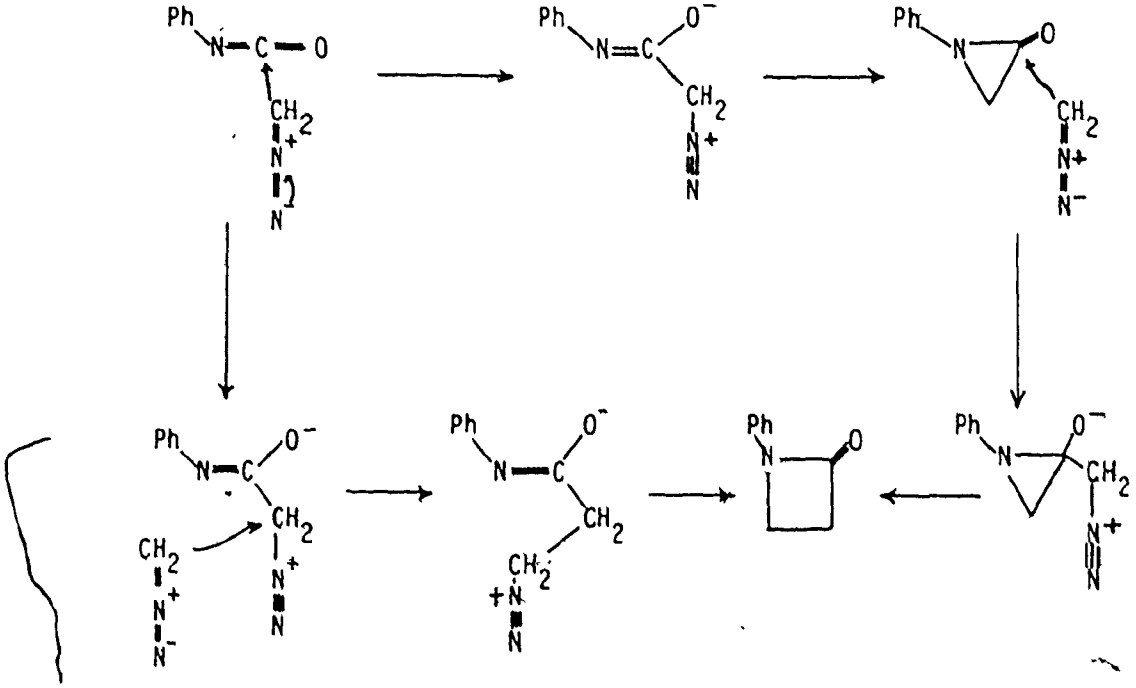
It was left to Sheehan and Izzo[30] in 1948 to establish that the product of the reaction between diazomethane and phenyl isocyanate was, in fact, the β-lactam of N-phenyl-β-alanine.



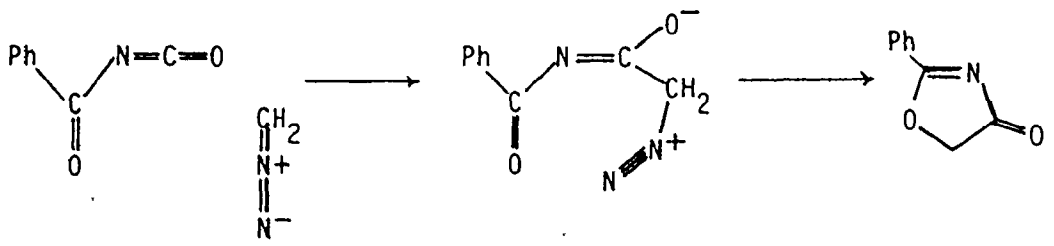
Extending the investigation to other isocyanates, they[31] found that although reaction with p-bromophenylisocyanate yielded the corresponding β-lactam, reaction with α-naphthyl, p-nitrophenyl and benzyl isocyanates did not. Diazomethane and benzoyl isocyanate reacted rapidly but instead of yielding the β-lactam, afforded a 1:1 adduct, 2-phenyl-4-oxazolone.



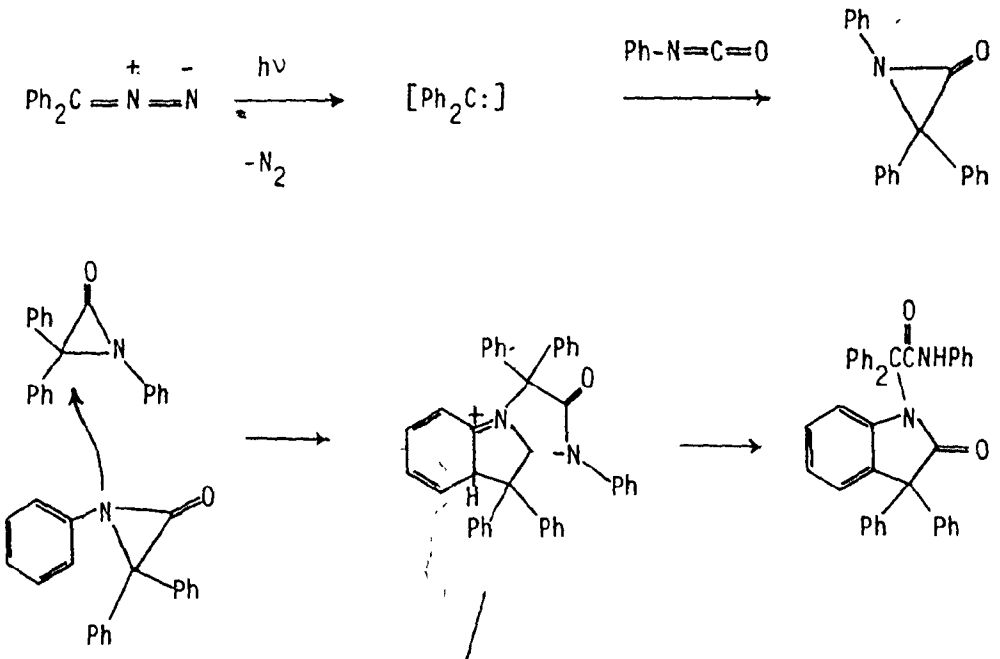
Formation of the β-lactam was rationalised in terms of the successive addition of two methylene groups to the polarized carbonyl double bond of phenyl isocyanate. Addition of the first molecule of diazomethane afforded a dipolar species which, unable to form a stable three-membered ring (α-lactam), reacted with a second molecule of diazomethane to form the β-lactam. Alternatively, the α-lactam may have actually formed but then reacted immediately with another molecule of diazomethane to enlarge the ring to the more stable four-membered ring.



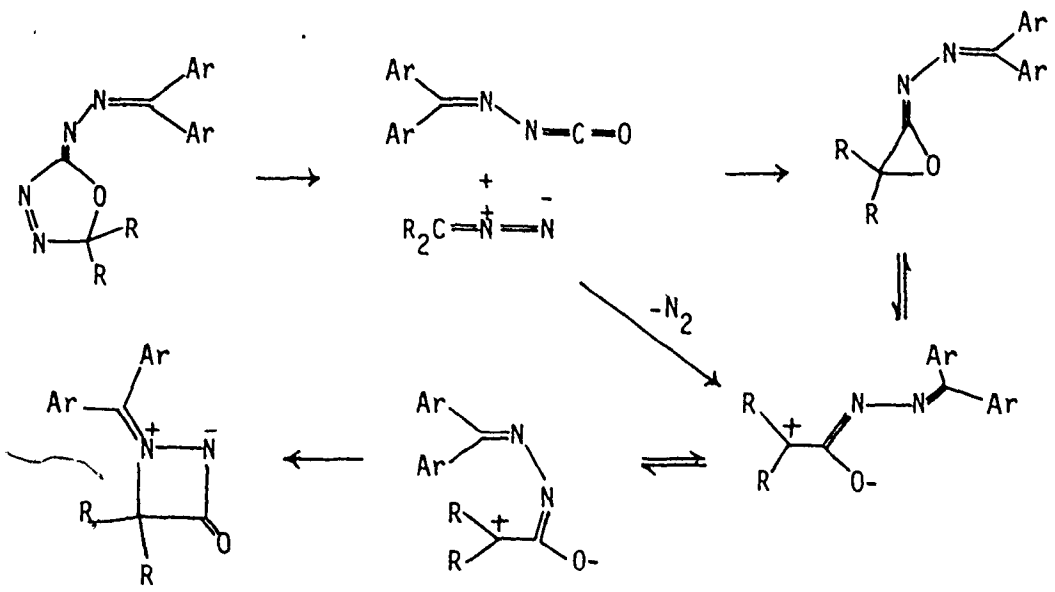
The formation of 2-phenyl-4-oxazolone by reaction of diazomethane with benzoyl isocyanate differs mechanistically in that after the addition of the first molecule of diazomethane, the intermediate so formed is favourably set up to form a stable five-membered oxazoline ring and consequently addition of the second molecule of diazomethane does not occur.



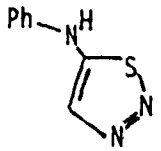
Sheehan and Lengyel[32] subjected a solution of diphenyldiazomethane in phenyl isocyanate to ultraviolet irradiation and were able to isolate 2-[1'-(3,3'-diphenyloxindolyl)]-2,2-diphenylacetanilide[34] as well as two dimeric products. They suggested that formation of the oxindole occurred through addition of the photogenerated carbene from diphenyldiazomethane to the phenyl isocyanate to produce an α-lactam. This α-lactam[33] then underwent an unusual dimerization involving ring expansion of the α-lactam with concomitant attack of the heterocyclic nitrogen on the carbon atom of another α-lactam molecule to yield a zwitterionic intermediate. A subsequent proton shift would afford the photo-product.

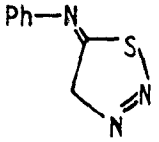


The most recent example of the reaction of a diazoalkane with an isocyanate is the formation of 3-oxo-1,2-diazetidinium hydroxide inner salts by thermolysis of 2-hydrazono-Δ^3-1,3,4-oxadiazolines.[35,36] Persuasive experimental evidence exists that the diazoalkane and the N-isocyanatoimine generated in the initial fragmentation of the oxadiazoline, recombine with the loss of nitrogen to form either a dipolar species directly, or an iminooxirane which subsequently ring opens, affording the dipolar species. Inversion of configuration about the amido nitrogen followed by inversion of configuration about the second nitrogen will give rise to a dipolar species with the s-trans configuration which is geometrically suited for closure to the observed product.



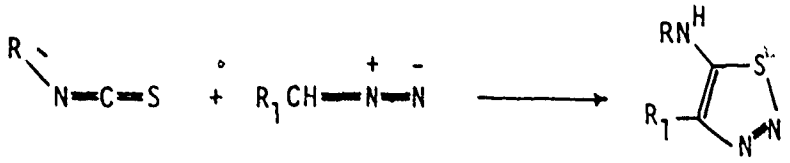
When von Pechmann[29] reacted diazomethane with phenyl isothiocyanate he obtained an equimolar adduct in contrast to the 2:1 adduct obtained from reaction of diazomethane with phenyl isocyanate. At first, von Pechmann assumed that the addition could have taken place in either of two ways to the nitrogen-carbon double bond of phenyl isothiocyanate. However, failure to convert the supposed thiocarbonyl group to a carbonyl group by treatment with mercuric oxide later led von Pechmann to formulate the reaction as proceeding by the addition of diazomethane across the thio carbonyl group of phenyl isothiocyanate to produce a sulphur-containing ring. Of the two possible formulae, von Pechmann favoured 5-anilino-1,2,3-thiadiazole over the tautomeric 5-phenylimino-1,2,3-thiadiazoline.





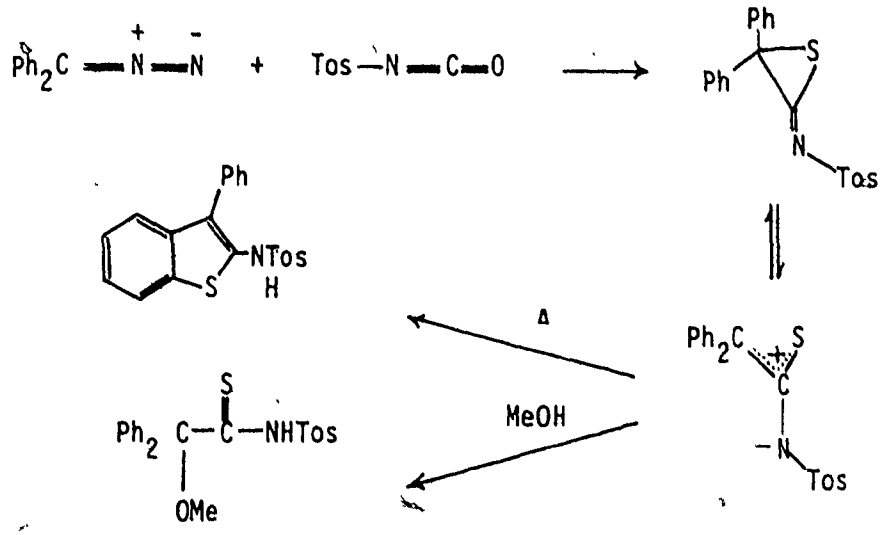
In 1949, Sheehan and Izzo[31] were able to confirm by means of several chemical reactions von Pechmann's suspicion that the product of reaction between diazomethane and phenyl isothiocyanate was indeed 5-anilino-1,2,3-thiadiazole. They suggested that formation of the thiadiazole occurred because on addition of the molecule of diazomethane to the carbon atom of the isothiocyanate moiety, the nucleophilicity of the neighbouring sulphur atom was such that ring closure to a stable five-membered system was made possible at a rate faster than nitrogen was eliminated.

Two different research groups investigated the scope of the reaction by using diazoalkanes other than diazomethane and alkyl and aryl isothiocyanates. Lieber, Calvanico and Rao[37] were able to synthesise a series of 5-arylamino-1,2,3-thiadiazoles by reaction of diazomethane with various aryl isothiocyanates. Tisler, Hrovat and Machiedo[38] carried out a somewhat more extensive investigation, studying the reactions of diazomethane, diazoethane, phenyldiazomethane and ethyldiazoacetate with several alkyl and aryl isothiocyanates. They found that the reactivity of the various isothiocyanates towards diazomethane and diazoethane differed markedly; para- and meta-substituted aromatic isothiocyanates readily yielded 1,2,3-thiadiazoles while alkyl isothiocyanates and ortho-substituted aromatic isothiocyanates failed to produce 1,2,3-thiadiazole derivatives.

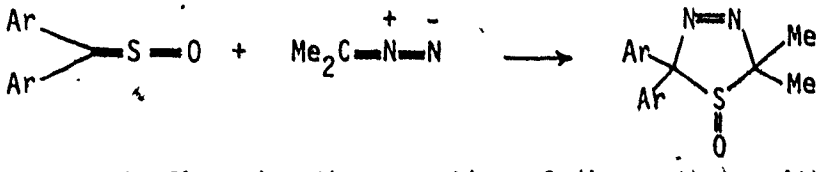


However, in the hands of Martin and Mucke,[39,40] reaction of diazomethane (either in the gas phase or in ethereal solution) with alkyl isothiocyanates and ortho-substituted aromatic isothiocyanates did afford N-substituted 5-amino-1,2,3-thiadiazoles. Furthermore, they found that the rate of formation of the thiadiazole increased with increasing electrophilicity of the isothiocyanato-carbon atom but that it was not affected by the polarity of the solvent. On the basis of this evidence they concluded that the reaction was a 1,3-dipolar cycloaddition rather than a stepwise process involving a zwitterionic intermediate, as Sheehan and Izzo had suggested.

In marked contrast, L'abbé, Dekerk, Declerq, Germain and Van Meerssche[41] have recently found that reaction of equimolar amounts of diphenyldiazomethane and tosyl isothiocyanate in anhydrous ether at 0°C affords 2-tosylimino-3,3-diphenylthiirane. Chemical reactions of this compound proceed via cleavage of the sulphur-quaternary carbon bond; thus the iminothiirane thermally decomposes in chloroform solution during three days to the benzo(b)thiophene and upon treatment with methanol furnishes the thioamide.

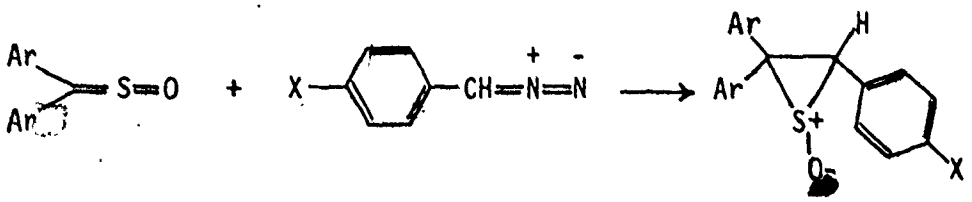


The accessibility of aromatic sulphines (thione S-oxides) through the oxidation of thiones with peroxy acids, prompted Bonini, Maccagnani, Wagenaar, Thijs and Zwanenburg[42] to investigate their reaction with diazoalkanes in the hope of synthesising novel heterocyclic systems. They found that aromatic sulphines such as thiobenzophenone-S-oxide and thiofluorenone-S-oxide reacted smoothly with 2-diazopropane affording Δ^3-1,3,4-thiadiazoline-1-oxides in high yield. Reaction with diazomethane was more sluggish and in most cases a complex mixture of products resulted although reaction of thiofluorenone-S-oxide with diazomethane did give the desired 1:1 cycloadduct in 50% yield.



Confirmation that reaction of diazomethane with aromatic sulphines yielded Δ^3-1,3,4-thiadiazoline-1-oxides came from the work of Venier and Gibbs.[43]

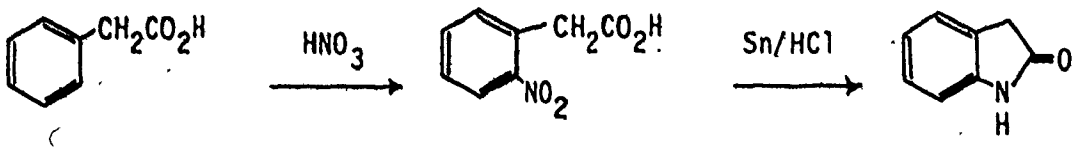
In contrast, Bonini and Maccagnani[44] found that reaction of aromatic sulphines with aryldiazomethanes under identical experimental conditions, yielded a mixture of diastereoisomeric episulphoxides.



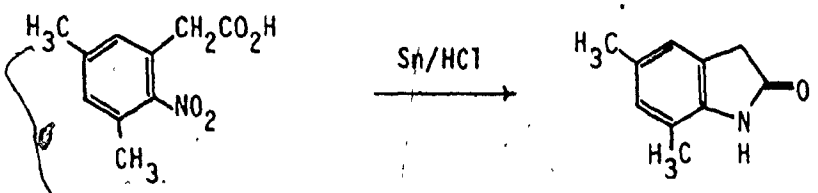
Synthesis of Oxindoles

Of the numerous routes to oxindoles which have appeared in the literature, the most commonly encountered are the cyclisation of 2-amino phenylacetic acid derivatives, the Lewis acid catalysed cyclisation of α-haloacetanilides and the condensation of acylphenylhydrazines using alkaline reagents and elevated temperatures.

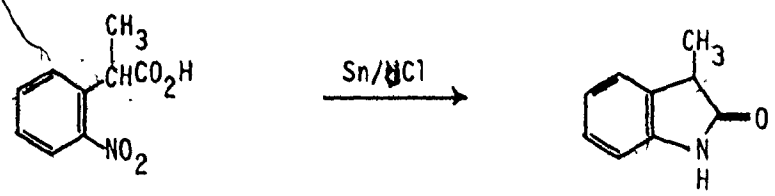
In 1878, Baeyer[45] achieved the first total synthesis of oxindole by reducing 2-nitrophenylacetic acid with tin and hydrochloric acid.



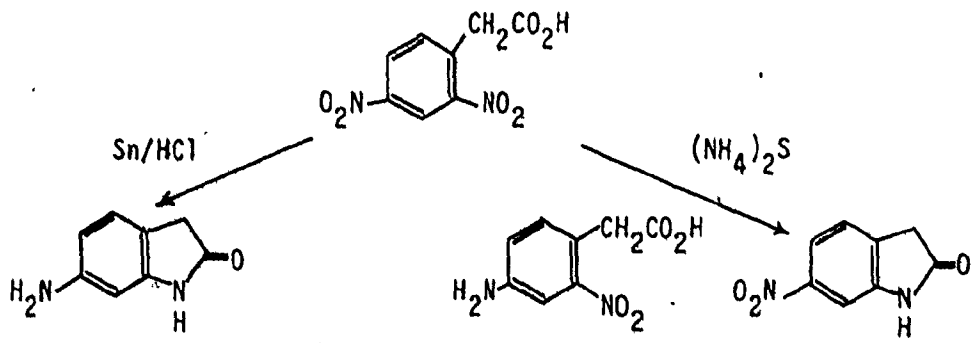
During the succeeding years, several substituted oxindoles were obtained from phenylacetic acid derivatives by nitration and reduction with tin and hydrochloric acid, Wispec[46] preparing 5,7-dimethyloxindole from the dimethylacetic acid derived from mesitylene, and



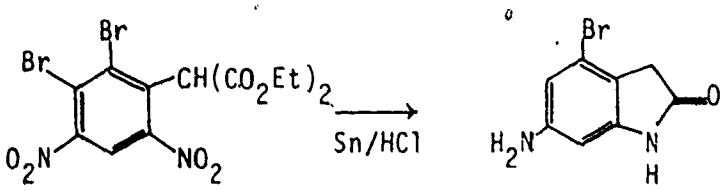
Trinius[47] obtaining 3-methyloxindole by reduction of 2-nitrohydratropic acid.



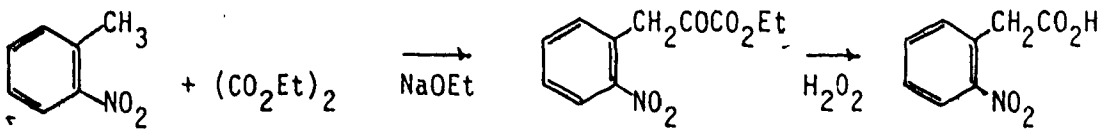
2,4-Dinitrophenylacetic acid, on reduction with ammonium sulphide, was found to yield a mixture of 2-nitro-4-aminophenylacetic acid and 6-nitrooxindole, but on treatment with tin and hydrochloric acid, afforded only 6-aminooxindole.[48,49]



Jackson and Bancroft[50] prepared 4-bromo-6-aminooxindole by reduction of ethyl 2,3-dibromo-4,6-dinitrophenylmalonate with tin and hydrochloric acid.



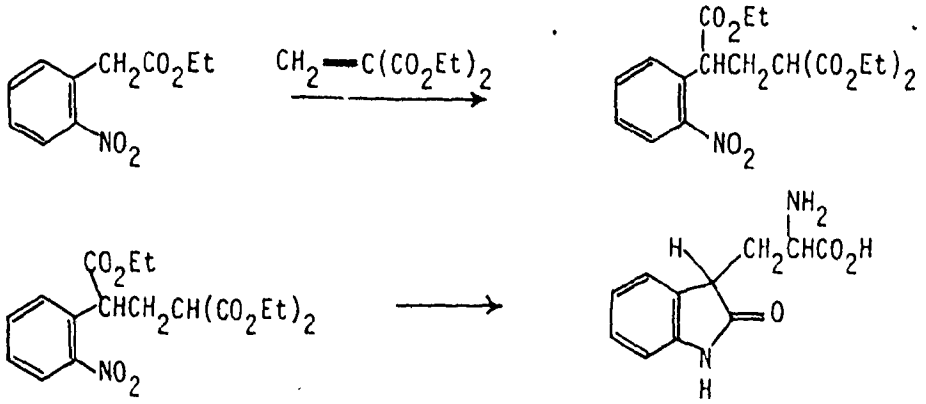
The scope of the Baeyer synthesis is somewhat limited by the fact that appropriately substituted o-nitrophenylacetic acids are often difficult to obtain. To a certain extent, this problem can be overcome by condensing o-nitrotoluene with ethyl oxalate to obtain ethyl o-nitrophenylpyruvate; this, upon hydrolysis and treatment with hydrogen peroxide, is easily converted to o-nitrophenylacetic acid.



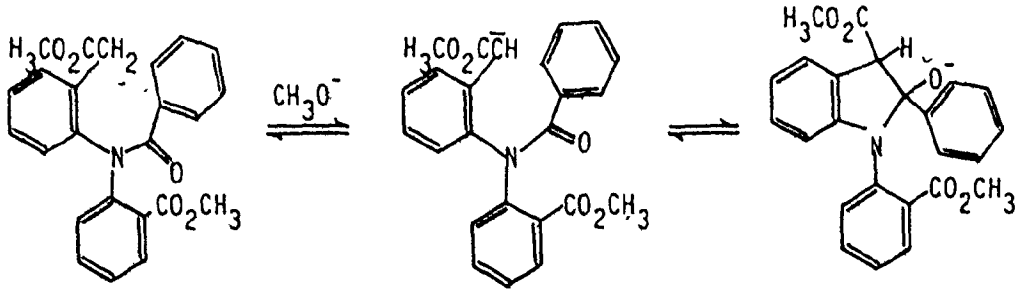
For example, Reissert and Scherk[51] synthesised 5-methyloxindole by reducing the acetic acid obtained from 2-nitro-m-xylene in this manner.

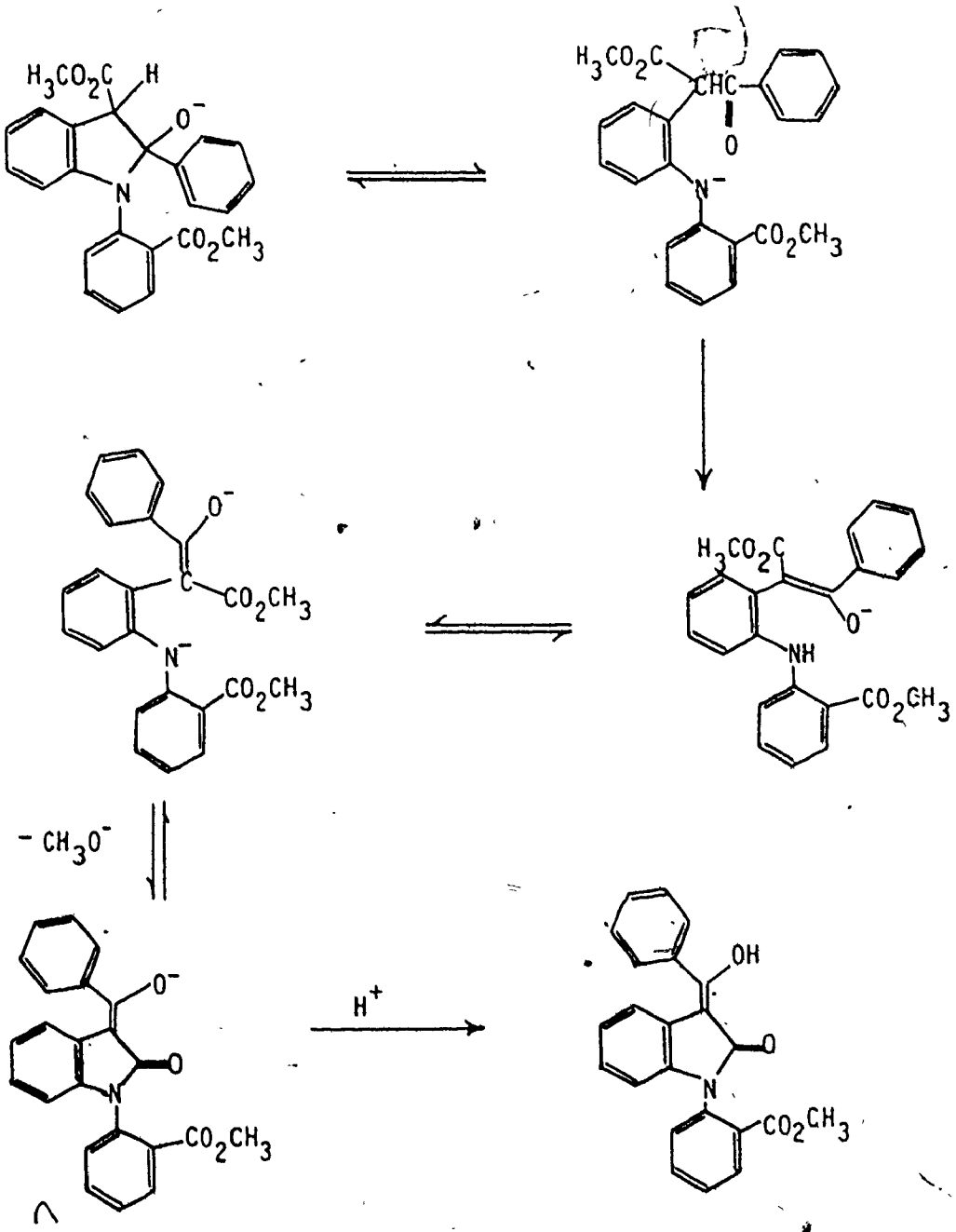
α-Substituted o-nitrophenylacetic acids which can be obtained by condensing o-nitrophenylacetic acid with aldehydes or compounds having active methylene groups, have been used to prepare 3-substituted oxindoles of fairly complex structure. Kotake, Sakan and Miwa[52] treated the ethyl ester of o-nitrophenylacetic acid with diethylmethylenemalonate in the presence of sodium ethoxide and obtained 1-(o-nitrophenyl)propane-1,3,3-tricarboxylic acid triethyl ester. Treatment of this ester with ethyl nitrite and sodium ethoxide followed by reduction with stannous chloride and hydrochloric acid in glacial acetic acid at 0°C, and subsequent hydrochloric acid hydrolysis, afforded the hydrochloride

of 3-(β-l-aminopropionic acid)oxindole.

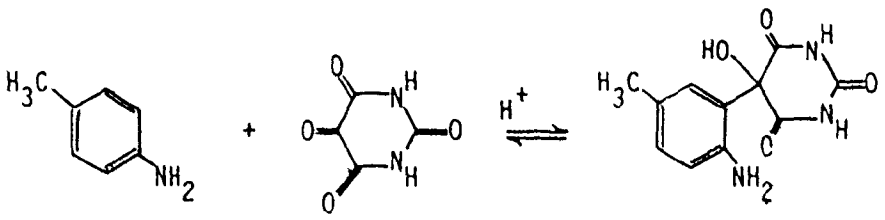


Compounds in which formation of the o-aminophenylacetic acid moiety is possible, may function as intermediates in the synthesis of some complex oxindoles. Schulenberg and Archer[53] treated N-benzoyl-o-carbomethoxy-o'-(carbomethoxymethyl)-diphenylamine with sodium methoxide and obtained 3-benzoyl-l-(2-carbomethoxyphenyl)oxindole. It is believed that the initially formed anion attacks the amide carbonyl rather than the carbomethoxy group affording an intermediate which then opens to give a different anion. Proton transfer gives the stable enolate anion and in the presence of an excess of sodium methoxide, the dianion is formed. Although the equilibrium between mono- and dianion must lie to the left, the dianion can react by a second path, intramolecular expulsion of methoxide affording the stable oxindole enolate anion.



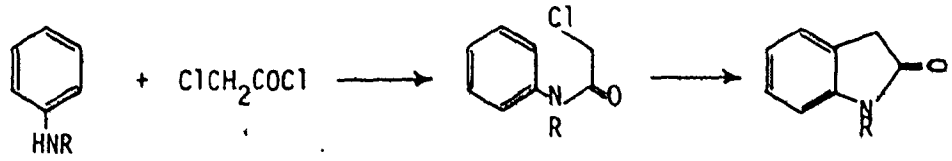


The formation of oxindole derivatives such as 5-methyldioxindole-3-carboxyureide from the reaction of p-substituted anilines with alloxan also involves intramolecular cyclisation of an o-aminophenylacetic acid system.[54]



From the foregoing it can be seen that the Baeyer synthesis constitutes a general and flexible method of synthesising oxindoles, despite the fact that appropriately substituted o-nitrophenylacetic acids are often difficult to obtain and N-alkyloxinoles cannot be prepared.

A general method for preparing the 1- and 3-alkyl derivatives of oxindole, as well as those containing nuclear substituents, is that of Stollé.[55] Condensation of an α-halogenated acid halide with an aromatic amine affords an α-haloacetanilide which, on treatment with anhydrous aluminum chloride, gives rise to the corresponding oxindole.

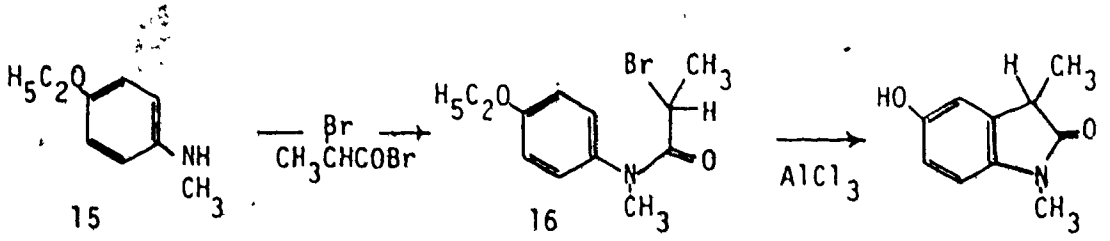


Considerable modification of both the aniline and α-haloacyl moieties can be carried out and reaction will still yield anilides which can be converted to oxindoles. Thus, the primary amines, aniline, o- and p-toluidine,[56] p-anisidine[57] and p-xylidene[58] have, on treatment with chloroacetyl chloride, followed by aluminum chloride, given oxindoles.

Secondary anilines which have led to oxindoles include methylaniline, ethylaniline,[56] diphenylamine,[55] β-phenylethylaniline,[59] N-methyl-p-anisidine[60] and di-β-naphthylamine.[61] In addition to chloroacetyl chloride, the α-chloro or α-bromo halides from propionic acid,[62] butyric acid[63] and isobutyric acid[64] have been reported to afford 3-alkyl oxindoles.

The ease with which ring closure takes place varies with the degree of substitution of the anilide used and in some instances ring closure does not even occur. Stollé[56] was not able to obtain oxindoles from β-naphthylamine, α-aminoanthraquinone or m-phenylenediamine and Porter, Robinson and Wyler[65] reported that they could not isolate 3,3-dimethyloxindole after treating α-bromoisobutyranilide with aluminum chloride.

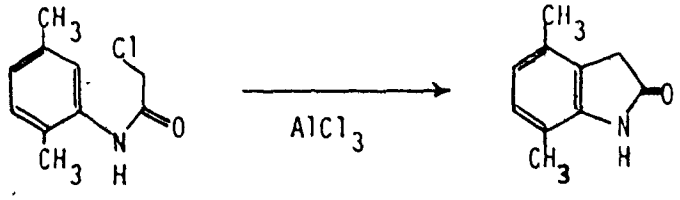
Under the conditions of the reaction, aluminum chloride can effect cleavage of phenolic ether groups. Julian and Pikl[62] reacted N-methyl-phenetidine[15] with α-bromopropionyl bromide obtaining the anilide[16], which, on treatment with excess aluminum chloride, afforded 1,3-dimethyl-5-hydroxyoxindole.

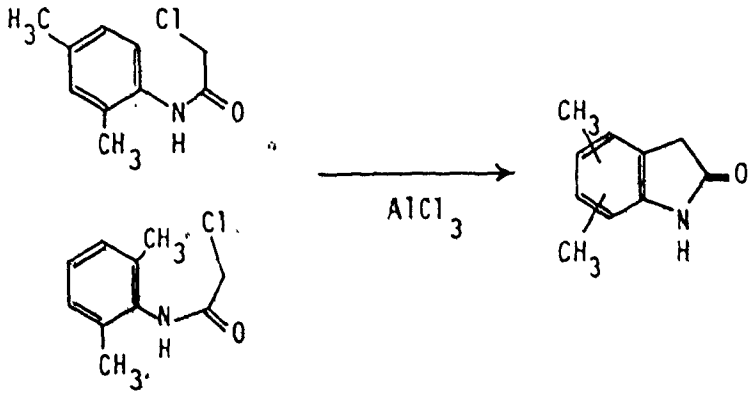


Giovannini and Portmann[57] reported that treatment of α-chloroacetyl-p-anisidine with aluminum chloride yielded 5-methoxyoxindole but it is most likely that the product was the 5-hydroxy derivative.

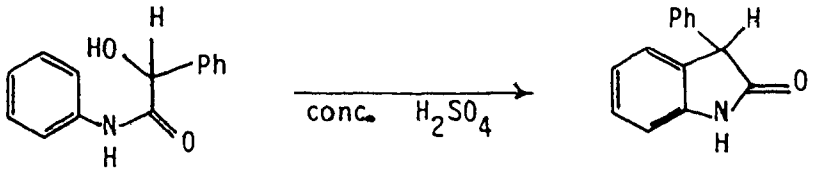
Partial failure has also been observed in the case of N-benzyl-chloroacetanilide which undergoes debenzylation and ring closure to oxindole.[56]

Wahl and Livovschi[66,67] investigated the Stollé reaction with several disubstituted chloroacetanilides. Treatment of α-chloro-N-(2,5-dimethylphenyl)acetamide with aluminum chloride afforded the expected product, 4,7-dimethyloxindole.[58] While it was first reported that 5,7-dimethyloxindole was obtained from α-chloro-N-(2,4-dimethylphenyl)-acetamide,[68] further investigation[66] showed that the compound was not identical with the 5,7-dimethyloxindole which Wispec[46] synthesised by the reductive cyclisation of 2-nitro-3,5-dimethylphenylacetic acid. The exact nature of this anomalous product was not determined. However, Wahl and Livovschi did demonstrate that aluminum chloride can cause the migration of methyl groups by obtaining a dimethyloxindole from α-chloro-N-(2,6-dimethylphenyl)acetamide.

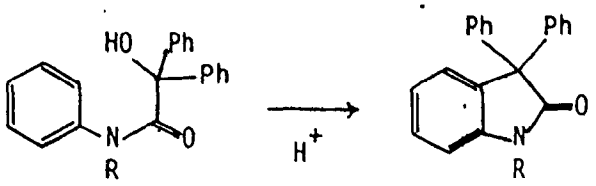




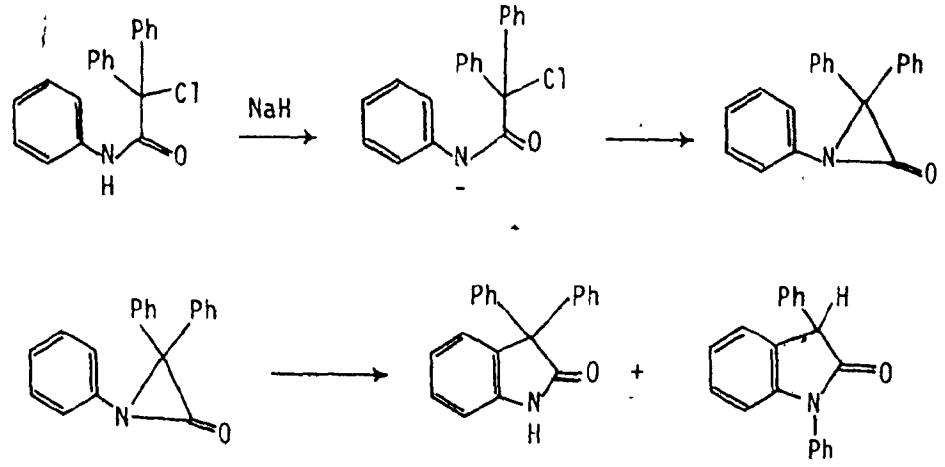
A method of preparing oxindoles which is very similar to the Stollé synthesis was first used by Meisenheimer and Meis.[69] By treating α-hydroxy-α-phenylacetanilide with concentrated sulphuric acid, they were able to obtain 3-phenyloxindole.



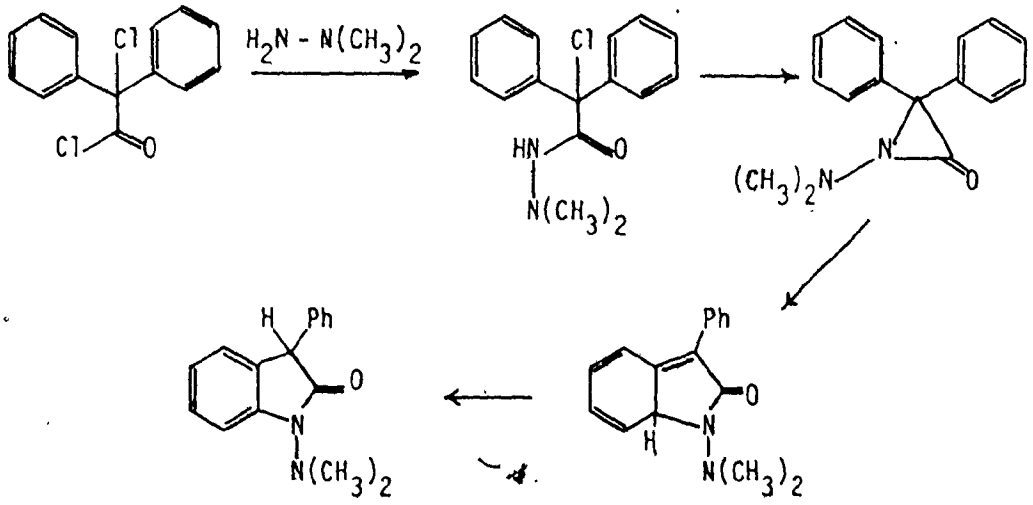
Petyunin and coworkers,[70,71,72,73] utilised this method to prepare many 3,3-diphenyloxindoles for α,α-diphenyl-α-hydroxyacetanilides. The cyclisation is doubtlessly an intramolecular Friedel Crafts reaction of the carbonium ion generated by ionization of the tertiary carbinol.



When Sheehan and Frankenfeld[74] treated α-chloro-α,α-diphenylacetanilide with sodium hydride they obtained three products; 2-[1'-(3,3'-diphenyloxindolyl)]-2,2-diphenylacetanilide (the major product which would appear to be the product of the subsequent alkylation of 3,3-diphenyloxindole by the starting material), 3,3-diphenyloxindole and 1,3-diphenyloxindole. The possibility that an α-lactam was an intermediate in the formation of both the 1,3- and 3,3-diphenyloxindoles, was mentioned, but there was no direct evidence for this proposal.

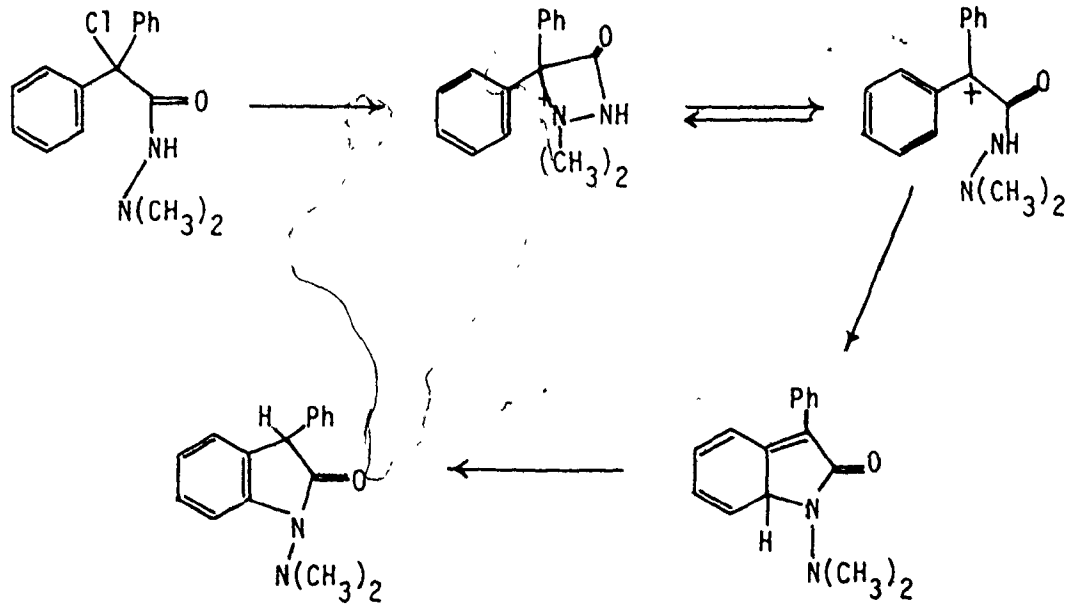


Meyer[75] reacted α-chlorodiphenylacetyl chloride with 1,1-dimethylhydrazine and instead of the expected 1-(α-chlorodiphenylacetyl)-2,2-dimethylhydrazine obtained (1-dimethylamino)-3-phenyloxindole. By analogy with the work of Sheehan and Frankenfeld, he suggested that the reaction proceeded via an α-lactam intermediate.



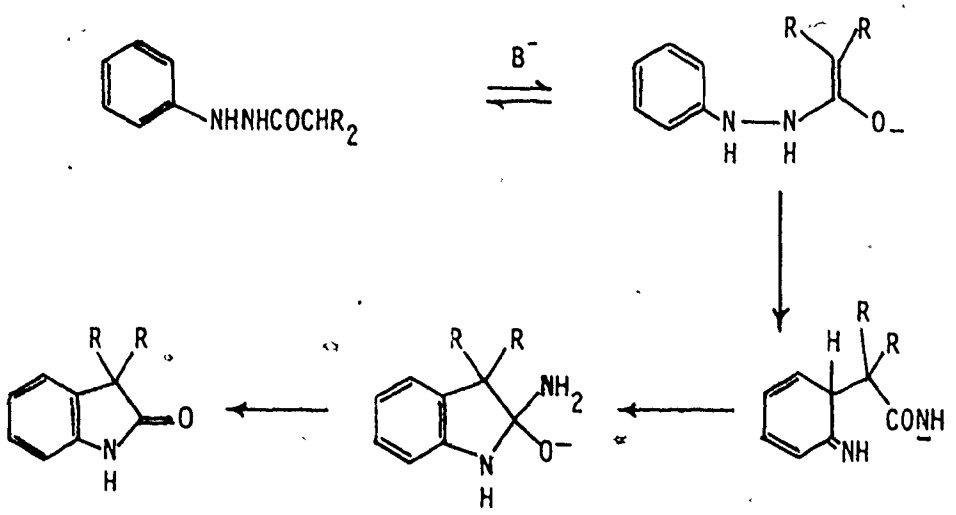
However, Bird[76] has reported that acid treatment of ethyl 3-oxo-2,4,4-triphenyldiazetidine-1-carboxylate (obtained by reaction of chlorodiphenylacetyl chloride with ethyl N'-phenylhydrazine-N-carboxylate) affords 1-carboethoxyamino-3,3-diphenyloxindole. Thus it would appear

that the following mechanism is more likely.

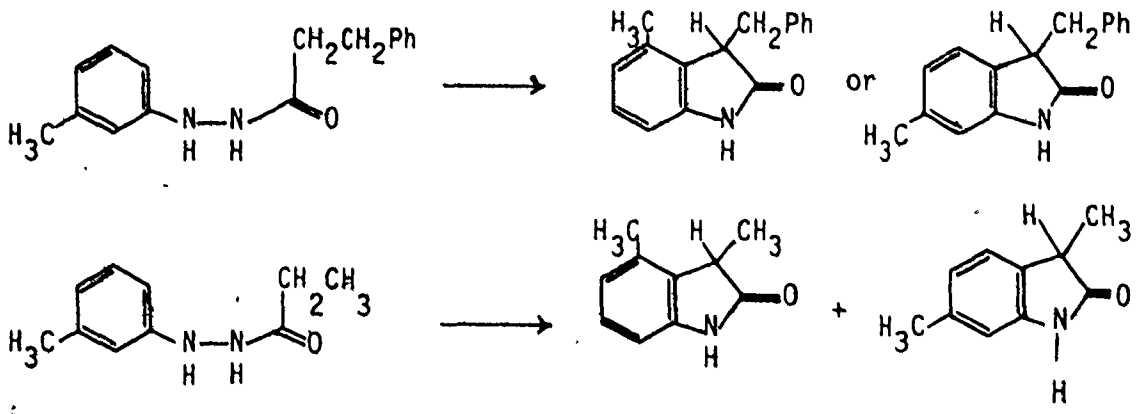


Another important method of preparing oxindoles, devised by Brunner,[77] involves treatment of an N-acylphenylhydrazine with an alkaline reagent at elevated temperatures. The original procedure of Brunner in which the acylphenylhydrazine is heated with lime at temperatures near 200°, has been applied most extensively. However, several other bases have been used as condensing agents, notably sodamide for the synthesis of oxindole from N-acetylphenylhydrazine,[78] calcium hydride for the preparation of 3-methyloxindole from β-propionylphenylhydrazine[79] and 1,3,3-trimethyloxindole from N'-methyl-N'-phenylisobutyrohydrazide[80] and a mixture of sodium in naphthalene for the synthesis of 3,3-diphenyloxindole from diphenylacetic acid diphenyl hydrazide.[81]

The mechanism of the cyclisation probably parallels that of the Fischer indole synthesis.

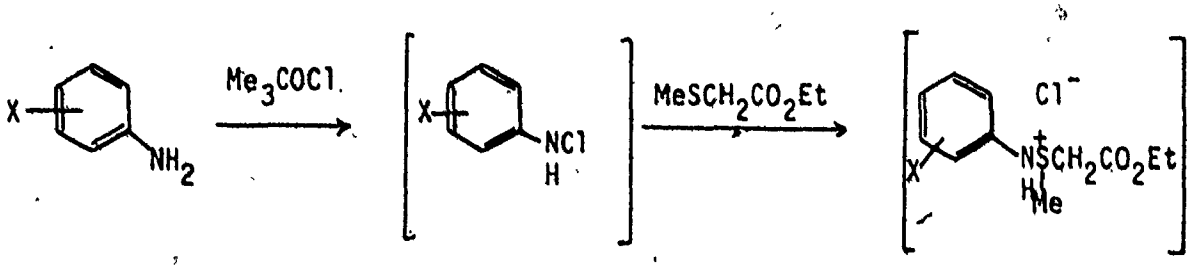


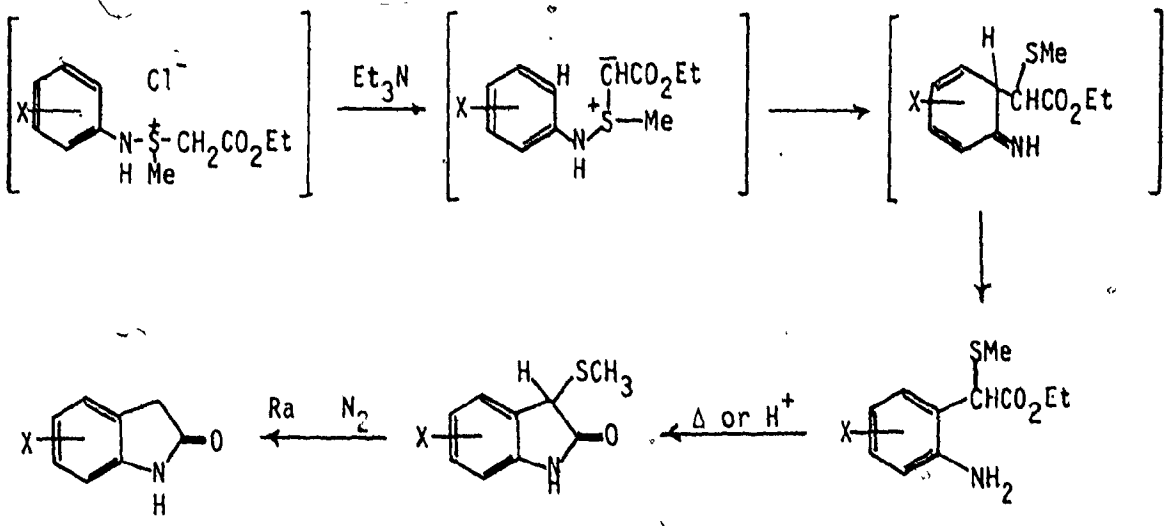
Phenylhydrazine, 1-methyl-1-phenylhydrazine, o-tolylhydrazine, m-tolylhydrazine, p-tolylhydrazine,[82] o-ethoxyphenylhydrazine, p-ethoxyphenylhydrazine,[83] 1-methyl-1-(p-ethoxyphenyl)hydrazine[84] and α- and β-naphthylhydrazine[85] have served in the preparation of oxindoles. These phenylhydrazines have been converted to oxindoles after acylation with acetic acid, propionic acid, butyric acid,[86] isobutyric acid,[77] 2-methyl- and 3-methyl-butyric acids, valeric acid,[84] phenylacetic acid,[86] α-phenylpropionic acid[87] and β-phenylpropionic acid.[82] Of the two reported instances in which meta substituted phenylhydrazines have been used as the starting materials in the synthesis of oxindoles, only the one hydrazine, β-phenylpropionyl-m-tolylhydrazine yielded a single isomer, either 3-benzyl-4- or 6-methyloxindole.[82] Propionyl-m-tolylhydrazine, on the other hand, gave a mixture of the two isomers, 3,4- and 3,6-dimethyloxindole.[88]



In general, phenylhydrazines give better yields of oxindoles than do the 1-methylphenylhydrazines. However, the effect of substitution in the 1-position is not so remarkable as are changes in the acyl group. For while Brunner was able to obtain 3-methyloxindole[86] and 1,3-dimethyloxindole[77] in yields of 78% and 50%, respectively, he could only obtain oxindole and 1-methyloxindole in equally poor yields.

Recently, Gassman and van Bergen[89] have developed another method for the synthesis of oxindoles. The procedure involves the sequential treatment of an aniline derivative with t-butylhypochlorite, an α-carboalkoxy sulphide and triethylamine to produce a relatively unstable amino ester. Treatment of this compound with dilute acid affords a 3-methylthiooxindole derivative which, on reduction with Raney-nickel, is converted to the corresponding oxindole.

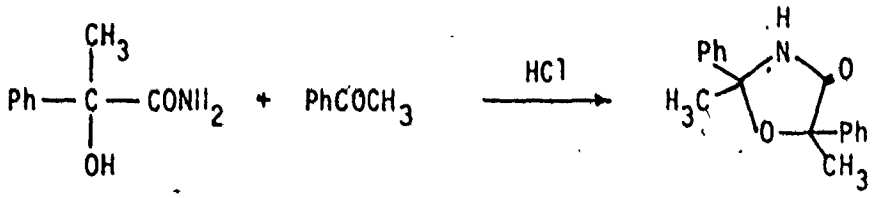




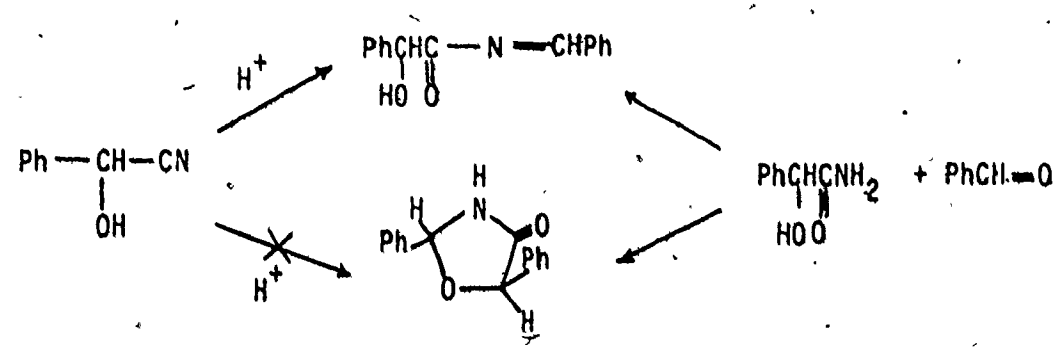
The yields of the oxindoles synthesised by this procedure range from good to excellent; oxindole being obtained in 64% overall yield and 5-methyloxindole in 19% overall yield. The reaction is reasonably versatile in that a broad range of substituents, which extends from mildly electron-donating to strongly electron-withdrawing, can be tolerated. When ortho- and para-substituted anilines are used, the reaction is quite straightforward, insofar as the para substituent is always found at the 5-position of the oxindole while the ortho substituent can only reside at the 7-position of the resulting oxindole. Meta-substituted anilines present a more complex problem as intramolecular attack of the ylide can occur at either the position ortho or para to the substituent. Studies thus far indicate that when the substituent is a strong electron-withdrawing group, attack occurs adjacent to the substituent to give the 4-substituted oxindole but when the substituent is an electron-donating group, the 6-substituted oxindole is the major product.

Synthesis of 2-Imino-4-Oxazolidones and 2-Imino-4-Thiazolinethiones

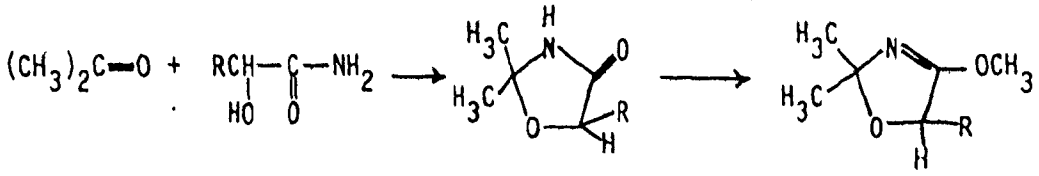
There are relatively few accounts in the literature of the synthesis of 4-oxazolidones and only a small fraction are concerned with 2-imino-4-oxazolidones. The first report which described the preparation of a 4-oxazolidone was that of Staudinger and Ruzicka.[90] Condensation of the amide of hydratropic acid with acetophenone by means of cold concentrated hydrochloric acid was found to yield 2,5-diphenyl-2,5-dimethyl-4-oxazolidone. The same product was isolated when acetophenone cyanohydrin was treated with concentrated hydrochloric acid.



Earlier, Michael and Jeanpretre[91] had obtained a substance of similar nature, both by treating mandelonitrile with concentrated hydrochloric acid and by heating mandelamide with benzaldehyde. However, they formulated this substance as benzilidene mandelamide, rejecting the oxazolidone formula because the product afforded an acetyl derivative and could not be converted into an N-nitroso compound.

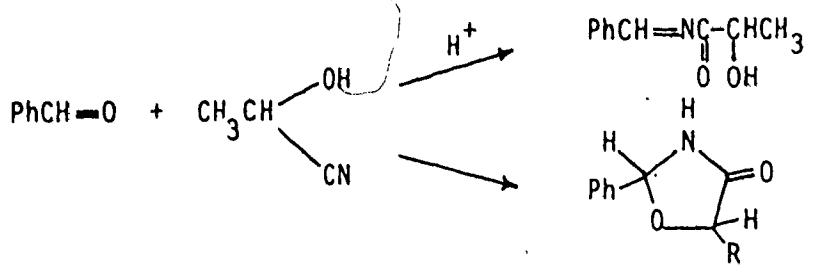


While Staudinger and Ruzicka disagreed with the proposed structure, preferring instead the 4-oxazolidone structure, it was some considerable time before further evidence as to the exact nature of the reaction product was forthcoming. Fischer, Dangschat and Stettiner[92] were able to show conclusively that the products obtained on the condensation of acetone with various α-hydroxyamides were, indeed, 4-oxazolidones. For, on methylation with silver oxide and methyl iodide, the reaction products afforded 4-methoxy-3-oxazolines which were easily hydrolysed to methanol, ammonia, acetone and the α-hydroxy acid. These degradations would be difficult to reconcile with an acyclic structure.



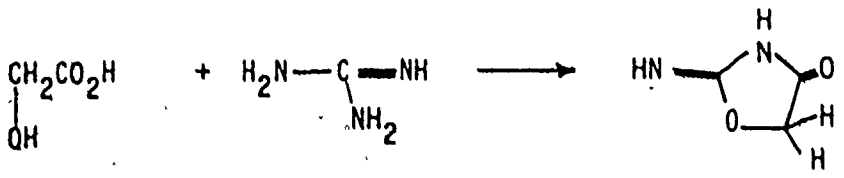
Thus, by analogy it would seem that the compound obtained by Michael and Jeanpretre was a 4-oxazolidone rather than an acylic species. Support for this view also came from the work of Cornforth and Cornforth[93] who found that this product of the reaction of benzaldehyde with mandelonitrile was readily soluble without decomposition in aqueous sodium hydroxide. Acidity in benzilidene mandelamide would be very surprising but it is frequently found among cyclic imides. Moreover, the reaction product was unaffected by either acetyl chloride or thionyl chloride.

In an attempt to prepare a phenylmethyloxazole from benzaldehyde and acetaldehyde cyanohydrin in ethereal hydrogen chloride, Fischer[94] obtained a compound which he identified as benzilidine lactamide.

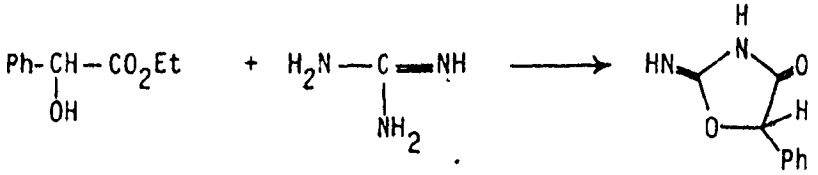


Many years later, work by Davies, Ramsay and Stove[95] indicated that the compound was actually 2-phenyl-5-methyloxazolid-4-one. They found that there was no chemical evidence for the presence of the hydroxyl group in the compound as it was inert to phenyl isocyanate and thionyl chloride though lacto-p-toluidide which bears some resemblance to the acyclic compound, reacted with them as expected. Absence of an activated azomethine group was indicated by the inability of the compound to add piperidine, or alcohols, in the presence of basic catalyst and also by its inertness to magnesium in boiling methanol. The probability of the cyclic structure was further shown by the condensation of lactamide and diphenylketimine to form ammonia and 2,2-diphenyl-5-methyloxazolid-4-one, the structure of which was shown by the absence of a hydroxyl group.

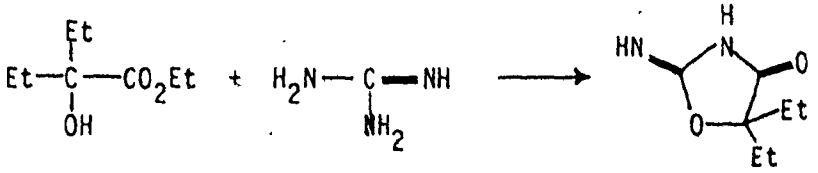
It was in 1913 that the first account of the synthesis of a 2-imino-4-oxazolidone appeared in the literature. Traube[96] reported that he had obtained the parent compound by the condensation of α-hydroxyacetic acid with guanidine in alcoholic solution.



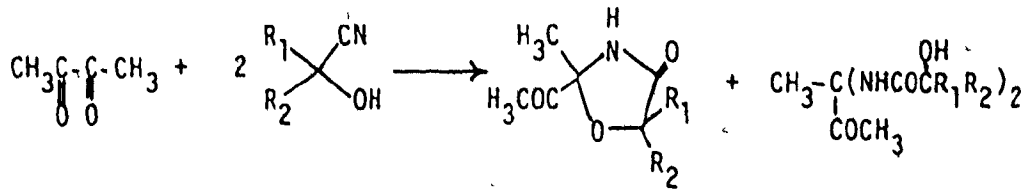
Later, a communication from Traube and Ascher[97] described the synthesis of 5-phenyl-2-imino-4-oxazolidone in an analogous manner, namely the reaction of ethyl mandelate with guanidine in alcoholic solution. Similarly, Erlenmeyer and Kleiber[98] were able to prepare



2-imino-5,5-diethyl-4-oxazolidone by the reaction of 1,1-diethyl-1-hydroxyacetic acid, ethyl ester with guanidine.

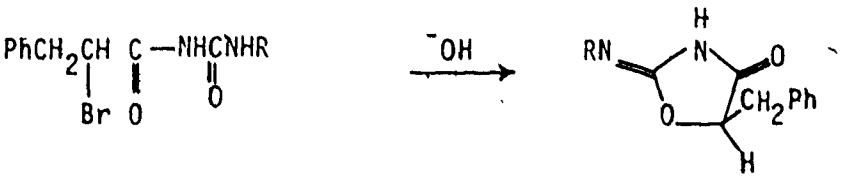


von Eichenberger, Ganz and Druey[99] investigated the reaction of biacetyl with cyanohydrins of several aliphatic ketones and found that the major product was a 2-methyl-2-acetyl-4-oxazolidone instead of the expected 2,2-di-(α-hydroxyacylamino)-butan-3-one which was only formed in very small quantities. The structure of the reaction product

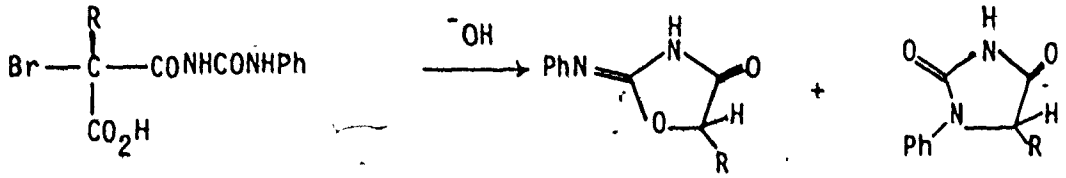


was established by its chemical transformation to another 4-oxazolidone and comparison of the spectral characteristics of that 4-oxazolidone with those of the same 4-oxazolidone synthesised according to the method of Fischer, Dangschat and Stettiner.[92]

A second method of synthesising 2-imino-4-oxazolidones was reported by Aspelund[100] who found that the treatment of compounds of the type N-α-bromo-β-phenyl-propionyl-N'-alkyl urea with alkali afforded these five-membered ring heterocycles.

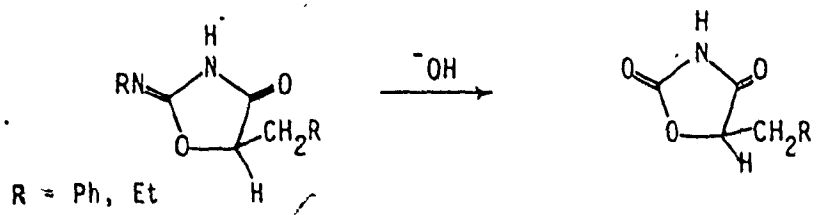


The course of the reaction was dependent to a great extent on the nature of the substituents on the urea. 5-Bromo-5-benzyl-1-phenyl-, 5-bromo-5-ethyl-1-phenyl-, and 5-bromo-1,5-diphenyl-barbituric acids, when treated with dilute aqueous alkali, all afforded the corresponding 2-phenylimino-4-oxazolidones as the major product together with a small amount of the corresponding 1-phenylhydantoin. Similarly alkaline treatment of N-(α-bromopropionyl)-N'-phenyl urea yielded 2-phenylimino-5-methyl-4-oxazolidone as well as 5-methyl-1-phenylhydantoin. It should be noted that Frerichs and Hollmann[101] were able to isolate only the hydantoin when N-(α-bromopropionyl)-N'-phenyl urea was subjected to treatment with alcoholic potassium hydroxide solution. However, when 5-bromo-

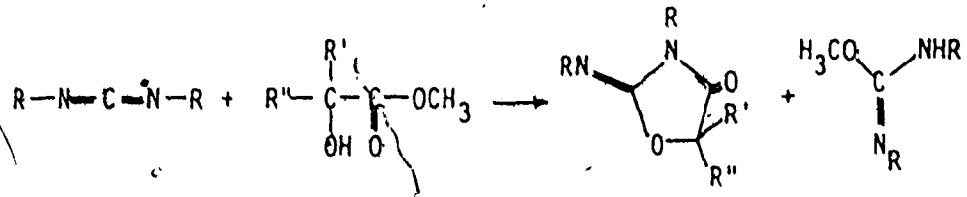


5-phenyl-1-methylbarbituric acid was treated with dilute aqueous alkali the only reaction product that was isolated (in very good yield) was 2-methylimino-5-phenyl-4-oxazolidone. In contrast, alkaline treatment of

5-bromo-5-benzyl-3-methyl-1-phenylbartituric acid under various conditions did not afford any of the 2-imino-4-oxazolidone but instead yielded 5-benzyl-1-phenyl-3-methylhydantoin as the main product as well as a small amount of the isomeric 5-benzyl-1-methyl-3-phenylhydantoin. When the substituent R was a methyl group alkaline hydrolysis occurred more readily and the major products were the corresponding 2,4-oxazolidones.



Yet another method of preparing 2-imino-4-oxazolidones was discovered by Schmidt and Carl[102] while investigating the reactions of aliphatic carbodiimides. They found that either Cu(I) or Cu(II) chloride catalysed the reaction of aliphatic carbodiimides with the esters of α-hydroxyacetic acids and that the main reaction products were the aforementioned heterocycles together with small amounts of the corresponding O,N,N'-trisubstituted isoureas.

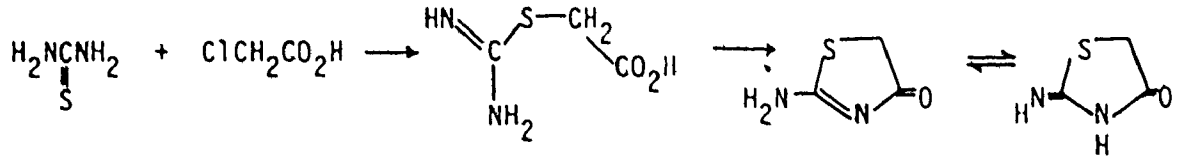


An interest both in their effect on the central nervous system and their tautomerism prompted Najer, Giudicelli and several co-workers[103,104,105,106,107] to carry out an extensive investigation of a number of differently substituted 5-aryl-2-imino-4-oxazolidones. The synthesis of these compounds was accomplished by known methods; the

reaction of the ester of an α-hydroxy-α-arylacetic acid with guanidine chlorohydrate in alcohol or by the treatment of N-(α-chloro-α-phenyl)-acetyl-N'-alkyl-urea with sodium ethoxide in alcohol.

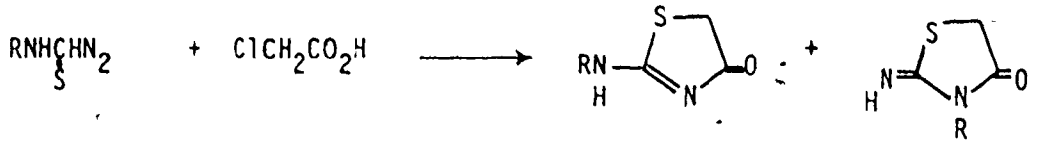
Somewhat surprisingly, there is no mention in the literature of a 2-imino-4-thiazolinethione although there are several accounts of the synthesis and reactions of 2-imino-4-thiazolidones.

The reaction between thiourea and chloracetic acid, its chloride or esters which proceeds through the intermediate formation of the acyclic pseudothiohydantoic acid, is the most convenient method for the preparation of 2-iminothiazolines. This was, in fact, the method by which

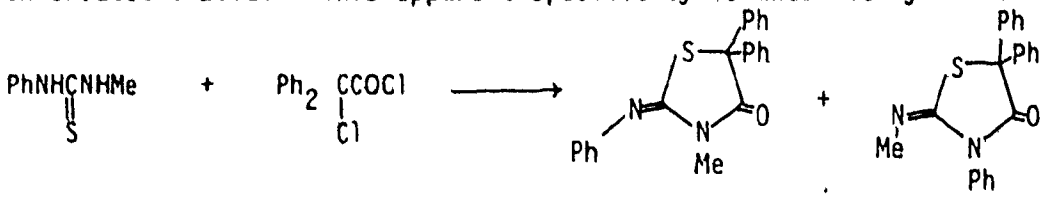


2-iminothiazolines were first synthesised although at the time it was thought that the products of the reaction were 2-thiohydantoins.[108,109,110] However, as unexpected results were obtained when the compounds were hydrolysed,[111] oxidised[112] and treated with metallic oxides in an attempt to desulphurise them,[110] the structure of the products was soon revised. When applied to other α-halo-acids or -esters and substituted thioureas, this reaction constitutes a general method for the preparation of 2-imino-thiazolines with a variety of substituents on either of the nitrogen atoms as well as in the 5-position.[113,114,115,116,117] Monosubstituted thioureas as a rule afford stable compounds in which the substituent is on the exocyclic nitrogen. Products of this type are obtained exclusively

when R is aryl or acyl. However, when R is alkyl the product can be that in which the substituent is on the ring nitrogen. For example, Eberly

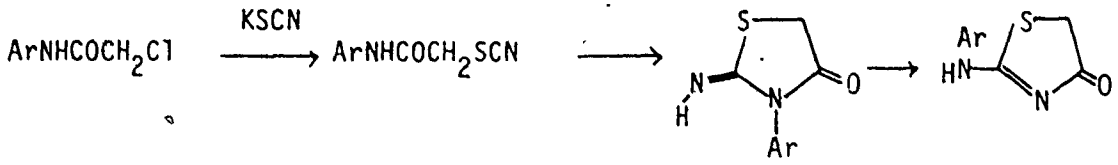


and Dains[118] found that reaction of allylthiourea with chloroacetic acid yielded only 2-allylimino-4-thiazolidones. N,N-disubstituted thioureas can, of course, form only the one product while N,N'-disubstituted thioureas in which the substituents are different may yield isomeric products. Generally, however, only one product has been isolated. Thus, Dains, Irvin and Harrel[113] obtained 2-phenylimino-3-methyl-5,5-diphenyl-4-thiazolidone and 2-methylimino-3-phenyl-5,5-diphenyl-4-thiazolidone in a ratio of 1:3 after reacting 1-phenyl-3-methylthiourea with α,α-diphenyl-α-chloroacetic acid. This apparent specificity is undoubtedly due in

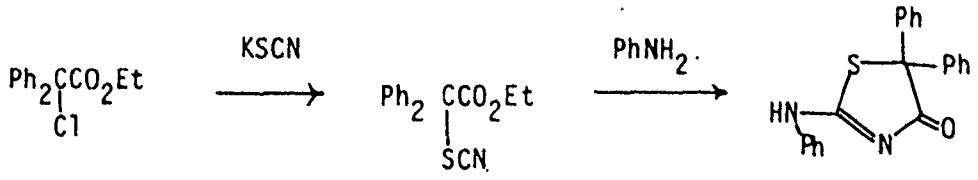


part to a greater ease of isolation of one of the two possible isomers as well as to a directive effect on the reaction itself by the marked difference in character of the two substituents in those thioureas that have been studied exhaustively. When one of the substituents on the thiourea is aryl or acyl, this group usually appears on the exocyclic imino group. Here again, the allyl group behaves uniquely; the reaction of N-phenyl-N'-allylthiourea with chloroacetyl chloride giving only 2-allylimino-3-phenyl-4-thiazolidone.

The reaction of thiocyanates with α-haloacid derivatives also gives rise to 2-imino-4-thiazolidones. Thus, chloroacetanilide and its derivatives with potassium or ammonium thiocyanate yield the corresponding thiocyanatoacetanilides which readily cyclise to the 2-imino-3-aryl-4-thiazolidones. These products are quite often labile and rearrange into the stable 2-arylamino-4-thiazolidones.



Esters of α-thiocyanato acids, which are obtained from the reaction of α-chloro esters with potassium thiocyanate, react with aryl amines to give the stable 2-arylamino-4-thiazolidones.[119,120]

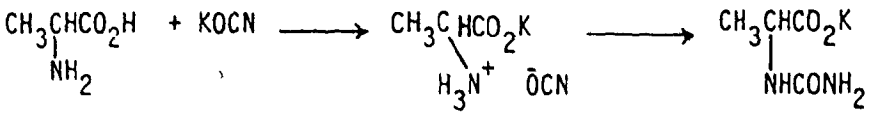


The tendency of the 2-imino-3-aryl-4-thiazolidones to rearrange to the 2-arylamino-4-thiazolidones depends markedly, however, on the conditions of the reaction (acid or neutral) and on the nature of the ring substituents.[120]

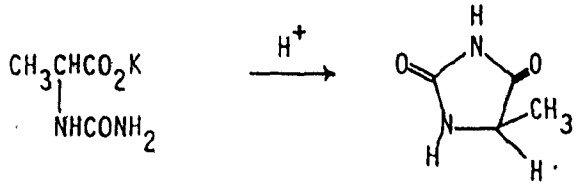
Synthesis of Hydantoins and 2,4-Dithiohydantoins

As the literature abounds with accounts of the synthesis of hydantoins only the more general methods will be discussed in any detail.

One of the methods for the synthesis of hydantoins which has found wide application is that involving the reaction of α-amino acids with potassium cyanate. This reaction which was first reported by Urech[121] in 1873, has been applied to the preparation of a large number of hydantoins with substituents in the C-5 position as well as to a limited number of hydantoins with a substituent in the N-1 position. When an α-amino acid reacts with potassium cyanate in aqueous solution, the product is generally the potassium salt of an α-ureido acid. Initially, it is believed, a substituted ammonium cyanate is formed and this rearranges to the potassium salt of the α-ureido acid. Conversion



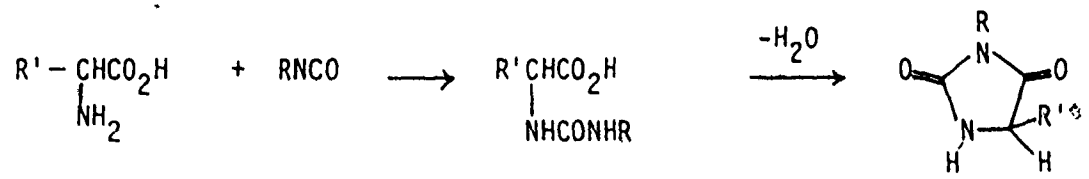
to the corresponding hydantoin is accomplished by heating the salt with 25% hydrochloric acid, a method first described by Mouneyrat.[122]



This general method of synthesis has been used with a large number of α-amino acids, as well as with certain amides and nitriles. So generally applicable is this reaction of α-amino acids with potassium cyanate,

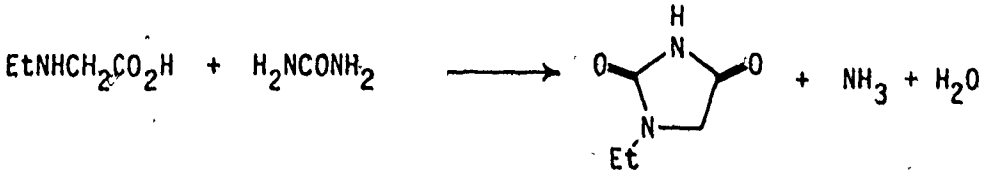
that it has been utilised as a method for separating the amino acids resulting from the hydrolysis of proteins.[123]

Alkyl and aryl isocyanates have found wide application in the synthesis of hydantoins from α-amino acids. The reaction is generally



carried out in alkaline aqueous solution from which the resulting ureido acid may usually be precipitated by the addition of mineral acid. In certain cases, however, it is the hydantoin which is obtained on acidifying the alkaline reaction mixture.[124,125] The esters of the amino acids have also been used, ether being the solvent generally chosen for the reaction medium and the corresponding esters of the ureido acids being obtained.[126] Both the free hydantoic acids and their esters are readily converted into hydantoins by heating with mineral acid.[122]

Urea and its derivatives have been used in a number of syntheses of hydantoins, most of these utilising the reaction of urea with an α-amino acid. In fact, it was not long after the discovery of hydantoin that the first synthesis of this type was reported by Heintz[127] who found that when urea and N-ethylglycine were heated together at 120-125°C, ammonia was evolved and 1-ethylhydantoin was formed. Later, Lippich[128]

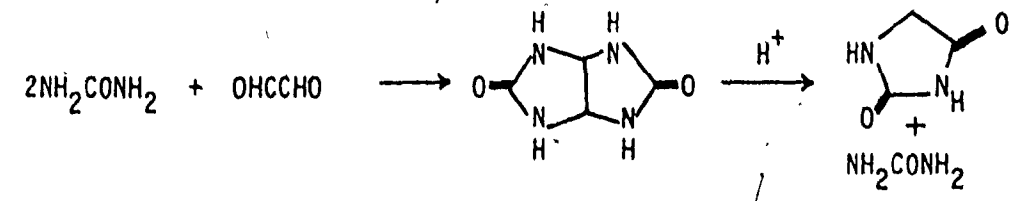


showed that hydantoic acids and through them hydantoins, could be

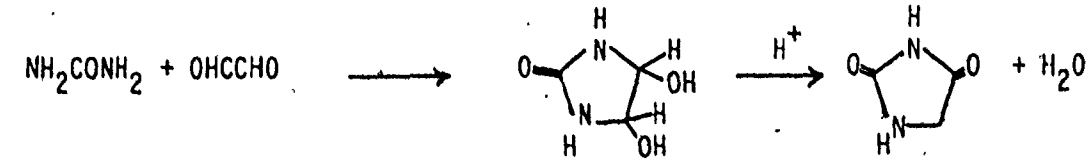
obtained in better yield by boiling the amino acids in barium hydroxide solution with an excess of urea, a method first employed by Baumann and Hoppe-Seyler;[129] the corresponding hydantoins were obtained by heating the barium salts of the hydantoic acids with dilute sulphuric acid.

Not only α-amino acids, but also α-hydroxy acids and their nitriles, will react with urea to form hydantoic acids or hydantoins.

Urea will also react with compounds containing adjacent carbonyl groups to form products which are readily converted into hydantoins. The first synthesis of this type was reported by Siemonson[130] who obtained glycoluril as an intermediate product in the preparation of hydantoin from urea and glyoxal. When the glycoluril was treated with dilute hydrochloric acid, urea was split off and hydantoin obtained in good yield. This reaction was studied further by Pauly and Sauter[131]

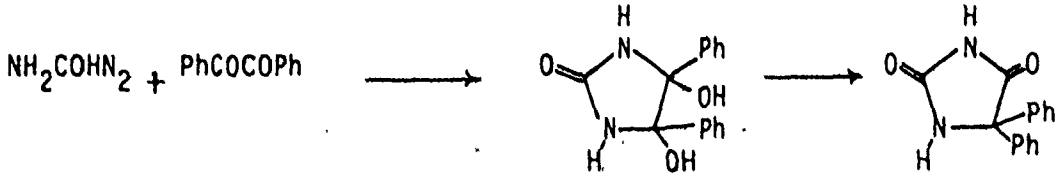


who reported that they had been able to obtain a dihydroxy compound as an intermediate product; when the latter was heated with acid, a pinacolone rearrangement took place and hydantoin was formed. Biltz[132,133,134,135]

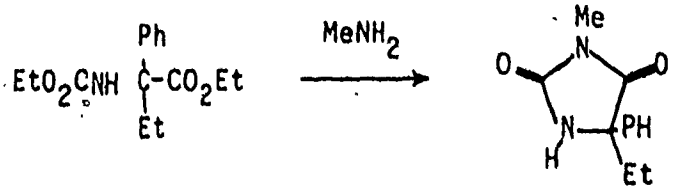


examined the reaction of urea with benzil and recommended it as a method for the preparation of 5,5-diarylhydantoins. The reaction can be carried out with N-substituted ureas leading to the formation of N-3 or of N-1,-

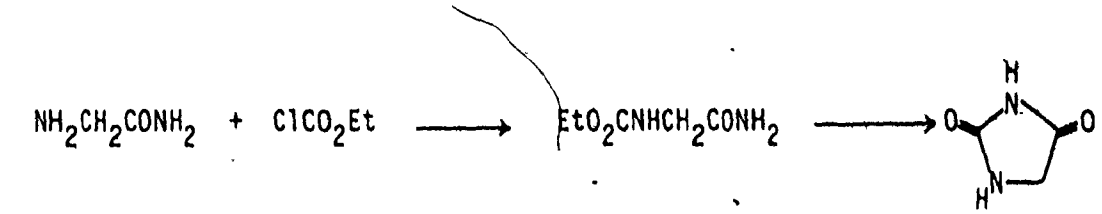
N-3 disubstituted hydantoins and diaryl α-diketones other than benzil may be used. The fact that the same hydantoin, 1,3-dimethyl-5,5-diphenylhydantoin, was obtained through the action of N,N'-dimethylurea with benzilic acid and with benzil, indicates that a pinacolone rearrangement must take place when the latter reacts with urea.



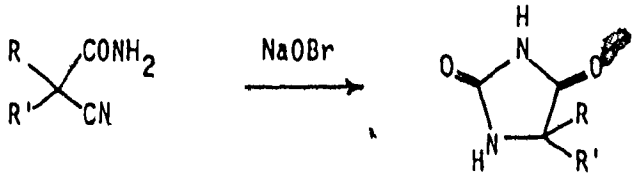
Treatment of ester of α-amino acids with ethyl chloroformate affords the N-carboethoxy derivatives of these amino acids which, on reaction with ammonia or a primary amine, give rise to substituted hydantoins. For example, the treatment of ethyl α-urethano-α-phenylbutyrate with methylamine in alcohol under pressure results in the formation of 3-methyl-5-phenyl-5-ethylhydantoin.[136]



On the other hand, when the amide of an α-amino acid reacts with ethyl chloroformate to produce an N-carboethoxy derivative, only treatment with dilute aqueous or alcoholic alkali is necessary in order to obtain a substituted hydantoin. This method of synthesis of hydantoins from N-carboethoxyamino acid amides has been found to be of quite general application and amongst the hydantoins prepared in this manner are 5-methylhydantoin, 5-ethylhydantoin, 5-isobutylhydantoin, 5-benzylhydantoin,[137] 5-phenylhydantoin,[138] 1-phenylhydantoin[139] and 5-hydantoincarboxamide.[140]

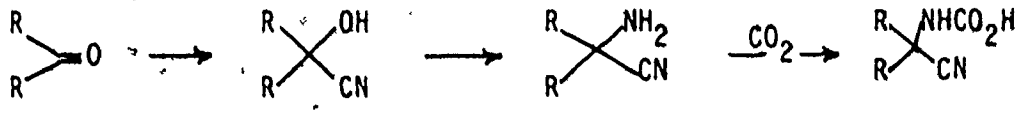


The synthesis of hydantoins through the action of alkali hypohalites on disubstituted cyanoacetamides has found wide application in the preparation of 5,5-disubstituted hydantoins.[141,142,143,144]

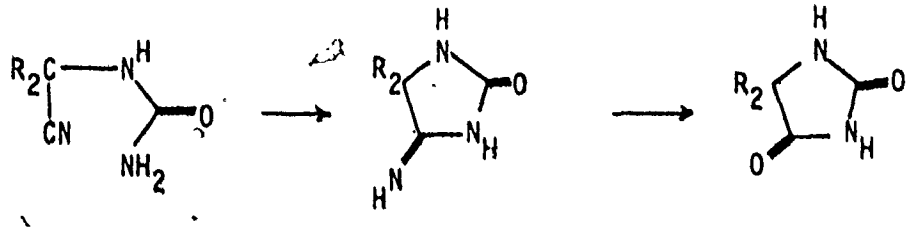


A reaction that was first described by Berg,[145] but is usually credited to Bucherer[146] who worked out most of the experimental conditions, is the most convenient method for the preparation of 5-substituted and 5,5-disubstituted hydantoins. An aldehyde or ketone in aqueous alcohol containing potassium cyanide and ammonium carbonate is heated at 60-70°C. In some instances, better yields are obtained by heating the mixture in a closed system at pressures of 2-8 atmospheres. This reaction works well for aliphatic and aromatic aldehydes or ketones and cyclic ketones.[147,148,149,150,151,152,153]

Since the action of ammonium carbonate on cyanohydrins and amino nitriles under identical conditions also yields hydantoins it seems probable that they are intermediates in the Bucherer reaction. Bucherer proposed the following course for the reaction. The last step appears to involve the formation of the corresponding carbamide following by ring

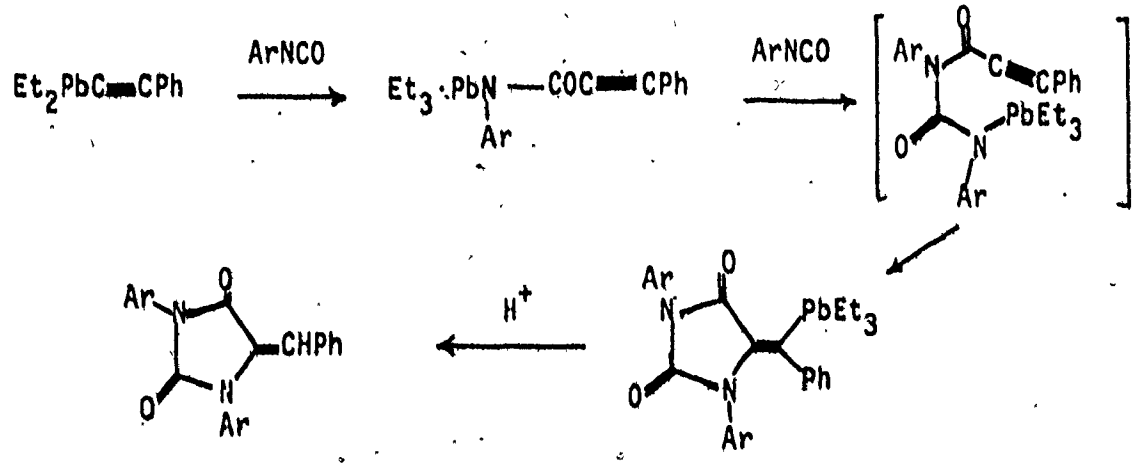


closure. The last intermediate prior to ring closure in both the amino nitrile and Bucherer methods may be an N-substituted carbamic acid, although this has not been established experimentally.



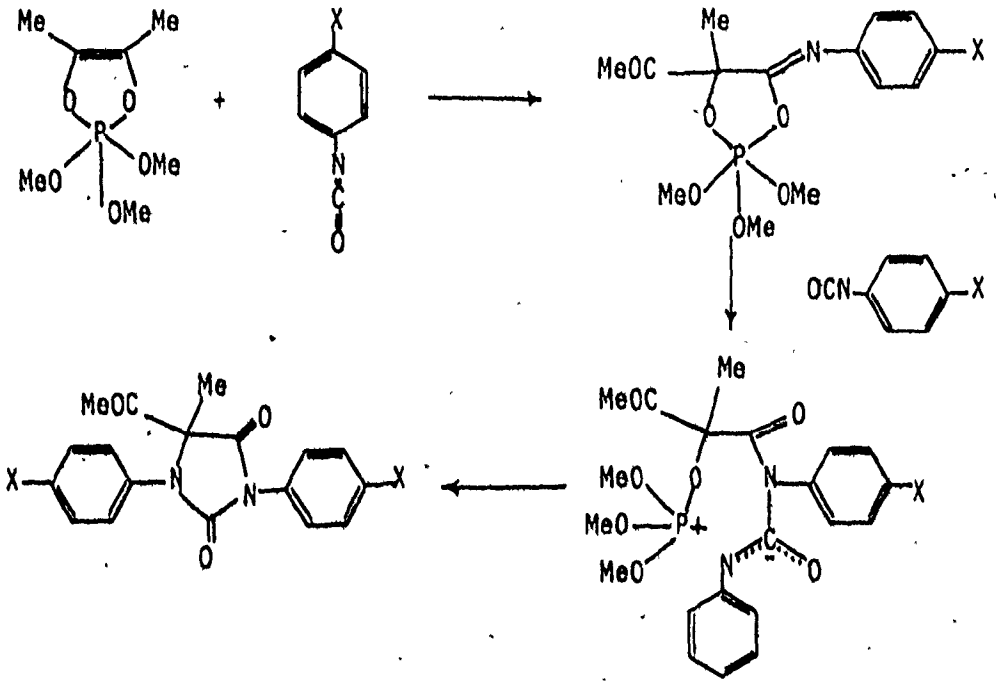
While the aforementioned methods of synthesising hydantoins are the ones most frequently used, recently several novel syntheses have been devised.

Davies and Puddlephatt[154] found that alkynyl-lead compounds (prepared by treating an organolead halide with a sodium acetylide in liquid ammonia or an organic solvent) reacted exothermally with phenyl or 1-naphthyl isocyanates to yield 5-alkenyl hydantoins. The initial addition

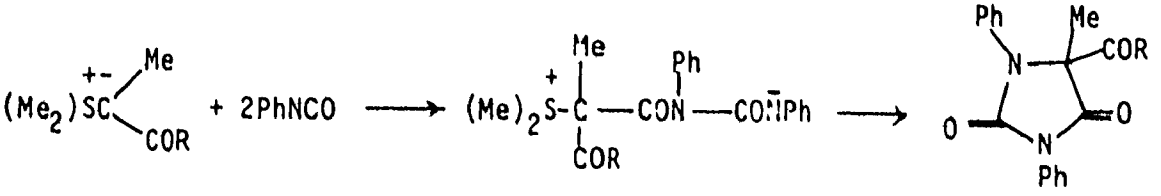


presumably occurs across the N=C bond of the isocyanate to give the plumbyl derivatives of propiolylanilide; the Pb-N bond of this is a more powerful addendum group than the initial Pb-C bond, and adds to a second molecule of isocyanate to give an N-plumbyl-N'-propiolylurea. Ring closure then occurs by intramolecular addition of the Pb-N bond across the ethynyl group.

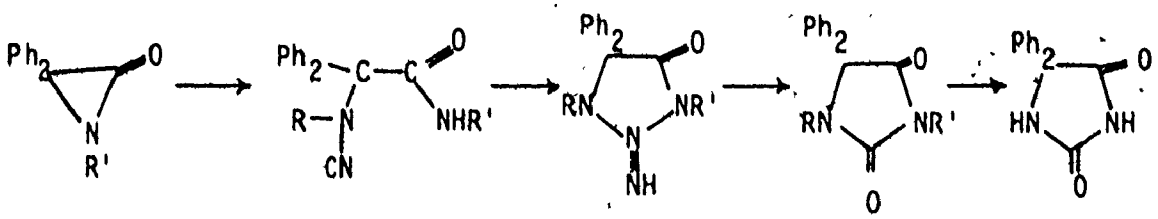
A new reaction which leads to 5-acylhydantoins, precursors of β-keto-α-amino acids, was reported in 1968 by Ramirez et al.[155] The phospholene 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene made from biacetyl and trimethyl phosphite was reacted with one mole equivalent of a para-substituted phenyl isocyanate to give a 2,2,2-trimethoxy-4-(p-substituted)phenylimino-5-acetyl-5-methyl-2,2-dihydro-1,3,2-phospholane. The latter was then treated with a second mole equivalent of isocyanate (either the same or a different isocyanate) to produce, via the ambient dipolar adduct, a hydantoin.



A group of Japanese workers[156] have found that treatment of sulphur ylides such as dimethylsulphonium-α-methylacylmethylide with two mole equivalents of phenyl isocyanate in dimethyl sulphoxide at 70°C affords 1,3-diphenyl-5,5-disubstituted hydantoins.

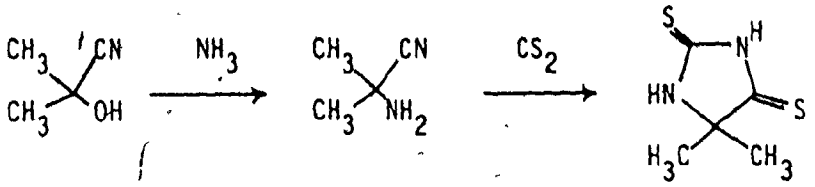


Recently, Simig and Lempert[157] developed an apparently general method for the synthesis of 1-alkyl, 1-araalkyl and 1-aryl derivatives of 5,5-diphenylhydantoin. An N-cyanoamine in 10 to 50% excess was reacted with 1-t-butyl-3,3-diphenylaziridinone in anhydrous benzene at room temperature and furnished an amide which was then cyclised in refluxing methanolic triethylamine. Deamination of the glycocyamidine with sodium nitrite in acetic acid and subsequent de-t-butylation in a refluxing 48% hydrobromic acid-acetic acid mixture yielded the hydantoin.

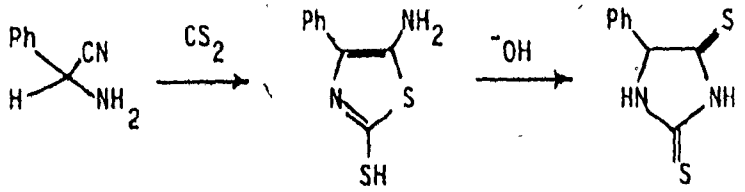


Just as the reaction of α-amino nitriles with carbon dioxide affords hydantoins, the reaction of α-amino nitriles with carbon disulphide has been found to lead to the formation of 2,4-dithiohydantoins.[158,159,160,161,162] For example, conversion of acetone cyanohydrin to α-aminoisobutyronitrile and subsequent reaction with carbon

disulphide has been reported to yield 2,4-dithio-5,5-dimethylhydantoin.[162]



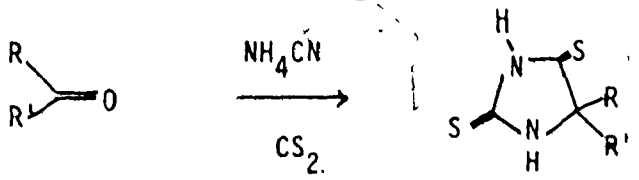
The reaction is, however, strongly dependent on the conditions used. Cook, Heilbron and Levy[159,160] obtained only 5-amino-2-mercapto-4-phenylthiazole on reacting α-aminobenzylnitrile with carbon disulphide whereas they isolated both 2,4-dithio-5-methylhydantoin and 5-amino-2-mercapto-4-methylthiazole from the reaction of α-aminopropionitrile with carbon disulphide. It was found that the 5-amino-2-mercaptothiazoles could be transformed into the corresponding 2,4-dithiohydantoins by treating them with aqueous alkali.



The conversion of aldehydes and ketones into 5-substituted hydantoins by the action of sodium cyanide and ammonium carbonate is well-known. During the development of this method, Bucherer and Lieb[163] made some attempts to extend the procedure to the preparation of 5-substituted 2,4-dithiohydantoins but were unable to isolate the expected compounds.

In a reinvestigation of the application of the Bucherer reaction to the preparation of dithiohydantoins, Carrington[164] found that when ketones are reacted with carbon disulphide and ammonium cyanide (or, in

practice, a mixture of salts capable of reacting as ammonium cyanide) the corresponding 2,4-dithiohydantoins can be readily isolated. Of a



wide variety of ketones employed by Carrington, only diisopropyl ketone and camphor failed to give the corresponding 2,4-dithiohydantoins.

Chapter II

Discussion

General

In the discussion of the thermolysis of 2-imino-Δ^3-1,3,4-oxadiazolines and Δ^3-1,3,4-oxadiazolin-2-ones in the presence of aryl isocyanates and phenyl isothiocyanate which ensues, the spectroscopic data and chemical properties of the reaction products are cited and arguments for the various structure assignments are developed. Then, in the light of the experimental evidence to date, possible mechanisms for their formation are considered. Lastly, the utility of the reaction as a method of synthesis of the various heterocyclic compounds will be examined.

The study was, initially, undertaken using 5,5-dimethyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline as the source of dimethyldiazomethane. Later, however, after it had been verified that thermolysis of either 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one or 5,5-dimethyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline in the presence of phenyl isocyanate afforded the same reaction products, the 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones were used routinely. For the synthesis of these compounds by the lead tetraacetate oxidation of the unsubstituted ketone semicarbazone in methylene chloride and subsequent "in situ" dilute hydrochloric acid hydrolysis is a more facile process than the

synthesis of 5,5-dialkyl-2-phenylimino-Δ^3-1,3,4-oxadiazolines which requires transamination of the unsubstituted ketone semicarbazone (a low yield reaction) prior to lead tetraacetate oxidation.

Characterization of the Products Obtained from the Thermolysis of 5,5-Dialkyl-Δ^3-1,3,4-Oxadiazolines in the Presence of Aryl Isocyanates and Phenyl Isothiocyanate

1-Arylcarbamoyl-3,3-Dialkyloxindoles

The assignment of the oxindole structure to the major product isolated from the thermal decomposition of 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones (or 5,5-dialkyl-2-phenylimino-Δ^3-1,3,4-oxadiazolines) in nitrobenzene at 150° containing an excess of an aryl isocyanate is based on microanalysis, spectroscopic and chemical evidence.

Both microanalysis and mass spectrometry indicated that the molecular composition of the product corresponded to that of a 2:1 adduct of the aryl isocyanate and the diazoalkane less one mole of nitrogen.

The infrared spectra of all the adducts showed a broad, intense band between 1700 cm^{-1} and 1730 cm^{-1} that was partially resolved into two bands and which can be attributed to the asymmetric stretching of two carbonyl groups in the molecule. Beckett, Daisley and Walker,[165] for example, have found that the infrared spectra of a number of N-methyl-substituted oxindoles all exhibit a single, intense absorption in the region 1700-1710 cm^{-1}. The absorption of weak to medium intensity in the region of 3240 cm^{-1} which was present

in the infrared spectra of all the compounds can be assigned to the stretching frequency of an NH group.

Ultraviolet spectra of the 1-arylcarbamoyl-3,3-dialkyloxindoles were not recorded on a routine basis because more useful information pertaining to the structure of the adducts was available from other sources. An example of the ultraviolet spectra of oxindoles is that of 1-phenylcarbamoyl-3,3-dimethyloxinole which exhibited an inflexion at 240 mμ (log ε 4.58) and a band at 244 mμ (log ε 4.45). Beckett, Daisley and Walker[165] found that oxindole displayed a band at 249 mμ (log ε 3.97) and an inflexion at 277 mμ (log ε 3.26) while its N-methyl analogue exhibited a band at 252.5 mμ (log ε 3.94) and an inflexion at 279 mμ (log ε 3.11).

All the compounds exhibited pmr spectra which, in the high field region, were characteristic of alkyl groups that are somewhat deshielded relative to saturated hydrocarbons. In addition to the broad signal in the region of 10.5δ which can be attributed to a nitrogen bound proton, the low field region of the pmr spectra contained an interesting feature; namely, two well-separated multiplets in the ratio of 8:1 (or 6:1 when a p-substituted phenyl isocyanate was used as the reactive scavenger). Comparison of the pmr spectrum of 1-(p-tolyl)carbamoyl-3,3,5-trimethyloxindole (page 61) with the pmr spectrum of 1-phenylcarbamoyl-3,3-dimethyloxindole (page 60) revealed that the introduction of a substituent into the aromatic ring reduced the fine structure of the low field multiplet to such an extent that it had the appearance of a slightly broadened doublet with a coupling constant of 8 Hertz. Furthermore the fine

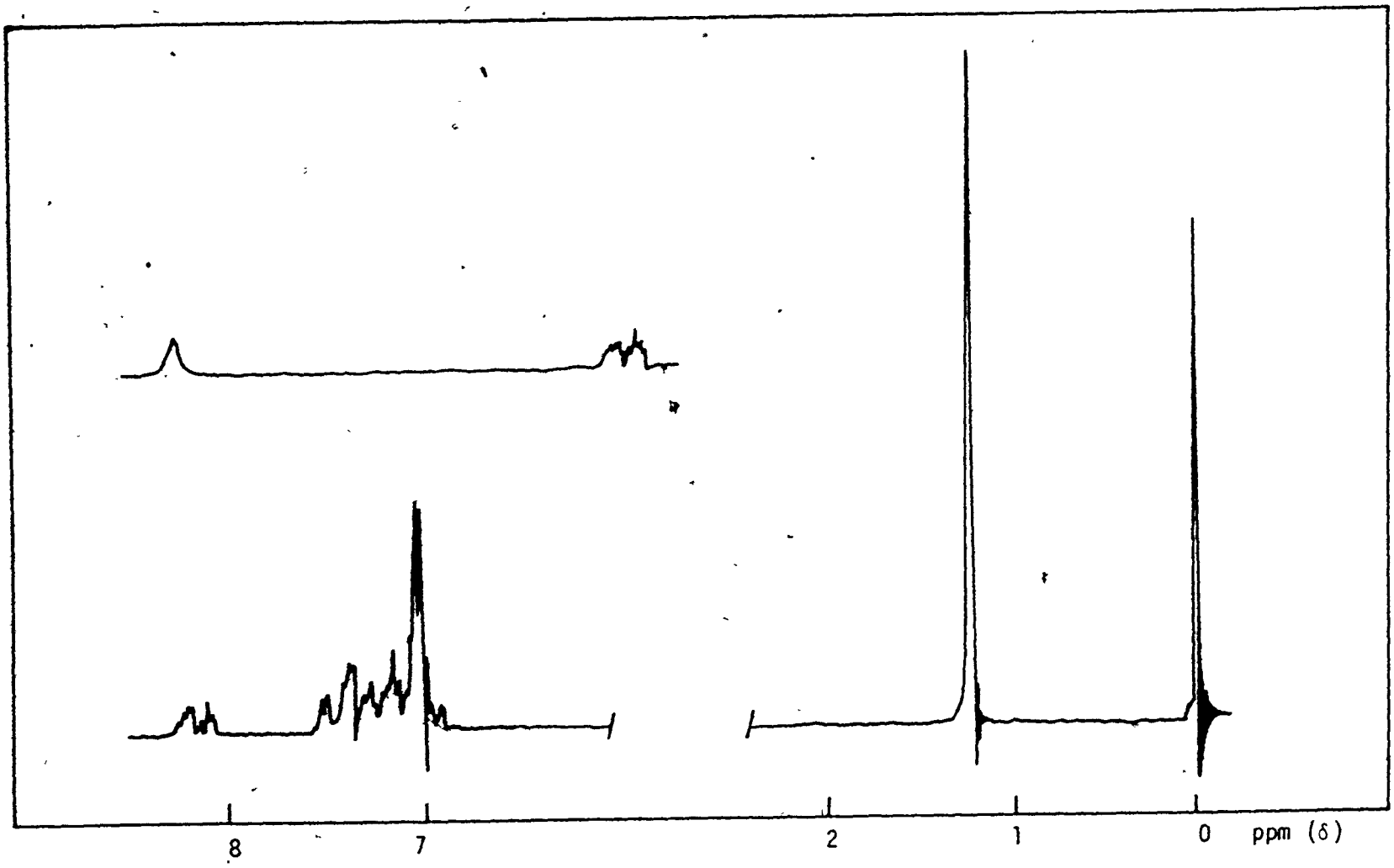


Fig. 1

60 MHz pmr spectrum of 1-phenylcarbamoyl-3,3-dimethyloxindole

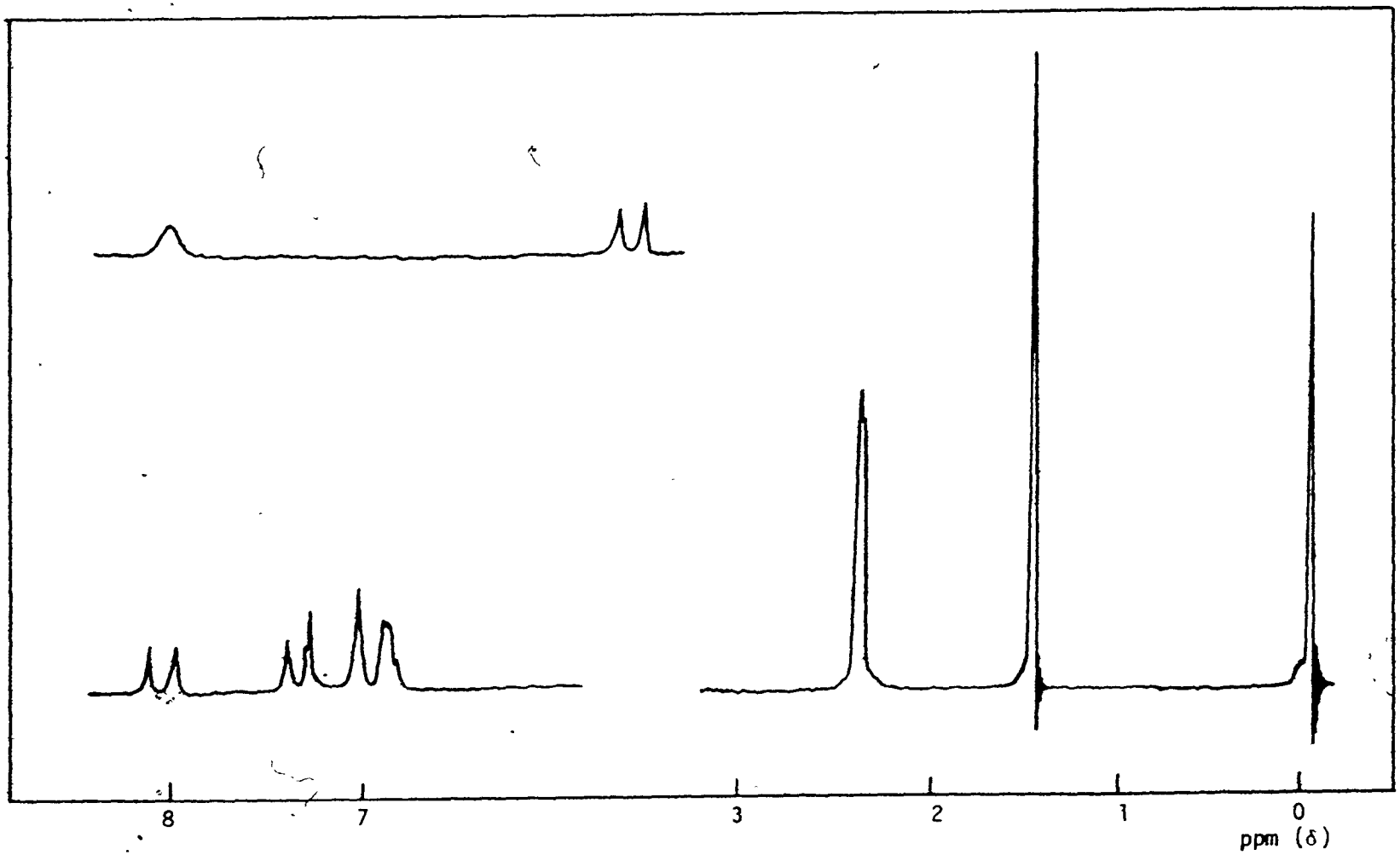
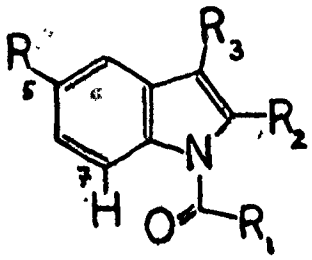


Fig. 2

60 MHz pmr spectrum of 1-(p-tolyl)carbamoyl-3,3,5-trimethyloxindole

structure of the multiplet to higher field was simplified somewhat. In view of the fact that the spin-spin coupling constant is 6.9 Hertz for an ortho proton, 1-3 Hertz for a meta proton and 0-1 Hertz for a para proton,[166] the low field signal was attributed to the proton attached to carbon-7. Such a downfield shift of a proton in the para position has been observed by Elguero, Marzin and Peek,[167] who found that the proton attached to carbon-7 of N-acyl-indoles (17) in the Z-configuration, resonated in the region of 8.46. Further support for the assignment was provided by the pmr spectrum of (18). This compound which has a fixed geometry and thus constitutes a good model for 1-phenylcarbamoyl oxindoles in the Z-configuration, exhibited a resonance at 8.216.



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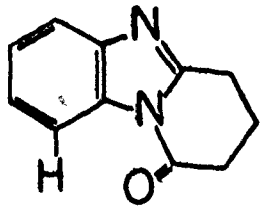

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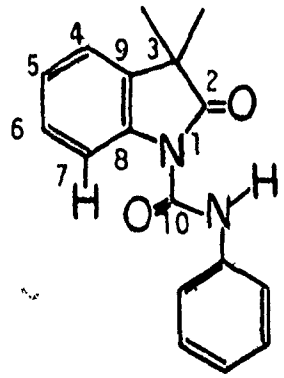
This restriction of rotation about the C-N bond linking the heterocycle to the phenylcarbamoyl group and the adoption of a preferred configuration must be the result of several factors. To ensure that there is maximum overlap between the nitrogen lone pair, the

π-system of the carbonyl group and the π-system of the aromatic ring, the five-membered ring will adopt a planar configuration. Moreover, the carbonyl group in the phenylcarbamoyl moiety will attempt to achieve coplanarity with the oxindole ring system. In the Z-configuration (19) this will have the effect of bringing the phenylcarbamoyl oxygen into proximity with the proton attached to carbon-7 and thus causing it to be deshielded relative to the aromatic proton. In the E-configuration (20), however, there will be steric interaction between the proton attached to carbon-7 and the phenylamino group and thus it will be much less likely.



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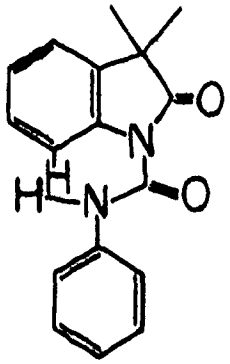
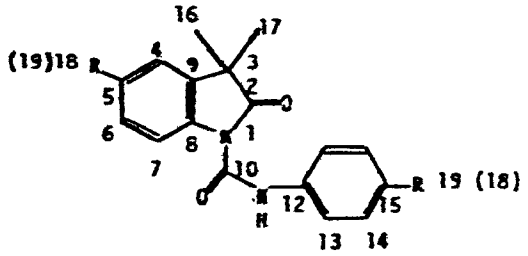


20

^{13}C Nmr spectra of the adducts were recorded routinely and were found to be consistent with the assigned structure of a 1-substituted oxindole. The signal at 184.0 ± 1.0 ppm was attributed to the carbonyl carbon in the five-membered ring. It can be seen (Table I) that replacement of one of the methyl groups of 1-phenylcarbamoyl-3,3-dimethyloxindole by various other alkyl groups has

TABLE I

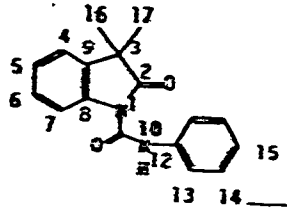
C^{13} CHEMICAL SHIFTS OF 1-ARYLCARBAMOYL-3,3-DIALKYLOXINDOLES



OXINDOLE	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{12}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}
R=H	184.3	45.4	124.4	125.0	128.4	116.7	137.3	134.3	149.7	138.9	120.5	129.1	122.0	25.1	25.1		
R=CH_3	184.3	45.4	122.6	134.8	128.8	116.4	134.6	134.3	149.7	136.6	120.5	129.6	133.9	25.1	25.1	20.8	21.1
R=CH_3O	183.9	45.6	108.7	157.4	112.5	117.4	130.4	135.8	149.7	132.2	122.8	114.2	156.5	25.0	25.0	55.3	55.5
R=Cl	183.7	45.6	122.5	130.7	129.2	117.9	136.1	135.7	149.3	137.2	121.7	129.7	128.5	25.0	25.0		

TABLE II

C^{13} CHEMICAL SHIFTS OF 1-PHENYLCARBAMOYL-3,3-DIALKYLOXINDOLES



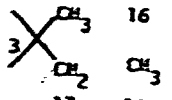
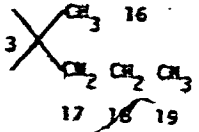
	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{12}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}	C_{20}	C_{21}
	183.9	59.2	124.4	125.0	128.4	116.6	137.4	132.5	149.5	139.9	120.5	129.1	122.2	24.0	32.4	8.8			
	184.0	49.9	124.4	125.0	128.3	116.6	137.3	132.8	149.6	139.7	120.5	129.1	122.1	24.6	41.6	17.9	14.1		

Table II. continued

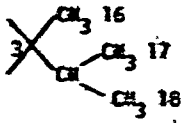
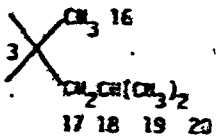
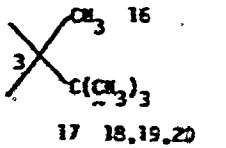
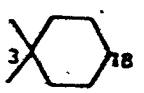
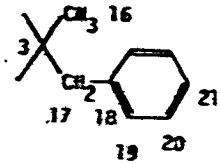
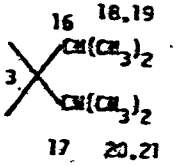
	C_2	C_2'	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{12}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}	C_{20}	C_{21}
	186.1	52.7	124.5	124.7	128.3	116.4	137.4	132.0	149.6	140.0	120.5	129.2	123.0	22.1	36.8	17.4	17.2		
	184.3	49.3	124.4	124.5	128.3	116.7	137.4	132.7	149.6	139.5	120.4	129.1	122.5	27.1	47.4	25.6	24.0	23.0	
	183.5	54.7	124.4	124.5	128.2	116.1	137.4	132.2	149.5	140.1	120.5	129.1	124.0	29.7	37.3	25.3	25.3	18.1	

Table II, continued

	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{12}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}	C_{20}	C_{21}
	183.3	48.0	124.2	124.5	128.0	116.5	137.4	134.1	149.6	139.0	120.4	129.0	122.9	33.8	26.0	20.8			
	183.2	51.2	124.4	124.6	128.5	116.5	137.3	131.7	149.3	139.6	120.5	129.1	122.9	23.6	45.3	135.1	129.7	128.5	127.1
	183.1	60.1	124.3	124.5	128.1	116.1	137.4	130.2	149.4	140.9	120.5	129.0	123.0	33.1	33.1	17.4	17.0	17.4	17.0

little effect on the chemical shift of the carbonyl carbon. This is to be expected since Stothers and Lauterbur[168] have reported that the substituent parameters for a methyl at the carbonyl carbon of a saturated aldehyde or ketone are very small, the α-effect being $\sim$+5 ppm, the β-effect $\sim$+2 ppm and the γ-effect $\sim$-1 ppm. The signal at 149.5 $\pm$ 0.2 ppm was assigned to the second carbonyl carbon and this is consistent with the value of 152.6 ppm determined for the carbonyl carbon of N,N'-diphenylurea. (It should be noted that this value was obtained from a d_6 dimethyl sulphoxide solution instead of a deuteriochloroform solution. However, Maciel and Ruben,[169] on measuring the carbonyl carbon shieldings of acetone in a variety of solvents, found that the carbonyl carbon absorbs at +0.7 ppm in dimethyl formamide and +2.3 ppm in chloroform (the shifts being relative to neat acetone). The chemical shift of carbon-3 was found to range from 45.4 ppm in 1-phenylcarbamoyl-3,3-dimethyl oxindole to 60.1 ppm in 1-phenylcarbamoyl-3,3-diisopropyloxindole. This variation was to be expected since the introduction of alkyl groups larger than a methyl group into the 3-position of the oxindole must cause some change in the shielding of carbon-3 although the effect is not as large as that when alkyl groups are substituted in linear and branched alkanes. The assignment of the atoms in the aromatic rings was accomplished by empirical calculations, i.e., by adding the contributions of the substituent shielding parameters[170] to the shift values for 1-phenylcarbamoyl-3,3-dimethyloxindole (see Tables I and II). In a few cases, the agreement between calculated and experimental values was far from satisfactory; discrepancies

may be ascribed to ortho interactions which give rise—as indicated by Lauterbur—to chemical shift values that are either up- or downfield with respect to those calculated according to the additivity rule.

Confirmation that the oxindole structure was the correct assignment was obtained when the adduct isolated from the reaction between 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one and phenyl isocyanate at 150° in nitrobenzene was hydrolysed in basic solution to 3,3-dimethyloxindole, a well-characterized compound. Moreover, reaction of 3,3-dimethyloxindole (synthesized by an independent route) with phenyl isocyanate at 150° in nitrobenzene was found to yield the adduct, 1-phenyl-carbamoyl-3,3-dimethyloxindole.

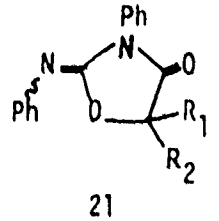
2-Phenylimino-3-Phenyl-4-Oxazolidones and 1,3-Diphenylhydantoins

Assignment of the 2-phenylimino-3-phenyl-4-oxazolidone structure and the 1,3-diphenylhydantoin structure to the two minor products formed during thermolysis of the 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones in nitrobenzene containing an excess of phenyl isocyanate was, to a large extent, dependent on a few differences observed in the spectra of the respective compounds. For, although both ring systems have been known for some time, there is not sufficient data in the literature describing them to permit the establishment of the one structure in the absence of the other without resorting to chemical methods (an approach hampered by the lack of relatively pure material) or to X-ray crystallography.

It was not possible, except in the case of 2-phenyl-imino-3-phenyl-5,5-dimethyl-4-oxazolidone, to obtain satisfactory microanalysis for the 2-imino-4-oxazolidones and the 1,3-diphenylhydantoins. As all

the compounds were heavy oils, they were purified by chromatography on analytical thin layer plates and the solvent that was used to elute them from the adsorbent was removed under reduced pressure. Thus it is likely that, despite prolonged evacuation, traces of solvent were still present when the compounds were submitted for analysis.

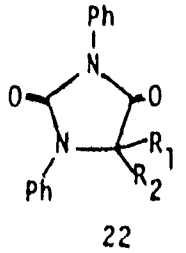
Mass spectrometry indicated that both the minor products of the reaction were isomeric with the major product, the 1-phenylcarbamoyloxindole; that is, they, too, were 2:1 adducts of phenyl isocyanate and the diazoalkane less one mole of nitrogen. A peak of medium intensity at m/e 161 in the mass spectra of 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone (21a) and 1,3-diphenyl-5,5-dimethylhydantoin (22a) and at m/e 203 in the mass spectra of 2-phenylimino-3-phenyl-5-methyl-5-t-butyl-4-oxazolidone (21b) and 1,3-diphenyl-5-methyl-5-t-butylhydantoin (22b) was attributed to the fragment formed on the loss of phenyl isocyanate by the parent ion. That this loss of phenyl isocyanate from both the 2-imino-4-oxazolidones and the 1,3-diphenylhydantoins is a facile process was evident from the intensity of the peak at m/e 119 in all the mass spectra.



21

a $R_1 = R_2 = CH_3$

b $R_1 = CH_3$, $R_2 = C(CH_3)_3$

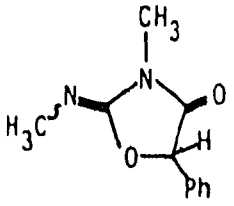


22

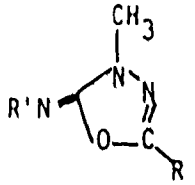
It was noticeable that the mass spectra of the 2-imino-4-oxazolidones exhibited an intense peak at m/e 194, attributable to N,N'-diphenylcarbodiimide formed on fragmentation of the parent ion, but that no such peak was evident in the mass spectra of the 1,3-diphenylhydantoins.

While the intense peak at m/e 133 in the mass spectrum of 1,3-diphenyl-5,5-dimethylhydantoin indicated that cleavage of the N(1)-C(2) and C(4)-C(5) bonds of the hydantoin ring had occurred, the absence of a peak at m/e 175 in the mass spectrum of 1,3-diphenyl-5-methyl-5-t-butylhydantoin suggested that this type of fragmentation was not an important process in the compound. This is not unexpected since the loss of a t-butyl substituent (as evidenced by the intense peak at m/e 265) should be a more facile process.

The infrared spectra of the 2-imino-4-oxazolidones exhibited a broad, intense absorption band between 1685 cm^{-1} and 1710 cm^{-1} which was partially resolved into two bands with maxima at 1690 cm^{-1} and 1705 cm^{-1} respectively and a sharp band of medium intensity at 1745 cm^{-1}. This broad band can be attributed to the stretching of both a carbonyl group and an exocyclic imine group. For the carbonyl stretching frequency of a cyclic γ-lactam in dilute solution is known to occur in the region of 1700 cm^{-1} and Najer, Giudicelli and coworkers[171,172,173] have found that N-alkylimino groups absorb at 1700-1710 cm^{-1} and that N-arylimino groups absorb at somewhat lower frequencies.



1700 cm^{-1}



R = Ph, R' = CH_3 1710 cm^{-1}

R = Ph, R' = Ph 1660-80 cm^{-1}

R = H, R' = Ph 1675 cm^{-1}

That there is no amino function in the compounds is indicated by the absence of any absorption above 3075 cm^{-1}.

The infrared spectra of those 1,3-diphenylhydantoins which could be isolated in a relatively pure form exhibited an intense band around 1710 cm^{-1} and a strong band at about 1775 cm^{-1}. The fact that the known 1,3-diphenylhydantoin exhibits an intense band at 1720 cm^{-1} and a strong band at 1780 cm^{-1} and that 1,3-diphenyl-5-benzylhydantoin displays two strong bands at 1720 cm^{-1} and 1770 cm^{-1} respectively, lends support to the structural assignment. These two maxima cannot be assigned to either of the carbonyl groups but rather must be attributed to the symmetric and antisymmetric coupled stretching vibrations of the carbonyl double bonds. The absorption band at the lower wave number was the more intense since the symmetric mode of vibration involves a greater change in the dipole moment than does its antisymmetrical counterpart. The absence of any absorption above 2075 cm^{-1} suggested that there was no amino function present in the compounds.

Ultraviolet spectra of the 2-phenylimino-3-phenyl-4-oxazolidones and the 1,3-diphenylhydantoins were not recorded on a routine basis because the data so obtained were not of much assistance in establishing the structures. Moreover, as it was not possible to isolate a 1,3-diphenylhydantoin in analytically-pure form, the ultraviolet spectra could only afford qualitative information. A typical example of the ultraviolet spectra of the 2-imino-4-oxazolidones is that of 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone which exhibits absorption bands at 223 mμ (log ε 4.50) and at 248 mμ

(log ε 4.49). 2-Phenylimino-3-methyl-5-phenyl-Δ^4-oxadiazoline by way of comparison exhibits absorption bands at 230 mμ, 260 mμ, and 311 mμ.

The 60 MHz pmr spectra of the 2-phenylimino-3-phenyl-4-oxazolidones and the 1,3-diphenylhydantoins were not particularly helpful in distinguishing between the respective structures since they exhibited only high field signals typical of alkyl groups that are somewhat deshielded relative to saturated hydrocarbons and a multiplet at low field characteristic of aromatic protons. However, it was noticeable that in the pmr spectra of the compounds ultimately assigned the iminooxazolidone structure, that the low field multiplet extended over 45 Hz and in effect appeared to be two partially separated multiplets rather than a discrete entity, indicating that the protons on the two aromatic rings were in quite different environments.

C^{13} Nuclear magnetic resonance spectra provide strong support for the assignment of the 2-phenylimino-3-phenyl-4-oxazolidone and 1,3-diphenylhydantoin structures to the two minor products. The low field signal exhibited by the iminooxazolidones and the hydantoins (see Table III) can be attributed to the amido carbon. In the one series of compounds, the signal in the vicinity of 148 ppm has been assigned to the imino-carbon of the iminooxazolidone rather than to the ureide carbon of the hydantoins for two reasons. First, while the C^{13} nmr spectra of model 2-phenylimino-4-oxazolidones do not seem to be recorded in the literature, Naulet, Filleux, Martin, and Pornet[174] have observed in iminoethers such as (23), the imino carbon resonates at 154.2 ppm and that in aromatic amidines such as (24), it resonates at 149.8 ppm.

TABLE III

C^{13} CHEMICAL SHIFTS OF 2-PHENYLIMINO-3-PHENYL-5,5-DIALKYL-4-OXAZOLIDONES AND 1,3-DIPHENYL-5,5-DIALKYLHYDANTOINS

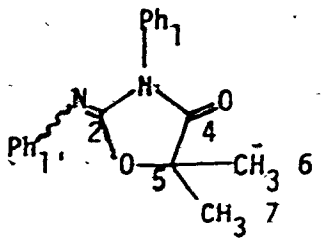
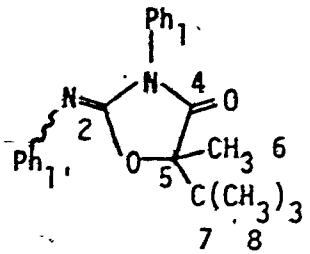
	C_2	C_4	C_5	C_6	C_7	C_8	Aromatic C_1	Aromatic $C_{1'}$	Aromatic
	147.0	174.3	83.5	24.0	23.7		132.2	144.6	129.1, 128.7 128.5, 126.8 123.8
	147.7	173.7	90.0	24.7	38.0	18.5	132.2	144.8	129.1, 128.6 128.1, 126.9 123.6, 123.5

Table III, continued

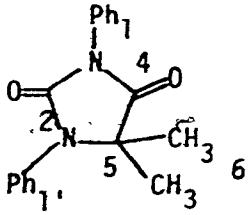
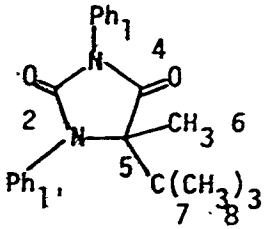
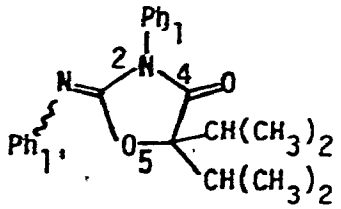
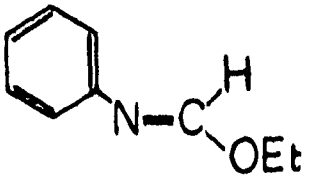
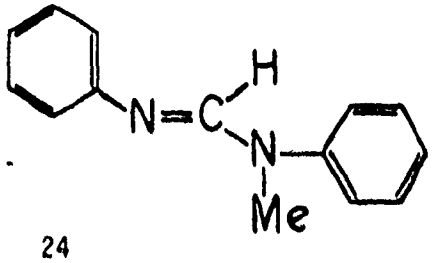
	C_2	C_4	C_5	C_6	C_7	C_8	Aromatic C_1	Aromatic $C_{1'}$	Aromatic
	153.5	175.3	63.5	24.2			137.4	132.0	129.9, 129.6 129.1, 128.2 126.2
	155.1	174.3	72.1	25.8	39.5	19.7	137.3	132.0	129.3, 129.0 128.8, 128.2 128.0, 126.4

Table III, continued

	C_2	C_4	C_5	C_6	C_7	C_8	Aromatic C_1	Aromatic $C_{1'}$	Aromatic
 6, 7, 8	148.7	173.0	93.4	31.9	16.5	16.2	132.2	145.0	129.2, 128.7 127.0, 126.7 124.5, 123.5



23



24

Although the combined effects of both the oxygen atom and the N-phenyl group on the imino carbon cannot be predicted, the observed chemical shifts are in the right region for such an imino carbon. Second, the chemical shifts in the region of 154 ppm in the other series of compounds which could, possibly, have been assigned to the imino-carbon of the iminooxazolidones is in excellent agreement with the chemical shifts of the ureide carbon of 1,3-diphenylhydantoin (153.1 ppm) and the carbonyl carbon of N,N'-diphenylurea (152.6 ppm). It should be noted that in the spectrum of each of the iminooxazolidones only one signal which could be attributed to an iminocarbon was observed (see Table III) suggesting that in each instance a single isomer was formed. However it is not possible to determine the configuration of the isomer from the data available because Naulet, Filleux, Martin and Pornet have found that in iminoethers and ethylenic oximes, the imino carbon of the Z-isomer resonates at higher field than does that of the E-isomer whereas in conjugated aromatic amidines and aliphatic imines, the reverse is true. Perhaps the main evidence in favour

of the particular assignments comes from a comparison of the chemical shifts of the C-5 carbon in the two different ring systems. In the compounds to which has been atrributed the iminooxazolidone structure this occurs in the region of 88 ppm whereas in the compounds assigned the hydantoin structure it occurs in the vicinity of 67 ppm. Such a marked downfield shift is to be expected when an alpha nitrogen is replaced by an oxygen atom. For example, the chemical shift of the methylamine carbon is reported to be 28.3 ppm[170] while that of the methanol carbon is 49.3 ppm, a downfield shift of 21 ppm, just what is observed in the case of the two heterocyclic systems.

In summary, a consideration of the C^{13} nuclear magnetic resonance, infrared, and mass spectral properties of the two series of compound leads to the conclusion that their structures are those of a 2-phenylimino-3-phenyl-4-oxazolidone and a 1,3-diphenylhydantoin.

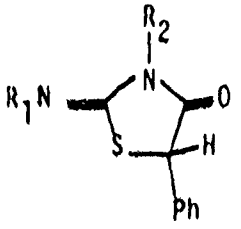
2-Phenylimino-3-Phenyl-4-Thiazolinethiones and 1,3-Diphenyl-2,4-Dithiohydantoins

Assignment of the 2-phenylimino-3-phenyl-4-thiazoline-thione and 1,3-diphenyl-2,4-dithiohydantoin structures to the two major compounds formed during the thermal decomposition of a 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one in nitrobenzene containing an excess of phenyl isothiocyanate at a temperature of 150° is based on microanalysis, spectroscopic and chemical evidence.

Both microanalysis and mass spectrometry indicate that the molecular composition of the two compounds corresponds to that of a

2:1 adduct of phenyl isothiocyanate and the diazoalkane less one mole of nitrogen.

A strong absorption band around 1640 cm^{-1} in the infrared spectra of the 2-imino-4-thiazolinethiones is indicative of an exocyclic ~~imino~~ group alpha to both a nitrogen and a sulphur atom as Najer, Giudicelli, Morel and Menin[175] have found that such a group absorbs in the region of 1600-1640 cm^{-1}.



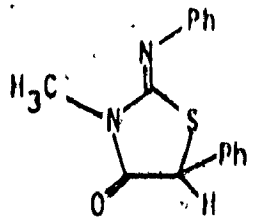
R_1 = H,	R_2 = CH_3	1615 cm^{-1}
R_1 = CH_3,	R_2 = CH_3	1640 cm^{-1}
R_1 = Ph,	R_2 = H	1600-1620 cm^{-1}
R_1 = Ph,	R_2 = CH_3	1610-1620 cm^{-1}

The high intensity is to be expected for, although many imino absorptions are quite weak, it has been shown that the stretching absorption of an exocylic imino group is greatly enhanced in intensity. The broad, strong absorption band in the vicinity of 1290 cm^{-1} can be attributed to the thione group.

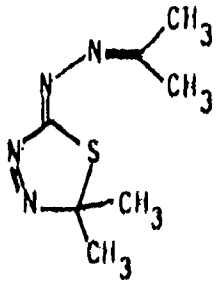
That the other series of compounds were 1,3-diphenyl-2,4-dithiohydantoins was suggested by the absence of any strong absorption in the region 2000 cm^{-1} to 1600 cm^{-1} and the presence of two relatively intense bands at 1290 cm^{-1} and 1100 cm^{-1} which can probably be ascribed to the coupling of vibrations of the two NCS groups.

As in the case of the 2-phenylimino-3-phenyl-4-oxazolidones and 1,3-diphenylhydantoins, ultraviolet spectra of the 2-phenylimino-3-phenyl-4-thiazolinethiones and 1,3-diphenyl-2,4-dithiohydantoins were

not recorded on a routine basis because the information so obtained was not of much assistance in establishing the respective structures. A typical example of the ultraviolet spectra of the 2-imino-4-thiazoline thiones is that of 2-phenylimino-3-phenyl-5,5-dimethyl-4-thiazoline-thione which shows two absorption bands, one at 214 mμ (log ε 4.36) and the other at 296 mμ (log ε 4.45). The latter is intermediate between the absorption bands at 272 mμ (log ε 3.88) and 335 mμ (log ε 3.67) in the ultraviolet spectra of the model compounds (25) and (26) respectively.[175]



25



26

An example of the ultraviolet spectra of the 2,4-dithiohydantoins is that of 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin which exhibits two absorption bands, one at 220 mμ (log ε 4.38) and the other at 300 mμ (log ε 4.58).

The 60 MHz pmr spectra of the 2-phenylimino-3-phenyl-4-thiazolinethiones and the 1,3-diphenyl-2,4-dithiohydantoins were not particularly useful in the assignment of structure since they exhibited only high field signals typical of alkyl groups that are somewhat deshielded relative to saturated hydrocarbons and a multiplet at low field characteristic of aromatic protons. However as was the

case with the oxygen analogues, it was noticeable that in the pmr spectra of the compounds ultimately assigned the iminothiazolinethione structure the low field multiplet extended over 50 Hz and, moreover, appeared to be two partially separated multiplets, indicating that the protons on the two aromatic rings were in significantly different environments.

C^{13} Nuclear magnetic resonance spectra provide conclusive evidence that the reaction products were, indeed, 2-phenylimino-3-phenyl-4-thiazolinethione and 1,3-diphenyl-2,4-dithiohydantoins. The low field signal exhibited by both series of compounds (see Tables IV and V) is characteristic of a thioamide carbon. In thioacetamide, for example, the thioamide carbon resonates at 207.2 ppm. The signal displayed by the compounds assigned the iminothiazolinethione structure in the vicinity of 158 ppm (see Table IV) can be attributed to the imino carbon; support for this assignment coming from the observation of L'abbé, Toppet, Willocx and Mathys[176] that the imino-carbon of 2-phenylimino-3-methyl-Δ^4-1,3,4,5-thiatriazoline resonates at 156 ppm. In an off-resonance decoupled spectrum of 2-phenylimino-3-phenyl-5,5-dimethyl-4-thiazolinethione the signal at 157.4 ppm still occurred as a singlet while the signal at 149.1 ppm exhibited fine structure thereby confirming that the former signal is due to the iminocarbon and that the latter arises from carbon-1 of the aromatic ring. On the other hand, the signal in the region of 182 ppm exhibited by the compounds assigned the 2,4-dithiohydantoin structure is typical of a thiourea carbon. In N,N'-diethylthiourea, for example, the thiourea carbon resonates at 182.8 ppm.

TABLE IV

C^{13} CHEMICAL SHIFTS OF 2-PHENYLIMINO-3-PHENYL-5,5-DIALKYL-4-THIAZOLINETHIONES

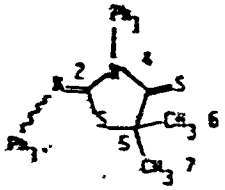
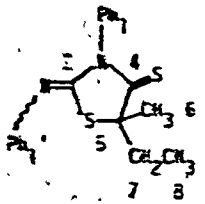
	C_2	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic C_1'	Aromatic C's
	157.4	212.9	61.4	32.9	32.9				139.1	149.0	129.6, 129.2, 126.4 124.8, 120.7
	156.0	211.7	66.9	31.3	38.0	9.2			139.1	149.1	129.6, 129.1, 126.4 124.7, 120.7

Table IV, continued

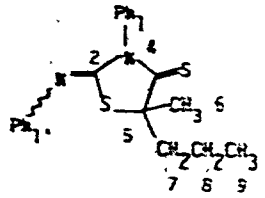
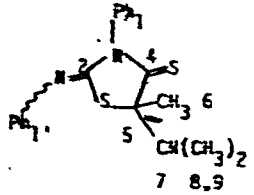
	C_2	C_3	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic $C_{1'}$	Aromatic C's
	157.9	211.7	66.2	31.5	46.9	18.2	13.9		139.0	149.0	129.5, 129.1, 128.4, 124.6, 120.6
	158.4	212.5	71.9	30.3	40.4	17.9	17.9		138.9	149.3	129.6, 129.2, 128.4 124.7, 120.7

Table IV, continued

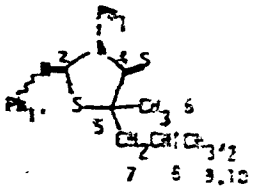
	C_2	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic $C_{1'}$	Aromatic C's
	158.1	212.4	66.0	33.2	52.2	26.3	24.5	23.7	139.1	149.1	129.6, 129.1, 128.4, 124.7, 120.7
	157.7	212.2	70.6	41.0	23.7	24.5			135.7	145.2	129.6, 129.1, 128.5 124.6, 120.8

TABLE V

C^{13} CHEMICAL SHIFTS OF 1,3-DIPHENYL-5,5-DIALKYL-2,4-DITHIOHYDANTOINS

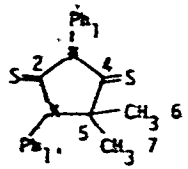
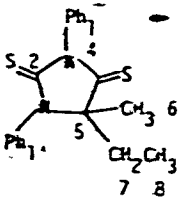
	C_2	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic $C_{1'}$	Aromatic carbons
	181.1	208.6	77.2	27.9	27.9				136.6	136.4	129.6, 129.4, 129.3, 128.9, 128.7
	182.2	207.2	81.3	27.3	33.5	7.8			136.8	136.6	129.8, 129.6, 129.4, 129.3, 128.8

Table # , continued

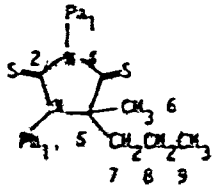
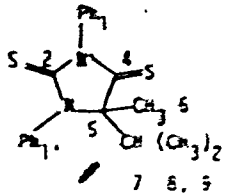
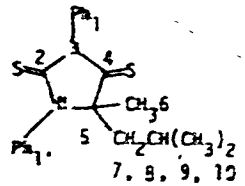
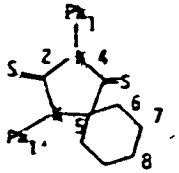
	C_2	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic $C_{1'}$	Aromatic carbons
	181.9	207.3	80.9	27.4	42.4	16.5	13.6		136.7, 136.5		129.7, 129.3 129.1, 128.7
	182.1	206.5	82.9	25.6	37.0	16.5	15.7		136.9, 136.9		129.7, 129.4 128.8

Table V . continued

	C_2	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	Aromatic C_1	Aromatic C_1	Aromatic carbons
 7, 8, 9, 10	181.8	207.2	80.5	29.1	48.4	24.4	24.4	23.7	136.6	136.6	129.4, 129.1 128.5
	181.3	208.1	78.1	35.4	20.3	23.9			136.9, 136.7		130.7, 129.6 129.3, 128.8

Kalinowski and Kessler[177] established that a linear relationship exists between the C^{13} chemical shifts of carbonyl groups and thiocarbonyl groups.

$$\delta_{C=S} = \delta_{C=O} - 46.5 \text{ ppm}$$

Using this expression, it is found that there is good agreement between the observed chemical shift of carbon-4 in 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin and that calculated using carbon-4 in 1,3-diphenyl-5,5-dimethylhydantoin as the model. However there is a difference of 5 ppm between the observed chemical shift of carbon-2 in the 2,4-dithiohydantoin and that calculated using carbon-2 in 1,3-diphenyl-5,5-dimethylhydantoin as the model. This perhaps is not too surprising as the expression was derived from a limited number of experimental observations and only two of these involved heterocyclic systems.

The chemical shift of carbon-5 ranges from 61.4 ppm in 2-phenylimino-3-phenyl-5,5-dimethyl-4-thiazolinethione to 71.9 ppm in the 5-isopropyl-5-methyl derivative and from 77.2 ppm in 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin to 82.9 ppm in the 5-isopropyl-5-methyl derivative (see Tables IV and V). It is apparent that the substituent parameters for a methyl group at this carbon are much smaller than those in aliphatic hydrocarbons; the β effect being $\sim$+5 ppm (in the case of the iminothiazolinethiones) and the γ effect $\sim$-0.5 ppm. In the case of the 2,4-dithiohydantoins, however, sequential replacement of β-hydrogens by methyl groups does not give rise to a linear change in the shielding of carbon-5. The reason for this is unknown and because only three

compounds are involved, it may just be an anomaly.

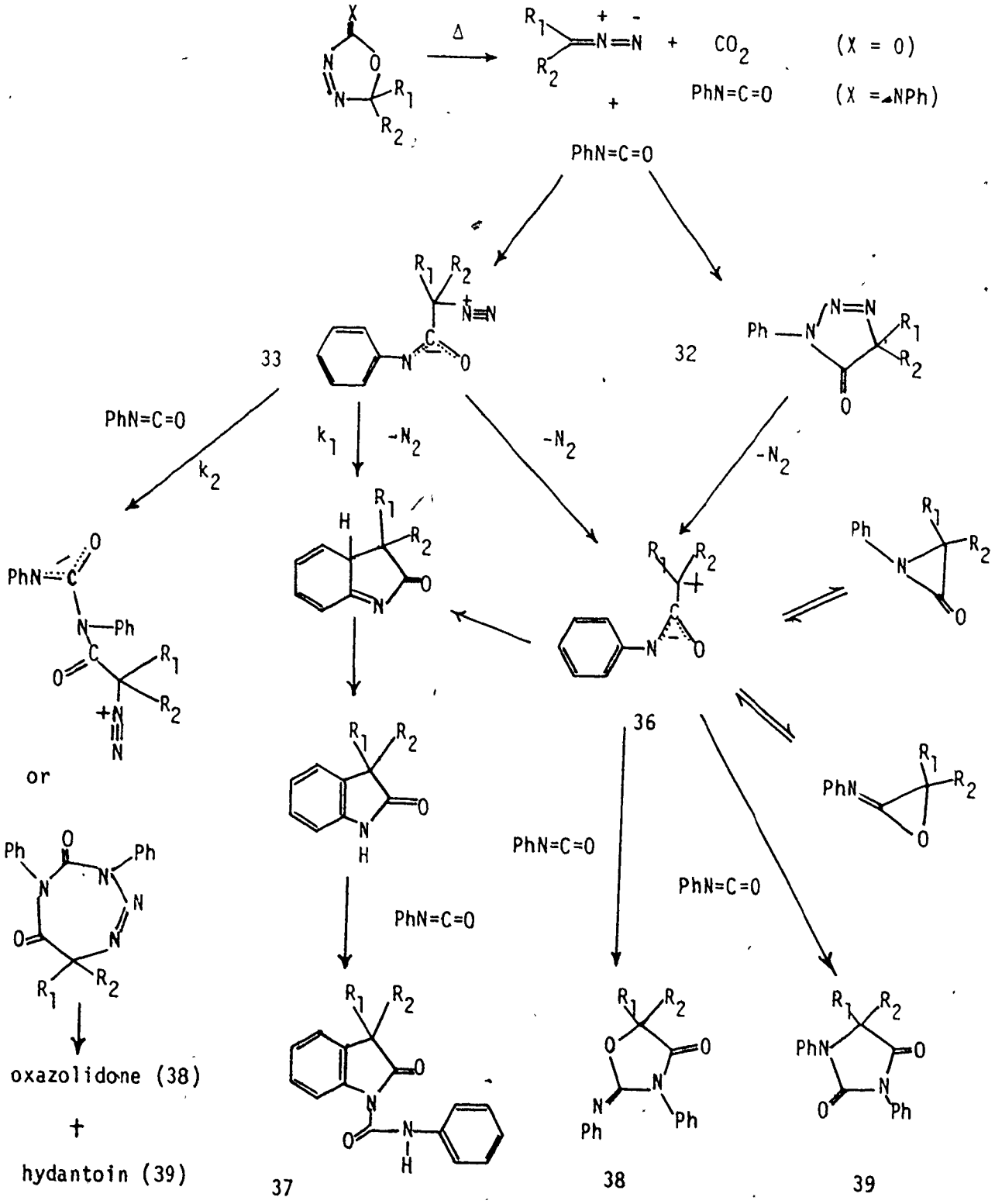
Further evidence supporting the assignment of the 2-phenylimino-3-phenyl-4-thiazolinethione structure to the one series of compounds is afforded by the acid hydrolysis of the 5,5-dimethyl derivative; the product of the reaction being the known 3-phenyl-5,5-dimethyl-2,4-thiazolinedione.

Mechanism of Formation of Heterocycles

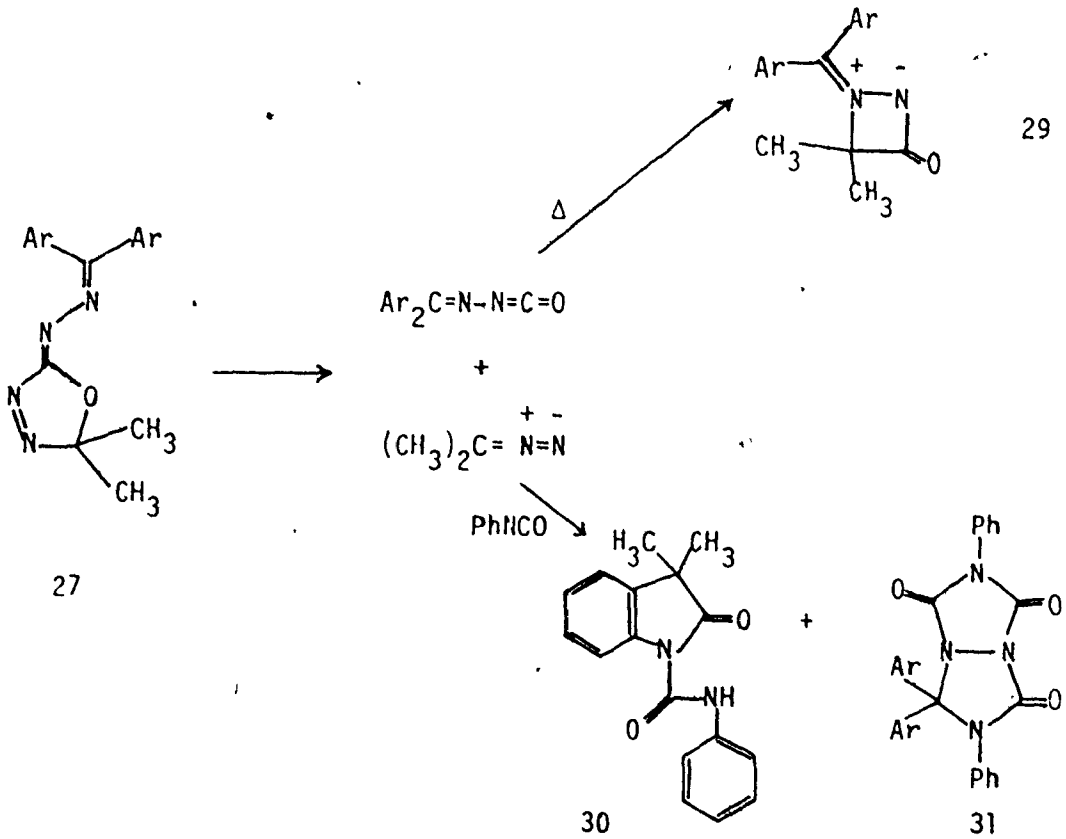
The fact that the thermolysis of Δ^3-1,3,4-oxadiazolines in the presence of either aryl isocyanates or phenyl isothiocyanate can give rise to a variety of heterocyclic compounds, namely oxindoles, 2-imino-4-oxazolidones and hydantoins in the one instance and 2-imino-4-thiazolinethiones and 2,4-dithiohydantoins in the other, poses an interesting question from a mechanistic point of view.

The structures of the heterocyclic products suggest that their formation originates with the interception of the diazoalkane, generated in the thermolysis of the Δ^3-1,3,4-oxadiazoline, by either isocyanate or isothiocyanate. On this basis the mechanistic scheme outlined on page 90 probably best accounts for their formation.

That it is, indeed, free diazoalkane rather than the Δ^3-1,3,4-oxadiazoline which reacts with the isocyanate is indicated by the results of a mechanistic study of the thermolysis of 5,5-dimethyl-2-diarylmethylenehydrazono-Δ^3-1,3,4-oxadiazolines[36] (27). In a manner analogous to the 2-phenylimino-Δ^3-1,3,4-oxadiazolines and Δ^3-1,3,4-oxadiazolin-2-ones, these compounds have been found to undergo a retro-1,3-dipolar cycloaddition affording dimethyldiazomethane and an N-


Δ
+ CO2 (X = O)
PhN=C=O (X = NPh)
PhN=C=O
33
32
PhN=C=O
k2
k1
-N2
-N2
-N2
or
oxazolidone (38)
+
hydantoin (39)
36
PhN=C=O
PhN=C=O
PhN=C=O
37
38
39

isocyanatodiarylmethyleneimine (28). The two fragments subsequently recombine with the loss of nitrogen to form a 1-diarylmethyleneimino-4,4-dimethyl-3-oxo-1,2-diazetidinium hydroxide inner salt (29). However, in the presence of phenyl isocyanate both intermediates are intercepted, 1-phenylcarbamoyl-3,3-dimethyloxindole (30) and the 1:2 adduct (31) of the N-isocyanatodiarylmethyleneimine and phenyl isocyanate being obtained. As the first order rate constant for the decomposition of 5,5-dimethyl-2-di(p-chlorophenyl)methylenehydrazono-Δ^3-1,3,4-oxadiazoline is the same whether or not phenyl isocyanate is present, phenyl isocyanate cannot react with the oxadiazoline at a rate competitive with the unimolecular decomposition of the oxadiazoline.

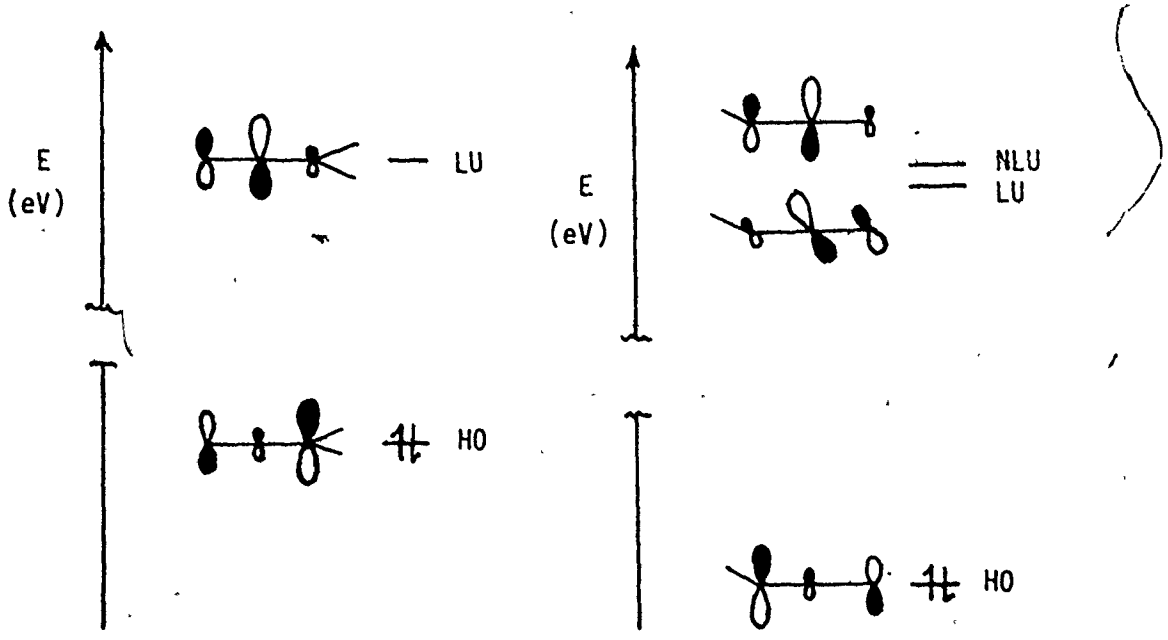


In the case of the 2-phenylimino-Δ^3-1,3,4-oxadiazolines there exists the possibility that a cage effect is operative; that is the diazoalkane and phenyl isocyanate generated in the thermolysis react together immediately rather than diffusing apart prior to interception of the diazoalkane by isocyanate. That the latter process takes places was demonstrated through thermolysis of 2-(p-tolyl)imino-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in nitrobenzene containing a 20 molar excess of phenyl isocyanate. Only 1-phenylcarbamoyl-3,3-dimethyloxindole was formed and no 1-phenylcarbamoyl-3,3,5-trimethyloxindole, the cage product, was formed within the limits of detection (pmr).

While it is conceivable that the dialkylcarbene (derived from the diazoalkane) rather than the diazoalkane itself reacts with the isocyanate, this process can be ruled out as a major contributor to the reaction mechanism. For no propylene resulting from a 1,2-hydrogen shift in dimethylcarbene has been detected in the thermolysis of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one despite the fact that formation of olefins from dialkylcarbenes is a facile process.[178] Furthermore, it has been found that decomposition of this oxadiazolinone in styrene affords mainly acetone and acetone azine, plus a small amount (< 5%) of phenyl-2,2-dimethylcyclopropane; thereby setting an upper limit on the amount of dimethylcarbene that could have been formed since some of the cyclopropane may have come from decomposition of a pyrazoline intermediate.[179]

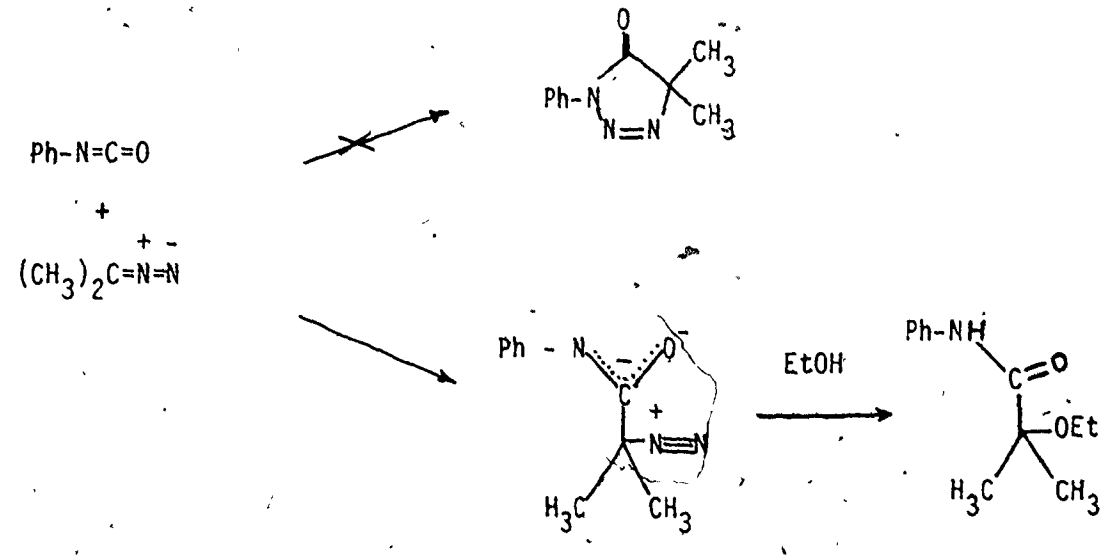
The reaction of a dialkyldiazomethane with phenyl isocyanate to form the cycloadduct (32) is a symmetry-allowed, concerted, 1,3-cycloaddition involving 6π electrons but it is by no means certain

that such a process actually occurs; theoretical calculations and experimental data tending to indicate otherwise.[180,181,182] Houk and coworkers have determined that the energies of both the highest occupied and lowest unoccupied π molecular orbitals of diazomethane are such that reactivity and regioselectivity with virtually all dipolarophiles will be controlled by the interaction between the diazomethane's highest occupied and the dipolarophile's lowest unoccupied π molecular orbitals.[180] Isocyanates are characterized by a low-lying vacant in-plane molecular orbital.[183] However nearly degenerate with this lowest unoccupied molecular orbital, is a π molecular orbital which should be stabilized more than the in-plane orbital by substituents such as aryl groups. As a result aryl isocyanates can be expected to undergo only non-concerted reactions because of stabilization of the intermediate dipolar species.

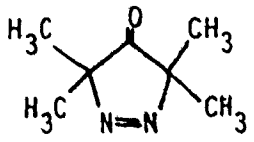


HØ and LU π orbitals of diazomethane. FMOS of isocyanate.

The fact that reaction, at room temperature, of dimethyldiazomethane with phenyl isocyanate in anhydrous ether containing ethanol* affords α-ethoxyisobutyranilide and not the cycloadduct, lends support to the hypothesis that the reaction occurs in a stepwise manner.



For, compounds such as (40) are known to be stable under these conditions.[26]



40

*The ethereal solution of dimethyldiazomethane was flash distilled prior to reaction with phenyl isocyanate and as a consequence the small amount of ethanol used to permit dissolution of the potassium hydroxide during the preparation of the diazoalkane, was not removed.

When the mole ratio of phenyl isocyanate to 5,5-dimethyl-Δ^3-1,3,4-oxadizaoline-2-one is increased from 20:1 to 50:1 and/or temperatures lower than 150° are used, both 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin are formed at the expense of 1-phenylcarbamoyl-3,3-dimethyloxindole. This suggests that a bimolecular process leading to the iminooxazolidone and hydantoin is competing with a unimolecular process of some intermediate. However the nature of the intermediate and the unimolecular process involved are open to question.

It is possible that the loss of nitrogen to form the 1,3-dipolar species (33) formed immediately upon nucleophilic addition of the diazoalkane to phenyl isocyanate is concomitant with aromatic substitution. Moreover, this 1,3-dipolar species may also react with a second molecule of phenyl isocyanate to form an adduct such as (34) or (35). Either of these adducts could then yield both the iminooxazolidone and the hydantoin. However there also exists the possibility that nitrogen is lost from the 1,3-dipolar species resulting in the formation of a second 1,3-dipolar intermediate (36) in which the positive end of the dipole is stabilized by the alkyl substituents and the negative end of the dipole is conjugated with the aromatic ring. This second dipolar species could then either undergo aromatic substitution to afford the oxindole or it could react with a second molecule of phenyl isocyanate yielding both the iminooxazolidone and the hydantoin.

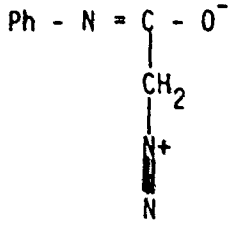
The fact that reaction of diazomethane with phenyl isocyanate fails to yield oxindole or α-ethoxyacetanilide[30] can be most easily accounted for if it is assumed that the dipolar species $Ph\bar{N}COCH_2N_2^+$

does not lose nitrogen readily. Since concerted closure of $Ph\bar{N}COCH_2N_2^+$ to oxindole should be much easier than it is for $Ph\bar{N}COC(CH_3)_2N_2^+$ (33) because of lower steric hindrance, the concerted process for the latter is very unlikely.

Hence if formation of the oxindole and α-ethoxyisobutyranilide does occur through this second 1,3-dipolar intermediate (36), the latter must have an appreciable lifetime. For, at room temperature, at least, aromatic substitution must be slow since bimolecular capture by ethanol, present at low concentration can compete successfully. It is reasonable, therefore, that phenyl isocyanate can divert the 1,3-dipolar species (36) from oxindole formation. Consequently there is no reason to retain the first 1,3-dipolar intermediate (33) as a product-forming species in the reaction scheme.

While the 1,3-dipolar species may well be in equilibrium with both the iminooxirane[184,185] and the α-lactam,[186,187,188] in view of their known instabilities, it is very unlikely that either species is present in significant amounts.

The foregoing mechanism is similar to that suggested by Sheehan and Izzo[31] for the reaction of diazomethane with phenyl isocyanate in that they, too, postulated a dipolar intermediate (41).



41

However their subsequent reactions did not include aromatic substitution for oxindole formation was not observed. A possible reason for the different behaviour in the present case is that the second dipolar intermediate is accessible because of the stabilization afforded by the alkyl groups.

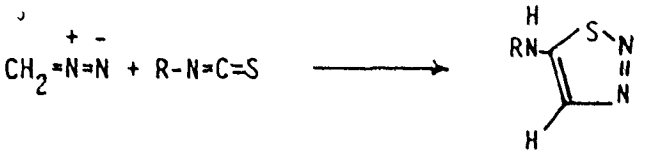
When a para-substituted phenyl isocyanate is used to trap the diazoalkane generated in the thermolysis of a 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one, the reaction is quite straightforward insofar as the para-substituent is always found at the 5-position of the oxindole. Meta-substituted phenyl isocyanates, however, present a more complex problem since aromatic substitution can occur either ortho to the substituent to give a 4-substituted oxindole or it can occur para to the substituent to give the 6-substituted oxindole. Reaction of m-tolyl isocyanate with 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one has been found to afford equal amounts of 1-(m-tolyl)carbamoyl-3,3,4-trimethyloxindole and 1-(m-tolyl)carbamoyl-3,3,6-trimethyloxindole. This is not too surprising for both the methyl and NCOR substituents (which are meta to each other) activate the ortho and para positions relative to benzene. Moreover, since in the nitration of toluene the rates of substitution at one of the ortho, meta and para positions relative to the rate of substitution at one of the six equivalent positions in benzene are 42, 2.5 and 58 respectively[189] the 4-substituted and the 6-substituted oxindoles might be formed in the ratio of 1:1.3 which is in approximate agreement with the ratio obtained experimentally.

In the case of the 2-phenylimino-Δ^3-1,3,4-oxadiazolines, which on thermolysis yield phenyl isocyanide, ketone and nitrogen in addition

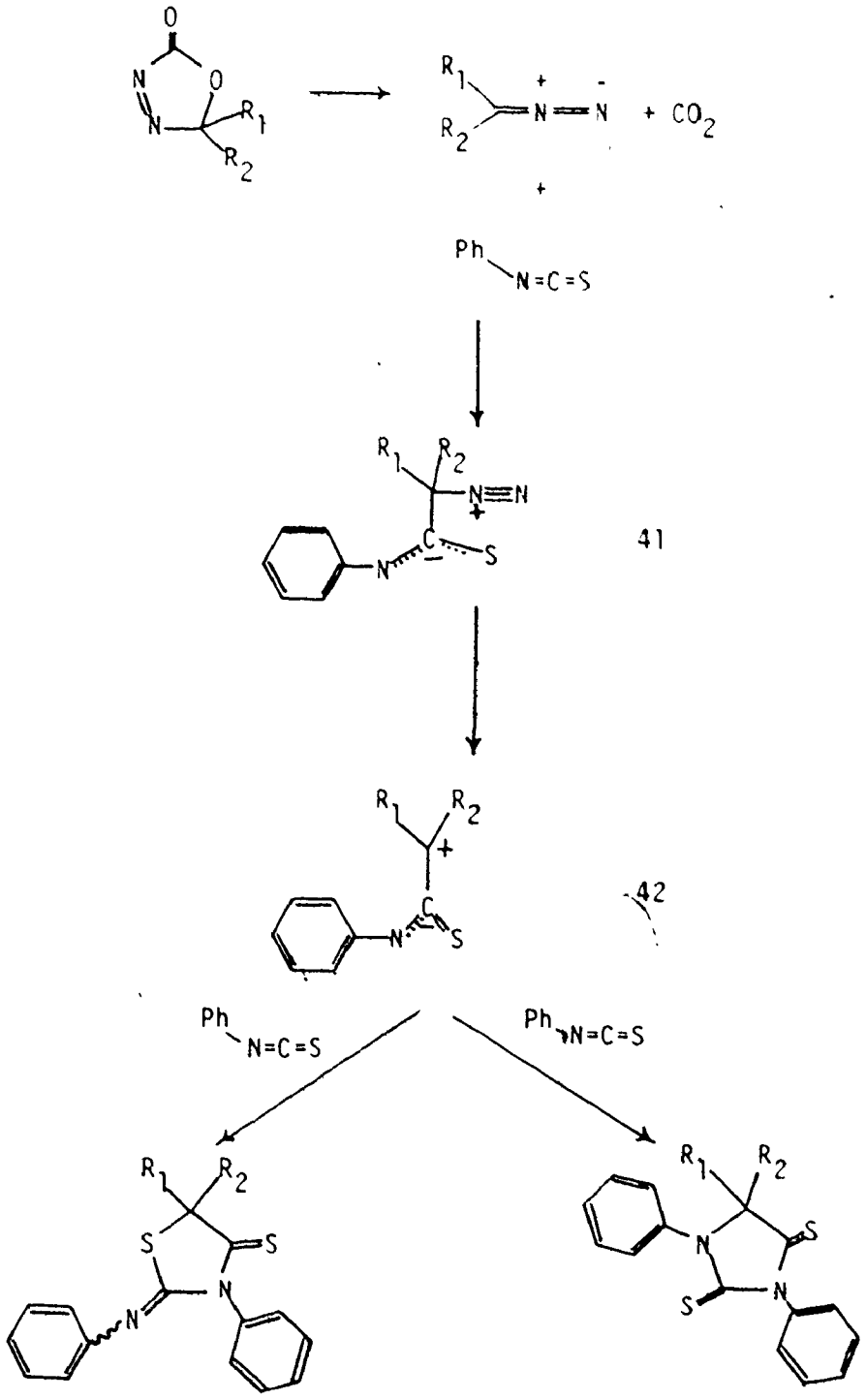
to phenyl isocyanate and diazoalkane there existed the possibility that the iminooxirane intermediate could have been formed through reaction of phenyl isocyanide with the ketone; such a reaction having precedent in the Passerini reaction.[190] However this was excluded from consideration when it was found that phenyl isocyanide and acetone did not react under the same experimental conditions.

The mechanism which accounts for the formation of a 1-phenylcarbamoyl-3,3-dialkyloxindole, a 2-phenylimino-3-phenyl-5,5-dialkyl-4-oxazolidone and a 1,3-diphenyl-5,5-dialkylhydantoin upon thermolysis of a 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one in nitrobenzene containing phenyl isocyanate can also accommodate the formation of a 2-phenylimino-3-phenyl-5,5-dialkyl-4-thiazolinethione and a 1,3-diphenyl-5,5-dialkyl-2,4-dithiohydantoin when the thermolysis is carried out in the presence of phenyl isothiocyanate instead of isocyanate (see page 99).

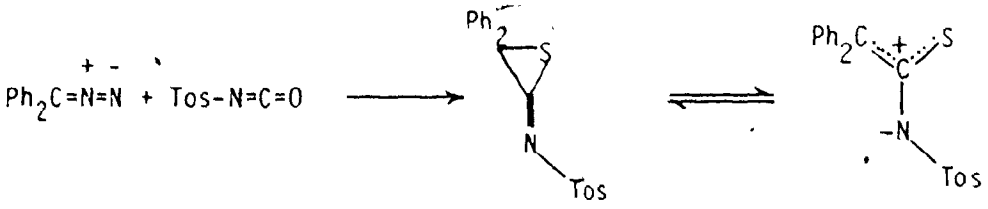
Martin and Rucke[40] have found that the reaction of diazomethane with several isothiocyanates proceeds by a 1,3-dipolar cycloaddition but since the product 1,2,3-thiadiazoles are generally high-melting solids and melt without decomposition,[37,38] it is unlikely that cycloadduct formation occurs in the case under consideration.



Moreover, as reaction of diphenyldiazomethane with tosyl isothiocyanate in anhydrous ether at 0° affords 2-tosylimino-3,3-diphenylthiirane[41]

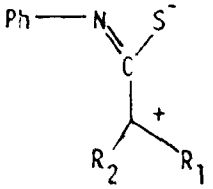

Ph
N=C=S
41
42
Ph
N=C=S
Ph
N=C=S

which, at room temperature, is in equilibrium with a ring-opened 1,3-dipolar species, it would appear that formation of a 1,3-dipolar species (42) through nucleophilic addition of a diazoalkane to the

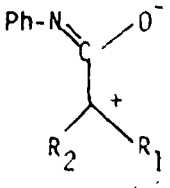


thiocarbonyl carbon and subsequent loss of nitrogen to afford a second 1,3-dipolar species (43) is a distinct possibility. For, stabilization of the positive end of the dipole is afforded by the two alkyl groups and stabilization of the negative end of the dipole is provided by nitrogen, by the aromatic ring, and by the sulphur atom.

That only a bimolecular process involving the 1,3-dipolar species (43) and a second molecule of phenyl isothiocyanate takes place is probably due to the fact that the ring of the sulphur system is much less activated toward aromatic substitution than is the ring of the oxygen system. That is, there is much more negative charge on the sulphur of (43) than is on the oxygen of (36).



43



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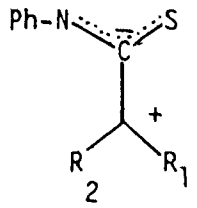
While thermolysis of 5,5-dimethyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline in nitrobenzene containing a 10 fold excess of phenyl isothiocyanate afforded 2-phenylimino-3-phenyl-5,5-dimethylthiazoline-

4-thione, 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin, 2-phenylimino-3-phenyl-5,5-dimethyloxazolin-4-thione and 1,3-diphenyl-5,5-dimethyl-4-thiohydantoin in the ratio of 1.5:1.5:1:3.5, thermolysis of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one in nitrobenzene containing a 10-fold excess of both phenyl isocyanate and phenyl isothiocyanate yielded 1-phenylcarbamoyl-3,3-dimethyloxindole, 1,3-diphenyl-5,5-dimethyl-4-thiohydantoin and 2-phenylimino-3-phenyl-5,5-dimethyloxazolin-4-thione in the ratio of 2.5:3:1. Hence it would appear that dimethyldiazomethane adds to phenyl isothiocyanate more rapidly than it does to phenyl isocyanate since when the two heterocumulenes are present in equimolar amounts a larger proportion of the products has the structure in which the quaternary carbon bearing the gem dimethyl groups is adjacent to a thiocarbonyl group. Moreover, these experiments indicate that the addition of phenyl isocyanate to the 1,3-dipolar intermediate (43) is a more facile



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process than is addition of phenyl isothiocyanate since 1,3-diphenyl-5,5-dimethyl-4-thiohydantoin and 2-phenylimino-3-phenyl-5,5-dimethyl-oxazolin-4-thione are formed in the ratio of 3:1 when the two heterocumulenes are present in equimolar amounts and a larger proportion of the products is formed from one molecule each of dimethyldiazomethane, phenyl isothiocyanate and phenyl isocyanate when phenyl isothiocyanate is present in considerable excess.

Synthetic Utility

Of the numerous routes to oxindoles, the most commonly encountered are the cyclisation to 2-aminophenylacetic acid derivatives (Baeyer route), the Lewis acid catalyzed cyclisation of α-haloacetanilides (Stollé synthesis) and the condensation of acylphenylhydrazines using alkaline reagents and elevated temperatures.

As the appropriately substituted o-nitrophenylacetic acids are often difficult to obtain, the scope of the Baeyer method is limited to the synthesis of 3-alkyl derivatives of oxindole as well as those containing nuclear substituents.

In the Stollé synthesis of oxindoles considerable modification of both the aniline and the α-haloacyl moieties can be carried out and the reaction will still yield anilides which can be converted to oxindoles. However there have been no reports of the successful synthesis of 3,3-dialkyl-substituted oxindoles by this method probably because under the conditions of the reaction, aluminum chloride would effect elimination at the tertiary centre.

The most direct method used for the synthesis of 3,3-dialkyl-substituted oxindoles is that of Brunner[77] in which an N-acylphenylhydrazine is treated with an alkaline reagent at elevated temperatures. Despite its wide use, however, the method does not afford 3,3-dialkyl-substituted oxindoles in good yield. For example, Brunner and Moser[84] obtained 3-ethyl-3-methyloxindole in only 21% yield when they heated the hydrazide of 2-methylbutyric acid with calcium oxide at 150°. 1,3,3-Trimethyloxindole was synthesized in only 36% yield[80] by heating N'-methyl-N'-phenylisobutyrohydrazide with calcium oxide under nitrogen.

By using the hydride instead of the oxide, Carson and Mann[80] were able to increase the yield to 44%, but on using sodamide, recommended by Stanek and Rybar[78] as superior to either the oxide or the hydride, they were unable to obtain the oxindole.

In view of the foregoing it can be seen that reaction of a dialkyldiazomethane (generated "in situ" by the thermolysis of a 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one) with phenyl isocyanate to afford a 1-phenylcarbamoyl-3,3-dialkyloxindole provides a viable approach to the synthesis of 3,3-dialkyloxindoles. For, although the yields from this reaction are not particularly good, ranging from a low of 24% for 1-phenylcarbamoyl-3-isobutyl-3-methyloxindole to a high of 46% for 1-phenylcarbamoyl-3-methyl-3-t-butyloxindole, they do compare favourably with those obtained using the Brunner process.

The reaction is not as versatile as the Brunnner route in that it permits the synthesis of only 3,3-dialkyl-substituted oxindoles. This is due to the fact that the Δ^3-1,3,4-oxadiazoline exists as the tautomeric 2-amino-1,3,4-oxadiazole when one or both of the substitutents on the quaternary carbon is a hydrogen atom and thus is not a source of diazoalkane. Another somewhat undesirable feature of the reaction is the 1-phenylcarbamoyl substituent on the 1-position of the oxindole which must be removed by base hydrolysis in order to obtain the unsubstituted oxindole. If, however, an elaboration of the oxindole via a reaction involving the ring carbonyl is planned, then the presence of the phenylcarbamoyl substituent in the 1-position is advantageous. When para-substituted phenyl isocyanates are used the reaction is quite straightforward in that the para-substituent is always found at

the 5-position of the oxindole but when meta-substituted phenyl isocyanates are used, a mixture of the two isomers, the one bearing the substituent in the 4-position and the other with the substituent in the 6-position, is obtained. This, though, is a feature which is common to all the other major methods of synthesis of oxindoles.

As a route to either 2-phenylimino-3-phenyl-5,5-dialkyl-4-oxazolidones or 1,3-diphenyl-5,5-dialkylhydantoins, thermolysis of 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones in the presence of phenyl isocyanate, is of very little use. For, although changes in the experimental conditions do effect an increase in the amounts of iminooxazolidone and hydantoin formed relative to the amount of oxindole, neither the 2-phenyl-imino-3-phenyl-5,5-dialkyl-4-oxazolidone nor the 1,3-diphenyl-5,5-dialkylhydantoin can be obtained as the major product of the reaction.

Thermolysis of the 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-ones in the presence of phenyl isothiocyanate affords two major products, a 2-phenylimino-3-phenyl-5,5-dialkyl-4-thiazolinethione and a 1,3-diphenyl-5,5-dialkyl-2,4-dithiohydantoin. Despite the fact that neither the iminothiazolinethione nor the dithiohydantoin can be obtained as the major product, the reaction does provide a viable route to both these heterocyclic systems. For, the only direct methods of preparing 2,4-dithiohydantoins are by reaction of a ketone with carbon disulphide and ammonium cyanide and by reaction of an α-aminonitrile with carbon disulphide and neither of these reactions affords the heterocycle in particularly good yield. Carrington,[164] for example, synthesised 5,5-dimethyl-2,4-dithiohydantoin in 24% yield and 5-isobutyl-5-methyl-2,4-

dithiohydantoin in 10% yield. As 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin is obtained in 29% yield and 1,3-diphenyl-5-isobutyl-5-methyl-2,4-dithiohydantoin in 30% yield by thermolysis of the appropriate Δ^3-1,3,4-oxadiazolinone in the presence of phenyl isothiocyanate, it can be seen that the reaction does compare quite favourably. It does, however, have the disadvantage that it affords 2,4-dithiohydantoins bearing phenyl substituents on both nitrogen atoms. In the case of the 2-phenylimino-3-phenyl-5,5-dialkyl-4-thiazolinethiones which have not been synthesised prior to the present study, thermolysis of 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones in the presence of phenyl isothiocyanate provides a direct route to the compounds.

In summary, a new method for the synthesis of 3,3-dialkyl-substituted oxindoles and for the synthesis of 2-imino-5,5-dialkyl-4-thiazolinethiones and 5,5-dialkyl-2,4-dithiohydantoins has been presented. The ease of carrying out the procedure and the readily available nature of the starting materials makes the method a viable alternative to the procedures which are currently available.

Chapter III

Experimental

General

Infrared spectra were recorded on a Beckman IR-5 instrument and on a Perkin-Elmer Model 283 instrument. The spectra were obtained from solutions of the compounds in either chloroform or carbon tetrachloride using 0.1 mm sodium chloride cells and from potassium chloride pellets. The data are presented in reciprocal centimeters relative to polystyrene.

Ultraviolet spectra were recorded on a Cary Model 14 instrument from solutions of the compounds in 95% ethanol using 1 cm quartz cells. The data are given in nanometers with the logarithm of the extinction coefficient ($\log \varepsilon$) in parentheses.

Proton magnetic resonance spectra were recorded on Varian Associates Model T-60, EM 390 and HA 100 instruments and on a Brüker WM 90 instrument using deuteriochloroform as the solvent (unless otherwise stated). The resonances are reported in parts per million (δ) from the tetramethyl silane, the internal standard, and are tabulated as chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, se = septet, m = multiplet) and proton integration. ^{13}C Nuclear magnetic resonance spectra were recorded on a Brüker WH 90 instrument at 25.2 MHz using deuteriochloroform as the solvent.

Mass spectra were recorded on a CEC Model 21-110 instrument and only the parent peaks are reported.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Elemental analyses were performed by Schwarzkopf Micro-Analytical Laboratory, Inc., Woodside, New York, and by Organic Microanalyses (Dr. C. Daessle), Montreal, Canada.

Synthesis of Semicarbazones

The method used was similar to that of Vogel.[191] The ketone (0.18 mol) was added to a solution of semicarbazide hydrochloride (20.0 g, 0.18 mol) and sodium acetate (32 g, 0.23 mol) in water (200 ml) and the mixture was shaken vigorously for several minutes. The crude semicarbazone which separated out was collected and recrystallized from either ethanol, an ethanol-water mixture, or water. If, however, no crude semicarbazone separated out after considerable agitation, the reaction mixture was heated on a steam bath for 30 minutes and then cooled to 0° to promote crystallization. The crude semicarbazone so obtained was collected and recrystallized. Identification of the semicarbazones was accomplished by comparison of the melting points and pmr spectra with those reported in the literature.

1. 2-Propanone semicarbazone: This compound was prepared in 75% yield, m.p. 187-188° (lit.[192] m.p. 190°). p.m.r. 1.90, s, 3; 1.98, s, 3; 5.62, broad s, 2; 8.09 broad s, 1.

2. 2-Butanone semicarbazone: This compound was prepared in 65% yield, m.p. 143-144° (lit.[192] m.p. 146°), p.m.r. 1.08, t, 3; 1.83, s, 3; 2.28, q, 2; 5.83, broad s, 2; 8.56, broad s, 1.

3. 2-Pentanone semicarbazone: This compound was prepared in 60% yield. m.p. 107-108° (lit.[192] m.p. 106°). p.m.r. 0.94, t, 3; 1.52, m, 2; 1.83, s, 3; 2.22, m, 2; 5.99, broad s, 2; 8.82, broad s, 1.

4. 3-Methyl-2-butanone semicarbazone: This compound was prepared in 45% yield. m.p. 113-114° (lit.[192] m.p. 113°). p.m.r. 1.06, d, 6; 1.77, s, 3; 2.46, se, 1; 6.03, broad s, 2; 8.78, broad s, 1.

5. 4-Methyl-2-pentanone semicarbazone: This compound was prepared in 75% yield. m.p. 129-131° (lit.[192] m.p. 132°). p.m.r. 0.94, m, 7; 1.81, s, 3; 2.10, m, 2; 5.79, broad s, 2; 8.48, broad s, 1.

6. 3,3-Dimethyl-2-butanone semicarbazone: This compound was prepared in 60% yield. m.p. 156.5-157° (lit.[193] m.p. 155°). p.m.r. 1.12, s, 9; 1.83, s, 3; 6.07 broad s, 2; 8.85, broad s, 1.

7. Cyclohexanone semicarbazone: This compound was prepared in 70% yield. m.p. 165-166° (lit.[192] m.p. 166°). p.m.r. complex absorption between 1.37 and 2.52, 10; 5.89, broad s, 2; 9.71, broad s, 1.

8. Phenyl-2-propanone semicarbazone: This compound was prepared in 70% yield. m.p. 196-198° (lit.[191] m.p. 198°). p.m.r. (DMSO d_6) 1.40, s, 3; 3.17, s, 2; 5.95, broad s, 2; 6.98, s, 5; 8.78, broad s, 1.

9. 2,4-Dimethyl-3-pentanone semicarbazone: This compound was prepared in 60% yield. m.p. 161° (lit.[192] m.p. 160°). p.m.r. 1.09, d, 12; 2.74, se, 2; 6.03, broad s, 2; 8.69, broad s, 1.

Synthesis of Lead Tetraacetate

The method used was similar to that of Fieser.[194] Glacial acetic acid (600 ml) and acetic anhydride (400 ml) were combined in a 3-litre, 3-necked round bottom flask and heated to 60°. While the mixture was stirred vigorously with a mechanical stirrer, lead tetraoxide (red lead)(700 g) was added in small portions. Fresh additions were made only after the orange colour due to the previous addition had disappeared and at a rate such that the temperature of the reaction mixture did not rise above 80°. Upon completion of the addition of lead tetraoxide, the brown mixture was cooled to room temperature and the crystalline product was filtered off, washed with cold glacial acetic acid and recrystallized from hot (but not boiling) glacial acetic acid. Lead tetraacetate was obtained in 80% yield.

Synthesis of 5,5-Disubstituted-Δ^3-1,3,4-Oxadiazolin-2-ones

To the semicarbazone (0.03 mol) in well-stirred, ice-cooled methylene chloride (200 ml) with nitrogen (L-grade) bubbling through, was added lead tetraacetate (0.035 mol). After the initially pale yellow colour of the reaction mixture was discharged (about 30 minutes), ice water (100 ml) was added, followed by 2.4 M hydrochloric acid (20 ml). The mixture, still in the ice bath, was stirred for an additional 30 minutes and then it was filtered through a bed of Celite to remove the insoluble inorganic material. The organic layer was separated, washed with ice-water (200 ml), saturated sodium bicarbonate solution (200 ml) and then again with ice-water (200 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent

at room temperature under reduced pressure afforded the crude product which was either a solid or an oil. The solid products were purified by sublimation at ambient temperature and 10^{-2} Torr. The oils were purified by bulb to bulb distillation at 10^{-2} Torr, the pot being at a temperature of 40° and the receiver being cooled in a dry ice-acetone bath. Crude yields were of the order of 55-65% and the yields of purified products were of the order of 40%. The oxadiazolinones were identified by comparison of their spectroscopic data with those reported in the literature.[4,195]

5,5-Dimethyl-Δ^3-1,3,4-oxadiazolin-2-one: i.r. 1540 (m), 1835 (s). p.m.r. (CCl_4) 1.85, s.

5-Ethyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one: i.r. 1528 (m), 1837 (s). p.m.r. (CCl_4) 0.81, t, 3; 1.65, s, 3; 2.10, q, 2.

5-Methyl-5-n-propyl-Δ^3-1,3,4-oxadiazolin-2-one: i.r. 1545 (m), 1835 (s). p.m.r. (CCl_4) 1.05, m, 5; 1.63, s, 3; 2.03, m, 2.

5-Isopropyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one: i.r. 1542 (m), 1836 (s). p.m.r. (CCl_4) 0.92, d, 3; 1.05, d, 3; 1.58, s, 3; 2.26, m, 1.

5-Isobutyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one: i.r. 1535 (m), 1840 (s). p.m.r. (CCl_4) 0.90, m, 7; 1.64, s, 3; 2.07, m, 2.

5-Methyl-5-t-butyl-Δ^3-1,3,4-oxadiazolin-2-one*: i.r. 1540 (m), 1838 (s). p.m.r. (CCl_4) 1.03, s; 1.60, s. The peak areas were in the ratio 3:1.

Cyclohexanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazoline-2'-one): i.r. 1540 (m), 1830 (s). p.m.r. (CCl_4) complex absorption between 1.32 and 2.45.

5-Benzyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one. i.r. 1539 (m), 1830 (s), p.m.r. (CCl_4) 1.63, s, 3; 3.28, s, 2; 7.17, m, 5.

5,5-Diisopropyl-Δ^3-1,3,4-oxadiazolin-2-one*: i.r. 1545 (m), 1840 (s). p.m.r. (CCl_4) 0.94, d, 6; 1.06, d, 6; 2.78, m, 2.

Thermal Decomposition of 5,5-Disubstituted-Δ^3-1,3,4-Oxadiazolin-2-ones in the Presence of Phenyl Isocyanate at 150°

General Method

A solution of the oxadiazolinone (0.004 mol) in nitrobenzene† (25 ml) was added dropwise with stirring during 1 hour to a solution of freshly distilled phenyl isocyanate (0.080 mol) and nitrobenzene (10 ml) purged with nitrogen (L-grade) and maintained at a temperature of 150°. After the addition was complete, the solution was kept at that temperature for a further 2 hours and then the excess phenyl isocyanate and nitrobenzene were removed under reduced pressure. The resultant crude reaction products were dissolved in a minimum volume of chloroform and chromatographed on either preparative thin layer plates (20 cm x 20 cm, 2 mm thick, aluminum oxide GF254 type 60/E, E. Merck, Darmstadt, Germany) or on a column (100 g, neutral aluminum oxide, Brockman Activity II 80-200 mesh, Fisher Scientific Company) using a mixture of light

*The author wishes to acknowledge the synthesis of both 5-methyl-5-t-butyl and 5,5-diisopropyl-Δ^3-1,3,4-oxadiazolin-2-ones by Mr. A. J. Paine.

†The nitrobenzene was purified by distillation from phosphorous pentoxide and subsequent fractional distillation.

petroleum ether, b.p. 30-45°, and ether in the ratio of 5:2, as the eluant. The individual components were then either recrystallized from the appropriate solvents or they were rechromatographed on thin layer plates (20 cm x 20 cm, neutral aluminum oxide with fluorescent indicator U.V.$_{254}$, Macherey, Nagel and Company) using different mixtures of light petroleum ether and ether as the solvent. The latter procedure was repeated until the compounds occurred as single bands on analytical thin layer plates.

1-Phenylcarbamoyl-3,3-Dimethyloxindole

The main product formed in the reaction between 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one and phenyl isocyanate was obtained as a viscous oil. Crystallisation from an ethanol-water mixture yielded 1-phenyl-carbamoyl-3,3-dimethyloxindole as colourless needles n.p. 74-76°. 0.20 g* (36%). i.r. 1715 (s), 1737 (vs), 3260 (m), U.V. 214 (4.58), 244 (4.45). p.m.r. 1.38, s, 6; 7.46, m, 8; 8.38, m, 1; 10.79, broad s, 1. ^{13}C n.m.r. 184.3, 149.7, 138.9, 137.3, 134.3, 129.1, 128.4, 125.0, 124.5, 122.0, 120.5, 116.7, 45.4, 25.1. m.s. 280. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.87, H. 5.66; N, 10.07.

*As thermolysis of 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one does not afford the dialkyldiazomethane exclusively, the yields of the 1-phenylcarbamoyl-3,3-dialkyloxindoles have been determined using the results from a study of the thermolysis of 5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-ones in 1,2-dichloroethane at 80°, taking into consideration the fact that with a 12° rise in temperature, there is a 2% increase in the amount of ketone formed.

5,5-dialkyl-Δ^3-1,3,4-oxadiazolin-2-one	Percentage of dialkyldiazomethane formed[196]
5=methyl, 5=methyl	56
5=methyl, 5=n-propyl	49

(Continued)

Hydrolysis of 1-Phenylcarbamoyl-3,3-Dimethyloxindole

The title compound (0.25 g, 0.0009 mol) in a solution of 10% potassium hydroxide (15 ml) and methanol (15 ml) was heated under reflux for 1 hour. The basic solution was then neutralised with dilute hydrochloric acid and extracted with ether (3x50 ml). The ethereal solution was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulphate and concentrated under reduced pressure. Recrystallization of the residue from methanol afforded 3,3-dimethyloxindole as colourless prisms m.p. 152-154° (lit.[197] m.p. 150°) 0.11 g (79%). i.r. 1720 (s), 3450 (m). p.m.r. 1.40, s. 6; 7.06, m, 4; 9.37, broad s, 1. m.s. 161.

Reaction of 3,3-Dimethyloxindole with Phenyl Isocyanate

3,3-Dimethyloxindole (0.15 g, 0.0009 mol) was added to a well-stirred solution of phenylisocyanate (1 ml, 0.0009 mol) and nitrobenzene (8 ml) at 150°. After 2 hours at that temperature, the reaction mixture was concentrated under reduced pressure, affording a viscous oil. Crystallization from an ethanol-water mixture produced colourless

5-methyl, 5-iso-propyl	58
5-methyl, 5-iso-butyl	57
5-methyl, 5-t-butyl	72
5-methyl, 5-benzyl	23
5-iso-propyl, 5-isopropyl	75

It has been assumed that both 5-ethyl-5-methyl-Δ^3-1,3,4-oxadizaolin-2-one and cyclohexanespiro-5'(4'-1',3',4'-oxadiazolin-2'-one) on thermolysis afford 50% ketone and 50% diazoalkane.

needles m.p. 73-75°. 0.2 g (80%). The spectral data were identical with those obtained from the compound, 1-phenylcarbamoyl-3,3-dimethyloxindole.

2-Phenylimino-3-Phenyl-5,5-Dimethyl-4-Oxazolidone

A minor product from the reaction of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was obtained as a white solid. Recrystallization from methanol afforded 0.04 g (7%) of 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone as colourless needles m.p. 148-149°. i.r. 1690 (vs), 1705 (vs), 1740 (m). UV 223 (4.50), 248 (4.49). p.m.r. 1.65, s, 6; 7.39, m, 10. ^{13}C n.m.r. 174.3, 147.0, 144.6, 132.2, 129.1, 128.7, 128.5, 126.8, 123.8, 123.4, 83.5, 24.0, 23.7. m.s. 280. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.67; H, 6.33; N, 10.12.

1,3-Diphenyl-5,5-Dimethylhydantoin

The second minor product from the reaction of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was obtained as an oil. Despite repeated chromatography on alumina thin layer plates using a 3:2 mixture of light petroleum ether and ether it was not possible to obtain an analytically pure sample of the oil, 1,3-diphenyl-5,5-dimethylhydantoin. i.r. 1715 (vs), 1775 (s). p.m.r. 1.44, s, 6; 7.33, m, 10. ^{13}C n.m.r. 175.3, 153.5, 137.4, 132.0, 129.9, 129.6, 129.1, 128.2, 126.2, 63.5, 24.2. m.s. 280.

Although the compounds 1-phenylcarbamoyl-3,3-dimethyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-

5,5-dimethylhydantoin were formed in the ratio 5:1:1, it was not possible to isolate them in this ratio due, in part, to the fact that extensive chromatography was needed to obtain the last-mentioned compound in reasonably pure form.

1-Phenylcarbamoyl-3-Ethyl-3-Methyloxindole

The major product from the reaction of 5-ethyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was isolated as a viscous oil. Despite repeated chromatography on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent, 1-phenylcarbamoyl-5-ethyl-5-methyloxindole could not be induced to solidify. 0.25 g (49%), i.r. 1705 (s), 1727 (vs), 3240 (m). p.m.r. 0.67, t, 3; 1.47, s, 3; 1.87, m, 2; 7.40, m. 8; 8.37, m, 1; 10.85, broad s, 1. ^{13}C n.m.r. 183.9, 149.5, 139.9, 137.4, 132.5, 129.1, 128.4, 125.0, 124.4, 122.2, 120.5, 116.6, 50.2, 32.4, 24.0, 8.8. m.s. 294. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 71.92; H, 6.02, N, 8.90.

1-Phenylcarbamoyl-3-Methyl-3-n-Propyloxindole

The major product from the reaction of 5-methyl-5-n-propyl-Δ^3-1,3,4-oxadiazolin-2-one had to be chromatographed three times on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as solvent before a relatively pure sample was obtained. i.r. 1705 (s), 1730 (vs), 3240 (m). p.m.r. 0.90, m, 5; 1.46, s, 3; 1.90, m, 2; 7.43, m, 8; 8.46, m, 1; 10.93, broad s, 1. ^{13}C n.m.r. 184.0, 149.6, 139.7, 137.3, 132.8, 129.1, 128.3, 125.0, 124.4, 122.1,

120.5, 116.6, 49.9, 41.6, 24.6, 17.9, 14.1. m.s. 308. Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 72.17; H, 6.81; N, 8.39.

1-Phenylcarbamoyl-3-Isopropyl-3-Methyloxindole

The main product formed in the reaction of 5-isopropyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate had to be chromatographed four times on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent before a reasonably pure sample of the oil could be obtained. i.r. 1705 (s), 1725 (vs). p.m.r. 0.86, d, 6; 0.96, d, 6; 1.50, s, 3; 2.18, m, 1; 7.47, m, 8; 8.47, m, 1; 10.97, broad s, 1. ^{13}C n.m.r. 184.1, 149.6, 140.0, 137.4, 132.0, 129.2, 128.3, 124.7, 124.5, 123.0, 120.5, 116.4, 58.5, 36.8, 22.1, 17.4, 17.2. m.s. 308.

1-Phenylcarbamoyl-3-Isobutyl-3-Methyloxindole

The major product isolated from the reaction of 5-isobutyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was rechromatographed on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent and 0.14 g (24%) of the oil, 1-phenylcarbamoyl-3-isobutyl-3-methyloxindole was obtained. i.r. 1710 (s), 1730 (vs), 3250 (m). p.m.r. 0.70, d of d 6; 0.97, m, 1; 1.43, s, 3; 1.94, m, 2; 7.35, m, 8; 8.34, m, 1; 10.77, broad, s, 1. ^{13}C n.m.r. 184.3, 149.6, 139.5, 137.4, 132.7, 129.6, 129.1, 128.3, 124.9, 124.4, 122.8, 120.5, 116.7, 49.4, 47.4, 27.1, 25.6, 24.0, 23.0. m.s. 322. Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69.

Found: C, 74.61; H, 6.85; N, 8.45.

1-Phenylcarbamoyl-3-Methyl-3-t-Butyloxindole

The main product isolated from the reaction of 5-methyl-5-t-butyl-Δ^3-1,3,4-oxadiazolin-2-one with phenylisocyanate was purified by chromatography on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent. Thus 0.21 g (46%) of the oil, 1-phenylcarbamoyl-3-methyl-3-t-butyloxindole was obtained. i.r. 1705 (m), 1734 (vs), 3220 (m). p.m.r. 1.00, s, 9; 1.43, s, 3; 7,40, m. 8; 8.44, m, 1; 10.94, broad s, 1. ^{13}C n.m.r. 183.6, 149.5, 140.1, 137.4, 132.2, 129.1, 128.2, 124.5, 124.4, 124.0, 120.5, 116.10, 54.7, 37.3, 29.7, 25.3, 18.1. m.s. 322. Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found, C, 73.94; H, 7.03; N, 8.09.

2-Phenylimino-3-Phenyl-5-Methyl-5-t-Butyl-4-Oxazolidone

One of the minor products isolated from the reaction of 5-methyl-5-t-butyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was rechromatographed on alumina thin layer plates using a 2:1 mixture of light petroleum ether and ether as the solvent. In this manner 0.11 g (24%) of 2-phenylimino-3-phenyl-5-methyl-5-t-butyl-4-oxazolidone was obtained as a white solid m.p. 89-93°. i.r. 1690 (vs), 1700 (vs), 1744 (m). p.m.r. 1.14, s, 9; 1.64, s, 3; 7.47, m, 10. ^{13}C n.m.r. 173.7, 147.7, 144.8, 132.2, 129.1, 128.6, 128.1, 126.9, 123.6, 123.5, 90.0, 38.0, 24.7, 18.5. m.s. 322. A satisfactory microanalysis could not be obtained.

1,3-Diphenyl-5-Methyl-5-t-Butylhydantoin

The second minor product formed in the reaction of 5-methyl-5-t-butyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate had to be chromatographed three times on alumina thin layer plates using a 3:2 mixture of light petroleum ether and ether before a reasonably pure sample of the oil could be obtained. i.r. 1708 (vs), 1769 (s). p.m.r. 1.03, s, 9; 1.86, s, 3; 7.40, m. 10. ^{13}C n.m.r. 174.3, 155.1, 137.3, 132.0, 129.3, 129.0, 128.8, 128.2, 128.0, 126.4, 72.1, 39.5, 25.8, 19.7. m.s. 322. A satisfactory microanalysis could not be obtained.

Cyclohexanespiro-3'-phenylcarbamoyl-1'(oxindole)

The main product isolated from the reaction between cyclohexanespiro-5'($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one) and phenyl isocyanate was recrystallised from methanol and 0.20 g (39%) of cyclohexanespiro-3'-phenylcarbamoyl-1'(oxindole) was obtained as colourless needles m.p. 101-103°. i.r. 1715 (s), 1735 (vs), 3270 (m). p.m.r. 1.82, broad s, 10; 7.36, m, 8; 8.34, m, 1; 10.78, broad s, 1. ^{13}C n.m.r. 183.3, 149.6, 139.0, 137.4, 134.1, 129.0, 128.0, 124.5, 124.3, 122.9, 120.4, 116.5, 48.0, 33.8, 25.0, 20.8. m.s. 320. Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.71, H, 6.31, N, 8.74.

1-Phenylcarbamoyl-3-Benzyl-3-Methyloxindole

The major product formed in the reaction of 5-benzyl-5-methyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate required extensive chromatography on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent before a reasonably

pure sample of the amber oil could be obtained. i.r. 1705 (s), 1725 (vs), 3250 (m). p.m.r. 1.53, s, 3; 3.12, s, 2; 7.15, m, 13; 8.13, m, 1; 10.61, broad s, 1. ^{13}C n.m.r. 183.2, 149.3, 139.6, 137.3, 135.1, 131.7, 129.8, 129.1, 128.5, 128.0, 127.1, 124.6, 124.4, 122.9, 120.5, 116.5, 51.2, 45.3, 23.6. m.s. 356. A satisfactory microanalysis could not be obtained.

1-Phenylcarbamoyl-3,3-Diisopropyloxindole

The main product isolated from the reaction of 5,5-diisopropyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocynate was chromatographed several times on alumina thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent before an analytically-pure sample of the oil could be obtained. i.r. 1705 (m), 1732 (vs), 3240 (m). p.m.r. 0.87, d, 6; 0.96, d, 6; 2.43, se, 2; 7.47, m, 8; 8.28, m, 1; 10.99, broad s, 1. ^{13}C n.m.r. 183.1, 149.4, 140.9, 137.4, 130.2, 129.0, 128.1, 124.5, 124.3, 123.0, 120.5, 116.1, 60.1, 33.1, 17.4, 17.0. m.s. 336. Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.18; H, 7.24; N, 7.83.

2-Phenylimino-3-Phenyl-5,5-Diisopropyl-4-Oxazolidone

The minor product formed in the reaction of 5,5-diisopropyl-Δ^3-1,3,4-oxadiazolin-2-one with phenyl isocyanate was repeatedly chromatographed on alumina thin layer plates using a 2:1 mixture of light petroleum ether and ether as the solvent in order to obtain a pure sample of the oil, 2-phenylimino-3-phenyl-5,5-diisopropyl-4-oxazolidone. i.r. 1696 (vs), 1730 (s). p.m.r. 0.99, d, 6; 1.05, d, 6; 2.33, m, 2;

7.23, m, 10. ^{13}C n.m.r. 173.0, 148.7, 145.0, 132.2, 129.2, 128.7, 127.0, 126.7, 124.5, 123.5, 93.4, 31.9, 16.5, 16.2. m.s. 336.

Thermal Decomposition of 5,5-Dimethyl-Δ^3-1,3,4-Oxadiazolin-2-one in the Presence of Aryl Isocyanate at 150°

General Method

A solution of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one (0.46 g, 0.004 mol) in nitrobenzene (25 ml) was added dropwise with stirring during 1 hour to a solution of the aryl isocyanate (0.080 mol) and nitrobenzene (10 ml) purged with nitrogen (L-grade) and maintained at a temperature of 150°. After the addition was complete, the reaction mixture was kept at that temperature for a further 2 hours. The isolation and the purification of the reaction products was essentially the same as the procedure described on page 111.

1-p-Tolylcarbamoyl-3,3,5-Trimethyloxindole.

The main product isolated from the reaction of the oxadiazoline with p-methylphenyl isocyanate was recrystallized from an ethanol-water mixture and 0.24 g (36%) of 1-p-tolylcarbamoyl-3,3,5-trimethyloxindole was obtained as colourless needles m.p. 125.5-126.5°. i.r. 1710 (m), 1740 (vs), 3240 (m). p.m.r. 1.42, s, 6; 2.33, d, 6; 7.15, m, 6; 8.10, d, 1; 10.56, broad s, 1. ^{13}C n.m.r. 184.3, 149.7, 136.6, 134.8, 134.6, 134.3, 133.9, 129.6, 128.8, 122.6, 120.5, 116.4, 45.4, 25.1, 21.1, 20.8. m.s. 308. Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.01; H, 6.65; N, 9.17

1-(p-Methoxyphenyl)carbamoyl-3,3-Dimethyl-5-Methoxyoxindole

The main compound isolated from the reaction of the oxadiazolinone with p-methoxyphenyl isocyanate was recrystallized from methanol and 0.36 g (48%) of 1-(p-methoxyphenyl)carbamoyl-3,3-dimethyl-5-methoxyoxindole was obtained as colourless needles. m.p. 118.5-120°. i.r. 1708 (m), 1733 (vs), 3250 (m). p.m.r. 1.47, s, 6; 3.79, d, 6; 7.22, m, 6; 8.23, d, 1; 10.57, broad s, 1. ^{13}C n.m.r. 183.9, 157.4, 156.5, 149.7, 135.8, 132.3, 130.4, 122.1, 114.4, 114.2, 112.5, 108.7, 55.5, 55.3, 45.6, 25.0. m.s. 340. Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.35; H, 6.09; N, 8.60.

1-(p-Chlorophenyl)carbamoyl-3,3-Dimethyl-5-Chlorooxindole

The main compound formed in the reaction between the oxadiazolinone and p-chlorophenyl isocyanate was recrystallized from ethanol, affording 0.25 g (33%) of 1-(p-chlorophenyl)carbamoyl-3,3-dimethyl-5-chlorooxindole as colourless prisms, m.p. 170.5-171.5°. i.r. 1715 (s), 1740 (vs), 3240 (m). p.m.r. 1.44, s, 6; 7.42, m, 6; 8.28, d, 1; 10.72, broad s, 1. ^{13}C n.m.r. 183.7, 149.3, 137.2, 136.1, 135.7, 130.7, 129.7, 129.2, 128.5, 122.5, 121.7, 117.9, 45.6, 25.0. m.s. 349. Anal. Calcd. for $C_{17}H_{14}N_2O_2Cl_2$: C, 58.46; H, 4.04; N, 8.02; Cl, 20.30. Found: C, 57.86, H, 4.43; N, 8.18; Cl, 20.42.

1-(m-Tolyl)carbamoyl-3,3,4-Trimethyloxindole and 1-(m-Tolyl)carbamoyl-3,3,6-Trimethyloxindole

The two major products formed in a ratio of 1:1 by the reaction of the oxadiazolinone with m-tolyl isocyanate had to be subjected to

repeated chromatography on alumina thin layer plates using a 15:1 mixture of light petroleum ether and ether before a partial separation of the two could be achieved. 1-(m-Tolyl)carbamoyl-3,3,4-trimethyloxindole. m.p. 77-80°. i.r. 1705 (s), 1740 (vs), 3240 (m). p.m.r. 1.54, s, 6; 2.40, d, 6; 7.17, m, 6; 8.25, m, 1; 10.79, broad s, 1. ^{13}C n.m.r. 184.5, 149.7, 139.3, 139.1, 137.3, 133.5, 129.0, 127.5, 125.6, 121.6, 121.2, 117.6, 114.3, 46.2, 23.0, 21.8, 21.5. 1-(m-Tolyl)carbamoyl-3,3,6-trimethyloxindole (an oil). i.r. 1706 (s), 1737 (vs), 3250 (m). p.m.r. 1.44, s, 6; 2.38, d, 6; 7.22, m, 6; 8.16, broad s, 1; 10.68, broad s, 1. ^{13}C n.m.r. 184.7, 149.9, 139.1, 138.6, 137.3, 131.5, 129.0, 125.6, 125.3, 121.7, 121.2, 117.7, 117.4, 45.3, 25.2, 21.8, 21.5. m.s. 308.

Thermal Decomposition of 5,5-Dimethyl-Δ^3-1,3,4-Oxadiazolin-2-one in the Presence of Various Concentrations of Phenyl Isocyanate and at Different Temperatures

1. Phenyl Isocyanate - final concentration 2.2 mol litre^{-1}, Temperature 149°

A solution of the oxadiazolinone (0.52 g, 0.0045 mol) in nitrobenzene (20 ml) was added dropwise with stirring during 1 hour to a solution of phenyl isocyanate (9 ml, 0.083 mol) and nitrobenzene (9 ml) purged with nitrogen (L-grade) and maintained at a temperature of 149°. On completion of the addition, the solution was kept at that temperature for a further 2 hours and then the excess phenyl isocyanate and nitrobenzene were removed under reduced pressure. The

crude reaction product so obtained, was analysed by p.m.r. spectroscopy and by thin layer chromatography using alumina plates and a 5:2 mixture of light petroleum ether and ether as the solvent.

This experiment was repeated two more times and the results obtained from the three separate experiments were averaged.

Under the above experimental conditions 1-phenylcarbamoyl-3,3-dimethyl oxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin were formed in the ratio 4.8:1:1.

2. Phenyl Isocyanate - final concentration 6.3 mol litre^{-1}. Temperature 149°.

A solution of the oxadiazolinone (0.49 g, 0.004 mol) in nitrobenzene (10 ml) was added dropwise with stirring during 1 hour to phenyl isocyanate (22 ml, 0.202 mol) purged with nitrogen (L-grade) and maintained at a temperature of 149°. When the addition was completed, the solution was kept at that temperature for a further 2 hours and then the excess phenyl isocyanate and nitrobenzene were removed under reduced pressure. The resulting crude reaction product was analysed in a similar manner to that in the previous experiment.

The above experimental conditions afforded 1-phenylcarbamoyl-3,3-dimethyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin in the ratio 2.4:1:1.

3. Phenyl Isocyanate - final concentration 2.2 mol litre^{-1}. Temperature 112°.

The procedure was the same as that in experiment 1 except that the reaction was carried out at 112°. Under these experimental conditions 1-phenylcarbamoyl-3,3-dimethyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin were obtained in the ratio 2.7:1:1.2.

4. Phenyl Isocyanate - final concentration 6.3 mol litre^{-1}. Temperature 112°.

The procedure was the same as that used in experiment 2 except that the reaction was carried out at 112°. Under these experimental conditions 1-phenyl-carbamoyl-3,3-dimethyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin were formed in the ratio 1.2:1.6:1.

5. Phenyl Isocyanate - 2.2 mole litre^{-1}. Temperature 65°.

The oxadiazolinone (0.5 g, 0.004 mol) was added to a well-stirred solution of phenyl isocyanate (9 ml, 0.083 mol) and nitrobenzene (29 ml) that was purged with nitrogen (L-grade) and maintained at a temperature of 65°. After 48 hours at that temperature, the solution was concentrated under reduced pressure and the crude products thus obtained, were analysed in a manner analogous to that used in the previous experiments.

Under these experimental conditions 1-phenylcarbamoyl-3,3-dimethyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone

and 1,3-diphenyl-5,5-dimethylhydantoin were formed in the ratio 1.1:1.6:1.

6. Phenyl Isocyanate - 6.3 mol litre^{-1}. Temperature 68°.

The oxadiazolinone (0.50 g, 0.004 mol) was added to a well-stirred solution of phenyl isocyanate (22 ml, 0.202 mol) and nitrobenzene (10 ml) that was purged with nitrogen (L-grade) and maintained at a temperature of 65°. After 48 hours at that temperature, the solution was concentrated under reduced pressure and the crude products thus obtained, were analysed in a similar manner to that used in the previous experiments.

Under these experimental conditions, 1-phenylcarbamoyl-3,3-dimetnyloxindole, 2-phenylimino-3-phenyl-5,5-dimethyl-4-oxazolidone and 1,3-diphenyl-5,5-dimethylhydantoin were formed in the ratio 1:1.7:2.

Synthesis of Dimethyldiazomethane [198,199]

Synthesis of Acetone Azine

Acetone (72 g, 1.24 mol) was added to a 250 ml round-bottom flask equipped with a magnetic stirrer and a dropping funnel and cooled in an ice bath. Hydrazine hydrate (33.0 g, 0.66 mol) was added with vigorous stirring at such a rate that the temperature did not rise above 35°. The mixture was stirred for an additional 10-15 minutes. Potassium hydroxide pellets (25 g, 0.45 mol) were then added with vigorous stirring and continued cooling. The resulting upper liquid layer was separated and allowed to stand over 12.6 g (0.22 mol) of

potassium hydroxide pellets for 30 minutes with occasional swirling and then over two successive 6 g (0.11 mol) portions of potassium hydroxide pellets. The liquid was then distilled through a fractionating column, the small forerun b.p. 80-127° being discarded and the fraction b.p. 128-131° being collected. 55.0 g (80%). p.m.r. 1.83, s; 1.97, s. The peak areas were in the ratio of 1:1.

Synthesis of Acetone Hydrazone

A mixture of acetone azine (55.0 g, 0.49 mol) and anhydrous hydrazine* (16.0 g, 0.50 mol) was placed in a 100 ml round-bottom flask fitted with a reflux air condenser, drying tube and maintained at a temperature of 100° for 12-16 hours. The crude product was then rapidly distilled through a fractionating column connected by a water-cooled condenser, the forerun being discarded and only that fraction boiling at 122-126° being collected. 46.5 g (65%). p.m.r. 1.70, s, 3; 1.84, s, 3; 4.86, broad s, 2.

Synthesis of Dimethyldiazomethane

A 250 ml three-necked round bottom flask was equipped with a mechanical stirrer, a dropping funnel and a distillation head that was connected via a condenser to a receiver in an acetone-dry ice bath. Yellow mercuric oxide (60.0 g, 0.28 mol), anhydrous ether (60 ml) and

*The anhydrous hydrazine was allowed to stand over barium oxide for several hours and then filtered just prior to use.

3 M ethanolic potassium hydroxide solution (4.5 ml) were placed in the flask. The pressure throughout the system was reduced by means of an aspirator and, with vigorous stirring, acetone hydrazone (15.0 g, 0.21 ml) was added slowly from the funnel. There was a violent reaction as the acetone hydrazone was oxidised to dimethyldiazomethane and mercury was deposited and then the dimethyldiazomethane and ether co-distilled rapidly. The bright pink ethereal solution of dimethyldiazomethane was quickly redistilled and dried over anhydrous magnesium sulphate before being used in the next experiment.

Reaction of Dimethyldiazomethane with Phenyl Isocyanate

The ethereal solution of dimethyldiazomethane was added dropwise with stirring during 1 hour to a solution of phenyl isocyanate (12 ml, 0.11 mol)* in ether (50 ml) contained in a 200 ml two-necked flask equipped with a condenser. When the addition was complete the solution was stirred at room temperature for a further 2 hours, during which time the bright pink colour disappeared, and then it was concentrated under reduced pressure. The addition of petroleum ether to the crude reaction product resulted in the precipitation of a white solid which was re-crystallized from a chloroform-petroleum ether solvent system. Thus α-hydroxyisobutyranilide was obtained as colourless plates m.p. 133-

*S. D. Andrews, A. C. Day, P. Raymond and M. C. Whiting reported that the above method of synthesis afforded dimethyldiazomethane in 70% yield. Since there was substantial decomposition during the drying of the ethereal solution, the amount of phenyl isocyanate used was based on a 50% yield.

134° (lit.[200] m.p. 135°). i.r. 1695 (vs), 3400 (m). p.m.r. 1.54, s, 6; 2.95, broad s, 1; 7.29, m, 5; 9.00, broad s, 1. m.s. 179.

The petroleum ether-soluble portion of the reaction product was concentrated under reduced pressure and chromatographed on a column (200 g, Florisil, 60/100 mesh, J. T. Baker Chemical Company, Phillipsburg, New Jersey) using light petroleum ether as the eluant. Thus the colourless liquid, α-ethoxyisobutyranilide was obtained. i.r. 1690 (s), 1730 (s), 3395 (m). p.m.r. 1.32, t, 3; 1.52, s, 6; 3.43, q, 2; 7.26, m, 5; 8.43, broad s, 1. m.s. 206.

When the reaction was repeated using an ethereal solution of dimethyl-diazomethane that had been dried rapidly over potassium hydroxide pellets instead of anhydrous magnesium sulphate, the major reaction product was found to be α-ethoxyisobutyranilide.

Synthesis of 1,3-Diphenylhydantoin[201]

A mixture of phenyl isocyanate (5.5 ml, 0.05 mol) and the ethyl ester of N-phenyl glycine (9.0 g, 0.05 mol) in anhydrous benzene (30 ml) was heated under reflux with stirring for 10 hours. Concentration under reduced pressure afforded a white solid which was recrystallised from carbon tetrachloride. Thus the ethyl ester of N-phenyl-N-phenylcarbamoylglycine was obtained as colourless needles. m.p. 107-109° (lit. m.p. 109°). 12.7 g (85%). p.m.r. 1.23, t, 3; 4.13, q, 3; 4.31, s, 2; 6.30, broad s, 1; 7.14, m, 10.

A mixture of the ethyl ester of N-phenyl-N-phenylcarbamoyl glycine (1.0 g, 0.003 mol), 0.1 M potassium hydroxide solution (10 ml)

and alcohol (10 ml) was heated under reflux with stirring for 4 hours. The solution was acidified with concentrated hydrochloric acid and a white solid precipitated out. Recrystallisation from ethanol afforded 0.60 g (80%) of 1,3-diphenylhydantoin as colourless needles m.p. 137-138° (lit.[201] m.p. 139°). p.m.r. 4.48, s; 7.48, m. The peak areas were in the ratio of 1:5. ^{13}C n.m.r. 167.4, 153.1, 137.5, 131.4, 129.3, 129.1, 128.4, 126.3, 124.5, 118.5, 49.5. m.s.206.

Synthesis of 1,3-Diphenyl-2-Thiohydantoin [201]

A mixture of the ethyl ester of N-phenylglycine (9.0 g, 0.05 mol) and phenyl isothiocyanate (6 ml, 0.05 mol) in anhydrous benzene (30 ml) was heated under reflux with stirring for 10 hours. Concentration under reduced pressure afforded a white amorphous solid which was recrystallised from a large volume of methanol. Thus, 1,3-diphenyl-2-thiohydantoin was obtained as colourless needles m.p. 213-215° (lit.[201] m.p. 212°), 10.0 g (75%). i.r. 1200 (s), 1757 (s). p.m.r. 4.60, s; 7.43, m. The peak areas were in the ratio 1:5. ^{13}C n.m.r. 182.3, 169.2, 138.2, 133.4, 129.5, 129.3, 128.6, 128.1, 125.5, 55.2. m.s. 222.

Thermal Decomposition of 5,5-Disubstituted-Δ^3-1,3,4-Oxadiazolin-2-ones in the Presence of Phenyl Isothiocyanate at 150°

General Method

A solution of the oxadiazolinone (0.004 mol) in nitrobenzene (25 ml) was added dropwise with stirring during 1 hour to a solution of freshly distilled phenyl isothiocyanate (0.080 mol) and nitrobenzene

(10 ml) purged with nitrogen (L-grade) and maintained at a temperature of 150°. After the addition was complete, the solution was kept at that temperature for a further 2 hours and then the excess phenyl isothiocyanate and nitrobenzene were removed under reduced pressure. Chromatography of the resultant crude reaction products on analytical thin layer plates (3 cm x 10 cm, neutral aluminum oxide with fluorescent indicator $U.V._{254}$, Macherey, Nagel and Company) using a 5:1 mixture of light petroleum ether and ether as solvent, indicated that in each instance two major products were formed in the reaction of a particular oxadiazolinone with phenyl isothiocyanate. These compounds were then isolated by dissolving the crude reaction mixture in a minimum volume of chloroform and chromatographing on a column (100 g, neutral aluminum oxide, Brockman Activity II, 80-200 mesh, Fischer Scientific Company) using mixtures of light petroleum ether and ether as the eluant.

2-Phenylimino-3-Phenyl-5,5-Dimethylthiazolin-4-thione and 1,3-Diphenyl-5,5-Dimethyl-2,4-Dithiohydantoin

Elution with a 6:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallised from methanol. 2-Phenylimino-3-phenyl-5,5-dimethylthiazolin-4-thione was obtained as yellow needles m.p. 142-144°. 0.25 g (37%*). i.r. 1280 (s), 1640 (s). u.v. 214 (4.36), 296 (4.45). p.m.r. 1.84, s; 7.24, m. The peak areas were in the ratio of 3:5. ^{13}C n.m.r. 212.9, 157.4, 149.0, 139.1, 129.6, 129.2, 128.4, 124.8, 120.7, 61.4, 32.9. m.s. 312. Anal. Calcd. for $C_{17}H_{16}N_2S_2$: C, 65.35; H, 5.16; N, 8.97; S, 20.52. Found: C, 65.08; H, 5.56; N, 9.08; S, 20.50.

Elution with a 5:1 mixture of light petroleum ether and ether afforded a second yellow solid which was also recrystallised from methanol. 1,3-Diphenyl-5,5-dimethyl-2,4-dithiohydantoin was obtained as yellow needles m.p. 183.5-185°. 0.20 g (29%*). i.r. 1280 (s). u.v. 220 (4.38), 300 (4.58). p.m.r. 1.59, s; 7.46, m. The peak areas were in the ratio of 3:5. ^{13}C n.m.r. 208.6, 181.1, 136.6, 136.4, 129.6, 129.4, 129.3, 128.9, 128.7, 77.2, 27.9. m.s. 312. Anal. Calcd. for $C_{17}H_{16}N_2S_2$: C, 65.35; H, 5.16; N, 8.97; S, 20.52. Found: C, 65.82; H, 5.24; N, 8.85; S, 20.62.

2-Phenylimino-3-Phenyl-5-Ethyl-5-Methylthiazolin-4-thione and 1,3-Diphenyl-5-Ethyl-5-Methyl-2,4-Dithiohydantoin

Elution with a 6:1 mixture of light petroleum ether and ether afforded a bright yellow oil, 2-phenylimino-3-phenyl-5-ethyl-5-methyl-thiazolin-4-thione, which could not be induced to crystallize. 0.15 g (23%). i.r. 1280 (s), 1637 (s). p.m.r. 1.05, t, 3; 1.83, s, 3; 2.16, q, 2; 7.28, m, 10. ^{13}C n.m.r. 211.7, 158.0, 149.1, 139.1, 129.6, 129.1, 128.4, 124.7, 120.7, 66.9, 38.0, 31.3, 9.23. m.s. 326. Anal. Calcd. for $C_{18}H_{18}N_2S_2$: C, 66.22; H, 5.56; N, 8.58; S, 19.64. Found: C, 66.03; H, 5.51; N, 8.33; S, 19.87.

*The yields of the 2-phenylimino-3-phenyl-5,5-dialkylthiazoline-4-thiones and 1,3-diphenyl-5,5-dialkyl-2,4-dithiohydantoins were determined in a manner similar to that by which the yields of the 1-phenylcarbamoyl-3,3-dialkyloxindoles were calculated. See page .

Elution with a 5:1 mixture of light petroleum ether and ether afforded another bright yellow oil, 1,3-diphenyl-5-ethyl-5-methyl-2,4-dithiohydantoin. 0.26 g (41%). i.r. 1270 (s). p.m.r. 1.06, t, 3; 1.63, s, 3; 1.96, m, 2; 7.46, m, 10. ^{13}C n.m.r. 207.2, 182.2, 136.8, 136.6, 129.8, 129.6, 129.4, 129.3, 128.8, 81.3, 33.5, 27.3, 7.8. m.s. 326. A satisfactory microanalysis could not be obtained.

2-Phenylimino-3-Phenyl-5-Methyl-5-n-Propylthiazolin-4-thione and 1,3-Diphenyl-5-Methyl-5-n-Propyl-2,4-Dithiohydantoin

Elution with a 6:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallized from methanol. Thus 2-phenylimino-3-phenyl-5-methyl-5-n-propylthiazolin-4-thione was obtained as yellow needles, m.p. 121-122.5°. 0.21 g (37%). i.r. 1285 (s), 1640 (s). p.m.r. 1.10, m, 5; 1.79, s, 3; 2.30, m, 2; 7.22, m, 10. ^{13}C n.m.r. 211.7, 157.9, 149.0, 139.0, 129.5, 129.1, 128.4, 124.6, 120.6, 66.2, 46.9, 31.5, 18.2, 13.9. m.s. 340 Anal. Calcd. for $C_{19}H_{20}N_2S_2$: C, 67.02; H, 5.92; N, 8.23; S, 18.83. Found: C, 66.65; H, 5.82; N, 8.34; S, 18.34.

Elution with a 4:1 mixture of light petroleum ether and ether afforded a second yellow solid which was recrystallized from methanol Thus, 1,3-diphenyl-5-methyl-5-n-propyl-2,4-dithiohydantoin was obtained as yellow needles, m.p. 158.5-160°. 0.17 g (30%). i.r. 1280 (s). p.m.r. 1.05, m,5; 1.60, s, 3; 2.00, m, 2; 7.43, m, 10. ^{13}C n.m.r. 207.3, 181.9, 136.7, 136.5, 129.7, 129.3, 129.1, 128.7, 80.9, 42.4, 27.4, 16.5, 13.6. m.s. 340. Anal. Calcd. for $C_{19}H_{20}N_2S_2$: C, 67.02; H, 5.92; N, 8.23; S, 18.83. Found: C, 67.25; H, 5.90; N, 8.04;

S, 18.93.

2-Phenylimino-3-Phenyl-5-Isopropyl-5-Methylthiazolin-4-thione and 1,3-Diphenyl-5-Isopropyl-5-Methyl-2,4-Dithiohydantoin

Elution with a 6:1 mixture of light petroleum ether and ether afforded a bright yellow oil, 2-phenylimino-3-phenyl-5-isopropyl-5-methylthiazolin-4-thione which would not crystallise. 0.14 g (23%). i.r. 1280 (s), 1637 (s). p.m.r. 1.03, d, 6; 1.83, s, 3; 2.57, se, 1; 7.25, m, 10. ^{13}C n.m.r. 212.5, 158.4, 149.3, 138.9, 129.6, 129.2, 128.4, 124.7, 120.7, 71.9, 40.4, 30.3, 17.9. m.s. 340. Anal. Calcd. for $C_{19}H_{20}N_2S_2$: C, 67.02; H, 5.92; N, 8.23; S, 18.83. Found: C, 66.82; H, 5.86; N, 8.08; S, 18.59.

Elution with a 5:1 mixture of light petroleum ether and ether afforded a bright yellow oil, 1,3-diphenyl-5-isopropyl-5-methyl-2,4-dithiohydantoin, which also would not crystallise. 0.15 g (25%). i.r. 1285 (s). p.m.r. 0.95, d, 6; 1.65, s, 3; 2.39, se, 1; 7.43, m, 10. ^{13}C n.m.r. 206.5, 182.1, 136.9, 129.7, 129.4, 128.8, 82.9, 37.0, 25.6, 16.5, 15.7. m.s. 340. A satisfactory microanalysis could not be obtained.

2-Phenylimino-3-Phenyl-5-Isobutyl-5-Methylthiazolin-4-thione and 1,3-Diphenyl-5-Isobutyl-5-Methyl-2,4-Dithiohydantoin

Elution with a 5:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallised from methanol. Thus 2-phenylimino-3-phenyl-5-isobutyl-5-methylthiazolin-4-thione was obtained as yellow needles, m.p. 149-151°. 0.20 g (35%). i.r. 1283

(s), 1640 (s). p.m.r. 1.02, m, 7; 1.80, s, 3; 2.14, m, 2; 7.20, m, 10. ^{13}C n.m.r. 212.4, 158.1, 149.1, 139.1, 129.6, 129.1, 128.4, 124.7, 120.7, 66.0, 52.2, 33.2, 26.3, 24.5, 23.7. m.s. 354. Anal. Calcd. for $C_{20}H_{22}N_2S_2$: C, 67.76; H, 6.25; N, 7.90; S, 18.08. Found: C, 68.35; H, 6.31; N, 7.83; S, 17.41.

Elution with a 4:1 mixture of light petroleum ether and ether afforded a bright yellow oil which was crystallized from methanol. Thus 1,3-diphenyl-5-isobutyl-5-methyl-2,4-dithiohydantoin was obtained as yellow needles. m.p. 102-104°. 0.17 g (30%). i.r. 1275 (s). p.m.r. 0.97, m, 7; 1.60, s, 3; 1.94, m, 2; 7.33, m, 10. ^{13}C n.m.r. 207.2, 181.8, 136.6, 129.4, 129.1, 128.5, 80.5, 48.4, 29.1, 24.4, 23.7. m.s. 354. Anal. Calcd. for $C_{20}H_{22}N_2S_2$: C, 67.76; H, 6.25; N, 7.90; S, 18.08. Found: C, 68.13; H, 6.22; N, 7.89; S, 17.54.

Cyclohexanespiro-5'(2'-phenylimino-3'-phenylthiazolin-4'-thione) and Cyclohexanespiro-5'(1',3'-diphenyl-2',4'-dithiohydantoin)

Elution with a 6:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallised from methanol. Thus cyclohexanespiro-5'-(2'-phenylimino-3'-phenylthiazolin-4'-thione) was obtained as yellow needles m.p. 205-206.5°. 0.19 g (33%). i.r. 1287 (s), 1640 (s). p.m.r. 1.98, m; 7.16, m. The peak areas were in the ratio of 1:1. ^{13}C n.m.r. 212.2, 157.7, 149.2, 138.7, 129.6, 129.1, 128.5, 124.6, 120.8, 70.6, 41.0, 24.5, 23.7. m.s. 353. Anal. Calcd. for $C_{20}H_{20}N_2S_2$: C, 68.14; H, 5.72; N, 7.95; S, 18.19. Found: C, 67.74; H, 5.75; N, 7.78; S, 18.31.

Elution with a 5:1 mixture of light petroleum ether and ether afforded a second yellow solid which was also recrystallized from methanol. Thus cyclohexanespiro-5'(1',3'-diphenyl-2',4'-dithiohydantoin) was obtained as yellow prisms. m.p. 181-183°. 0.18 g (32%). i.r. 1280 (s). p.m.r. 1.77, m; 7.44, m. The peak areas were in the ratio of 1:1. ^{13}C n.m.r. 208.1, 181.3, 136.9, 136.7, 130.7, 129.6, 129.3, 128.8, 78.1, 35.4, 23.9, 20.3. m.s. 353. Anal. Calcd. for $C_{20}H_{20}N_2S_2$: C, 68.14; H, 5.72; N, 7.95; S, 18.19. Found: C, 68.22; H, 5.76; N, 7.68; S, 18.28.

Acid Hydrolysis of 2-Phenylimino-3-Phenyl-5,5-Dimethylthiazolin-4-thione

A mixture of the thiazolinethione (0.50 g, 0.0016 mol) and concentrated hydrochloric acid (10 ml) was heated under reflux with stirring for 16 hours. Then the reaction mixture was cooled in ice and the white solid, which precipitated out, was filtered off and washed to neutrality. Recrystallisation from ethanol afforded 3-phenyl-5,5-dimethyl-2,4-thiazolinedione as colourless needles m.p. 97.5-100° (lit.[202] m.p. 102°). 0.23 g (66%). i.r. 1685 (s), 1710 (m), 1740 (s). p.m.r. 1.79, s, 6; 7.33, m, 5. ^{13}C n.m.r. 177.7, 169.6, 133.1, 129.3, 129.1, 127.3, 53.7, 28.1. m.s. 221.

Synthesis of 2-Propanone-4-Phenylsemicarbazone.[203]

2-Propanone semicarbazone (30.0 g, 0.26 mol) was added with vigorous stirring to aniline (45 ml, 0.49 mol) maintained at a temperature of 150°. After 15 minutes the clear solution was poured into 1 litre of a 10% acetic acid-ice mixture and a white solid rapidly

separated out. Recrystallisation from ethanol afforded colourless needles of 2-propanone-4-phenylsemicarbazone m.p. 154-155° (lit.[203] m.p. 155-156°). 17.5 g (35%).

Synthesis of 5,5-Dimethyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline[204]

A solution of 2-propanone-4-phenylsemicarbazone (6.0 g, 0.03 mol) in methylene choride (200 ml) was added dropwise with stirring during 1 hour to an ice cold solution of lead tetraacetate (15.5 g, 0.035 mol) in methylene chloride (400 ml). When the addition was completed, ice-cold water (400 ml) was added and the mixture was stirred for a further 15 minutes before being filtered through a bed of Celite. The organic layer was separated, washed with water (500ml), saturated sodium bicarbonate solution (500 ml) and then again with water (500 ml) and dried over anhydrous magnesium sulphate. Concentration under reduced pressure afforded a yellow solid which was recrystallised from a light petroleum ether-chloroform mixture. Thus 5,5-dimethyl-2-phenylimino-Δ^3-1,3,4-oxadiazoline was obtained as yellow plates m.p. 75-76° (lit.[204] m.p. 72-73°). 5.3 g (90%). i.r. 1701 (s). p.m.r. 1.66, s, 6; 7.35, m, 5.

Thermal Decomposition of 5,5-Dimethyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in the Presence of Aryl Isocyanates at 150°

General Method

The iminooxadiazoline (1.0 g, 0.005 mol) was added with stirring to a solution of the aryl isocyanate (0.055 mol) and bromobenzene (50 ml) maintained at a temperature of 150°. The reaction mixture was

kept at that temperature and stirred vigorously for 5 hours after which time the evolution of gas was no longer apparent. Removal of the excess aryl isocyanate and bromobenzene under reduced pressure afforded the crude reaction product which was then dissolved in the minimum volume of chloroform and chromatographed on a column (100 g, neutral aluminum oxide, Brockman Activity II, 80-200 mesh, Fisher Scientific Company) using a 5:2 mixture of light petroleum ether and ether as the eluant.

Phenyl Isocyanate

The product, 1-phenylcarbamoyl-3,3-dimethyloxindole, was isolated as a viscous oil but on crystallisation from an ethanol-water mixture was obtained as colourless needles m.p. 74-75°. 0.30 g (43%).

p-Tolyl Isocyanate

The product 1-p-tolylcarbamoyl-3,3,5-trimethyloxindole was isolated as a white solid and upon crystallisation from methanol 0.25 g (32%) of colourless needles m.p. 124-126° was obtained.

p-Methoxyphenyl Isocyanate

The product 1-(p-methoxy)phenylcarbamoyl-5-methoxy-3,3-dimethyloxindole was obtained as a white solid which, when recrystallised from methanol, was in the form of colourless needles n.p. 118-120°. 0.37 g (44%).

p-Chlorophenyl Isocyanate

The product 1-(p-chloro)phenylcarbamoyl-5-chloro-3,3-dimethyloxindole was obtained as a white solid and when recrystallised from methanol yielded colourless crystals m.p. 169-171°. 0.25 g (29%).

Thermal Decomposition of 5,5-Dimethyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline at 150°

The iminooxadiazoline (2.28 g, 0.012 mol) was added with stirring to bromobenzene (100 ml) maintained at a temperature of 150°. After 5 hours at that temperature the reaction mixture was concentrated under reduced pressure. Chromatography of the resulting dark brown gum on a Florisil column (200 g, 60-100 mesh, J. T. Baker and Company, Phillipsburg, New Jersey) using light petroleum ether as the eluant afforded the viscous oil, crystallisation of which from an ethanol-water mixture gave colourless needles m.p. 74.5-75° of 1-phenylcarbamoyl-3,3-dimethyloxindole 0.25 g (15%).

Thermal Decomposition of 5,5-Dimethyl-2-(p-Tolyl)imino-Δ^3-1,3,4-Oxadiazoline in the Presence of Phenyl Isocyanate at 150°

The iminooxadiazoline (0.40 g, 0.002 mol) was added with stirring to a solution of phenyl isocyanate (4 ml, 0.04 mol) and nitrobenzene (50 ml) maintained at a temperature of 150°. After 5 hours at that temperature the excess phenyl isocyanate and nitrobenzene were removed from the reaction mixture under reduced pressure. Chromatography of the resulting brown gum on a Florisil column (50 g) using light petroleum ether as the eluant afforded the viscous oil,

1-phenylcarbamoyl-3,3-dimethyloxindole which, as usual, was recrystallised from an ethanol-water mixture. Colourless needles m.p. 73-75°. 0.05 g (18%). No 1-phenylcarbamoyl-3,3,5-trimethyloxindole, the cage product, was formed within the limits of detection (p.m.r.).

Synthesis of Phenyl Isocyanide[205,206]

A solution of aniline (44 ml, 0.5 mol) and 98% formic acid (45 ml, 1.2 mol) in toluene (150 ml) under a condenser was attached to a Dean-Stark water separator. After water stopped collecting (about 5 hours) toluene and the excess formic acid were removed under reduced pressure. The crude-N-phenylformamide which gradually solidified on standing in an ice-bath, was recrystallized from a light petroleum ether-chloroform mixture. Colourless plates m.p. 48-50° (lit.[207] m.p. 52°). 42.4 g (70%).

N-phenylformamide (9.0 g, 0.07 mol), carbon tetrachloride (11.3 g, 0.08 mol), triethylamine (7.1 g, 0.07 mol) and triphenylphosphane (23.0 g, 0.09 mol) were dissolved in 1,2-dichloroethane (100 ml) and the solution was maintained at a temperature of 40° for 2 1/2 hours during which time it became dark brown in colour. Removal of the 1,2-dichloroethane on the rotary evaporator afforded a brown liquid which was extracted with light petroleum ether (5 x 200 ml). The petroleum ether extract was dried over anhydrous magnesium sulphate and then concentrated on the rotary evaporator. The resultant brown liquid was distilled under vacuum (10^{-1} Torr) with the pot at a temperature of 35° and the receiver cooled in a dry-ice acetone bath. Phenyl isocyanide was obtained as a colourless, vile smelling liquid 6.5 ml

(85%). i.r. 2140 (s).

Treatment of Phenyl Isocyanide with Acetone in Nitrobenzene at 150°

A solution of acetone (1.1 ml, 0.015 mol) and phenyl isocyanide (1.8 ml, 0.017 mol) in nitrobenzene (10 ml) was placed in a thermolysis tube and the system was then degassed by means of three freeze-pump thaw cycles at a pressure of 10^{-2} Torr. The sealed tube was then placed in an oil bath maintained at a temperature of 150° and left there for 5 hours during which time the solution darkened appreciably. Aliquots of the solution were then removed from the opened tube and analysed by n.m.r. spectroscopy and by chromatography on analytical neutral aluminum oxide thin layer plates using a 5:2 mixture of light petroleum ether and ether as the solvent.

The experiment was carried out in duplicate.

In both instances there was no evidence of the formation of 3,3-dimethyloxindole.

Thermal Decomposition of 5,5-Dimethyl-2-Phenylimino-Δ^3-1,3,4-Oxadiazoline in the Presence of Phenyl Isothiocyanate at 150°

The iminooxadiazoline (1.97 g, 0.01 mol) was added with stirring to a solution of phenyl isothiocyanate (14 ml, 0.01 mol) and nitrobenzene (50 ml) maintained at a temperature of 150°. After 5 hours at that temperature the excess phenyl isothiocyanate and nitrobenzene were removed under reduced pressure. Chromatography of the resultant crude reaction mixture on an analytical thin layer plate (3 cm x 10 cm, neutral aluminum oxide with fluorescent indicator

U.V.$_{254}$, Macherey, Nagel and Company) using a 5:1 mixture of light petroleum ether and ether as the solvent indicated that there were three products of the reaction. These compounds were isolated by the following procedure. The crude reaction mixture was dissolved in the minimum volume of chloroform and chromatographed on a column (200 g, neutral aluminum oxide, Brockman Activity II, 80-200 mesh, Fisher Scientific Company) using mixtures of light petroleum ether and ether as the eluant.

Elution with a 6:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallised from methanol. 2-Phenylimino-3-phenyl-5,5-dimethylthiazolin-4-thione was obtained as yellow needles m.p. 142-144°.

Elution was a 5:1 mixture of light petroleum ether and ether afforded a very small amount of a white solid which was recrystallised from ethanol. 2-Phenylimino-3-phenyl-5,5-dimethyloxazolin-4-thione was obtained as colourless needles m.p. 197-198°. i.r. 1730 (s). p.m.r. 1.72, s; 7.32, m. The peak areas were in the ratio of 3:5. ^{13}C n.m.r. 206.7, 149.3, 144.4, 134.8, 129.4, 128.7, 128.0, 124.2, 123.5, 94.7, 27.6. m.s. 296.

Elution with a 4:1 mixture of light petroleum ether and ether afforded a yellow solid which was recrystallised from methanol. The resultant yellow needles did not, however, have a sharp melting point. Subsequent work showed that the yellow needles were, in fact, a mixture of two compounds, 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin and 1,3-diphenyl-5,5-dimethyl-4-thiohydantoin.

This experiment was repeated twice more and the crude reaction products so obtained were analysed by p.m.r. spectroscopy and by thin layer chromatography using alumina plates and a 5:1 mixture of light petroleum ether and ether as the solvent.

Under the above experimental conditions 2-phenylimino-3-phenyl-5,5-dimethylthiazoline-4-thione, 1,3-diphenyl5,5-dimethyl-2,4-dithiohydantoin,* 2-phenylimino-3-phenyl-5,5-dimethyloxazoline-4-thione and 1,3-diphenyl-5,5-dimethyl-4-thiohydantoin were formed in the ratio 1.5:1.5:1:3.5.

Thermal Decomposition of 5,5-Dimethyl-Δ^3-1,3,4-Oxadiazolin-2-one in the Presence of Phenyl Isocyanate and Phenyl Isothiocyanate at 150°

A solution of the oxadiazolinone (0.50 g, 0.004 mol) in nitrobenzene (25 ml) was added dropwise with stirring during 1 hour to a solution of phenyl isocyanate (4.5 ml, 0.04 mol), phenyl isothiocyanate (5 ml, 0.04 mol) and nitrobenzene (10 ml) purged with nitrogen (L-grade) and maintained at a temperature of 150°. When the addition was completed, the solution was kept at that temperature for a further 2 hours and then the excess phenyl isocyanate, phenyl isothiocyanate and nitrobenzene were removed under reduced pressure. The resultant crude

*The amount of 1,3-diphenyl-5,5-dimethyl-2,4-dithiohydantoin was determined by assuming that the ratio of that compound to 2-phenylimino-3-phenyl-5,5-dimethylthiazoline-4-thione was the same in this reaction as in the identical decomposition of 5,5-dimethyl-Δ^3-1,3,4-oxadiazolin-2-one in the presence of phenyl isothiocyanate.

products were dissolved in the minimum volume of chloroform and chromatographed on a column (100 g, neutral aluminum oxide, Brockman Activity II 80-200 mesh, Fisher Scientific Company).

Elution with a 6:1 mixture of light petroleum ether and ether afforded a white solid which was recrystallised from methanol. 2-Phenylimino-3-phenyl-5,5-dimethyloxazolin-4-thione was obtained as colourless needles m.p. 195.5-197°.

Elution with a 5:1 mixture of light petroleum ether and ether afforded a pale yellow solid which was recrystallised from methanol. 1,3-Diphenyl-4-thiohydantoin was obtained as very pale yellow prisms, m.p. 146-148°. i.r. 1280 (s), 1700 (s). p.m.r. 1.60, s; 7.34, m. The peak areas were in the ratio of 3:5. ^{13}C n.m.r. 208.7, 154.0, 134.5, 124.3, 129.5, 129.1, 128.7, 127.7, 72.1, 27.9. m.s. 296. Anal. Calcd. for $C_{17}H_{16}N_2SO$: C, 68.89; H, 5.44; N, 9.45; O, 5.39; S, 10.82. Found: C, 69.43; H, 5.48; N, 9.40; S, 11.01.

Elution with a 5:2 mixture of light petroleum ether and ether afforded the viscous oil, 1-phenylcarbamoyl-3,3-dimethyloxindole which was crystallised from an ethanol-water mixture - colourless needles m.p. 74-75°.

This experiment was repeated several times and the relative yields of the three compounds were determined by p.m.r. spectroscopy. Under the above experimental conditions 1-phenylcarbamoyl-3,3-dimethyloxindole, 1,3-diphenyl-5,5-dimethyl-4,thiohydantoin and 2-phenylimino-3-phenyl-5,5-dimethyloxazolin-4-thione were formed in the ratio 2.5:3:1.

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