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SOME 1,3-DIPOLAR CYCLOADDITION REACTIONS OF SUBSTITUTED AZIRIDINES

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

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EDMONTON, ALBERTA

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled SOME 1,3-DIPOLAR CYCLOADDITION REACTIONS OF SUBSTITUTED AZIRIDINES submitted by GEORGE DALLAS, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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To my Mother and Father

ABSTRACT

A number of 3-aroyl-2-arylaziridines have been prepared and their [2+3] or 1,3-dipolar cycloaddition reactions with a variety of aldehydes have been investigated and shown to provide useful synthetic routes to oxazolidines. The scope of the reaction and the gross structure of the products have been examined, as has the orientation of the cycloaddition, which was shown to proceed in one direction only.

The reaction has been interpreted as proceeding by thermal cleavage of the aziridines at the 2,3-bond to intermediate azomethine ylides, which then reacted in [2+3] cycloadditions with the carbonyl group of various aldehydes to produce the oxazolidines.

The stereochemistry of the reaction was examined and was observed to be stereoselective. This was attributed to a combination of the tendency of the *cis* azomethine ylide to isomerize to its thermodynamically more stable *trans* counterpart, and the known sluggish nature of the carbonyl group in such [2+3] cycloaddition reactions.

Tentative assignments of the stereochemistry of the groups at the 4- and 5-positions have been offered.

An independent synthesis of the oxazolidine ring by a route which offered steric control at these positions was attempted but proved unsuccessful.

The range of carbonyl groups was extended to diphenylcyclopropenone which was shown to react with the aziridines in [2+3] cycloaddition reactions at the carbonyl group of diphenylcyclopropenone, followed by rearrangement to produce the 4-oxazoline ring system. The scope of this reaction was investigated and shown to depend on the nature of the group at the 3-position of the aziridine ring.

These 4-oxazolines displayed marked thermochromism and photochromism, and were found to themselves undergo [2+3] cycloaddition reactions with suitably substituted acetylenes and olefins to provide useful syntheses of furans and 4,5-dihydrofurans, respectively. The latter series of compounds were obtained from completely stereospecific reactions.

These reactions were considered to proceed via externally stabilized ketocarbene intermediates, obtained from cleavage of the 4-oxazoline ring at the $O-C_2$ bond, followed by cycloaddition to the acetylenic or olefinic multiple bond.

The 4,5-dihydrofurans themselves were also found to exhibit thermochromism, and to undergo [2+3] cycloaddition reactions with olefinic species to produce other dihydrofurans. This has been rationalized as proceeding via an externally stabilized ketocarbene intermediate analogous to that postulated to explain the formation of the dihydrofurans.

Finally a survey of the [2+3] cycloaddition reactions of 4-oxazolines with species containing heteromultiple bonds was undertaken.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. J. W. Lown for his constant encouragement and guidance throughout the course of this work.

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CHAPTER I

INTRODUCTION

The object of this study was to investigate and develop new synthetic routes to certain five-membered heterocyclic ring systems, containing one, and especially two hetero atoms within the ring, by expansion of small ring heterocyclic compounds, and to study the properties and reactions of the products thus obtained.

In current practice, five-membered heterocyclic ring systems are prepared by one of three main methods:

A) Cyclization, B) Isomerization, C) Cycloaddition.

Type A usually involve the cyclic condensation of two preformed sections, often under acid or base catalysis, to yield the desired heterocycle.

Type B consist of the expansion of small ring heterocycles, under catalytic conditions, to isomeric five-membered heterocyclic ring compounds. These isomerizations may be effected by acid or nucleophile catalysis or be thermally induced.

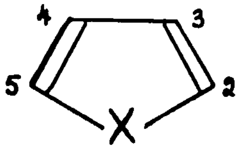
Type C represents the 1,3-dipolar or [2+3] cycloaddition technique by which a neutral five-membered ring system is formed by the combination of a dipolar species in the form of a triatomic 1,3-dipole, and a suitable unsaturated acceptor species known as the dipolarophile.

This thesis will be concerned with the third approach (type C), but it is relevant first of all to review the principal synthetic approaches to five-membered heterocyclic ring compounds that are representative of the first two methods.

CYCLIZATION METHODS

Five-Membered Rings with One Hetero Atom

There are several methods of ring formation which can be applied, sometimes with minor modifications, to the synthesis of compounds of general structure I (X = O, NR, S).

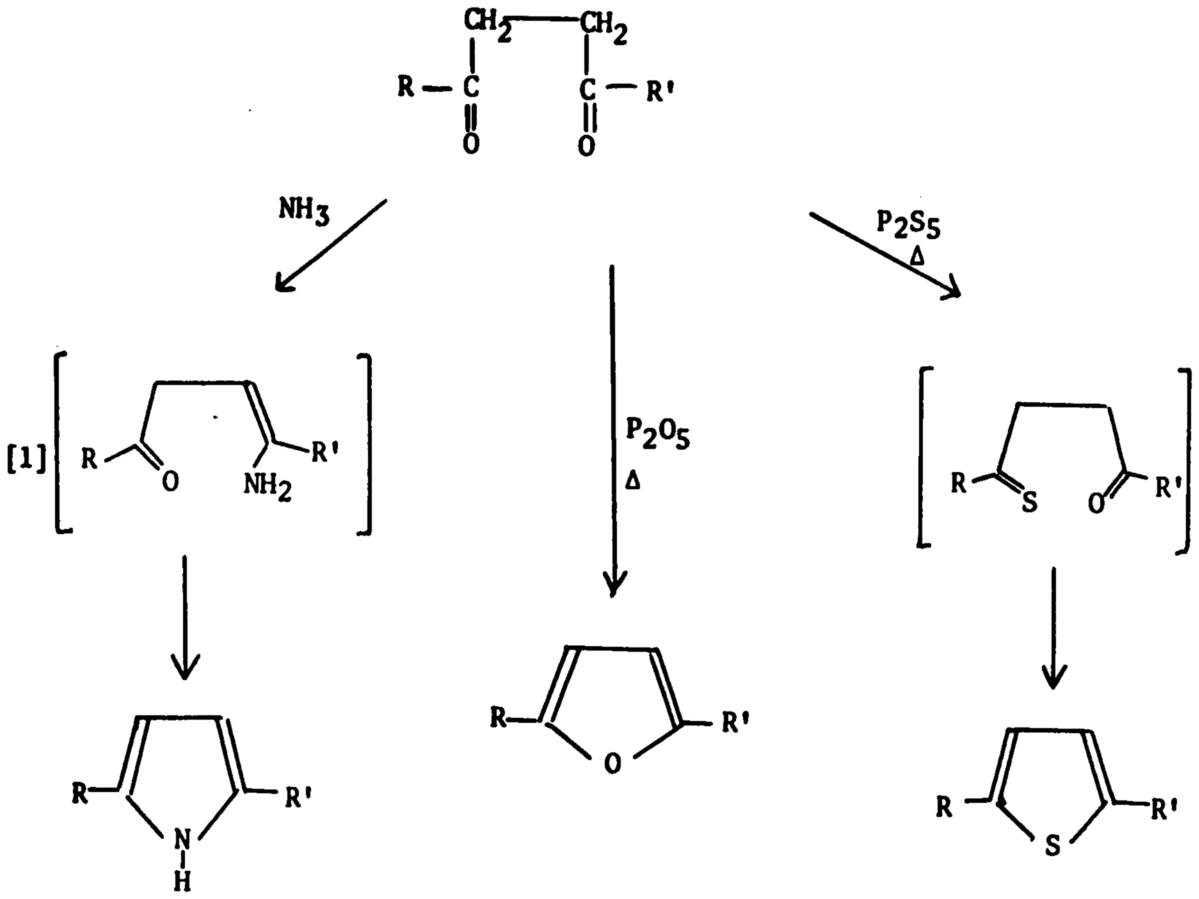


I

Of these, there are two main classes of cyclization synthesis:

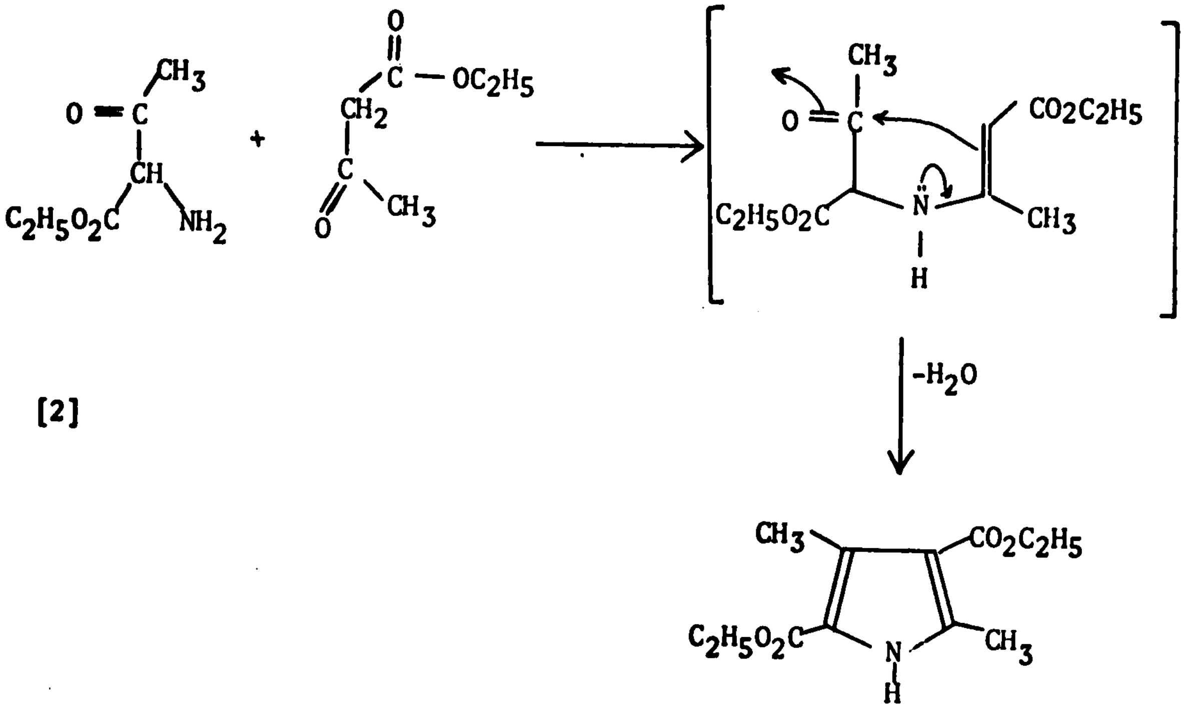
1) those involving bond formation between the hetero atom X, and atoms C_2 and C_5.
2) those involving bond formation between the hetero atom and C_2 and between atoms C_3 and C_4.

The former class is illustrated by the Paal-Knorr synthesis[1] of furans, pyrroles and thiophenes, eq. [1].



This convenient method involves the treatment of enolizable 1,4-diketones with a) ammonia or primary amines to give pyrroles, b) a dehydrating agent (H_2SO_4, P_2O_5, $ZnCl_2$) to produce furans, c) an inorganic sulfide, e.g. P_2S_5 to yield thiophenes. The yields in these reactions are fair to good, and due to the ready availability of enolizable 1,4-dicarbonyl compounds, the reaction is of wide applicability.

The second class of cyclization reactions is exemplified by the Knorr pyrrole synthesis.[2] This is the most general and widely applicable pyrrole synthesis and involves the acid catalyzed condensation of α-aminoketones or α-amino-β-keto esters with ketones or keto esters (equation [2]).

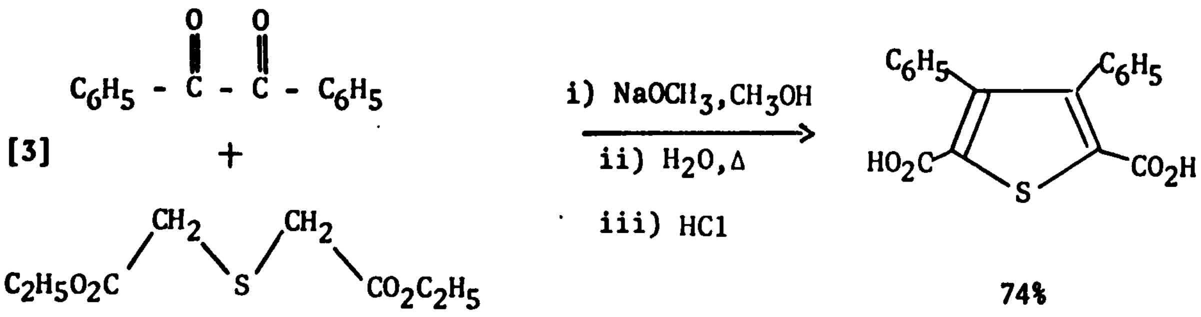


[2]

In general, the α-aminoketone is prepared *in situ* and is thought to form the intermediate shown (C_2-X bond closure), which then cyclizes with subsequent expulsion of water to form the pyrrole. The main disadvantage in this method is the tendency of α-aminoketones to dimerize if the ketone or keto ester is not reactive enough to condense at an appreciable rate.[4]

An important exception to these two principal classes of cyclization reactions is the Hinsberg thiophene synthesis[5], where the new bonds formed are between atoms C_2 and C_3, and C_4 and C_5 respectively as illustrated by equation [3].[6]

[3]

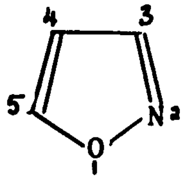


Synthetic methods leading to the dihydro-compounds of this series will be discussed in Chapter IV of this thesis.

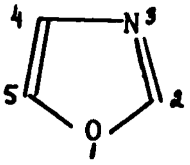
Five-Membered Rings with Two Hetero Atoms

This brief review of principal cyclization techniques will be confined to ring systems containing oxygen and nitrogen as the hetero atoms, since such systems were the main subject of this investigation.

Five-membered ring compounds containing oxygen and nitrogen as the hetero atoms can formally be regarded as being derived from furan by substitution of one of the ring =CH- groups by a nitrogen atom. Insertion of the nitrogen atom at the 2-position leads to a group of compounds known as isoxazoles, whereas replacement at the 3-position affords the oxazole group of compounds.



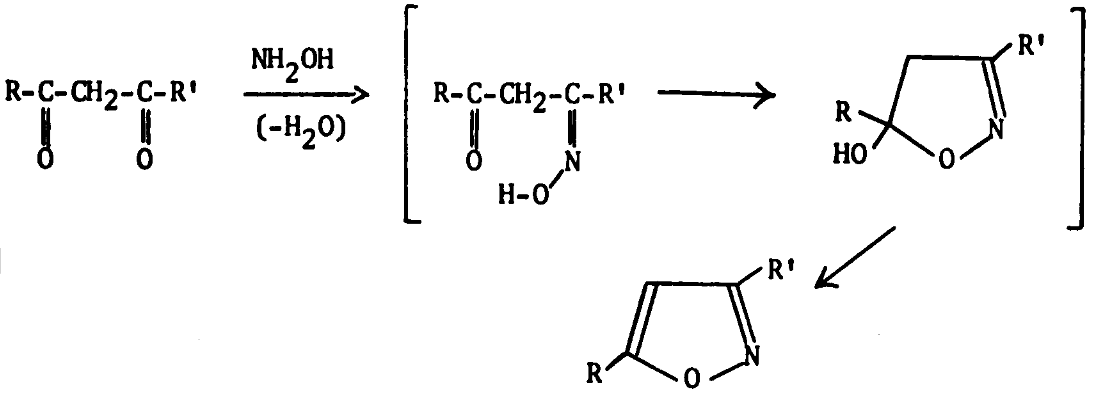
Isoxazole



Oxazole

Isoxazoles and their Derivatives

The methods of formation of isoxazoles are all based upon the addition of a species containing the preformed O-N bond to an acceptor molecule of the desired oxidation level. The most general and widely applicable synthetic method involves the addition of hydroxylamine to a 1,3-dicarbonyl compound or to a precursor of such a species, equation [4].



[4]

A wide variety of 1,3-dicarbonyl compounds may be used, the only limitation being that the attached substituents must not sterically hinder the cyclization of the monoxime intermediate.

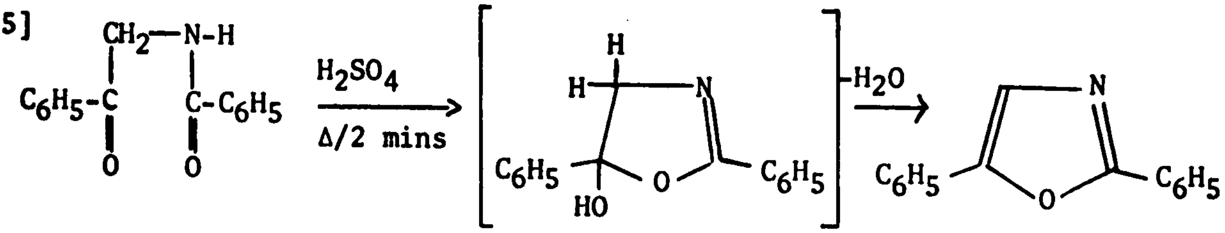
This and other methods, both cyclizations and 1,3-dipolar cycloadditions, for the synthesis of isoxazoles and their derivatives, isoxazolines and isoxazolidines, as well as a thorough discussion of their properties and reactions are to be found in reviews by Barnes[7] and Quilico.[8]

Oxazoles and their Derivatives

The oxazole ring system has received less attention than the isomeric isoxazole system and most of the progress in this field was as a consequence of the Anglo-American work on the synthesis of penicillin,[9] for although this molecule contains no oxazole ring, many such derivatives were prepared in the course of the work, some being possible intermediates in a synthesis of the antibiotic.

The most general synthetic method is the Robinson-Gabriel synthesis[10,11] which involves the cyclization of α-acylamino ketones as shown in equation [5].

[5]

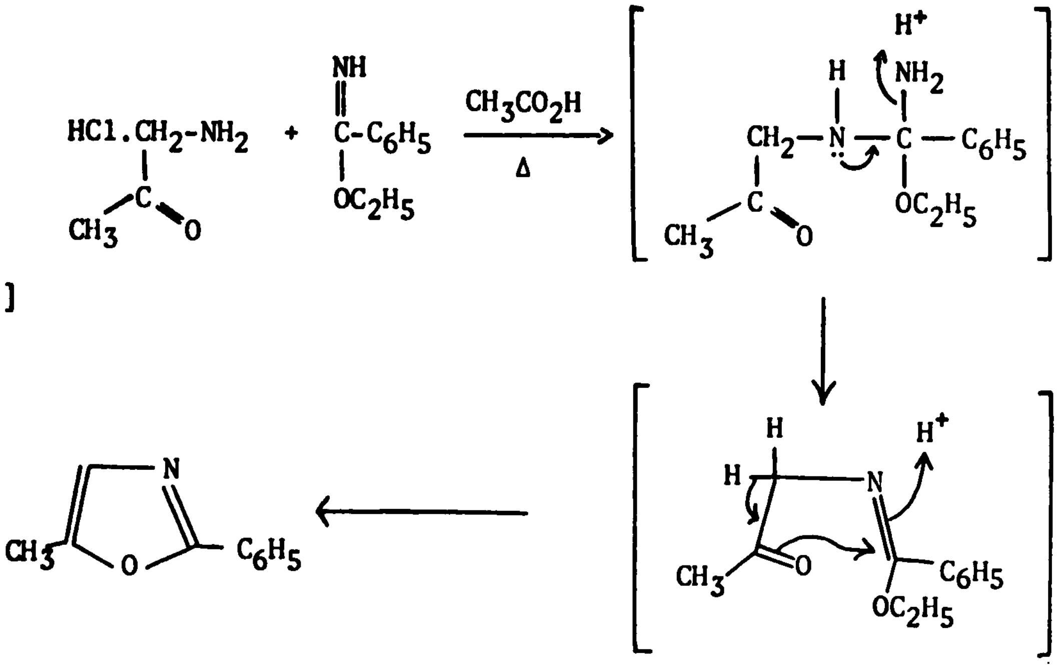


Ref. 10.

Various dehydrating agents can be used and the reaction provides good yields, but is generally restricted to derivatives bearing substituents on the 2- and 5-positions. There are many modifications of this general method in the literature.[12]

Another very useful approach involves the addition of imino ethers to 2-aminocarbonyl compounds, a modification of which can be applied directly to the synthesis of oxazole itself which is not available by the other methods. A representative reaction, taken from the work of Cornforth and Huang,[13] is shown in equation [6].

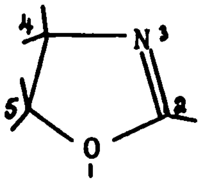
[6]



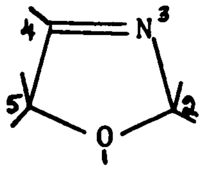
According to Paquette,[14] this mechanism is feasible since several of the intermediates have been isolated in the course of the reaction. The yields of this reaction are good.

These methods and others of lesser importance are thoroughly discussed in the review by Cornforth.[12]

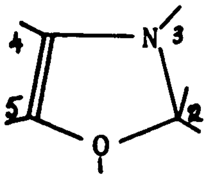
The dihydro-derivatives of oxazoles are known as oxazolines, all three of which are now known.



2-oxazoline



3-oxazoline

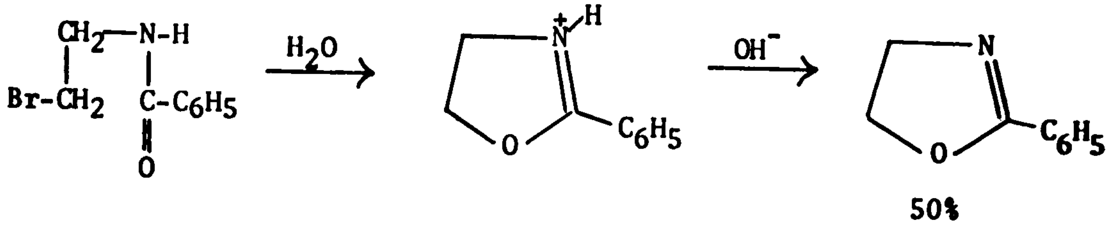


4-oxazoline

A literature survey has shown that the 3-oxazoline system is relatively rare, and with the exception of a few cases[15,16] where an imino-substituent was present at the 2-position, the 4-oxazolines were unknown prior to 1968.

The 2-oxazoline ring system has been known since 1889, and Gabriel's method[17] is still utilized for the preparation of simple 2-oxazolines, equation [7].

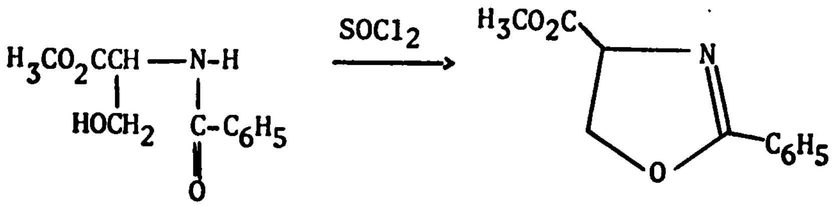
[7]



It was later found[18] that β-chloroalkylbenzamide gave improved yields of 2-oxazolines.

2-Oxazolines can also be obtained from N-acyl derivatives of β-hydroxyamines under mild conditions by several methods, one of which[19] is shown in equation [8].

[8]



The completely reduced oxazoles are known as oxazolidines, a class of compounds that form the subject of Chapter II of this thesis, and thus their preparative methods will be fully reviewed in that section.

The other major oxazole derivatives, oxazolones, oxazolidones, and oxazolidinediones, will not be discussed here, and the review by Cornforth[12] is recommended for the properties, reactions, and methods of preparation of these systems.

ISOMERIZATION METHODS

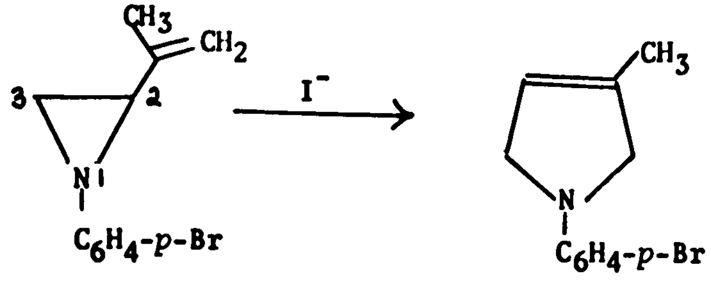
These isomerization reactions, whereby a small heterocyclic ring system is expanded into a five-membered heterocyclic ring, are essentially confined to aziridine derivatives and are catalyzed by acids, nucleophilic reagents, and by pyrolysis. The aziridine ring is cleaved in general at a carbon-nitrogen bond, although there are now several examples of carbon-carbon bond cleavage in the literature.

These isomerization reactions are discussed here because they are directly relevant to the main body of this thesis in that they illustrate many of the reactions to be expected of substituted aziridines.

Five-Membered Rings with One Hetero Atom

A literature survey has shown that there are relatively few examples of five-membered heterocyclic ring compounds containing one hetero atom that are produced by isomerization of substituted aziridines. One recorded example occurs when the aziridine ring bears an isopropylidene group at the 2-position. This under nucleophilic catalysis has been shown by Scheiner[20] to produce the pyrroline derivative as indicated in equation [9].

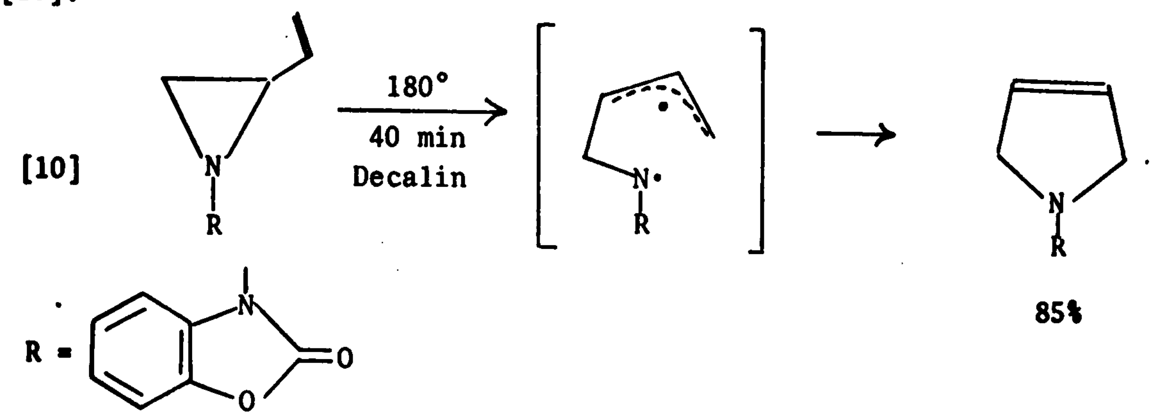
[9]



The mechanism of nucleophile catalyzed isomerizations will be briefly discussed in the next section.

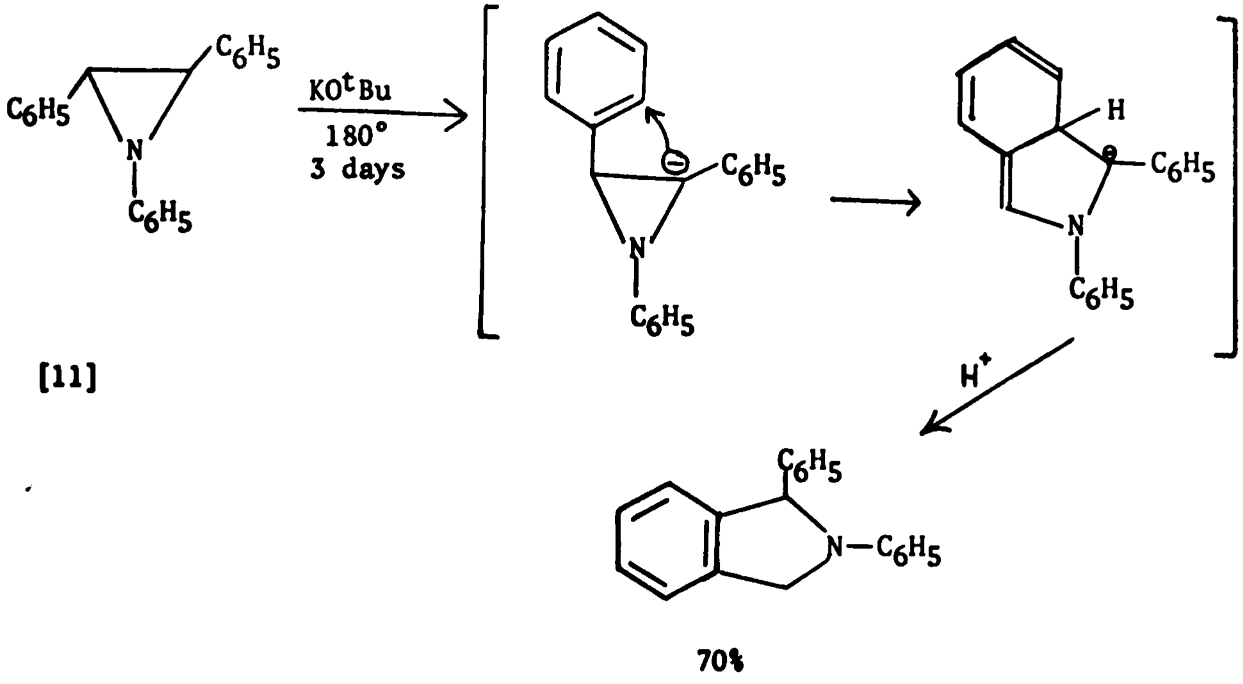
Atkinson and Rees[21] have reported a thermal isomerization of vinylaziridines to produce substituted pyrrolines as shown in equation [10].

[10]


180°
40 min
Decalin
N
R
N·
R
N
R
R =
N
O
O
85%

A different type of reaction possibly involving carbon-carbon bond cleavage has been utilized to produce isoindolenes in good yield,[22] equation [11].

[11]

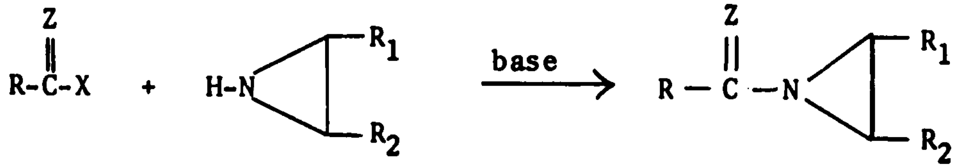

C6H5
C6H5
N
C6H5
KOtBu
180°
3 days
C6H5
N
C6H5
H
C6H5
N
C6H5
H+
C6H5
N—C6H5
70%

Five-Membered Rings with Two Hetero Atoms

These isomerization reactions of substituted aziridines have led to useful syntheses of 2-oxazolines,[23] imidazolines,[23] imidazolidines,[23] thiazolines,[23] pyrazolines,[23] triazolines,[23] and oxazoles.[24,25] This brief review will be confined to the cases where the hetero atoms are oxygen and nitrogen and sulfur and nitrogen.

With few exceptions,[24,25] the substrates required for these reactions are N-acyl and N-aroylaziridines or their thio-analogues, all of which can be conveniently prepared by the action of aziridine or its 2- and 2,3-substituted derivatives on carbonyl[26,38,39] and thiocarbonyl systems,[27] equation [12].

[12]



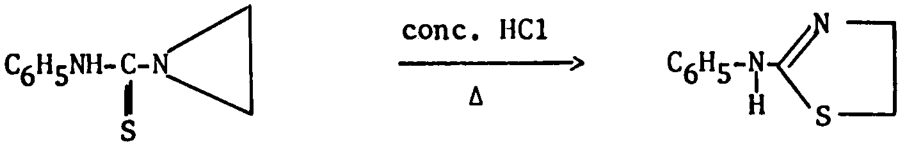
Z = O, NR, S; X = Cl, OAc, OR; R = alkyl, aryl

$\left.\begin{matrix} R_1 \\ R_2 \end{matrix}\right\}$ H, alkyl, aryl.

Much of the detailed elucidation of these aziridine derivative isomerizations is due to the work of Heine and his school.[23]

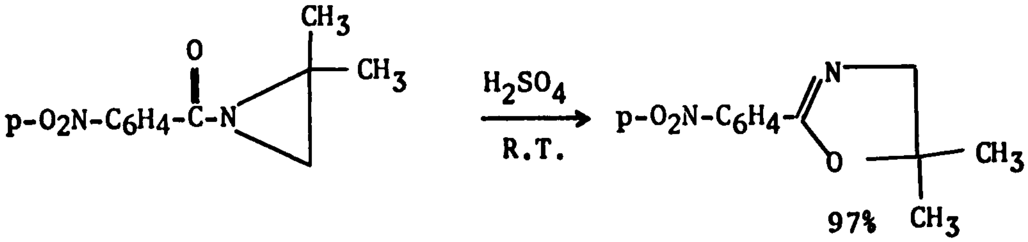
Acid Catalyzed Isomerizations

The earliest example of this type was described by Gabriel and Stelzner,[28] who converted 1-aziridinethiocarboxanilide into 2-anilino-2-thiazoline by heating the compound in concentrated hydrochloric acid. Although their original product structure assignment was shown to be erroneous, more recent work by Deutsch and Fanta[29] has produced a 90% yield of this product, equation [13].

[13] 

This reaction has been extended to a number of 1-substituted aziridines and aqueous sulfuric acid or phosphoric acid may serve as the catalyst.[23] It has also been shown,[29] that when the aziridine ring bears substituents on the 2- and 3-positions, the expected thiazoline is obtained but in reduced yield along with other by-products. The mechanism postulated by Heine[23] could account for this result.

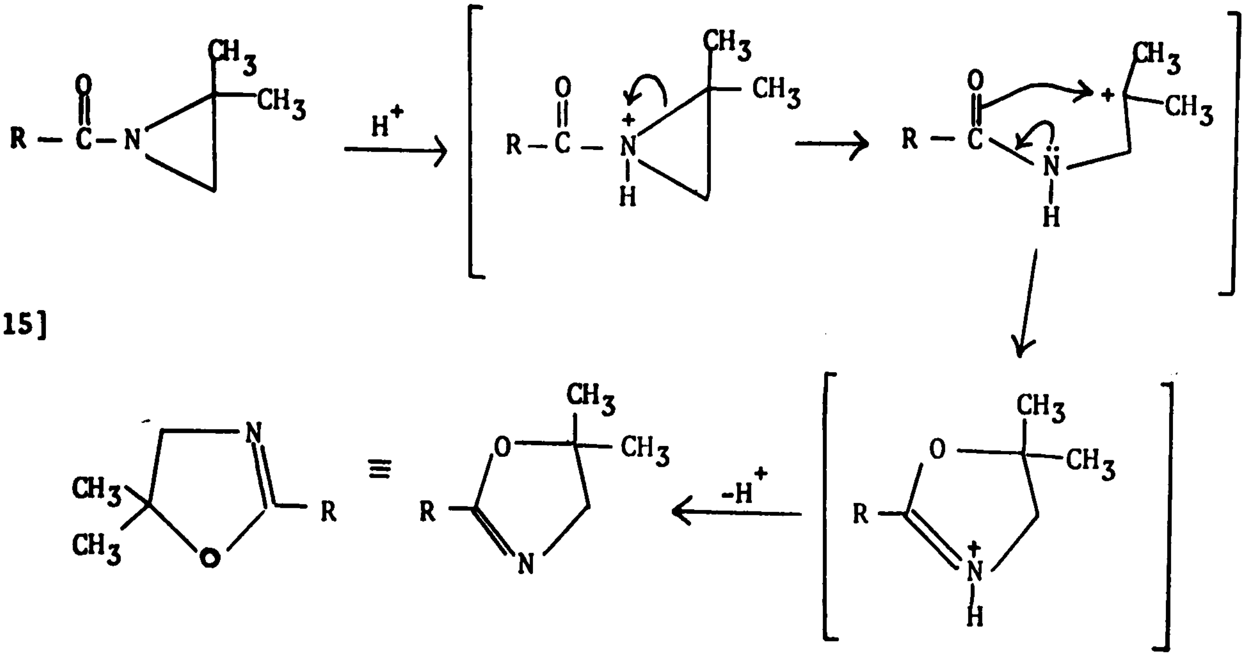
1-Aroylaziridines are readily isomerized into 2-aryl-2-oxazolines by the action of aluminium halides in heptane under reflux,[30] or by concentrated sulfuric acid at room temperature,[31] equation [14].

[14] 

In contrast to the case of the sulfur system described before,[29] this was the only product obtained from the reaction.

These acid catalyzed isomerizations, especially in strong acid have been rationalized by Heine[23] as shown in equation [15].

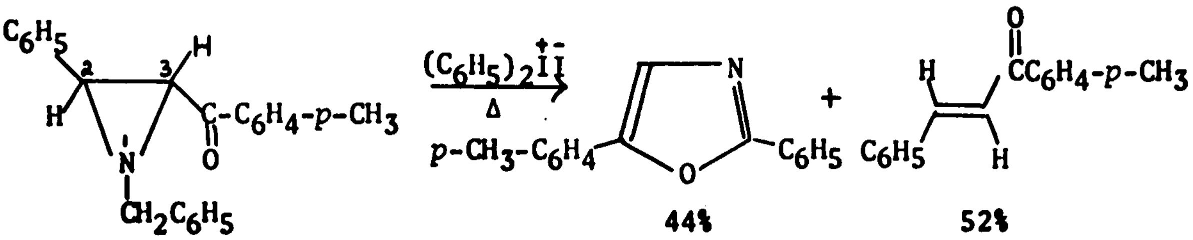
[15]



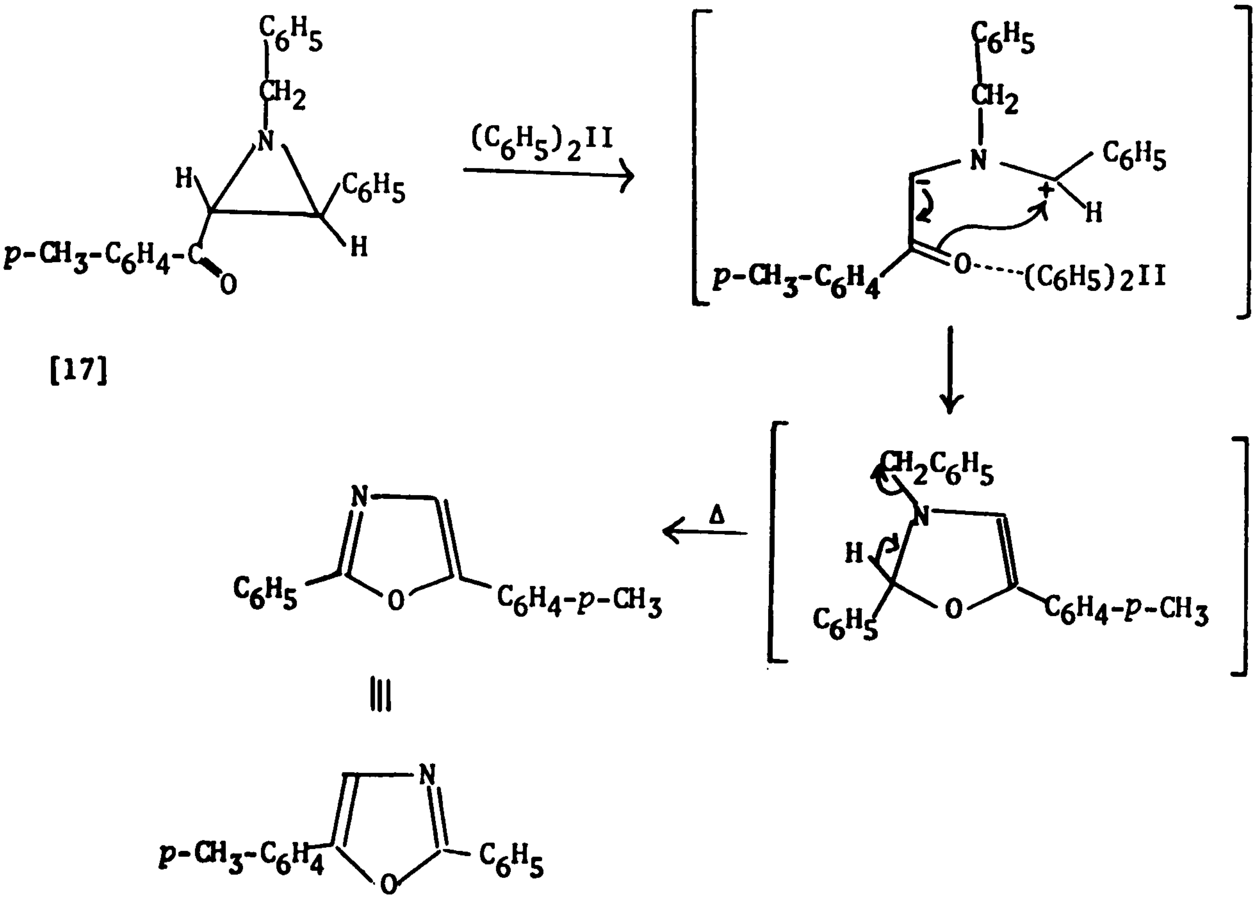
Protonation of the amido nitrogen and scission of the aziridinium ring to yield the more stable tertiary carbonium ion, followed by ring closure possibly by the mechanism shown, and subsequent deprotonation, would yield the required 2-oxazoline. The direction of ring opening is in agreement with other reported work on the acid cleavage of unsymmetrical aziridines.[32,33]

Whilst the isomerization of 1-aroylaziridines to 2-aryl-2-oxazolines under Lewis acid catalysis has been well established,[30] related isomerizations of the 3-aroylaziridine system has only recently been reported,[24,25] equation [16].

[16]



A possible explanation offered by Padwa for the oxazole formation illustrates the case where the aziridine ring cleaves across the carbon-carbon bond, due possibly to coordination of the diphenyliodonium iodide with the carbonyl group, (equation [17]). Subsequent ring closure to the intermediate 4-oxazoline and oxidation would readily account for the product.

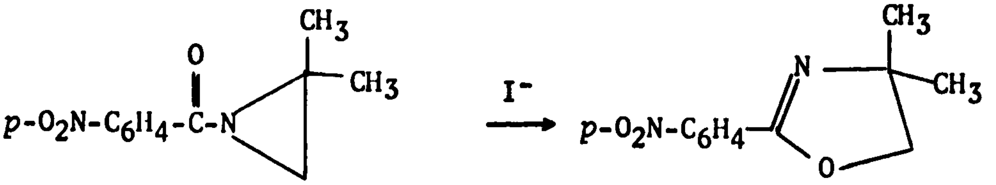

C_6H_5
CH_2
N
H
C_6H_5
H
p-CH_3-C_6H_4-C
O
$(C_6H_5)_2II$
C_6H_5
CH_2
N
C_6H_5
H
p-CH_3-C_6H_4
O
$(C6H5)2II$
Δ
$CH_2C_6H_5$
N
H
C_6H_5
O
C_6H_4-p-CH_3
N
C_6H_5
O
C_6H_4-p-CH_3
N
p-CH_3-C_6H_4
O
C_6H_5

[17]

Nucleophile Catalyzed Isomerizations

The sensitivity of all activated aziridines to ring opening by nucleophiles has provided a useful synthetic pathway to a wide variety of five-membered heterocyclic ring compounds, especially the 2-oxazoline and 2-thiazoline systems. By this method, which was first observed in

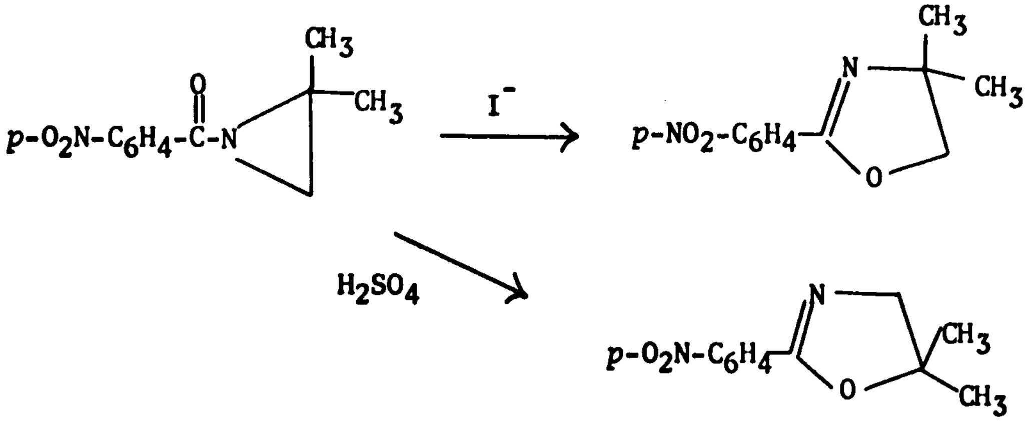
1959, 1-aroylaziridines are readily isomerized in high yields to 2-aryl-2-oxazolines in acetone solution containing sodium iodide or potassium thiocyanate[31,34] as shown in equation [18].

[18]


O
CH3
CH3
p-O2N-C6H4-C-N
I-
p-O2N-C6H4
N
CH3
CH3
O

93% Ref. 31.

It is of interest to compare the sole product of this reaction (equation [18]), with that of equation [14], where the same substrate was isomerized under acid catalysis. In the above case (equation [18]), the gem-dimethyl groups are attached at the 4-position, whereas in the acid catalyzed case (equation [14]) they are at the 5-position. This is due to mechanistic differences in the pathways of the reactions.



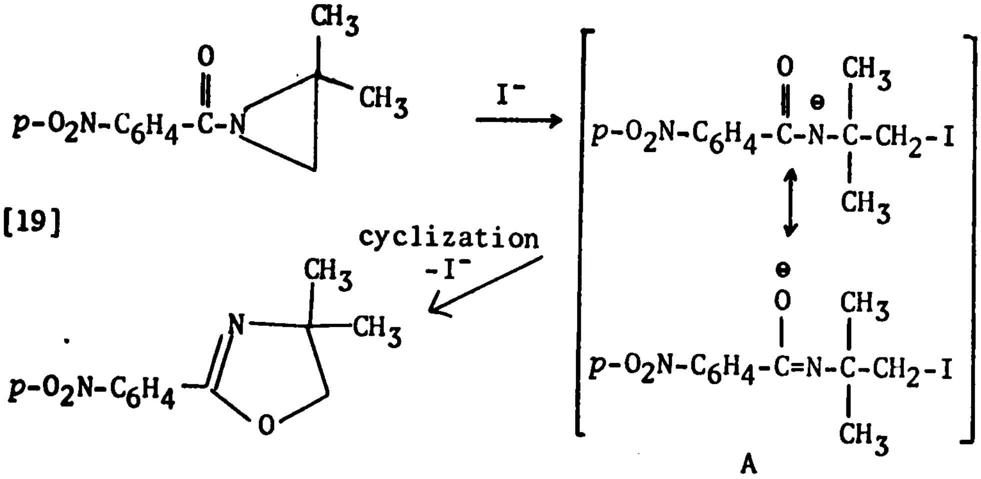
CH3
CH3
p-O2N-C6H4-C-N
O
I-
H2SO4
p-NO2-C6H4
N
O
CH3
CH3
p-O2N-C6H4
N
O
CH3
CH3

[18]

[14]

The actual mechanism by which these nucleophile catalyzed isomerizations proceed is still in doubt. The initial step has been envisionaged as either attack by the nucleophile on the carbonyl group or on one of the carbon atoms of the aziridine ring (the less hindered one if the ring bears substituents). The consensus of current opinion[35] seems to favour the latter pathway and the subsequent steps may proceed as in equation [19].

[19]

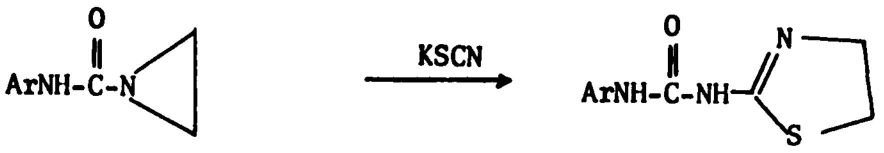


Cyclization of intermediate A with expulsion of the iodide ion would lead to the product 2-oxazoline. Since this reaction seems to involve addition and then elimination of the nucleophile, the latter must be of necessity a good leaving group, e.g., I^-, Br^-, $\bar{S}CN$, N_3^-.

The stereochemistry involved in these isomerizations is in accordance with the proposed mechanism for the reaction occurs, in the vast majority of cases, with overall retention (two inversions) of configuration. Where this is not the case, steric factors may be involved.[35]

An interesting exception to the nucleophile addition-elimination scheme occurs when 1-aziridine carboxanilides are treated with potassium thiocyanate instead of sodium iodide in acetone solution, for here 2-(3-arylureido)-2-thiazolines are obtained instead of the expected 2-oxazoline,[36] equation [20].

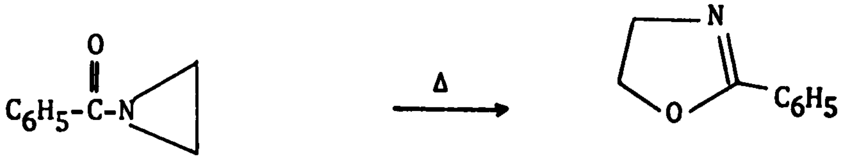
[20]



Thermal Isomerizations

The first reported thermal isomerization of 1-substituted aziridines occurred when Gabriel and Stelzner[28] observed that 1-benzoylaziridine isomerized to 2-phenyl-2-oxazoline upon distillation at 240°, equation [21].

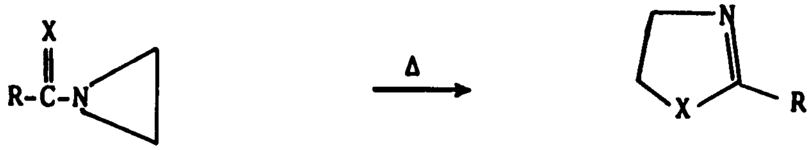
[21]



25%

Thermal isomerization of carbon-unsubstituted 1-acyl or 1-aroylaziridines is a fairly general route to 2-oxazolines.[37,38,39] Similarly, 2-amino- or 2-arylamino-2-thiazolines have been obtained from the corresponding aziridines.[40,41] The general situation is shown in equation [22].

[22]

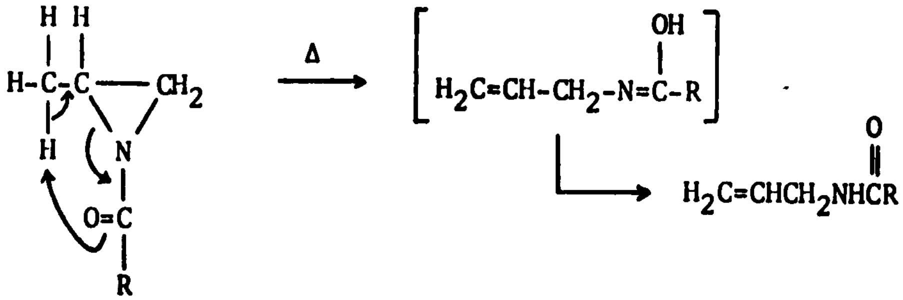


R = alkyl, aryl, OR, NR_2, NHR : X = O, S, NR.

It would appear that the two previous methods provide superior yields to the thermal method and also avoid the possibility of polymerization, which is reported to occur frequently in the latter procedure.[42]

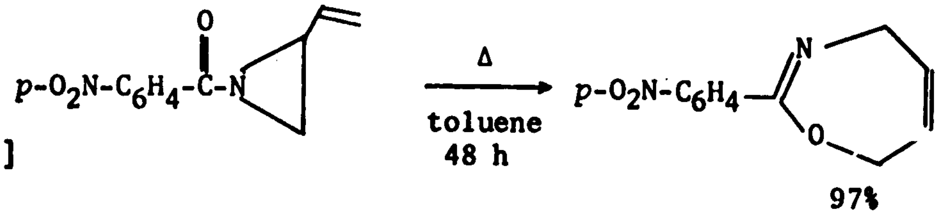
When the aziridine ring bears alkyl substituents at the 2- and 3-positions a different process occurs, leading to acyclic amides in good yields instead of heterocyclic compounds,[43,44,45] as illustrated by equation [23].

[23]



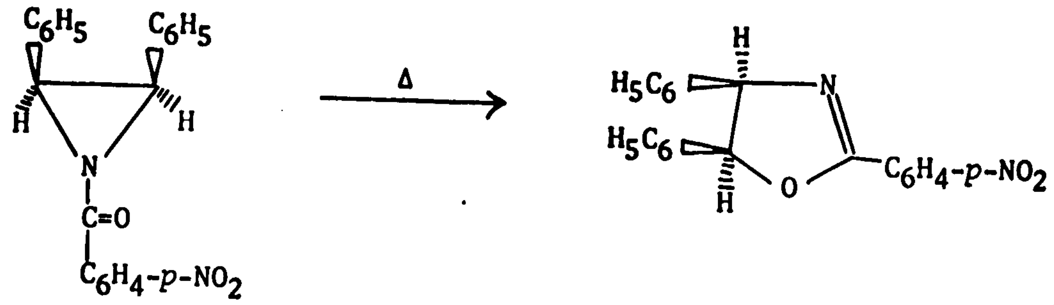
Another thermal pathway has recently been observed by Heine and coworkers[46] in an isomerization (equation [24]) which closely resembles that previously reported by Scheiner.[20]

[24]



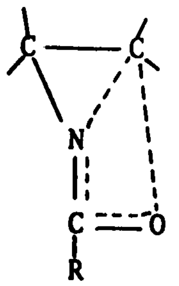
Despite a report to the contrary,[47] the thermal isomerization of 1-acylaziridines to 2-oxazolines has been found to be stereospecific,[48,49] and recent work has shown that isomerization of a *cis* or *trans*-2,3-diphenylaziridine derivative occurs with retention of configuration,[50] equation [25].

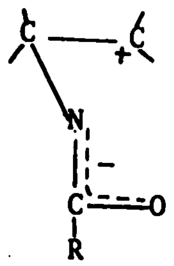
[25]



This result of Heine and Kaplan has mechanistic significance since the same reaction when catalyzed by iodide ion produces the *trans*-2-oxazoline.[51]

Mechanisms for these thermal isomerizations have been proposed by Heine, and by Fanta, and involve either a four-center transition state,[23,50] or an intermediate tight ion pair.[48,50]



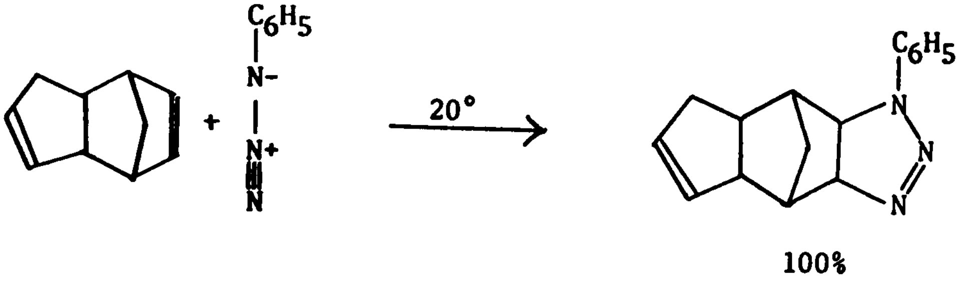


In concluding this section on isomerization reactions of substituted aziridines leading to five-membered heterocyclic ring compounds, it may be said that for preparative purposes the acid, and nucleophile catalyzed methods hold distinct advantages over the thermal technique in that the yields are superior, the reaction conditions are less severe, especially in the nucleophile catalyzed case, and in instances where the aziridine ring bears alkyl or vinyl substituents on the 2- or 3-positions, the former pair are the only possible methods available.

CYCLOADDITION METHODS

In this thesis, a cycloaddition will be defined as the combination of two molecular groupings with respectively, m and n atoms, to form a ring system of [m+n] members.[52] In these cases the reactants unite to form the cyclic compound by creating two new σ bonds at the expense of two π bonds. Furthermore the cycloaddition concept is employed where the new σ bonds are formed simultaneously as well as where new bond formation is not synchronous. An illustrative example would be the quantitative [2+3] cycloaddition of phenyl azide and dicyclopentadiene as shown in equation [26].[53]

[26]



In accordance with the above definition, cycloaddition reactions can be classified according to the number of ring atoms contributed by each of the reactants and a variety of classes have now been experimentally verified. Of these the [2+2], [2+3], and [2+4] classes form the most important groups. Examples of classes of lesser importance are given in the review by Woodward and Hoffmann.[54]

Since this thesis is concerned with the study of certain five-membered heterocycles, only [2+3] cycloaddition reactions will be discussed here. Reviews of the [2+2] class,[54,55,56] and the [2+4] class,[56,57,58] are to be found in the literature.

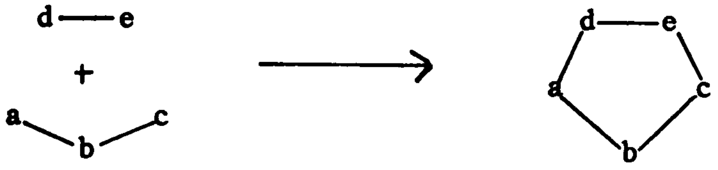
For these cycloaddition reactions leading to five-membered heterocyclic ring systems, two interchangeable titles are commonly used in the current literature: -

1) [2+3] Cycloaddition reactions, 2) 1,3-Dipolar Cycloaddition reactions.

The former specifies the number of atoms in the combining moieties in a clear and concise manner and implies the exact size of the ring being formed, i.e., 2+3 → 5.

The latter name is due to Huisgen, whose researches produced an understanding of the generality, scope, and mechanism of these reactions. His formulation is useful in predicting the overall result of a reaction, but the name itself needs care in interpretation, as will be explained later.

In general throughout this thesis reactions of the type shown,



will be referred to as [2+3] cycloadditions, though where it is appropriate, Huisgen's terminology will be adopted.

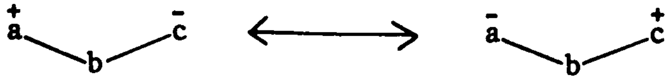
As becomes evident when the synthetic approaches to five-membered ring heterocycles are examined, there are few general methods available, though there are an abundance of special methods to specific types of compounds. This is particularly true of cases where the ring contains more than one hetero atom. One of the most attractive features of [2+3] cycloaddition reactions, is the extremely wide variety of heterocyclic compounds that become available by this method.

[2+3] Cycloaddition reactions have been known for some seventy years among the first of which, was the synthesis of triazoles by Michael[59] who added organic azides to acetylenes. The first comprehensive review on the subject[60] appeared in 1938, and covered mainly the chemistry of azides, aliphatic diazo compounds, nitrones and nitrile oxides. Although Smith[60] recognized that these systems were capable of undergoing 1,3-additions, he did not clearly separate the cycloaddition reactions from other ones, especially from the additions of bases to the reactants. Perhaps for this reason, Smith's review attracted little attention as judged by the scarcity of publications in this field between 1938 and 1958.

In 1957 Huisgen and his school commenced their work on [2+3] cycloaddition reactions, by investigating the mechanism of the addition of diazoalkanes to angularly strained double bond systems. Over the next three years sufficient progress was made to permit recognition of a general reaction scheme, and to allow new classes of triatomic 1,3-dipoles to be predicted, and experimentally verified in new reactions.[61]

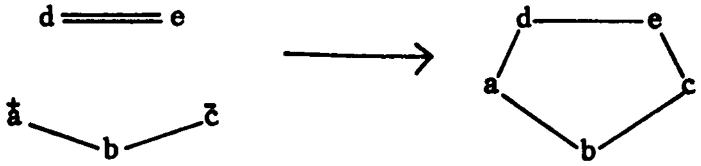
It is convenient at this point to define and classify the known 1,3-dipoles, and to introduce some terminology associated with [2+3] cycloaddition reactions.

Huisgen has stated that [2+3] cycloaddition reactions leading to uncharged five-membered ring compounds cannot occur with octet stabilized reactants which possess no formal charge.[62] It is therefore necessary to define a triatomic system a-b-c,such that atom a possesses an incomplete valence shell and a positive formal charge, (a has an electron sextet) and that atom c has an unshared electron pair and thus a formal negative charge. Such a species is called a 1,3-dipole and can be represented as shown.



It is important to realize that these zwitterionic structures are ambivalent in the 1- and 3-positions, and Huisgen has emphasized that it is not meaningful to assign electrophilic and nucleophilic centers in the 1,3-dipole. When however atoms a and c bear electron donating and electron releasing substituents, this becomes a debatable point about which more will be said in later sections of this thesis. When such a 1,3-dipole combines with any double (or triple) bond system, d=e, known as the dipolarophile, to yield an uncharged five-membered ring, the reaction is known as a [2+3] cycloaddition as shown in equation [27].

[27]



Compounds containing an electron sextet at a carbon, nitrogen or oxygen atom tend to be unstable.[62] This difficulty can be overcome if the central atom b, contains an unshared electron pair that can assist atom a to complete its octet. This will leave atom b with a positive charge in creating a new resonance structure in which all the atoms a, b, c have complete octets of electrons. Such systems are known as

1,3-dipoles with internal octet stabilization, and the earliest known and most stable 1,3-dipoles possess this system.

$$\overset{+}{a}=\underset{\cdot\cdot}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow a\equiv\overset{+}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \qquad b=N$$

$$\overset{+}{a}-\underset{\cdot\cdot}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow a=\overset{+}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \qquad b=NR,\ O.$$

Sextet Form Octet Form

The vast majority of 1,3-dipoles that have been studied can be classified into three groups, depending on whether or not the central atom b possesses an unshared electron pair, and if there is a double bond between atoms a and b in the sextet formula.

Group A comprise 1,3-dipoles possessing both a double bond and an unshared electron pair on the central atom in the 1,3-dipolar (sextet) form.

$$\overset{+}{a}=\underset{\cdot\cdot}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow a\equiv\overset{+}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow \underset{\cdot\cdot}{\overset{-}{a}}-\underset{\cdot\cdot}{b}=\overset{+}{c}$$

In this group, atoms a and c may represent carbon, nitrogen and oxygen, but the central atom b must be nitrogen since no other atom in the first row of the periodic table possesses an unshared electron pair while remaining in the triply bonded neutral state. The 1,3-dipolar systems in group A are shown in Table I.[63a]

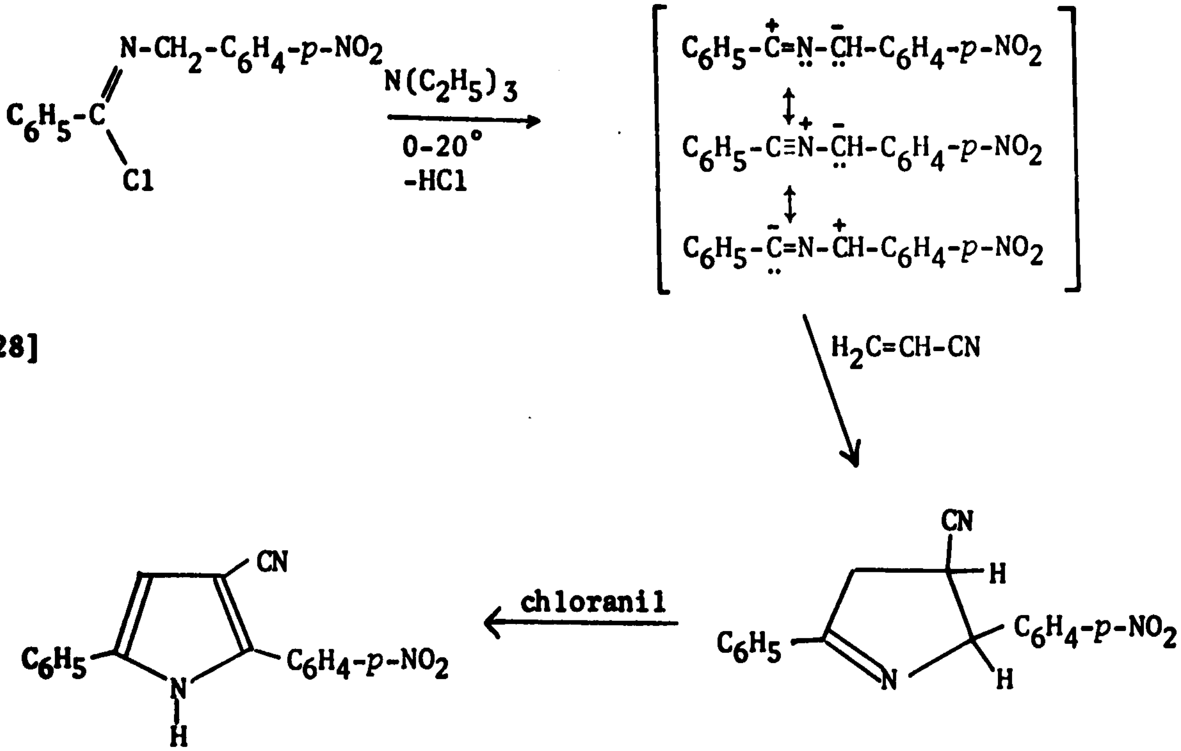
TABLE I

Group A: $\overset{+}{a}{=}\underset{\cdot\cdot}{b}{-}\overset{-}{\underset{\cdot\cdot}{c}} \longleftrightarrow a{\equiv}\overset{+}{b}{-}\overset{-}{\underset{\cdot\cdot}{c}}$

Atom System	1,3-Dipolar Form	Octet Form	Class Name
C-N-C	$-\overset{+}{C}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{C}}<$	$-C{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{C}}<$	Nitrile ylide
C-N-N	$-\overset{+}{C}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{N}}}-$	$-C{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{N}}}-$	Nitrile imine
C-N-O	$-\overset{+}{C}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{O}}}:$	$-C{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{O}}}:$	Nitrile oxide
N-N-C	$:\overset{+}{N}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{C}}<$	$:N{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{C}}<$	Diazoalkane
N-N-N	$:\overset{+}{N}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{N}}}-$	$:N{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{N}}}-$	Azide
N-N-O	$:\overset{+}{N}{=}\underset{\cdot\cdot}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{O}}}:$	$:N{\equiv}\overset{+}{N}{-}\overset{-}{\underset{\cdot\cdot}{\ddot{O}}}:$	Nitrous oxide

The synthetic utility of some 1,3-dipoles from this group in [2+3] cycloaddition reactions is illustrated by the following selected examples from the literature, equations [28], [29]. As may be observed, the 1,3-dipoles themselves are mostly generated *in situ*, although some are capable of being isolated.

Nitrile ylide

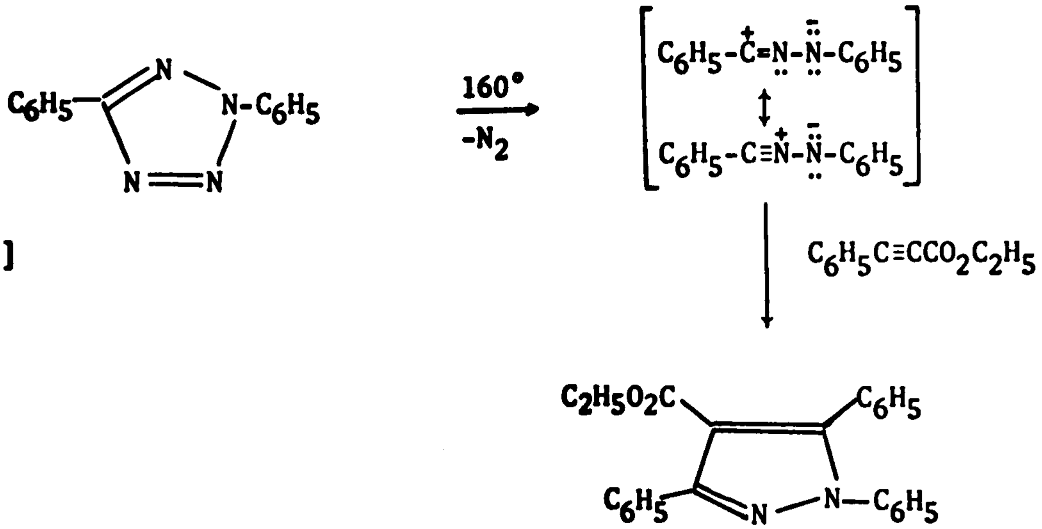


N-CH2-C6H4-p-NO2
C6H5-C
Cl
N(C2H5)3
0-20°
-HCl
C6H5-C=N-CH-C6H4-p-NO2
C6H5-C≡N-CH-C6H4-p-NO2
C6H5-C=N-CH-C6H4-p-NO2
H2C=CH-CN
CN
H
C6H5
N
H
C6H4-p-NO2
chloranil
CN
C6H5
N
H
C6H4-p-NO2

[28]

Isomeric, 86%   Ref. 64.

Nitrile imine



C6H5
N
N-C6H5
N
N
160°
-N2
C6H5-C=N-N-C6H5
C6H5-C≡N-N-C6H5
C6H5C≡CCO2C2H5
C2H5O2C
C6H5
C6H5
N
N-C6H5

[29]

84%   Ref. 65.

Group B comprise 1,3-dipoles possessing an unshared electron pair on the central atom b, but no double bond in the 1,3-dipolar form.

$$\overset{+}{a}-\underset{\cdot\cdot}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow a=\overset{+}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow \underset{\cdot\cdot}{\overset{-}{a}}-\underset{\cdot\cdot}{b}-\overset{+}{c}$$

Since there is no double bond in the 1,3-dipolar form, both nitrogen and oxygen may now serve as the central atom,and consequently group B is larger in number than group A. Atoms a and c may again represent carbon, nitrogen and oxygen, as the first row of the periodic table forms the framework of the group. Although most of these 1,3-dipoles have been successfully employed in cycloaddition reactions, there are some systems that have yet to be experimentally verified and they appear in Table II denoted by an asterisk.[63b]

TABLE II

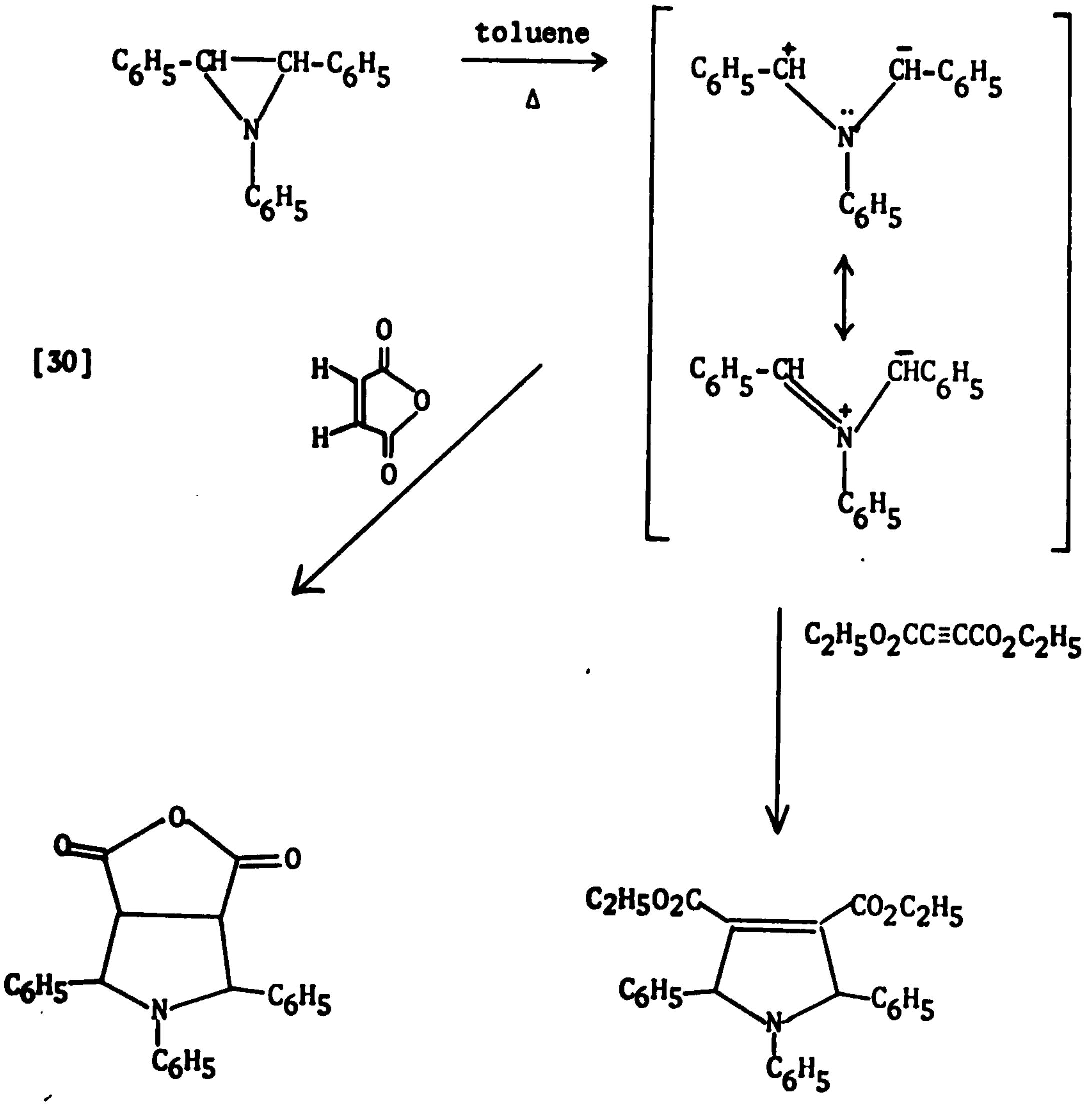
Group B: $\overset{+}{a}-\underset{..}{b}-\underset{..}{\overset{-}{c}} \leftrightarrow a{=}\overset{+}{b}-\underset{..}{\overset{-}{c}}$

Atom System	1,3-Dipolar Form	Octet Form	Class Name
C-N-C	$>\overset{+}{C}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{-}{C}}<$	$>C{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{-}{C}}<$	Azomethine ylide
C-N-N	$>\overset{+}{C}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	$>C{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	Azomethine imine
C-N-O	$>\overset{+}{C}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$>C{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Nitrone
N-N-N	$-\underset{..}{\overset{+}{N}}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	$-\underset{..}{N}{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	Azimines*
N-N-O	$-\underset{..}{\overset{+}{N}}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$-\underset{..}{N}{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Azoxy
O-N-O	$:\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$:\underset{..}{O}{=}\overset{+}{\underset{\vert}{N}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Nitro
C-O-C	$>\overset{+}{C}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{-}{C}}<$	$>C{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{-}{C}}<$	Carbonyl ylide
C-O-N	$>\overset{+}{C}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	$>C{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	Carbonyl imine*
C-O-O	$>\overset{+}{C}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$>C{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Carbonyl oxide
N-O-N	$-\underset{..}{\overset{+}{N}}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	$-\underset{..}{N}{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\overset{-}{..}}{N}}-$	Nitrosimine*
N-O-O	$-\underset{..}{\overset{+}{N}}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$-\underset{..}{N}{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Nitroso oxide*
O-O-O	$:\underset{..}{\overset{+}{O}}-\underset{..}{\overset{..}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	$:\underset{..}{O}{=}\underset{..}{\overset{+}{O}}-\underset{..}{\overset{\overset{-}{..}}{O}}:$	Ozone

Illustrative [2+3] cycloaddition reactions that are representative of the 1,3-dipoles of group B are shown in equations [30], [31]. Once again the majority of these species are generated *in situ*.

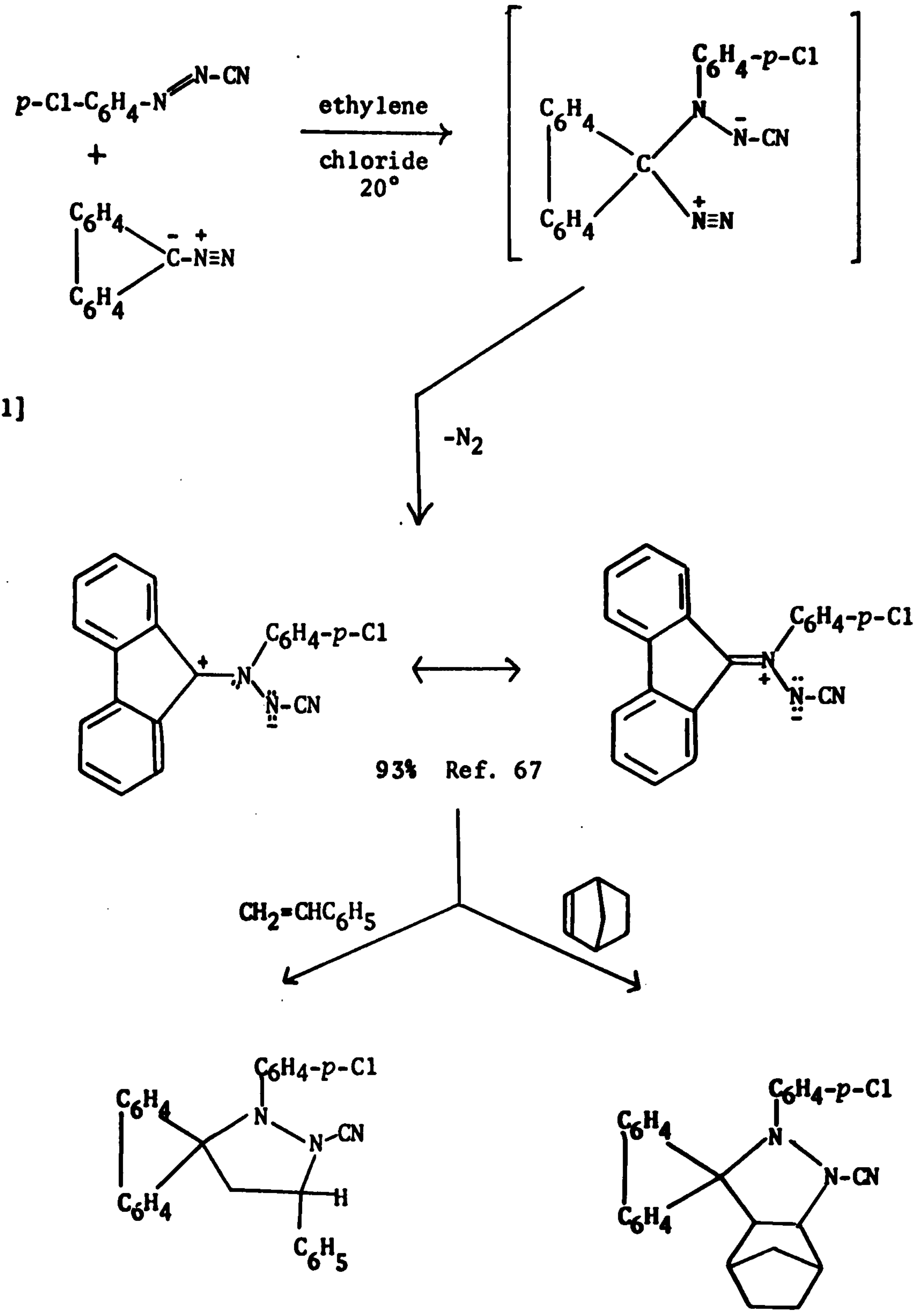
Azomethine ylide

[30]


C_6H_5-CH—CH-C_6H_5
N
C_6H_5
toluene
Δ
C_6H_5-$\overset{+}{C}H$
$\overset{-}{C}H$-C_6H_5
N
C_6H_5
C_6H_5-CH
$\overset{-}{C}HC_6H_5$
$\overset{+}{N}$
C_6H_5
H
H
O
O
O
$C_2H_5O_2CC{\equiv}CCO_2C_2H_5$
O
O
O
C_6H_5
N
C_6H_5
C_6H_5
$C_2H_5O_2C$
$CO_2C_2H_5$
C_6H_5
N
C_6H_5
C_6H_5

94% Ref. 66 98%

Azomethine imines


p-Cl-C6H4-N=N-CN
+
ethylene
chloride
20°
-N2
93% Ref. 67
CH2=CHC6H5
C6H4-p-Cl
N-CN
C6H5

[31]

92% **Ref. 67.** **79%**

All of the 1,3-dipoles thus far considered (groups A and B) have one common feature, namely internal octet stabilization, and even within group B, not all of them have been experimentally verified. The abandoning of this feature of internal octet stabilization leads to the third major group of 1,3-dipoles.

Group C comprising 1,3-dipoles without an electron pair on the central atom but containing a double bond.

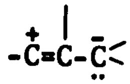
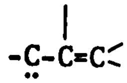
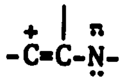
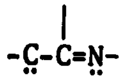
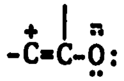
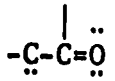
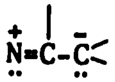
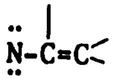
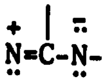
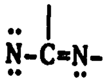
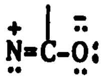
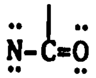
$$\overset{+}{a}{=}b{-}\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow \underset{\cdot\cdot}{a}{-}b{=}c$$

Working again within the bounds of the first row of the periodic table, the 1,3-dipoles of group C all contain an unsaturated (sp^2 hybridized) carbon atom as the central atom and thus no internal octet stabilization is permitted. Atoms a and c may represent carbon, nitrogen and oxygen. As will be shown later, this group bears a somewhat dubious relationship to groups A and B.

These 1,3-dipoles of group C are particularly difficult to study owing to their short lifetimes and high reactivity. They must therefore be generated *in situ* and trapped by reactive dipolarophiles, and many successful [2+3] cycloaddition reactions have been reported with certain members of the group. This class is especially relevant to this thesis, since Chapter IV contains examples of externally stabilized ketocarbenes which were encountered in the course of the research. Table III[63c] contains the 1,3-dipoles of group C which, since they are the least studied, may provide a fruitful area for future research.

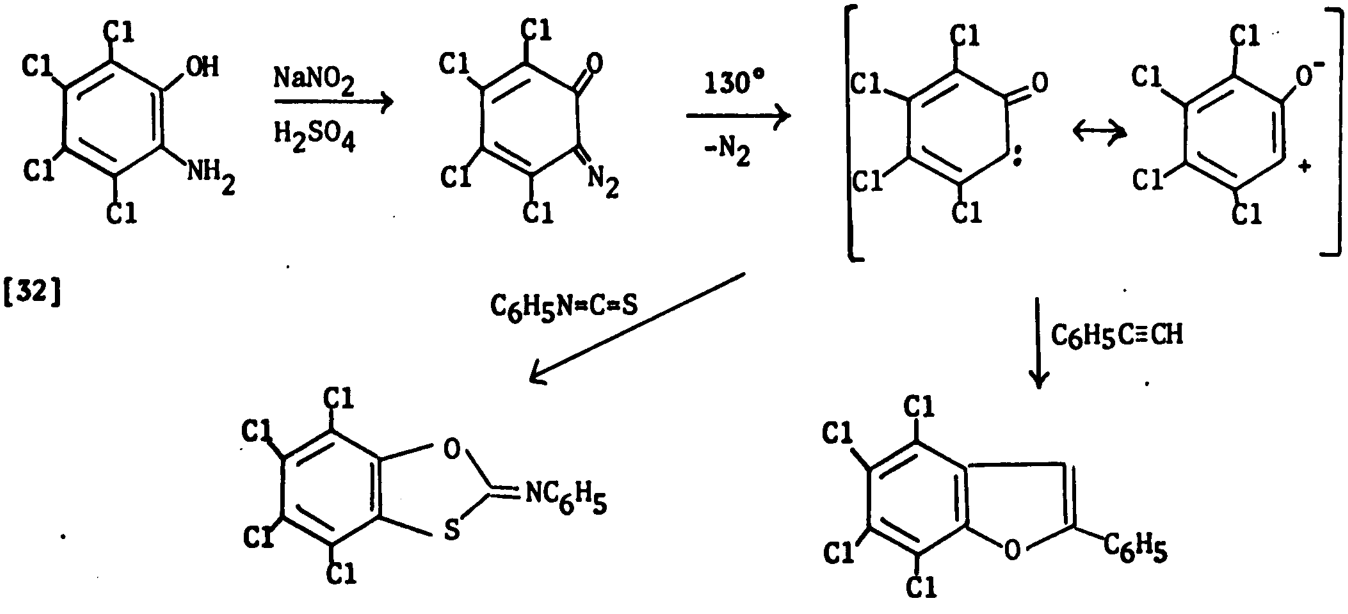
TABLE III

Group C: $\overset{+}{a}=b-\underset{\cdot\cdot}{\overset{-}{c}} \leftrightarrow \underset{\cdot\cdot}{a}-b=c$

Atom System	1,3-Dipolar Form	Alternate Form	Class Name
C-C-C	 $-\overset{+}{C}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{-}{C}}<$	 $-\underset{\cdot\cdot}{C}-\overset{\vert}{C}=C<$	Vinylcarbene
C-C-N	 $-\overset{+}{C}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{\bar{\cdot\cdot}}{N}}-$	 $-\underset{\cdot\cdot}{C}-\overset{\vert}{C}=\underset{\cdot\cdot}{N}-$	Iminocarbene
C-C-O	 $-\overset{+}{C}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{\bar{\cdot\cdot}}{O}}:$	 $-\underset{\cdot\cdot}{C}-\overset{\vert}{C}=\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}$	Ketocarbene
N-C-C	 $\underset{\cdot\cdot}{\overset{+}{N}}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{-}{C}}<$	 $\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}-\overset{\vert}{C}=C<$	Vinylnitrene
N-C-N	 $\underset{\cdot\cdot}{\overset{+}{N}}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{\bar{\cdot\cdot}}{N}}-$	 $\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}-\overset{\vert}{C}=\underset{\cdot\cdot}{N}-$	Iminonitrene
N-C-O	 $\underset{\cdot\cdot}{\overset{+}{N}}=\overset{\vert}{C}-\underset{\cdot\cdot}{\overset{\bar{\cdot\cdot}}{O}}:$	 $\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}-\overset{\vert}{C}=\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}$	Ketonitrene

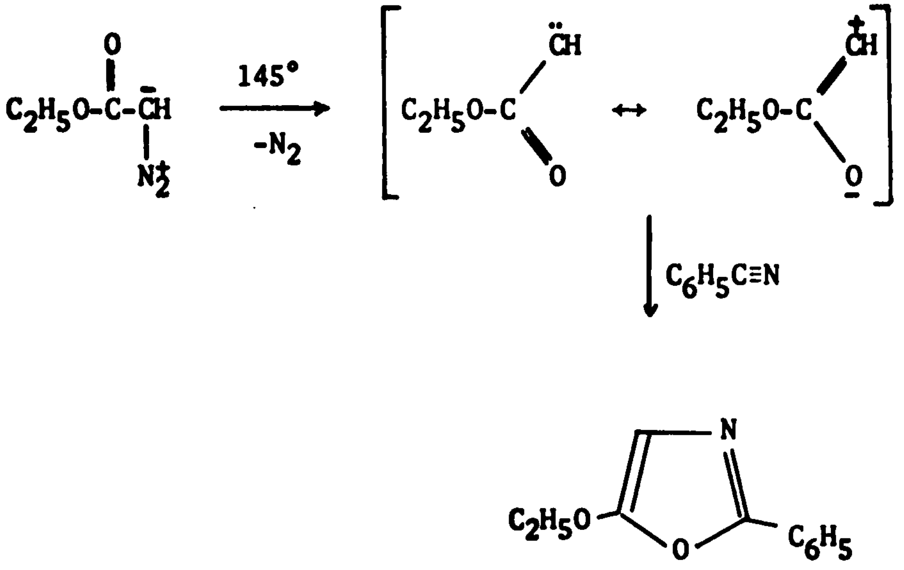
Most of the published cycloaddition reactions involving group C 1,3-dipoles has concerned the ketocarbene and ketonitrene systems, and thus it is from these classes that the representative reactions will be taken, equations [32], [33], [34].

Ketocarbenes


NaNO$_2$
H$_2$SO$_4$
130°
-N$_2$
C$_6$H$_5$N=C=S
C$_6$H$_5$C≡CH
Cl
OH
NH$_2$
O
N$_2$
O$^-$
+
S
NC$_6$H$_5$
C$_6$H$_5$

[32]

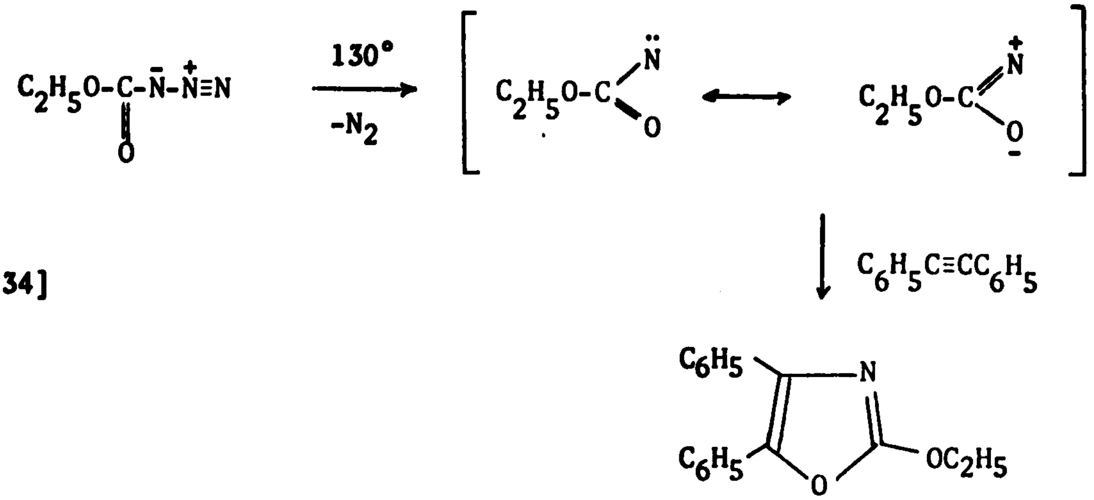
46%   Ref. 68   39%


145°
-N$_2$
C$_6$H$_5$C≡N
C$_2$H$_5$O-C-CH
N$_2^+$
O
N
C$_2$H$_5$O
C$_6$H$_5$

[33]

42% Ref. 69

Ketonitrene

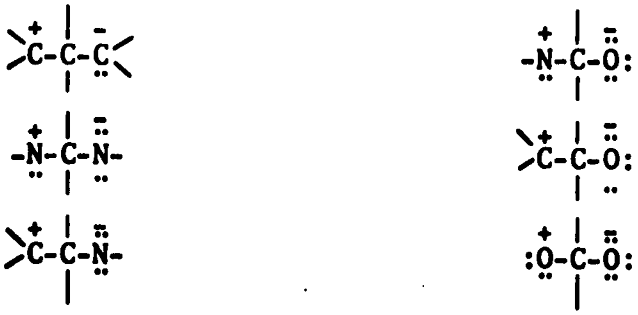


[34]

33% Ref. 70.

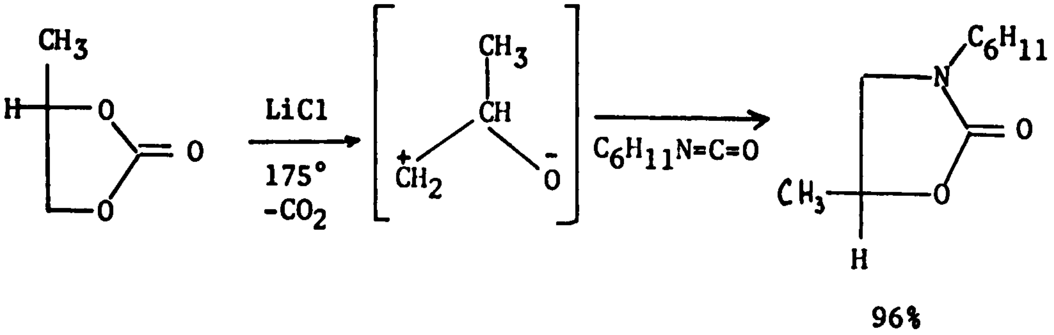
While groups A, B, and C constitute by far the majority of 1,3-dipoles studied to date, many others can be visualized, especially if elements of further rows of the periodic table are taken into consideration, (e.g., S,P) and Huisgen has already made advances in this region with his work on thioketocarbenes.[71]

We could also consider systems devoid of internal octet stabilization which possess a saturated carbon atom at the central position b. These would formally constitute a subclass of group C and may be grouped as follows: -



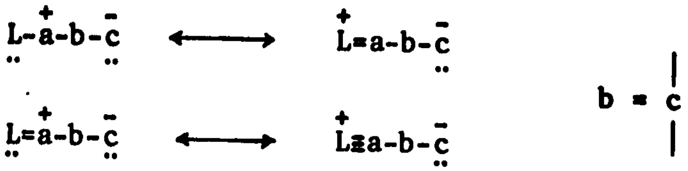
Here it is impossible to exchange the charges in such systems due to the insulating effect of the sp^3 hybridized central carbon atom. Such 1,3-dipolar species could occur as short-lived intermediates, and five-membered ring compounds from such species have been obtained,[72] as shown in equation [35].

[35]



As can be seen the variety of [2+3] cycloaddition reactions forces recognition of the potential "1,3-dipolar character" of any suitable substrate, and while the general presentation by Huisgen[62] seems valid, each case should be examined on its own merits as regards the reacting species, especially in the group C 1,3-dipoles and the subclass with the tetrahedral carbon atom at the central position. Cautionary remarks on this point have appeared in the literature by Baldwin[73] and Overberger.[74]

It has previously been mentioned that if the central atom b, of the 1,3-dipole is carbon, then internal octet stabilization of the species is impossible. Huisgen has postulated however, that if there is a ligand, L, which possesses a free electron pair, attached to atom a, this 1,3-dipole may be stabilized by external octet stabilization.[75]

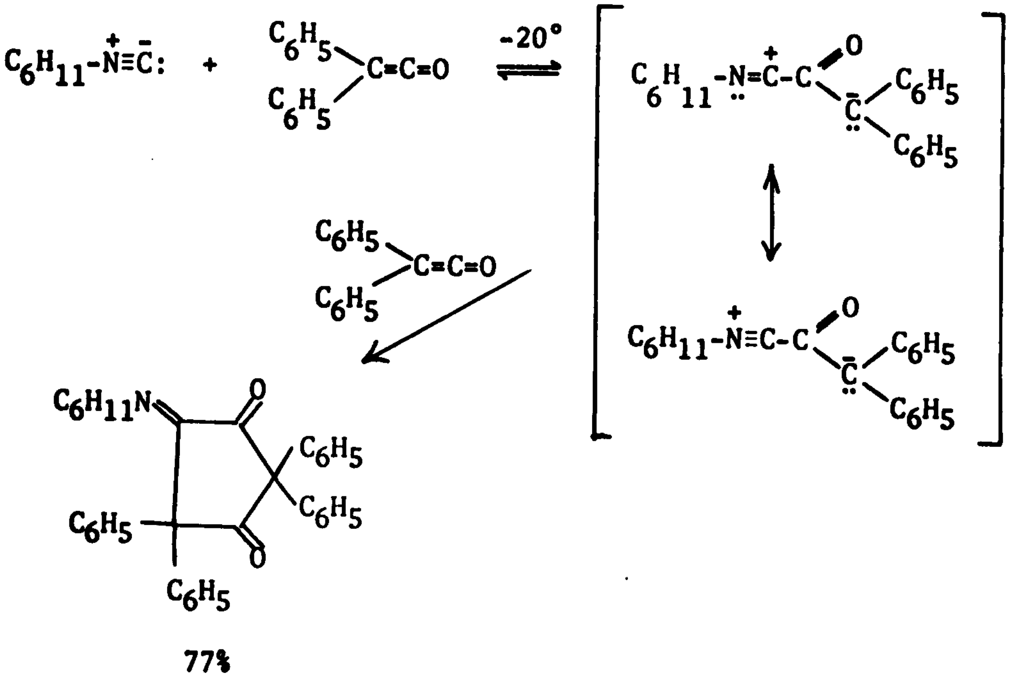


$$\underset{\cdot\cdot}{L}-\overset{+}{a}-b-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow \overset{+}{L}=a-b-\underset{\cdot\cdot}{\overset{-}{c}}$$

$$\underset{\cdot\cdot}{L}=\overset{+}{a}-b-\underset{\cdot\cdot}{\overset{-}{c}} \longleftrightarrow \overset{+}{L}\equiv a-b-\underset{\cdot\cdot}{\overset{-}{c}} \qquad b = \overset{|}{\underset{|}{C}}$$

This postulate has been experimentally verified by Ugi and Rosendahl,[76] equation [36].

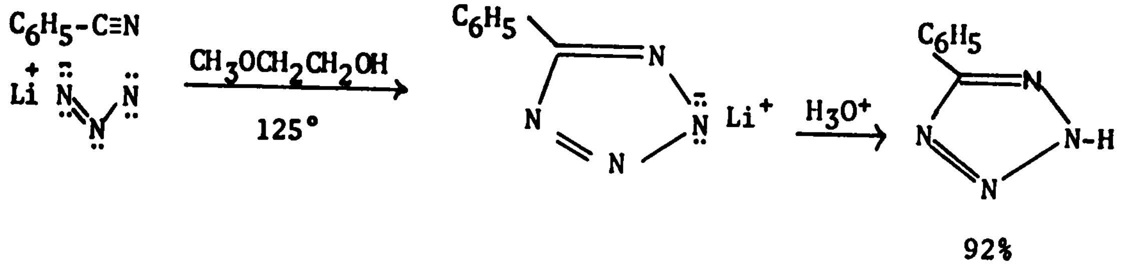
[36]



This topic of external octet stabilization will be considered in greater detail in Chapter IV of this thesis.

In all previous examples of [2+3] cycloadditions the five-membered ring produced was uncharged. A few variations from this scheme are observed in the reactions of anionic 1,3-dipoles with certain dipolarophiles where a charged product is obtained,[77] equation [37].

[37]



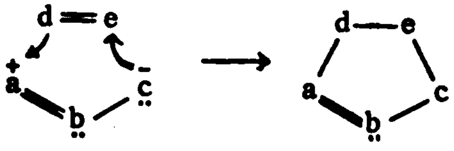
The charged ring product would be expected to benefit from the resonance stabilization of the tetrazole anion.

Having defined and classified 1,3-dipoles, and illustrated their synthetic utility in [2+3] cycloaddition reactions by selected examples, the available evidence for a mechanism of such reactions will next be examined, for although the concept of "cycloaddition" provides a formal description of an overall process, it does not present a mechanistic interpretation.

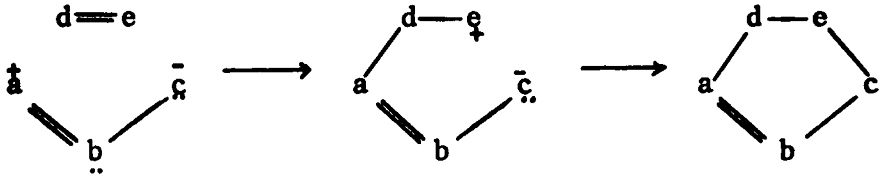
The mechanistic discussions in the literature tend to be confined to 1,3-dipoles with internal octet stabilization, (groups A and B), for those of group C present problems for a mechanistic study due to their very short lifetimes and high reactivities.

The following mechanisms have been proposed for [2+3] cycloaddition reactions.

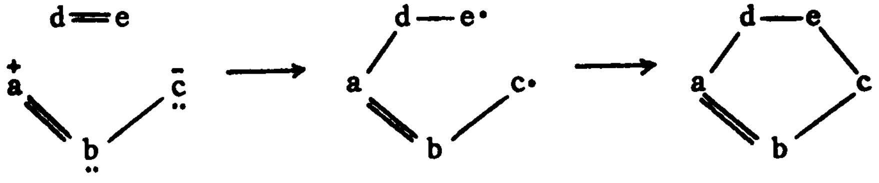
1) A multi-center or concerted reaction, with a cyclic electron shift as proposed by Huisgen.[62]



II) A two-step process in which the two new σ bonds are formed one after the other, and which involves a dipolar intermediate.[62]



III) A two-step mechanism involving a spin-paired diradical intermediate as proposed by Firestone.[78]

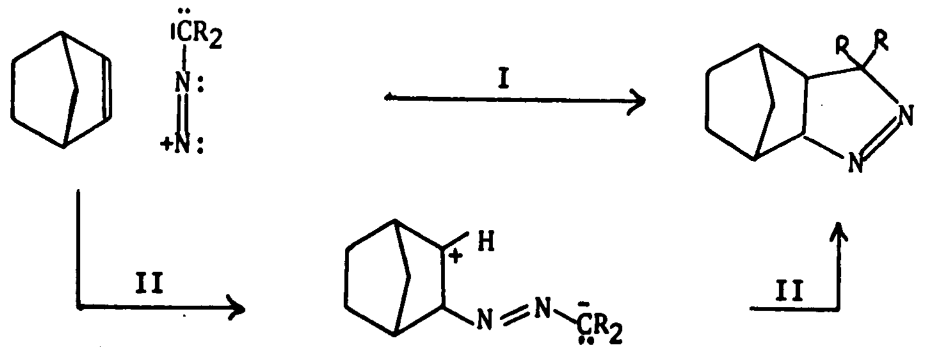


For the majority of [2+3] cycloadditions, the weight of experimental evidence favours the first mechanism in that it presents a strong case against the other two. It is fair to mention however that the concerted nature of the cycloaddition, even for 1,3-dipoles of Tables I and II, has not been definitely established in all cases and each case should be examined in its own right.

Any mechanism formulated for a [2+3] cycloaddition reaction must account not only for the reaction product, but also for the following phenomena: - a) activation parameters, b) the effect of solvent and substituents on the rate constant, c) the selectivity observed with *cis-trans* isomeric dipolarophiles, d) orientation phenomena.

Huisgen has stated that the energy profile for the [2+3] cycloadditions studied by his group contain a single activation peak and has used the [2+3] cycloaddition reaction of a diazoalkane with the angularly strained, electron rich, bicycloheptene to compare the concerted mechanism I with the two-step process II,[79] equation [38].

[38]



In the accompanying energy profile the dip corresponds to the intermediate in the two-step process.

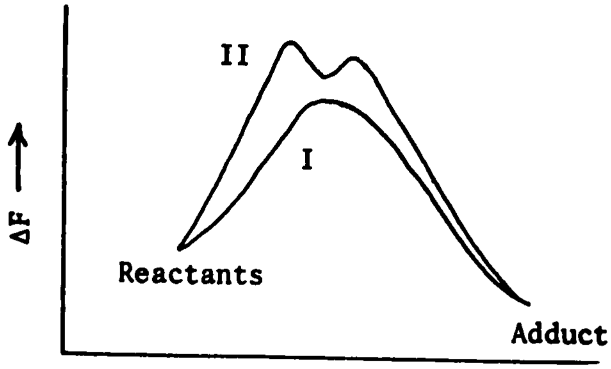
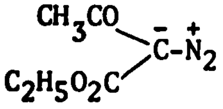


Figure I Reaction coordinate →

It has also been shown[79] (see Table IV), that the order of reactivity of substituted diazomethanes in cycloaddition reactions with model dipolarophiles is opposite to that expected for reaction path II.

TABLE IV

Rates of Addition of Diazoalkanes on to Angularly Strained Double Bond Systems*

Diazoalkane	Relative Rate of Addition
$H_2\overset{-}{C}\text{-}\overset{+}{N}_2$, $(C_6H_5)_2\overset{-}{C}\text{-}\overset{+}{N}_2$	rapid
$C_2H_5O_2C\text{-}\overset{-}{C}H\text{-}\overset{+}{N}_2$	rather slow
$C_6H_5CO\overset{-}{C}H\text{-}\overset{+}{N}_2$	slow
$p\text{-}O_2N\text{-}C_6H_4CO\overset{-}{C}H\text{-}\overset{+}{N}_2$	very slow
 $(CH_3CO)(C_2H_5O_2C)\overset{-}{C}\text{-}\overset{+}{N}_2$	no addition

*e.g. Norbornadiene

A characteristic of multi-center reactions is that they possess a high degree of order in the transition state. Thus in [2+3] cycloadditions, the reactants would be expected to be precisely aligned with respect to each other and exhibit large negative entropies of activation and moderate enthalpy requirements. That this is the case for [2+3] cycloaddition reactions in general,[80] is evidence for a concerted mechanism for most reactions.

Huisgen has also presented activation energy calculations and chemical evidence[81] to refute the diradical mechanism as proposed by

Firestone.[78]

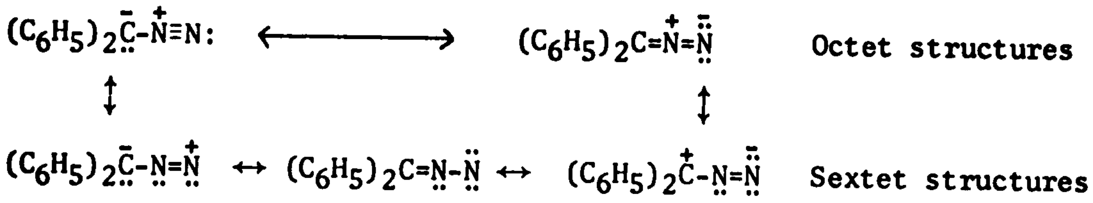
It would be expected that dependence of the rate of the reaction on the solvent would prove a rigorous test for the proposed mechanisms, especially the second one, in which the zwitterionic intermediate should be facilitated by solvents of high polarity. Conversely, for the concerted mechanism, the nature of the solvent should have little effect on the reaction rate, with the proviso that the components form a homogeneous solution. The results of kinetic studies performed by Huisgen show that [2+3] cycloaddition reactions are only moderately influenced by solvent polarity.[79,82] Indeed it was often found that spreads of rate constants by a factor of no less than 1/6, and no more than 10, were found as the polarity of the solvent was increased. This must indicate that the charge separation in the reactants and in the transition state must be similar. Table V illustrates the small variation in the rate constant for the [2+3] cycloaddition of diphenyldiazomethane and dimethyl fumarate at 40°C in various solvents.[80]

TABLE V

Solvent	Reaction Rate ($k \times 10^2$)
Benzene	1.44
Dioxane	1.15
Ethyl acetate	1.25
Acetone	1.10
Acetonitrile	2.63
Dimethylformamide	2.45

Even cycloadditions of 1,3-dipoles whose dipole moment exceeded 5D were only moderately retarded as the solvent polarity increased.[79,81]

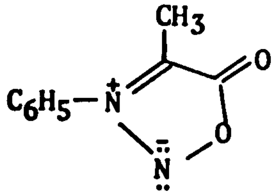
This evidence would tend to disfavour a two-step mechanism involving a zwitterionic intermediate for the vast majority of these reactions. In considering the effect of solvent on the rates of [2+3] cycloaddition reactions it should be realized that the term 1,3-dipole must not be misunderstood to imply a high dipole moment for the majority of the species. This can be illustrated by reference to diphenyldiazomethane.



$$(C_6H_5)_2\bar{C}-\overset{+}{N}\equiv N: \longleftrightarrow (C_6H_5)_2C=\overset{+}{N}=\overset{-}{N} \quad \text{Octet structures}$$

$$(C_6H_5)_2\bar{C}-N=\overset{+}{N} \leftrightarrow (C_6H_5)_2C=N-N \leftrightarrow (C_6H_5)_2\overset{+}{C}-N=\overset{-}{N} \quad \text{Sextet structures}$$

As can be seen there is charge compensation when all the structures (especially the octet structures) are considered,and this resonance effect reduces the dipole moment of diphenyldiazomethane to 1.42D from 6-7D,which is the value calculated for a single resonance structure.[79] There are admittedly some species that possess dipole moments that exceed 5D, a good example being the class of cyclic azomethine imines known as sydnones.[79]



$\mu = 6.57D$

Thus far little has been said about the nature of the dipolarophile (d=e), which is of considerable theoretical and practical interest, and whose study has contributed immensely to the understanding of [2+3] cycloaddition reactions. Huisgen has classified dipolarophiles in order of their relative reactivities with certain 1,3-dipolar systems.[79,83] The results show that though certain dipolarophiles always react faster than others with 1,3-dipolar systems in [2+3] cycloadditions, the actual ratios vary considerably depending on the particular 1,3-dipole utilized in the study. The relative rates are obtained by a competition technique in which pairs of dipolarophiles in a known molar ratio, are allowed to compete for the 1,3-dipolar species which is generated *in situ*. Table VI lists the relative rate constants for three dipolarophiles with four different 1,3-dipolar systems in [2+3] cycloaddition reactions.[79]

TABLE VI

1,3-Dipole	Temp.°C	Solvent	k_2(relative) for dipolarophile $H_2C{=}CH\text{-}R$		
			R = alkyl	C_6H_5	$CO_2Alk.$
$C_6H_5\text{-}C{\equiv}\overset{+}{N}\text{-}\bar{N}\text{-}C_6H_5$	80°	C_6H_6	0.30	3.2	100
$C_6H_5\text{-}C{\equiv}\overset{+}{N}\text{-}\bar{O}$	20°	$(C_2H_5)_2O$	3.9	14.0	100
$N{\equiv}\overset{+}{N}\text{-}\bar{C}(C_6H_5)_2$	40°	DMF	<0.01	0.2	100
$N{\equiv}\overset{+}{N}\text{-}\bar{N}\text{-}C_6H_5$	25°	CCl_4	2.4	4.1	100

Huisgen has also published a much more detailed study of relative rate constants for the [2+3] cycloaddition of one particular 1,3-dipole, diphenylnitrile imine, with various dipolarophiles in benzene at 80°, as shown in Table VII[83] (k_2 ethylcrotonate ≡ 1.00).

TABLE VII

Dipolarophile	k_2 (relative)
1-Heptene	0.137
Butadiene	1.4
Styrene	1.6
Ethyl acrylate	48.0
β,β-Dimethyl methyl acrylate	0.010
Ethyl crotonate	1.00
α-Chloromethyl acrylate	57.0
Dimethyl maleate	8.0
Fumaronitrile	112.0
Dimethyl fumarate	287.0
cis-Stilbene	0.010
trans-Stilbene	0.23
Acenaphthalene	1.0
Cyclohexene	0.015
Norbornene	3.12
Phenyl acetylene	0.12
Methyl Propiolate	5.8
Dimethylacetylene dicarboxylate	81.0
Benzaldehyde	0.052
Benzonitrile	0.0066

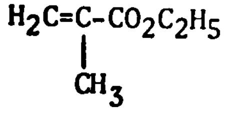
A study of Tables VI and VII reveals the marked increase in dipolarophilic activity when conjugation is introduced. Both electron-attracting and releasing substituents in conjugation with the olefinic double bond increase the effectiveness of the dipolarophile in [2+3] cycloaddition reactions. Nonconjugated olefins show the poorest reactivity and their relative rate constants are at times difficult to measure. Electron attracting nonconjugated substituents activate weakly, while the aromatic nucleus accelerates the rate from 1.5- to 20-fold. The most marked increase in activity occurs when there is a keto, ester, or nitrile function adjacent to the olefinic double bond, for here the rate constants increase over those of nonconjugated olefins by one to four orders of magnitude. Dimethyl fumarate is by far the most reactive dipolarophile and reacts in high yield with most 1,3-dipolar systems. Compared with olefins and substituted acetylenes, heteromultiple bonds tend to be relatively poor as dipolarophiles, though the -CH=N- system,[158] especially when suitably activated,has been shown to be an effective dipolarophile,as is the C=S double bond.[62]

The results of studies of [2+3] cycloaddition reactions using a variety of 1,3-dipoles has revealed that the dipolarophilic character of the C≡C triple bond is similar in magnitude to that of the C=C double bond.[84] A consequence of this surprising result is that reactions which produce aromatic rings do not proceed at a faster rate,and it would appear that the transition state in the [2+3] cycloaddition does not profit from the aromatic resonance of the ring produced. Acetylenic derivatives show similar substituent effects to their olefinic counterparts.

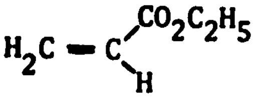
Huisgen has explained the promoting effect of conjugation on the dipolarophilic activity by two effects which may be related:[79,83] (1) the polarizability of the π bond of the dipolarophile is increased with conjugation. The bonding electrons tend to become more mobile when conjugation is present and thus the tendency to enter into cyclic electron shifts is increased; (2) relates from the postulate that concerted formation of the two new σ bonds is not necessarily synchronous. It is reasonable to assume that although the new σ bonds begin to form simultaneously, in the transition state they may not be developed to the same extent. This would lead to the development of partial charges, which could be stabilized by conjugation and thus lead to a reduction of the overall energy level.

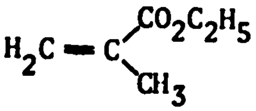
As can be observed from Table VII, steric factors are very important in determining the activity of a dipolarophile in [2+3] cycloaddition reactions. The addition of two methyl groups in the β-position of methyl acrylate renders the molecule even more sluggish than 1-heptene in the cycloaddition reaction with diphenylnitrile imine. Table VIII illustrates the influence of the position of methyl substituents on the rate constants for the [2+3] cycloaddition reactions of various 1,3-dipoles with ethyl acrylate.[79]

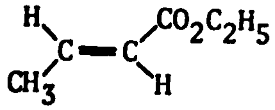
TABLE VIII

	Relative k_2 values based on k_2 for ethyl acrylate = 100	
1,3-Dipole	 $H_2C=C(CH_3)-CO_2C_2H_5$	$CH_3CH=CHCO_2C_2H_5$
$C_6H_5C\equiv\overset{+}{N}-\overset{-}{N}-C_6H_5$	34.0	2.1
$C_6H_5C\equiv\overset{+}{N}-\overset{-}{O}$	48.0	1.52
$(C_6H_5)_2\overset{-}{C}-\overset{+}{N}\equiv N$	7.2	0.35
$C_6H_5\overset{-}{N}-\overset{+}{N}\equiv N$	7.4	2.6

It is easily seen that methyl groups in the α-position cause less steric hindrance than those on the β-position,and this appears to be a general phenomenon in [2+3] cycloaddition reactions. Huisgen has stated that the steric effect of methyl groups on the activity of the dipolarophile is much more important than any polar effect that the methyl groups may exert. Increasing the number of substituent groups, as expected, significantly retards the reaction rate as shown in the following scheme for the reaction of C-phenyl-N-methylnitrone with methylated ethyl acrylate.[79]

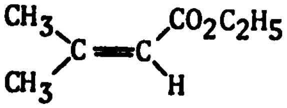


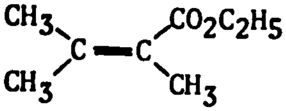




k_2 4300 1290 360

[1/mole/sec]





27 1.0

Examination of Table VII reveals that *trans*-stilbene reacts twenty-three times faster than *cis*-stilbene in [2+3] cycloaddition reactions with diphenylnitrile imine. The difference in reactivity between dimethyl fumarate and dimethyl maleate with the same 1,3-dipole is even greater. This greater reactivity of *trans*-alkenes over their *cis* isomers is a general finding of kinetic studies on [2+3] cycloaddition reactions. There are two reasons why *cis*-alkenes react more slowly than their *trans* counterparts:[79] (1) steric hindrance of resonance, which diminishes the activating effect of any conjugated electron-withdrawing or donating group. (2) the change in hybridization from sp^2 to sp^3 of the olefinic carbon atoms as the cycloaddition proceeds,which reduces the bond angle from 120° to 109° and results in considerable compression of the van der Waals radii of the eclipsed *cis*-substituents,thus leading to a larger energy of activation for cycloaddition to the *cis*-isomer. The *trans*-dipolarophiles are relatively free from these disadvantages.

In a [2+3] cycloaddition reaction if the two new σ-bonds are closed simultaneously during the cycloaddition, the result must be a stereospecific *cis*-addition.[84] If on the contrary the reaction were to proceed by a two-step mechanism, the intermediate would possess single bond character, and be susceptible to bond rotation prior to ring closure in the second step of the reaction. This would result in non-stereospecific addition, for the required energy to initiate bond rotation is relatively low. This argument would apply both to zwitterionic and diradical intermediates. Thus from a pure isomeric dipolarophile we should expect to obtain an isomerically pure cycloadduct if the concerted mechanism holds, but an isomeric mixture if the two-step process is in force.

Stereospecificity has been observed in the [2+3] cycloadditions of a wide variety of 1,3-dipoles containing internal octet stabilization with isomeric olefinic dipolarophiles, despite scrupulous searches for mixtures of isomers resulting from non-stereospecific cycloaddition.[79,81]

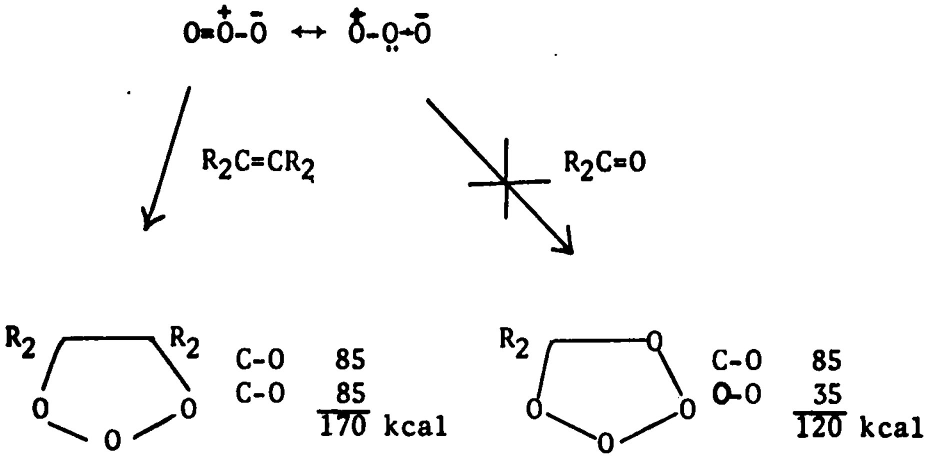
Despite an ingenious argument by Firestone[78] in favour of a diradical pathway, this concept of *cis* stereospecificity must be regarded as strong evidence for a concerted mechanism in [2+3] cycloaddition reactions which show this phenomenon.

There have been cases where *cis*-sterespecificity would appear not to have been conserved,[65,85] but these have been rationalized by consideration of the following two important factors: (1) subsequent epimerization of the primary cycloadduct may have occurred; (2) the olefinic dipolarophile may be susceptible to isomerization under the reaction conditions. This second factor will be dealt with in greater detail in Chapter IV of this thesis.

Although certain dipolarophiles, e.g. dimethyl fumarate, are generally found to be very reactive in [2+3] cycloaddition reactions with most 1,3-dipolar systems, there is no universal activity sequence of dipolarophiles, and Huisgen[79] has emphasized that dipolarophile activity sequences should be established for each new 1,3-dipolar system.

Examination of kinetic data has revealed that with few exceptions hetero-multiple bonds constitute relatively poor dipolarophiles when compared to their olefinic and acetylenic counterparts in [2+3] cycloaddition reactions. Nitriles often give only fair yields, and aldehydes and ketones are in general poor dipolarophiles and frequently fail to react. A reason for this is obtained from a consideration of the principle of maximum gain in σ-bond energy. This states essentially that for a successful cycloaddition to take place, the gain in energy by the formation of the two new σ-bonds must exceed that lost by destruction of the π-bonds of the reactants. The larger this energy difference is, the greater the driving force for the reaction to succeed. This can be conveniently illustrated by comparison of the reactions of ozone with olefinic C=C bonds to yield ozonides, and with C=O or C=N systems, where no cycloaddition reactions occur.[79] The energy calculations for the two new σ-bonds are shown beside the products, equation [39].

[39]

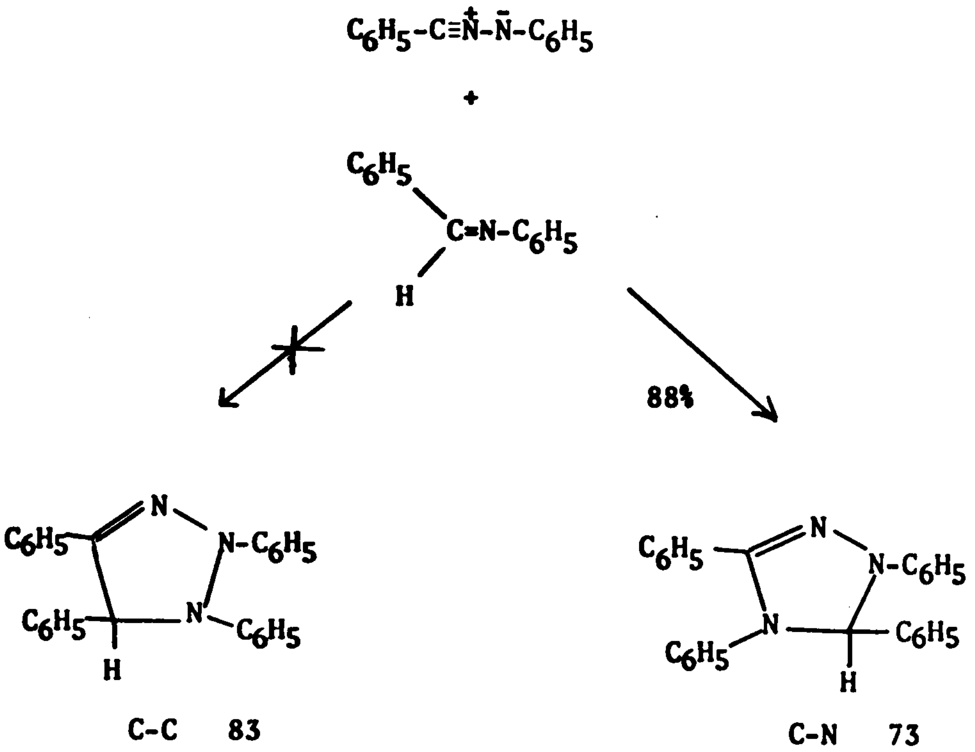

$O=\overset{+}{O}-\overset{-}{O} \leftrightarrow \overset{+}{O}-O-\overset{-}{O}$
$R_2C=CR_2$
$R_2C=O$
R_2
R_2
O
O
O
C-O 85
C-O 85
170 kcal
R_2
O
O
O
C-O 85
O-O 35
120 kcal

In the reaction with the olefin, two new C-O single bonds are formed with a gain in σ-bond energy of 170 kcals. In the other case the gain in σ-bond energy is only 120 kcals,which must be insufficient to overcome the loss of energy from the π-bonds of the reactants,since the reaction does not take place.

One of the most important features of [2+3] cycloaddition reactions concerns orientation phenomena. In general 1,3-dipoles lack bond symmetry, and thus can react with unsymmetrical dipolarophiles in two possible orientations, one of which is usually found to be exclusive or to predominate, as statistical 50-50 mixtures of products are rarely observed. This orientation phenomenon presents possibly the most challenging, and at present, the least understood section in the field of [2+3] cycloaddition reactions. It involves a consideration of electronic and steric factors, the principle of maximum gain in σ-bond energy,and possibly other factors which are as yet unknown. Since systematic study of effects of substituents in cycloaddition reactions is still in its infancy, there is as yet some inconsistency in prediction of the orientation of addition, and thus pertinent detailed discussions tend to be confined to certain examples which suggest the concerted nature of the [2+3] cycloaddition reaction in question.

In cycloaddition reactions involving dipolarophiles with multiple bonds including a hetero-atom,the direction of orientation can often be predicted by considering the application of the principle of maximum gain in σ-bond energy to the reaction under study. Fortunately it is frequently found that with such dipolarophiles only one orientation is observed,and is the one predicted by the theory. This is nicely illustrated by the reaction of diphenylnitrile imine and N-benzylideneaniline to yield a substituted Δ^2-1,2,4-triazoline as the sole product,[79] equation [40].

[40]



C_6H_5-C≡$\overset{+}{N}$-$\overset{-}{N}$-C_6H_5
+
C_6H_5
C=N-C_6H_5
H
88%
N
C_6H_5
N-C_6H_5
C_6H_5
N
C_6H_5
H
N
C_6H_5
N-C_6H_5
C_6H_5
N
C_6H_5
H

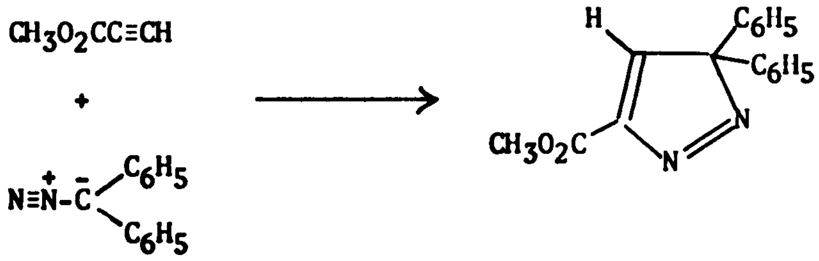
C-C	83	C-N	73
N-N	39	C-N	73
	122 kcal		146 kcal

The gain in σ-bond energy of 122 kcal, was insufficient to overcome the loss of π-bond energy of the reactants and thus no Δ^3-1,2,3-triazoline was obtained.

Huisgen has suggested,[86] that in the very few cases where the orientation of addition is not that predicted by the principle of maximum gain in σ-bond energy for reactions involving dipolarophiles containing a hetero atom,then a different mechanism may be in operation.

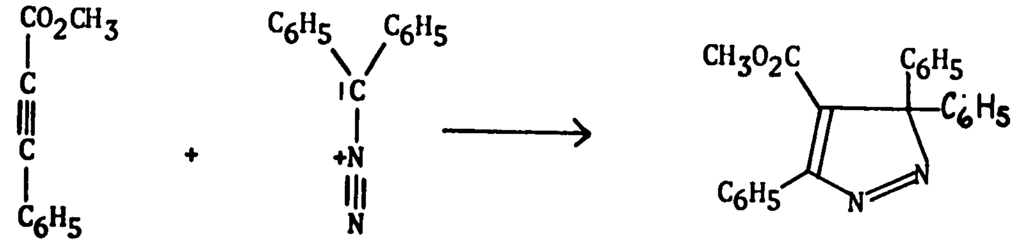
The situation becomes more complex in the larger class of cycloaddition reactions which involve olefinic and acetylenic dipolarophiles, for here either orientation of addition would produce the same gain of σ-bond energy, and as might be expected, mixtures of structural isomers are more frequently encountered. The major factors to be considered now are electronic effects and steric effects of the dipolarophile substituents and of the 1,3-dipole itself. As mentioned before, Huisgen considers the steric effect to outweigh the electronic effect and thus to be primarily responsible for directing the orientation of addition. It has been found that diphenyldiazomethane reacts with methylpropiolate to give a single product, the orientation of which is feasible both from steric and electronic considerations,[87] equation [41].

[41]



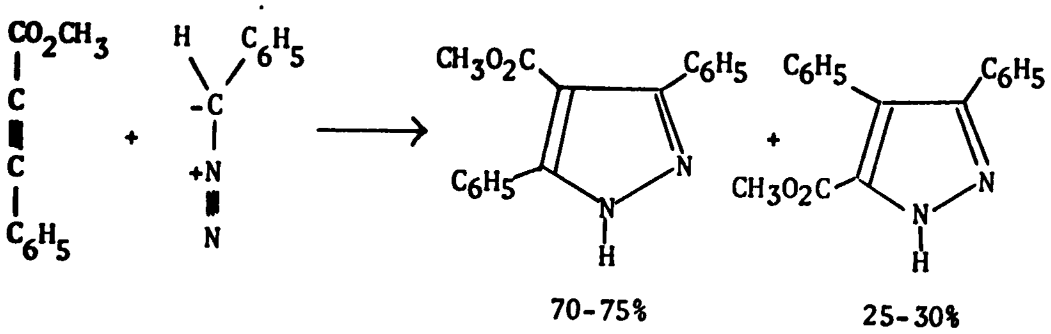
"Experimental evidence has shown that the central carbon atom of diphenyldiazomethane is more strongly nucleophilic than the outer nitrogen."[79] Thus the electronic requirement is satisfied. From a steric viewpoint the orientation is also satisfactory, since the carbomethoxy group is as far removed from the phenyl groups as possible.

When phenylmethylpropiolate is used as the dipolarophile, the sole reaction product is that which shows the opposite orientation to the case above,[87] equation [42].

[42] 

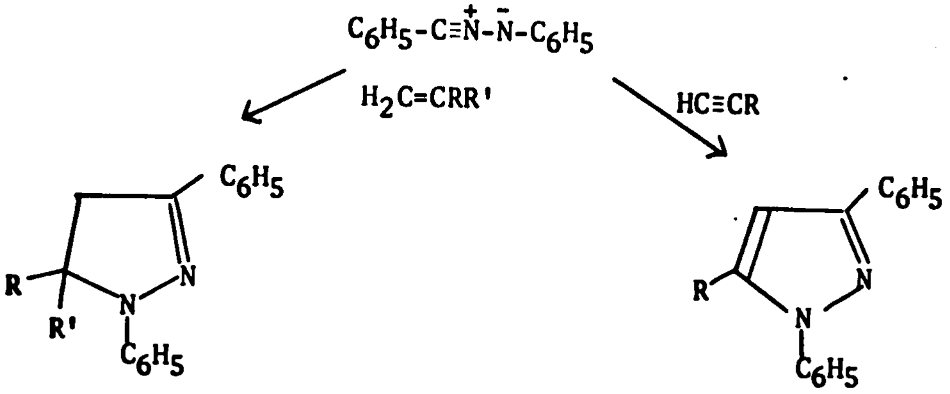
The explanation offered is that the phenyl group of the dipolarophile, which has larger steric requirements than the carbomethoxy group, is placed as far as possible from the phenyl groups of the 1,3-dipole. The steric effect is sufficient to outweigh the electronic one, and only a single product is obtained. It has been pointed out by Firestone,[78] that the phenyl and carbomethoxy groups of the dipolarophile should interact since they are in conjugation, and thus the electronic factor should be more important than has been suggested by Huisgen. Both suggestions seem to be satisfied in the case where the 1,3-dipole is less hindered, for a mixture of structural isomers is obtained, though with the sterically favoured one the predominant compound,[87] equation [43].

[43]


CO_2CH_3
C_6H_5
H
C_6H_5
-C
+N
N
CH_3O_2C
C_6H_5
C_6H_5
N
N
H
70-75%
C_6H_5
C_6H_5
CH_3O_2C
N
N
H
25-30%

Examination of the literature reveals that diphenylnitrile imine reacts with monosubstituted olefins and acetylenes in [2+3] cycloaddition reactions predominately in the same direction no matter whether the substituents on the dipolarophile be aryl or alkyl, electron withdrawing or donating,[78,65,88] equation [44].

[44]

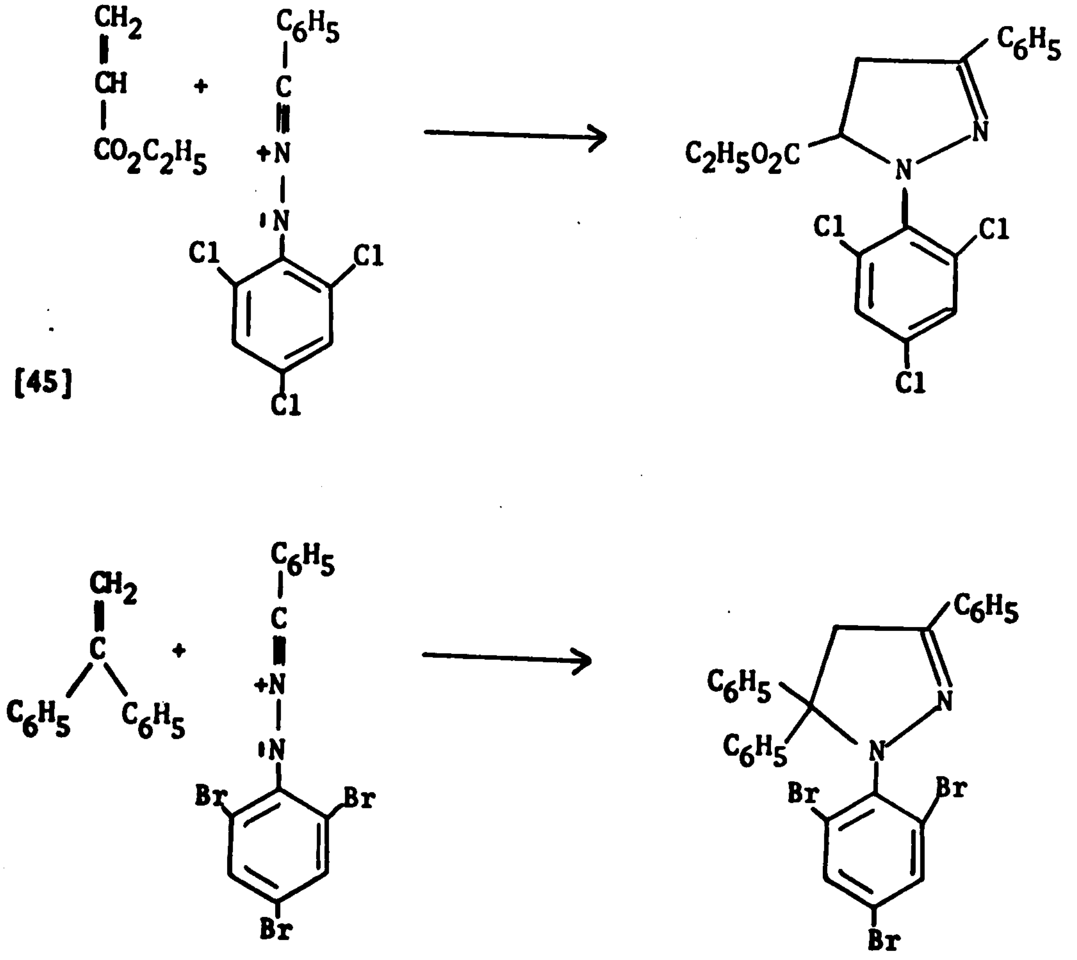

$C_6H_5-C\equiv\overset{+}{N}-\overset{-}{N}-C_6H_5$
$H_2C=CRR'$
$HC\equiv CR$
C_6H_5
R
R'
N
N
C_6H_5
C_6H_5
R
N
N
C_6H_5

R=H, R'=C_6H_5, CN, $CO_2C_2H_5$,
$CH=CH_2$, n-C_5H_{11}

R=C_6H_5, CO_2CH_3, $CH(OC_3H_7)_2$

Huisgen has contended[79] that the steric effect is still in control despite the fact that the 1,3-dipole now possesses phenyl groups at both 1- and 3-positions. The explanation is that the phenyl bearing carbon atom of the 1,3-dipole is more sterically hindered towards the approach of the dipolarophile than is the phenyl bearing nitrogen atom.

This point has been disputed by Firestone[78], who contends that the steric hindrance should be approximately the same in both positions. In an attempt to force the reversal of the direction of orientation, substituents of considerable steric bulk were placed on the N-phenyl group of the above nitrile imine and reacted with various monosubstituted dipolarophiles,[88,89] equation [45].

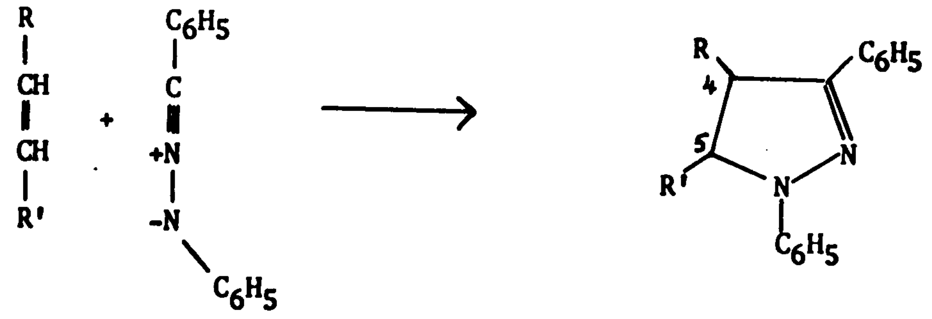

CH2
CH
CO2C2H5
C6H5
C
+N
N
Cl
Cl
Cl
C6H5
C2H5O2C
N
N
Cl
Cl
Cl
CH2
C
C6H5
C6H5
C6H5
C
+N
N
Br
Br
Br
C6H5
C6H5
C6H5
N
N
Br
Br
Br

[45]

It was found that the direction of orientation was still the same as before. Huisgen has offered no explanation for this unusual result, and has admitted that these findings cast doubt on a purely steric interpretation.

In a more recent attempt to clarify the situation, Huisgen and coworkers[83] examined the [2+3] cycloaddition of diphenylnitrile imine with a larger variety of dipolarophiles and divided the tendency of methyl, isopropyl, phenyl, and carboalkoxy substituents to occupy the 4- or 5-positions of the product Δ^2-pyrazoline into electronic and steric components, equation [46].

[46]



By combining the relative rate constants of Table VII with earlier ascertained directions of addition of diphenylnitrile imine, or their ratios, Huisgen obtained information on what was termed partial addition constants. This system was the first example of a cycloaddition in which a useful approximation to an additivity of substituent effects was permitted. Table IX illustrates some partial addition constants for the cycloaddition of diphenylnitrile imine to acrylic ester derivatives. All the rates are relative to k_2(1-heptene)= 0.137 (Table VII), and the ratios of the orientations of addition are also shown.[90a]

TABLE IX

Dipolarophile	Product Δ^2-pyrazoline		Partial addition const.	Ratio of orientation
	4-position	5-position		
$H_2C{=}CHCO_2C_2H_5$	H	$CO_2C_2H_5$	48	-
$CH_3CH{=}CHCO_2C_2H_5$	CH_3	$CO_2C_2H_5$	0.64	$\frac{64}{36}$
	$CO_2C_2H_5$	CH_3	0.36	
$(CH_3)_2C{=}CHCO_2CH_3$	$(CH_3)_2$	CO_2CH_3	0.001	$\frac{10}{90}$
	CO_2CH_3	$(CH_3)_2$	0.009	
$C_6H_5CH{=}CHCO_2CH_3$	C_6H_5	CO_2CH_3	1.85	$\frac{67}{33}$
	CO_2CH_3	C_6H_5	0.88	

By utilizing partial addition constants and assuming that alkyl groups exert no electronic effect in the transition state but only a steric effect, Huisgen and coworkers were able to calculate substituent effects for the 4- and 5-positions of the Δ^2-pyrazoline ring, equation [47].

$$[47] \qquad k_{2(A)} = k_2(\text{1-heptene}) \prod_{i=1}^{n} f_{A_{i(\text{steric})}} \cdot f_{A_{i(\text{electronic})}}$$

where f_{A_i} are the substituent factors $A_1, A_2 \ldots A_n$.

Huisgen has remarked that while the overall substituent effect is a measureable quantity, this cannot be said for the component electronic and steric effects, for whose values only reasonable suggestions can be offered based on a few initial assumptions.[83]

From Table IX it can be seen that ethyl acrylate reacts with diphenylnitrile imine 350-fold faster than does 1-heptene and furthermore, both the pentyl residue of 1-heptene and the carboethoxy group of ethyl acrylate appear in the 5-position of the product pyrazoline to an extent of >99%. Since no steric effect is assumed for the n-pentyl residue, Huisgen consequently assigned the overall effect of 350 for the carboethoxy group solely to the electronic effect (see Table X).

It is also inferred from Table IX that the methyl group of ethyl crotonate retards the addition constant by a factor of 75 compared with ethyl acrylate, and in a direction governed by ethyl acrylate. This retardation by the methyl group in the 4-position of the product is ascribed to a steric effect. Huisgen concludes that the cause for the directionally unambiguous addition to 1-heptene is that there is a steric effect in the 4-position, but none at all in the 5-position of the pyrazoline product.

The comparsion of k_2 values for the second direction of addition of ethyl crotonate, (0.36) with that of 1-heptene furnishes the overall effect of 2.60 for the carboethoxy group in the 4-position.

If a somewhat larger steric factor is assumed for the carboethoxy group in the 4-position than for the methyl group in the 4-position, namely 1/100, then $f_{A\ (\text{electronic})}$ gives a value of 260. The overall effect of the substituents is shown in the following scheme for ethyl crotonate.[90b]

	Δ^2-Pyrazoline		Δ^2-Pyrazoline	
	$H_3C\text{-}\underset{4}{CH}\text{=}\underset{5}{CH}\text{-}CO_2C_2H_5$		$C_2H_5O_2C\text{-}\underset{4}{CH}\text{=}\underset{5}{CH}\text{-}CH_3$	
k_2	0.64		0.36	
$f_{A(overall)}$	1/75	350	2.6	1
$f_{A(steric)}$	1/75	1	1/100	1
$f_{A(electronic)}$	1	350	260	1

Table X shows the substituent effects for the cycloaddition of diphenylnitrile imine and various olefinic dipolarophiles.[90b]

TABLE X

	Pyrazoline 4-position			Pyrazoline 5-position		
Substituent	$f_{A(overall)}$	steric	electronic	$f_{A(overall)}$	steric	electronic
CH_3	0.013	1/75	1	1	1	1
$CH(CH_3)_2$	0.010	1/100	1	1	1	1
CO_2R	2.60	1/100	260	350	1	350
C_6H_5	0.091	1/150	14	12	2/3	18
$N(Alk)_3$	small	-	-	530	1	350
OAlk.	-	-	-	2.2	1	2.2

It has been stressed by Firestone[78] that there seems no obvious explanation for the observed fact that there should be so much more hindrance to substituents taking up the 4-position of the product pyrazoline than to forming the 5-position in these concerted [2+3] cycloadditions. Another observation from Table X is that not all substituents have a constant electronic factor. Huisgen has conceded[91] that the numerical substituent effect separation contains some arbitrariness, but claims that within certain limits the net effect satisifies the additivity principle.

Turning briefly to structural variations in the 1,3-dipole, it has been frequently shown by Huisgen that the rate of cycloaddition of these species is little effected by polar substituents and he uses this fact as good evidence for a concerted mechanism. It should be noted however that exceptions to this statement do exist, a good example being the aromatic azide class of 1,3-dipoles. Table XI shows the rate constants for [2+3] cycloaddition reactions of some organic azides with various olefinic dipolarophiles in benzene solution at 25°C.[79,92]

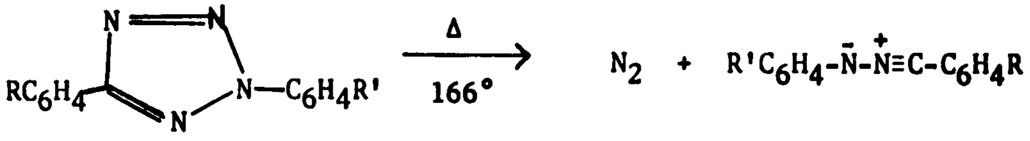
TABLE XI

1,3-Dipole $R\text{-}\overset{-}{N}\text{-}\overset{+}{N}{\equiv}N$	Dipolarophile $k_2 \times 10^7$ (liter/mole/sec)			
R	Maleic anhydride	N-Phenyl maleimide	Norbornene	Pyrrolidinyl cyclohexene
$p\text{-}O_2N\text{-}C_6H_4$	1.3	11	1,530	1,480,000
C_6H_5	7.2	28	254	9,930
$p\text{-}CH_3O\text{-}C_6H_4$	21	67	187	3,400
$C_6H_5CH_2$	53	95	22	25
ρ*	-1.2	-0.7	+0.8	+2.6

*Based on the relationship $\log k/k_0 = \sigma\rho$

Two main points arise from scrutiny of this table: 1) the aromatic azide displays opposing substituent effects depending on the electron density of the olefinic bond in the dipolarophile, 2) the Hammett ρ value of +2.6 in the case of pyrrolidinyl cyclohexene is so much larger than that observed for other 1,3-dipolar species in cycloaddition reactions that a change in the reaction mechanism is probably involved. Kosower has suggested that this reaction proceeds via a charge transfer process.[93] Baldwin and Hong[94] have attempted to assess the electronic effects on the [2+3] cycloadditions of diarylnitrile imines by measuring the rates of evolution of nitrogen from a series of 2,5-diaryltetrazoles, equation [48].

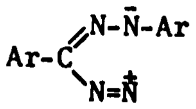
[48]



A. R = H; R' = *p*-CH_3, *m*-CH_3O, H, *p*-Cl

B. R = *p*-CH_3O, *p*-CH_3, H, *m*-Br, *p*-CN ; R' = H

Baldwin used tetrazoles for his study because the steric aspects of the reaction remained fairly constant due to the cyclic nature of the molecule. This consequently allowed the electronic effects of the benzene ring substituents to be measured, and a marked rate dependence on the substituent groups was observed. For the A series the Hammett ρ value was +1.16 while in the B series the ρ value was -0.23. Baldwin and Hong concluded that the differing ρ values indicated an unsymmetrical activated complex I, for the 1,3-cycloeliminations where the nitrogen of the 1,3-dipole carries more charge than does the carbon.



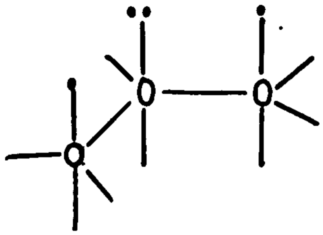
I

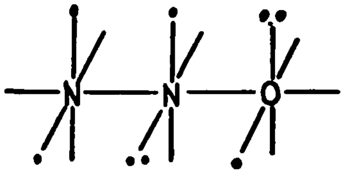
The evidence cited shows the delicate balance between structure and mechanism in such reactions. Huisgen[83] has used a similar activated complex to explain the ratio of reaction of various aryl-substituted styrenes with diphenylnitrile imine.

In the addition of aryl azides to enamines, it has been shown by Munk and Kim[95] that electronic effects overcome steric effects, and these, taken together with the results of Overberger and coworkers[74] on diazoalkanes, indicate that various pathways are possible for cycloaddition reactions. Which mechanism operates will depend on the reactants and conditions, and although it is probable that many [2+3] cycloaddition reactions do proceed by a concerted mechanism each new case should be examined in its own rights.

The next topic to be considered will be the molecular orbital presentation of those [2+3] cycloaddition reactions which experimental evidence suggests proceed in a concerted manner.

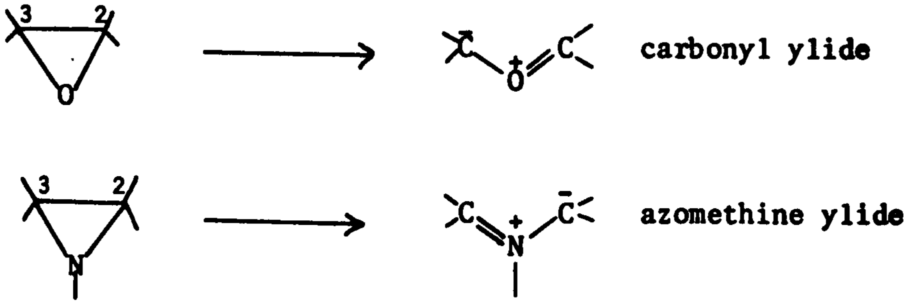
The vast majority of 1,3-dipolar species that undergo these cycloadditions are isoelectronic with either ozone or nitrous oxide and hence unambiguously contain four π-electrons in three parallel p-orbitals.[54]



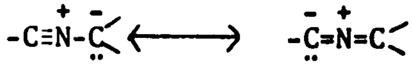


A second class of 1,3-dipoles are those formed from ring opening of labile small ring compounds by cleavage of the 2-3 bond in a manner which will be described later. Equation [49] exemplifies the formation of the carbonyl ylide and azomethine ylide systems.[54]

[49]

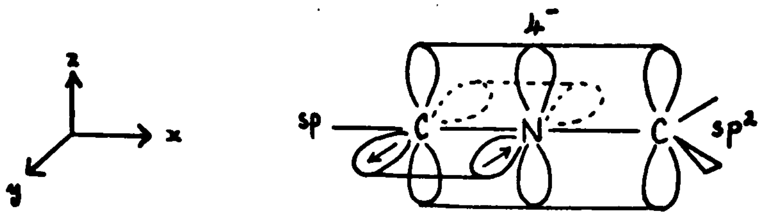


As with ozone, nitrous oxide,and the isoelectronic allyl anion, the four π-electrons occupy pairwise the two lowest molecular orbitals.[81] The nitrile ylide class of 1,3-dipoles will be utilized as a model system with which to observe the molecular orbital description of a concerted [2+3] cycloaddition reaction.[96] In terms of resonance theory the two principal octet forms of the nitrile ylide are as shown:



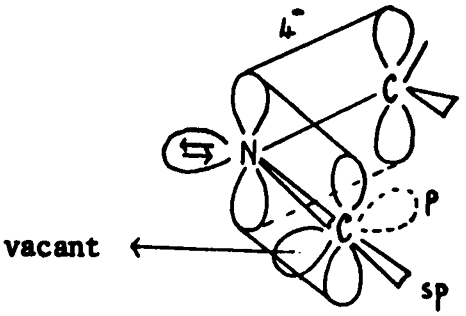
$$-C\equiv\overset{+}{N}-\underset{\cdot\cdot}{\overset{-}{C}}< \longleftrightarrow -\underset{\cdot\cdot}{\overset{-}{C}}=\overset{+}{N}=C<$$

The molecular orbital description of the above mesomerism is described in Figure A.



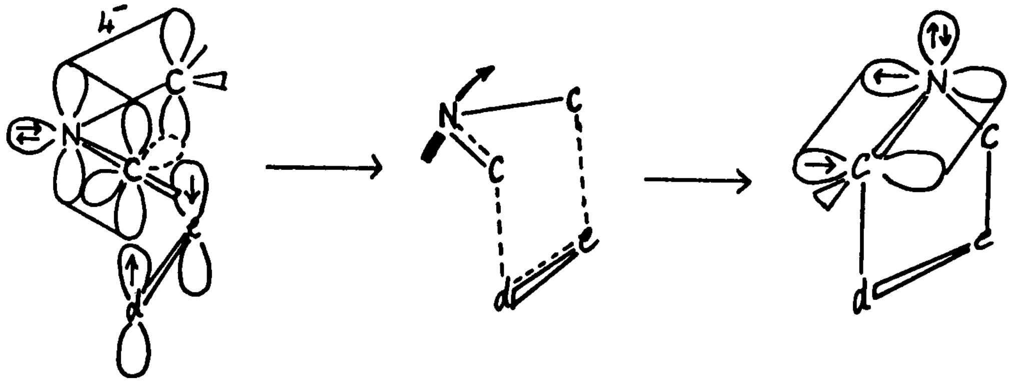
A

Huisgen has calculated[96] that the delocalization energy in A is, to a first approximation, that of the isoelectronic allyl anion. During the process of activation the linear 1,3-dipole system in Figure A must bend to align precisely the carbon atoms at the 1- and 3-positions with the π-bond of the dipolarophile. This motion necessitates the loss of the π_y oribtal and places the 1,3-dipole in a position to receive the dipolarophile as shown in Figure B.



B

LCAO calculations by Roberts[97] on the azide system have shown that the loss of π-bond energy in the bending process is small and is partly compensated for by energy gained from rehybridization and placing of a lone pair of electrons in an orbital of high s-character. The important conclusion is that the "allyl anion" resonance energy is not seriously disturbed by the bending.[96,97] The bent 1,3-dipole is now in the correct orientation to make contact with the π-bond of the dipolarophile d=e, and Huisgen has proposed[96] that the activation complex, transition state, and end product be represented as in Figures C, D, and E, equation [50].



[50] C D E

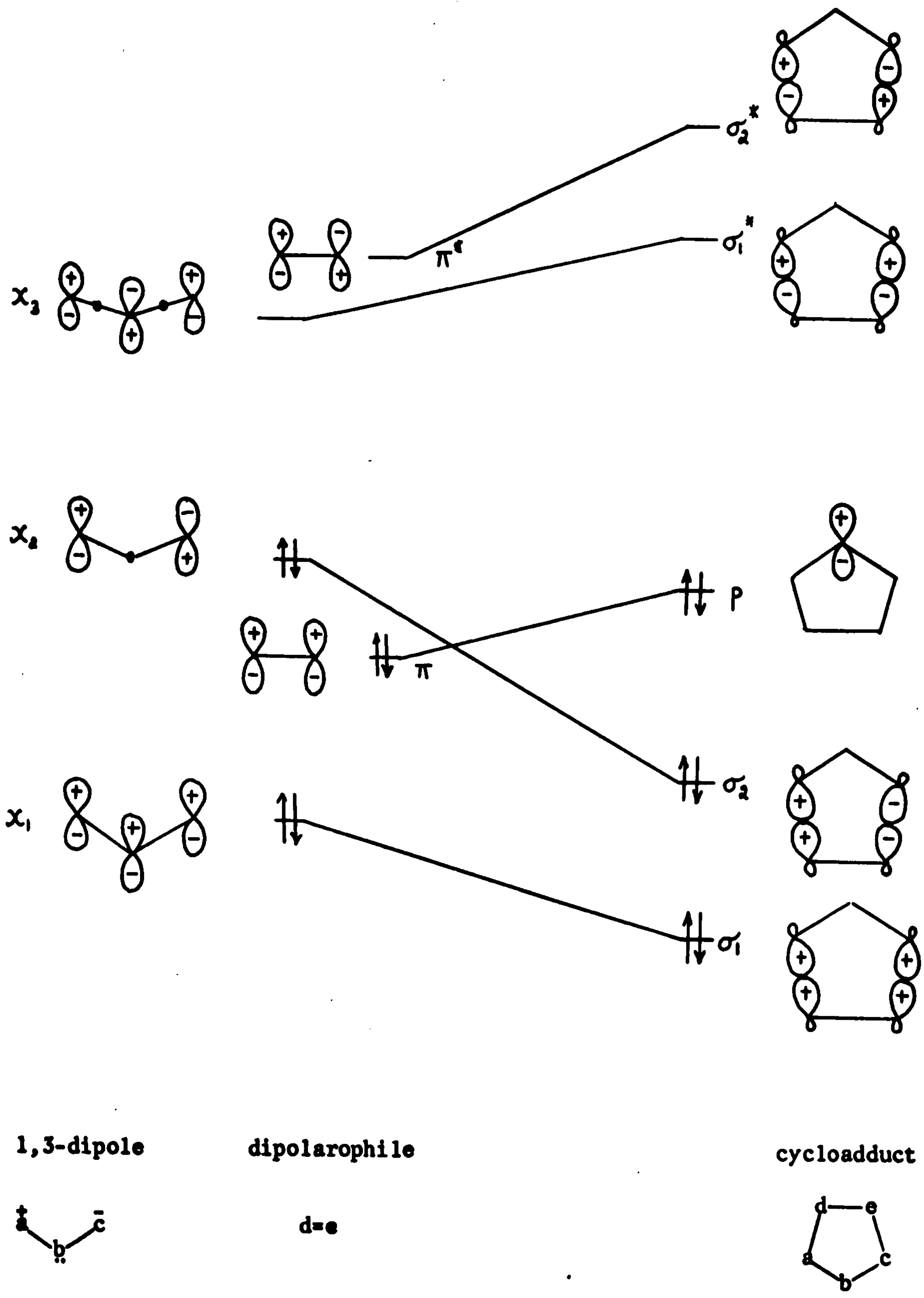
As the p-orbitals of C are transformed into the sp^2 or sp^3 hybridized orbitals of the new σ-bonds, the central nitrogen atom is gradually lifted into the plane of the other four centers (Figures D and E). One important feature of this process is that it is a mistake to assume that a planar transition state is formed from all five centers of the 1,3-dipole and the dipolarophile.[81] The transition state is as shown in Figure D. These [2+3] cycloaddition reactions are similar to the Diels-Alder reaction in that the so-called "two-planes" orientation complex C shows that (4+2)π-electrons are involved.

A noteworthy point arising from equation [50] is that the C=N double bond of the 1,3-dipole is not the same one that appears in the adduct.[96] This initial delocalized π-bond is lost as the reaction proceeds and a new π-bond is formed. This then explains why the rates of [2+3] cycloadditions of nitrile imines and acetylenes do not profit from the aromatic resonance of the product.[96] The new p-orbitals, later to be incorporated into the π-electron cloud, are not developed enough in the transition state.

The larger class of 1,3-dipoles, (Table II), which do not contain a double bond in the 1,3-dipolar form, are already bent in the ground state and hence the initial problem in the above case is avoided. Huisgen's presentation outlined above also applies to those 1,3-dipoles since they can form delocalized four π-electron systems of the allyl anion type.

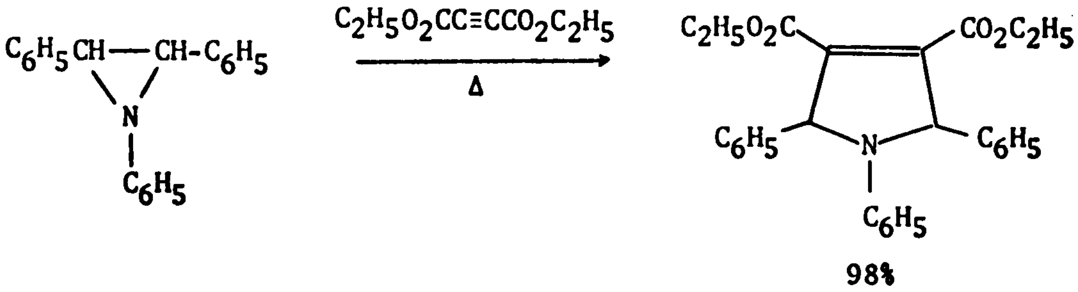
A more precise analysis of concerted [2+3] cycloaddition reactions is obtained by applying the Woodward-Hoffmann method of conservation of orbital symmetry.[54] In this method the approximately known energy levels of the reactants and products are recorded. A geometry of approach is assumed, and the energy levels of the reactants and product classified with respect to the symmetry maintained throughout the approach. Levels of like symmetry are then connected. This approach will be exemplified by the following molecular orbital correlation diagram for a [2+3] cycloaddition reaction involving 1,3-dipoles of general type $\overset{+}{a}-\underset{\cdot\cdot}{b}-\underset{\cdot\cdot}{\overset{-}{c}} \leftrightarrow a=\overset{+}{b}-\underset{\cdot\cdot}{\overset{-}{c}}$ (Table II). The orbitals shown refer to the π-electrons of the reactants, and the σ-bonds and lone pair p-orbital of the product. The diagram is adapted from the text by Kosower.[98]

Figure II

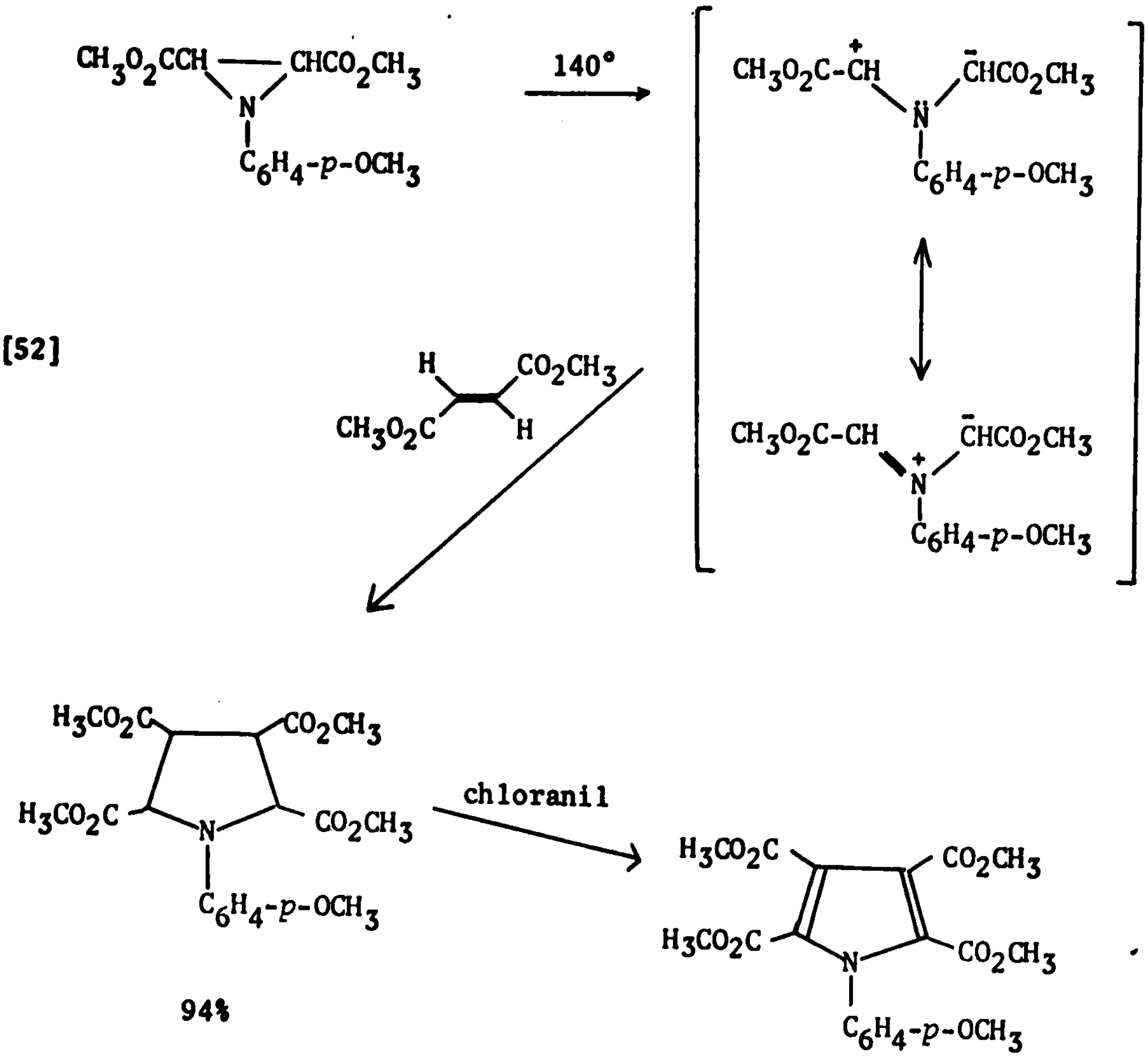

χ_3
π^*
σ_2^*
σ_1^*
χ_2
π
P
χ_1
σ_2
σ_1
1,3-dipole
dipolarophile
cycloadduct
$\overset{+}{a}$
b
$\bar{c}$
d=e
d
e
a
b
c

Our interest in [2+3] cycloaddition reactions stemmed from a desire to study the ring expansion reactions of small ring heterocyclic compounds, especially in the aziridine series. As has been previously summarized, ring expansion reactions of suitably substituted aziridines to isomeric five-membered heterocycles have been well established, principally by Heine and his school[23] and involve mainly ring opening at the 1-2, or 1-3 bond. Cleavage of the aziridine ring across the 2-3 bond has been alluded to in earlier work[99,100] but the first experimental verification appeared in 1965 by Heine and Peavy[66] who obtained cycloadducts from the thermal reaction of 1,2,3-triphenylaziridine with olefins and acetylenes, equation [51].

[51]

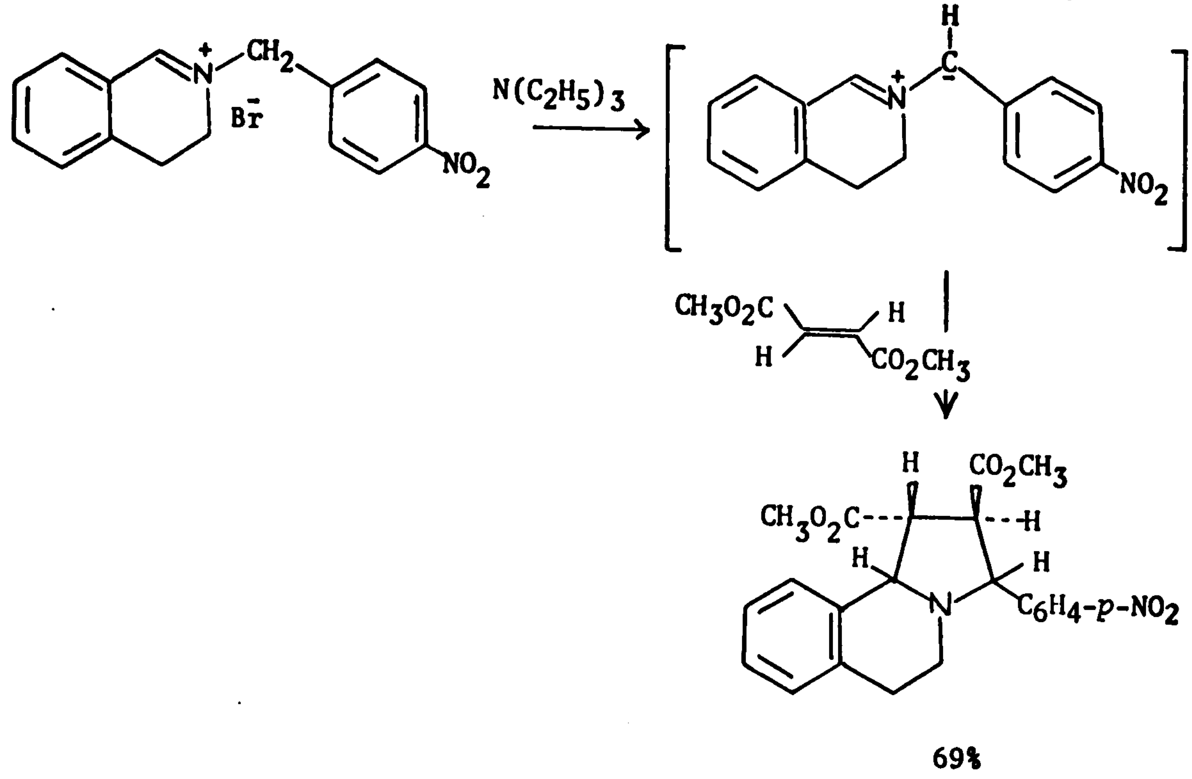


Confirmation of this finding soon appeared in the literature.[101,102] It was suggested by Heine[102] and verified by Huisgen[103] that cleavage of the aziridine ring across the 2-3 bond produced the class of 1,3-dipoles known as azomethine ylides, (Table II), which could readily react with dipolarophiles in [2+3] cycloaddition reactions, equation [52].



[52]

Azomethine ylides have been known since 1960 and were first prepared by treatment of N-(*p*-nitrobenzyl)-3,4-dihydroisoquinolinium bromide with triethylamine in hot pyridine.[104] The unstable ylide readily reacted with suitable dipolarophiles such as dimethylfumarate, phenyl isothiocyanate, and carbon disulfide in cycloaddition reactions, equation [53].

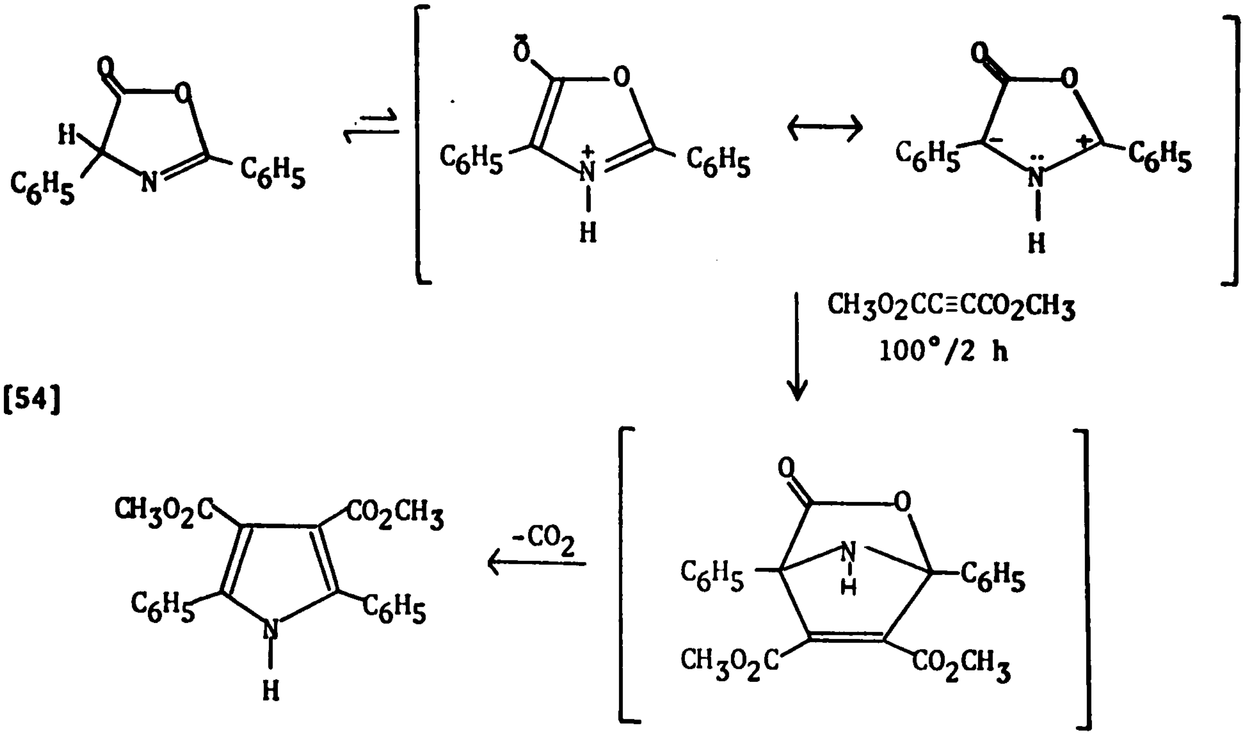


[53]

This and other examples of azomethine ylides in condensed ring systems are summarized in the review by Huisgen.[62]

Substituted aziridines are however more convenient to work with and more easily synthesized, and it has been shown that cleavage across the 2-3 bond to the azomethine ylide and subsequent [2+3] cycloaddition reactions with acetylenic and olefinic bonds have proven to be synthetically useful routes to pyrroles, pyrrolines, and pyrrolidines.[66,101,102,103,105,106,107,108]

In 1964 it was recognized by Huisgen and coworkers that in the well known azlactone system lay a potential route to cyclic azomethine ylides, which could then react in [2+3] cycloadditions to yield pyrroles and pyrrolines by intramolecular elimination of carbon dioxide just as in the analogous sydnone system.[109] This prediction was verified as shown in equation [54].[110]

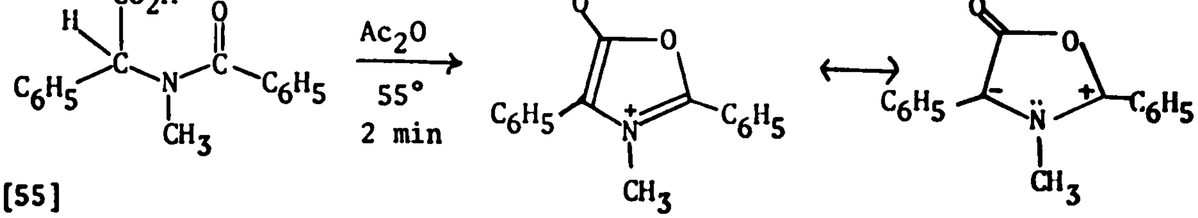


[54]

83%

For these reactions to be successful a proton shift to generate a reasonable equilibrium concentration of the mesoionic oxazolone must take place.[110] Utilization of this system for the generation of masked azomethine ylides often affords the best yields and shortest reaction times of any method involving these 1,3-dipoles, for even poor dipolarophiles like 1,1-diphenylethylene react smoothly.[111]

Many mesoionic oxazolones are stable enough to be isolated and can be prepared in high yield by the reaction of substituted glycines with acetic anhydride at 55°, equation [55].[112]



[55]

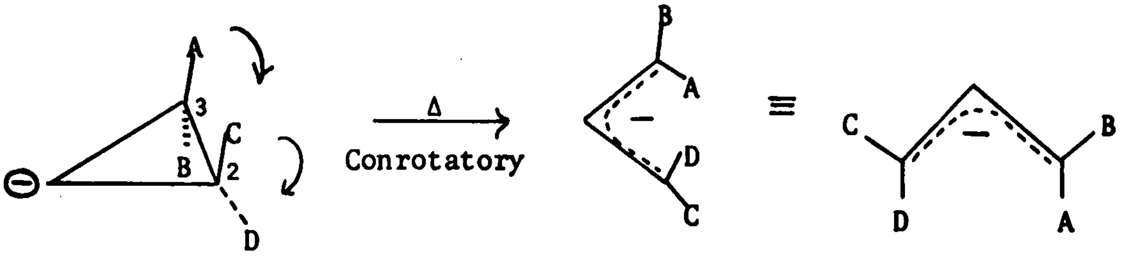
90%

These compounds are easily hydrolyzed, and at higher temperatures in the presence of acetic anhydride they undergo the Dakin-West reaction which may be the reason why they had not been previously reported. [2+3] Cycloaddition reactions of mesoionic oxazolones with variously substituted olefins, acetylenes and carbonyl compounds at temperatures ranging from 0-100°C have been reported.[110,111,112,113]

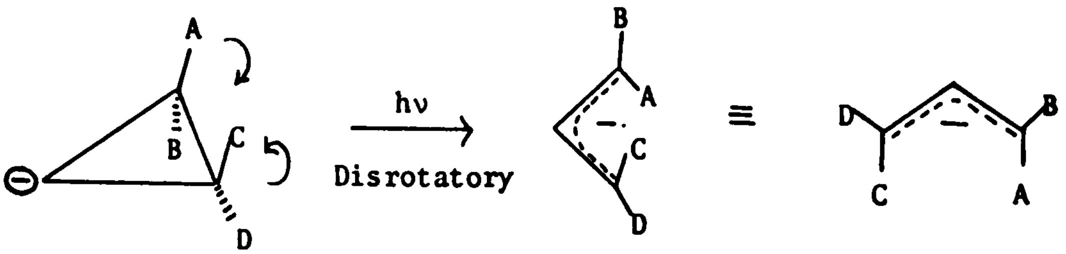
With some exceptions,[102,106] the azomethine ylide class of 1,3-dipoles obey all the criteria for concerted [2+3] cycloaddition reactions.

In 1965, Woodward and Hoffmann[114] made the prediction, based on their orbital symmetry calculations, that the thermal isomerization of the cyclopropyl anion to the allyl anion should proceed via a conrotatory ring opening, equation [56], while the photochemical interconversion should proceed by a disrotatory ring opening, equation [57].

[56]



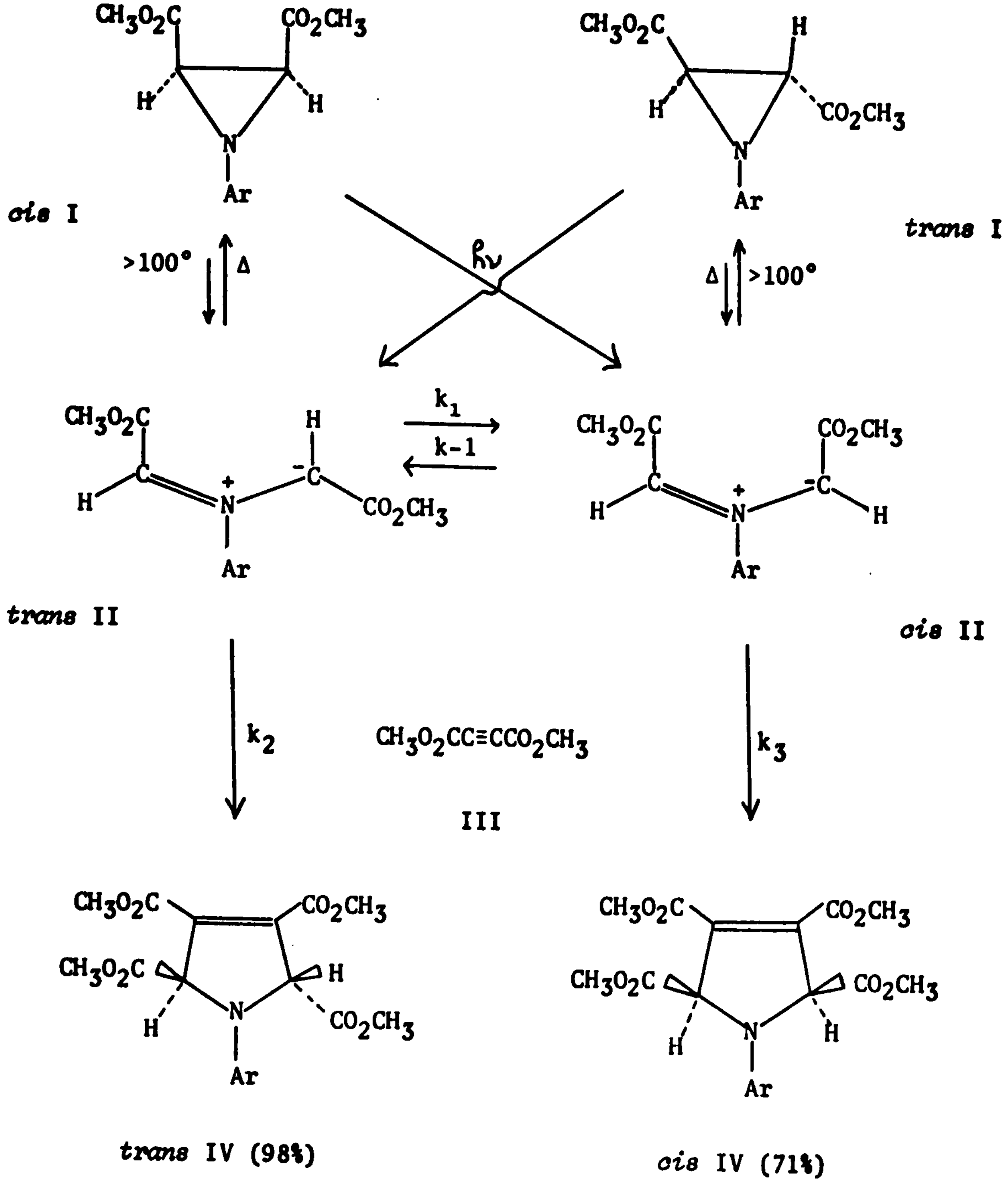
[57]



For a thermal conrotatory reaction, substituents that are *cis* oriented in the substrate are in a *trans* configuration in the product, while those which are *trans* in the substrate become *cis* oriented in the allyl anion. For the photochemical disrotatory ring cleavage, *cis* substituents in the ring retain their relative configurations in the open chain isomer and the same applies for their *trans* counterparts. As yet no direct experimental proof of this prediction has appeared in the literature.

The aziridine ring system is isoelectronic with the allyl anion system and hence with the cyclopropyl anion system. In 1967, Huisgen, Scheer, and Huber[115] provided the first experimental verification of the above predictions using the aziridine ring system as the working model, equation [58].

[58]



CH_3O_2C
CO_2CH_3
H
H
N
Ar
cis I
CH_3O_2C
H
H
CO_2CH_3
N
Ar
trans I
>100°
Δ
hν
Δ
>100°
k_1
k-1
trans II
cis II
k_2
$CH_3O_2CC{\equiv}CCO_2CH_3$
III
k_3
trans IV (98%)
cis IV (71%)

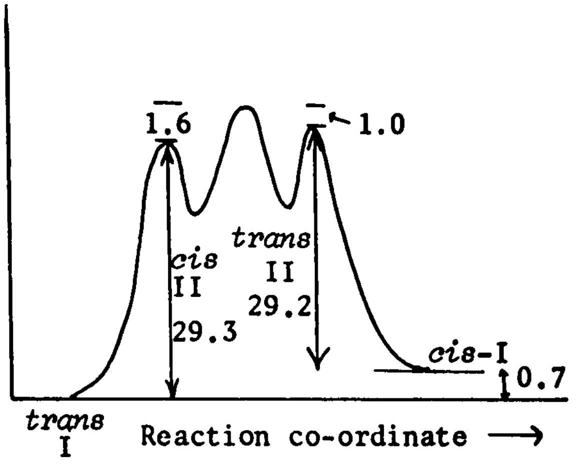
Ar = $-C_6H_4$-*p*-OCH_3

Both *cis*- and *trans*-IV gave the same pyrrole on chloranil dehydrogenation in 84% and 81%, respecively.[115]

The fact that *cis*-I gives *trans*-IV in 98% yield and *trans*-I produces *cis*-IV in 71% in these [2+3] cycloaddition reactions illustrates the predictions of Woodward and Hoffmann as to the intermediate azomethine ylide and its mode of generation, especially in the thermal reaction, since concerted [2+3] cycloadditions are known to proceed in a stereospecifically *cis* manner.[79] The photochemical case produced lower yields (69% *trans*-IV from *trans*-I), but was in accordance with the predictions. The photolysis of *cis*-I was however less clear, and in dioxane solution mixtures were obtained, while in dimethyl acetylenedicarboxylate itself no reaction occurred.

As may be observed from equation [58], equilibration of the intermediate azomethine ylides competes with the cycloaddition reaction, and it was found that only by employing very active dipolarophiles could the equilibration process be suppressed and uncontaminated cycloadducts be obtained. *Cis*-I and *trans*-I equilibrate at 100°C[116], though they are stable to isomerization at room temperature. The kinetics of the aziridine ring cleavage have been investigated by Huisgen and coworkers,[116] and it was found that the rate constants were independent of the dipolarophile concentration, implying that the bimolecular cycloaddition to the dipolarophile was not the rate determining step. The dipolarophile utilized in this study, tetracyanoethylene, was so active in the [2+3] cycloaddition reaction, that the *cis*-II $\rightleftarrows$ *trans*-II isomerization, and the electrocyclic regeneration of the aziridines was totally suppressed. As the polarity of the solvent was increased so also was the percentage of the *cis* isomer. From the kinetic data, Huisgen[116] has constructed a free energy diagram for aziridine ring opening and isomerization.

Figure III

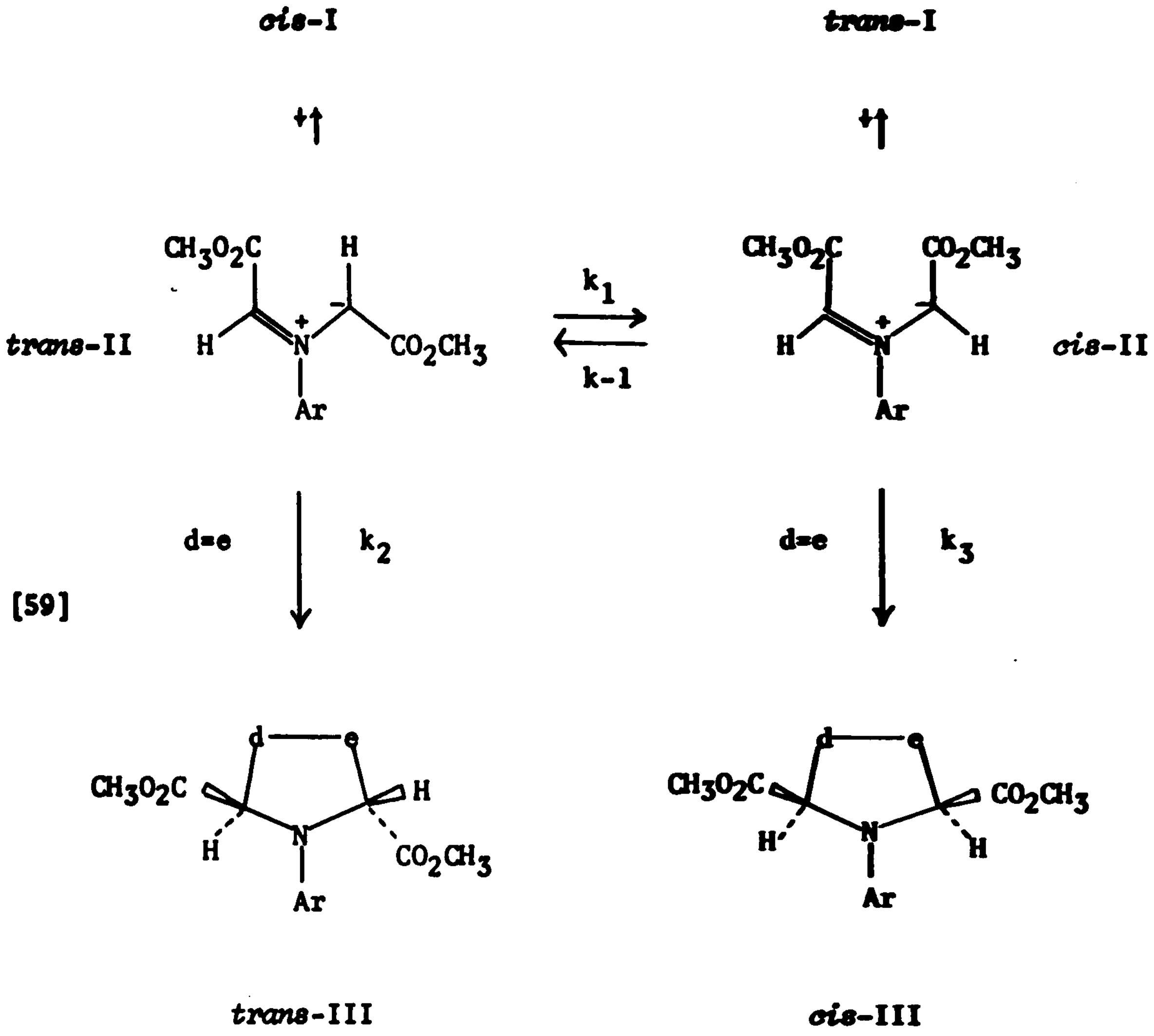


trans-I $\rightleftharpoons$ *cis*-II $\rightleftharpoons$ *trans*-II $\rightleftharpoons$ *cis*-I at 100°C

It was found that only one of eight molecules of *trans*-I that become *cis*-II can surmount the energy barrier leading to *trans*-II. Those left revert to *trans*-I. For intermediate *trans*-II, conversion to *cis*-I is four fold faster than reversion to *cis*-II. The energy values of the troughs corresponding to *cis*-II and *trans*-II are unknown.

As has been mentioned, the ratio of cycloaddition of the intermediate azomethine ylide to its isomerization depends markedly on the activity of the dipolarophile. In an accompanying paper[117] Huisgen and coworkers have estimated the extent of cycloaddition versus isomerization, by observing how the product ratio varies with change in dipolarophilic activity as shown in Table XII for the reaction in equation [59].

[59]



cis-I
trans-I
trans-II
cis-II
k1
k-1
d=e
k2
d=e
k3
trans-III
cis-III

TABLE XII[1]

Dipolarophile d=e	Product from *cis*-I* (yield %)	Product from *trans*-I	
		(yield %)	*trans*-III: *cis*-III†
Tetracyanoethylene	88	100	0 : 100
Dimethyl acetylenedicarboxylate	98	78	0 : 100
Diethyl azodicarboxylate	96	78	6 : 94
Diethyl mesoxalate	94	75	7 93
Dimethyl fumarate	100	93	9 : 91
Tetraethyl ethylene-tetracarboxylate	99	90	25 : 75
Norbornene	86	98	45 : 55
Cyclohexene	78	71	83 : 17
Phenanthrene	–	36	100 : 0

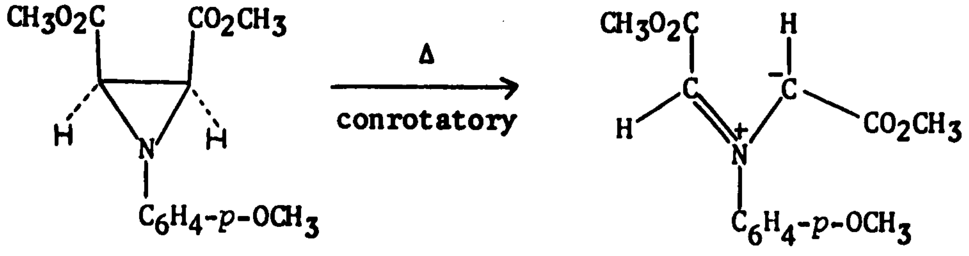
[1] Reactions were conducted at temperatures between 100 and 140°C.
*The ratio of *trans*-III to *cis*-III was 100:0 in all cases.
†Product ratios determined by p.m.r.

Table XII reveals that even with dipolarophiles of low reactivity, intermediate *trans*-II undergoes stereospecific [2+3] cycloaddition reactions. Conversely with *cis*-II isomerization competes effectively with cycloaddition as the dipolarophilic activity decreases. Furthermore no post isomerization was detected either under reaction conditions or during isolation procedure. The fact that the energy profile (p.78) shows little difference in energy between *cis*-II and *trans*-II has led Huisgen to suspect that the rate constants for the

[2+3] cycloaddition must hold the key to the stereospecificity observed (i.e., $k_2 > k_3$), and he contends that only with very active dipolarophiles, is the reaction expressed by rate constant k_3 sufficiently rapid to compete effectively with the isomerization reaction expressed by k-1.

cis-2,3-Dicarbomethoxy-1-(4-methoxyphenyl)aziridine under thermal conditions cleaves across the 2-3 bond in a conrotatory manner, to yield a structurally unambiguous *trans* azomethine ylide, equation [60].[115]

[60]

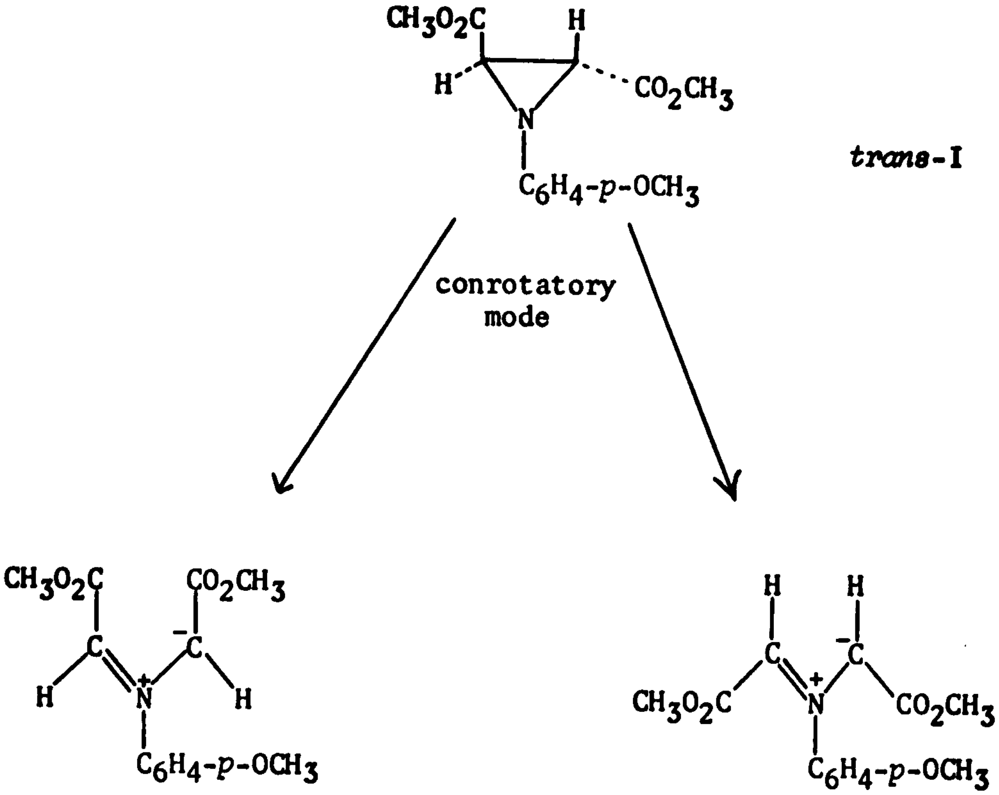


cis-I

trans-II

The *trans*-aziridine, under the same conditions cleaves in a conrotatory manner to yield the *cis*-azomethine ylide,which however could exist in two possible forms as shown in equation [61].

[61]



trans-I

cis-II

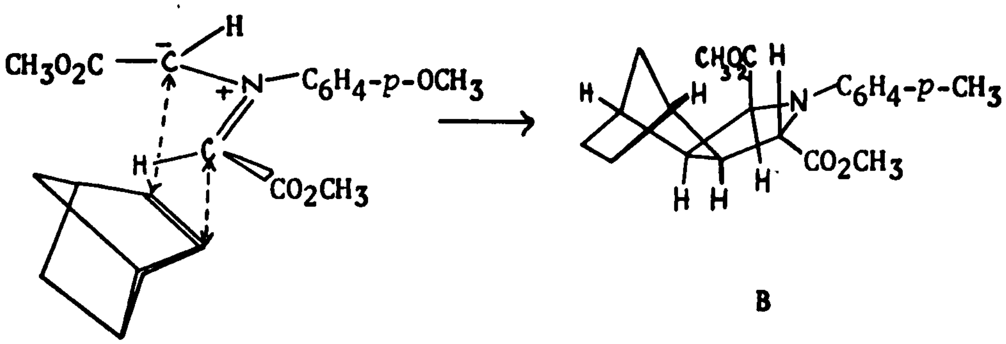
"Horse-shoe form"

"W-form"

In the W-form the van der Waals strain would be expected to be lower than in the "horse-shoe" form.

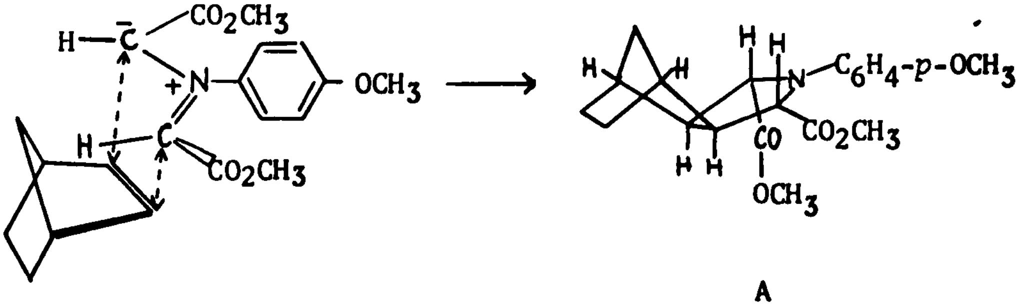
Huisgen and Mader[118] have investigated this point by studying the reaction of *trans*-I with norbornene at 100°C,and as shown in Table XII obtained a 98% yield of a 55:45 mixture of isomeric exo-cycloadducts A and B. The minor component B, which contained *trans*-dicarbomethoxy groups was obtained by isomerization of *cis*-II to *trans*-II followed by cycloaddition, equation [62].

[62]


CH3O2C
H
N
C6H4-p-OCH3
CO2CH3
CH3O2C
C6H4-p-CH3
B

The major product A contained *cis* fused dicarbomethoxy groups directed below the plane of the pyrrolidine ring,and Huisgen and Mader contend that examination of models reveal that the W-form of *cis*-II best explains the structure of the only *cis*-dicarbomethoxy adduct obtained, equation [63].

[63]

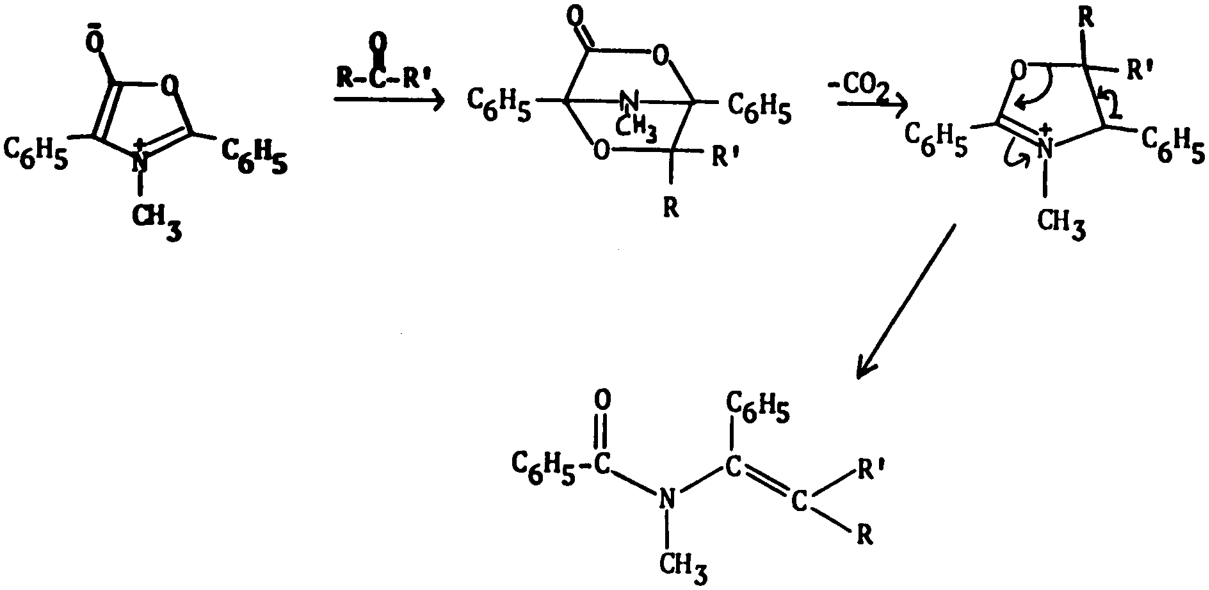

CO2CH3
H
N
OCH3
CO2CH3
C6H4-p-OCH3
CO
OCH3
A

It appears that where two modes for the azomethine ylide *cis*-II are possible, the W-form is preferred though Huisgen and Mader have reported an example where the *cis*-azomethine ylide is fused in the "horse-shoe" form.[118]

A study of the available literature on [2+3] cycloaddition reactions reported over the last twelve years reveals that olefinic and acetylenic systems constitute by far the majority of the dipolarophiles employed. Dipolarophiles containing hetero-atoms in the multiple bond had by comparison received little attention especially prior to 1967, when the work reported in this thesis was first commenced. Much progress has been made in the last three years with reactions involving such dipolarophiles, as judged by the number of publications that have appeared in the literature.

In the azomethine ylide class of 1,3-dipoles, successful reactions with phenyl isothiocyanate and carbon disulfide had been reported in 1963,[104] and cycloaddition reactions of mesoionic oxazolones to carbon disulfide and ethylcyanoformate in 1965.[119]

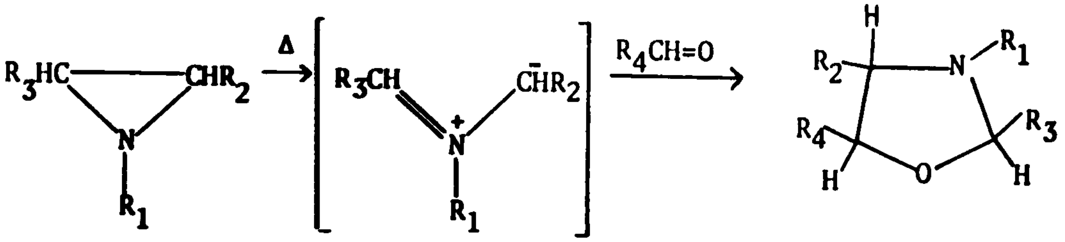
Our group was interested in the possible utilization of the carbonyl group as a dipolarophile in [2+3] cycloaddition reactions with azomethine ylides derived from cleavage of suitably substituted aziridines, despite cautionary comments by Huisgen as to their low reactivity with other 1,3-dipolar systems.[62] Within the azomethine ylide class of 1,3-dipoles the very reactive mesoionic oxazolone system had been shown by Huisgen and Funke[113] to undergo [2+3] cycloaddition reactions with aldehydes, α-diketones and keto esters, though in only a few cases were the intial products of cycloaddition stable enough to be isolated, as the majority tended to cleave to produce acyclic N-benzoyl enamines, equation [64].



[64]

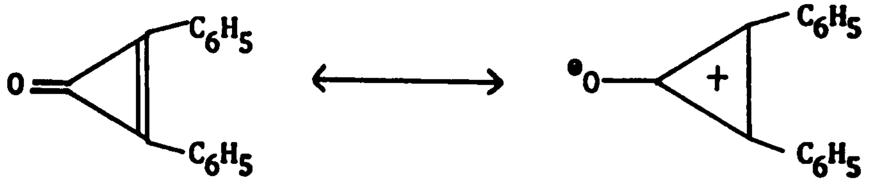
When a large excess of the dipolarophile was used bis-adducts were obtained.

Our intentions therefore were to study the [2+3] cycloaddition reactions of azomethine ylides,derived by cleavage of substituted aziridines,with a variety of carbonyl systems. Such reactions if successful would lead to a new synthesis of oxazolidines, a class of compounds that had previously been obtained by direct condensation techniques over which no stereochemical control could be exercised.



[65]

We were also interested in the potential [2+3] cycloaddition reaction of the intermediate azomethine ylides with the reactive carbonyl system of diphenylcyclopropenone,[120] which is known to be highly polarizable due to resonance of the type shown.



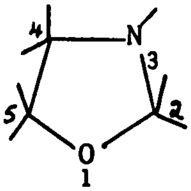
Here the possibility existed of cycloaddition at either or both the C=O group and the C=C group.

These ideas we commenced to test and the novel results are discussed in the next three chapters.

CHAPTER II

THE PREPARATION OF OXAZOLIDINES BY [2+3] CYCLOADDITION REACTIONS

The oxazolidine ring system is that of the completely saturated oxazole system (tetrahydrooxazole).



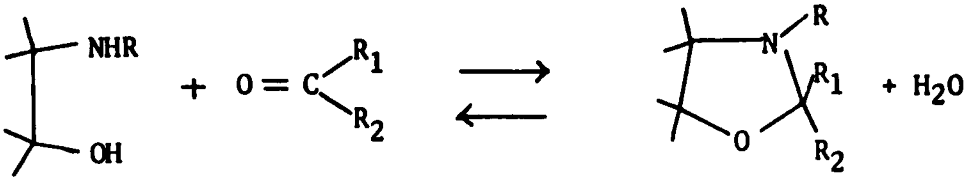
Oxazolidines have been known for over seventy years, and have considerable practical importance especially in the medical field. Their pharmacological value may be illustrated by the drug "Troxidone," 2,4-dioxo-3,5,5-trimethyloxazolidine which is used to control epilepsy.[121] Other substituted oxazolidines have an adrenergic blocking activity and are thus valuable in the treatment of cardiac arrhythmias and angina pectoris,[122] while 2-imino-5-phenyloxazolidine has been shown to possess a memory stimulating effect.[123]

In the field of synthetic polymers, oxazolidines have been used as polymerization accelerators for polyester resins,[124] and applied successfully in shrink and creasproofing of textiles.[125]

Oxazolidines were first reported in 1888 as reduction products of oxazoles,[126] and again in 1897,[127] but the products were not fully characterized and their structures remain in doubt.

There are to date very few synthetic pathways available for the preparation of oxazolidines. The most general method involves the reversible condensation of β-amino alcohols with aldehydes and ketones as shown in equation [66].[128]

[66]

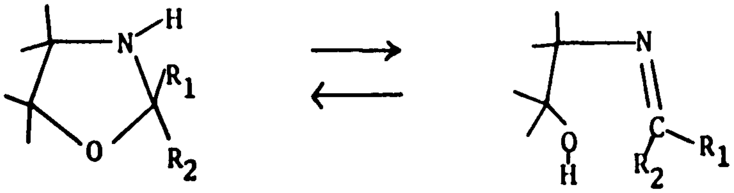


These reactions can be run under basic conditions,[129,130] but are more frequently performed under thermal conditions in an inert solvent with continuous separation of water.[131,132,133]

It has been pointed out by Cornforth,[128] that many substances prepared by these methods, especially in the older literature, have been described as oxazolidines without adequate structure proof. However in cases where the substrate is a N-substituted β-amino alcohol, the structure of the product oxazolidine is in no doubt as has been frequently demonstrated in the literature.[130,134,135,136] In these reactions the yields are fair to good, and a variety of alkyl and aryl substituted oxazolidines can be prepared by this method.

When the β-amino alcohol bears no substituent on the nitrogen atom, the intended oxazolidine product is in potential tautomeric equilibrium with the open-chain Schiff base as shown in equation [67].

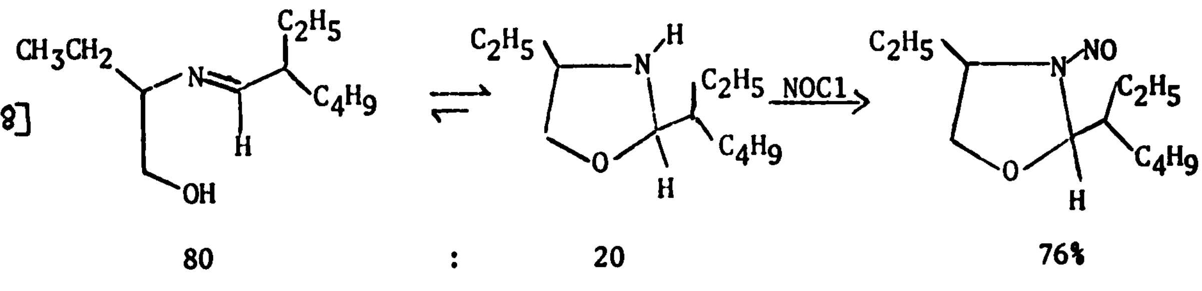
[67]



This mobile equilibrium in solution was first recognized by Cope and Hancock,[131] and later investigated more thoroughly by Bergmann and his school,[133,137,138] who showed that in many cases the products were indeed an equilibrium mixture of oxazolidine and Schiff base. From their studies with ethanolamine and 2-amino-3-hydroxybutane they proposed the following generalizations[128]: 1) aromatic and α,β-unsaturated carbonyl compounds on the whole tend to form Schiff bases, 2) saturated carbonyl compounds tend to form oxazolidines with ethanolamine, 3) introduction into the ethanolamine system of C-alkyl groups favours oxazolidine formation even with aromatic aldehydes and ketones. This view was questioned by McCasland and Horswill[139] who doubted whether there were any known examples of simple, N-unsubstituted oxazolidines of well-established structure.

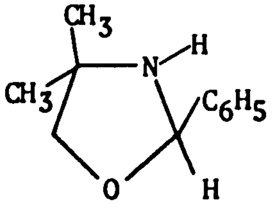
Goldberg and Nace have obtained chemical evidence for such an equilibrium in their reactions of oxazolidine-Schiff base mixtures with nitrosyl chloride,[140] equation [68].

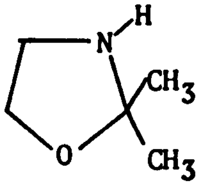
[68]

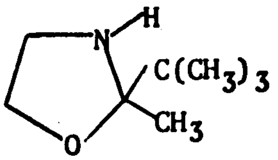


The fact that the product is an oxazolidine and is obtained in 76% yield, suggests that the reaction must proceed via an equilibrium shift from Schiff base to oxazolidine.

The main difficulty in the analysis of this problem was the lack of a suitable physical method with which to examine the proposed equilibrium mixture, and only with the advent of proton magnetic resonance spectroscopy has the problem been solved. Recently Paukstelis and Hammaker[141] published the results of a p.m.r. study of a series of "oxazolidines" unsubstituted at the 3-position which were prepared by standard methods.[132,133]



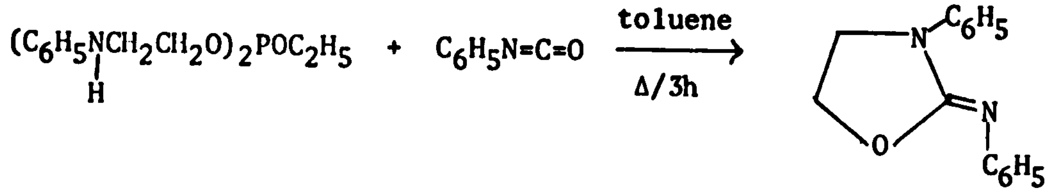




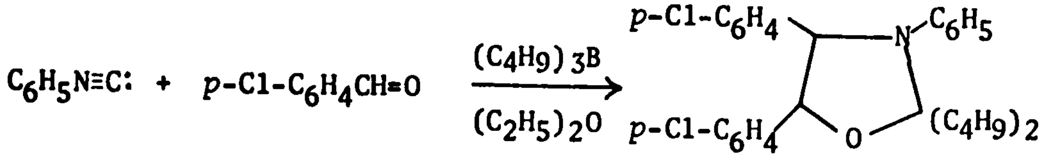
The spectra of each of the "oxazolidines" as pure liquids could be readily explained if each product was regarded as a mixture of a Schiff base and an oxazolidine, with equilibrium constants of 1.99, 1.40, and 0.47, respectively, in each case. This was substantiated by later work by Paukstelis and Lambing.[141a]

One of the principal disadvantages of this condensation method for the synthesis of oxazolidines, even where the product structure is unambiguous, is that the ring substituents tend to be simple alkyl or aryl groups and no other functionality in the molecule is possible. This is a serious drawback since the presence of such groups often lends considerable stabilization to the molecule, as well as introducing sites for further reaction.

The literature contains isolated examples of oxazolidines being synthesized by other than the above method, as shown in equations [69][142] and [70].[143]

[69] 

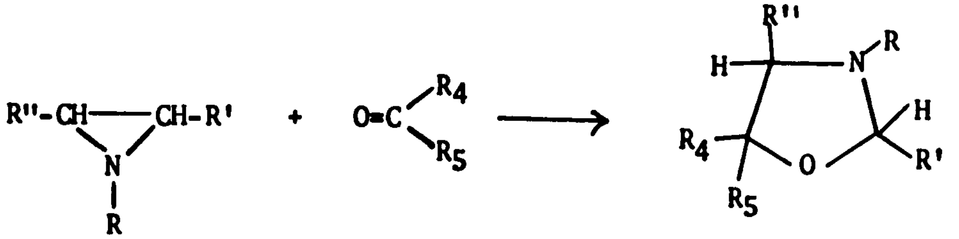
$(C_6H_5NCH_2CH_2O)_2POC_2H_5$
H
+
$C_6H_5N{=}C{=}O$
toluene
Δ/3h
N
C_6H_5
O
N
C_6H_5

[70] 

$C_6H_5N{\equiv}C{:}$
+
p-Cl-$C_6H_4CH{=}O$
$(C_4H_9)_3B$
$(C_2H_5)_2O$
p-Cl-C_6H_4
p-Cl-C_6H_4
N
C_6H_5
O
$(C_4H_9)_2$

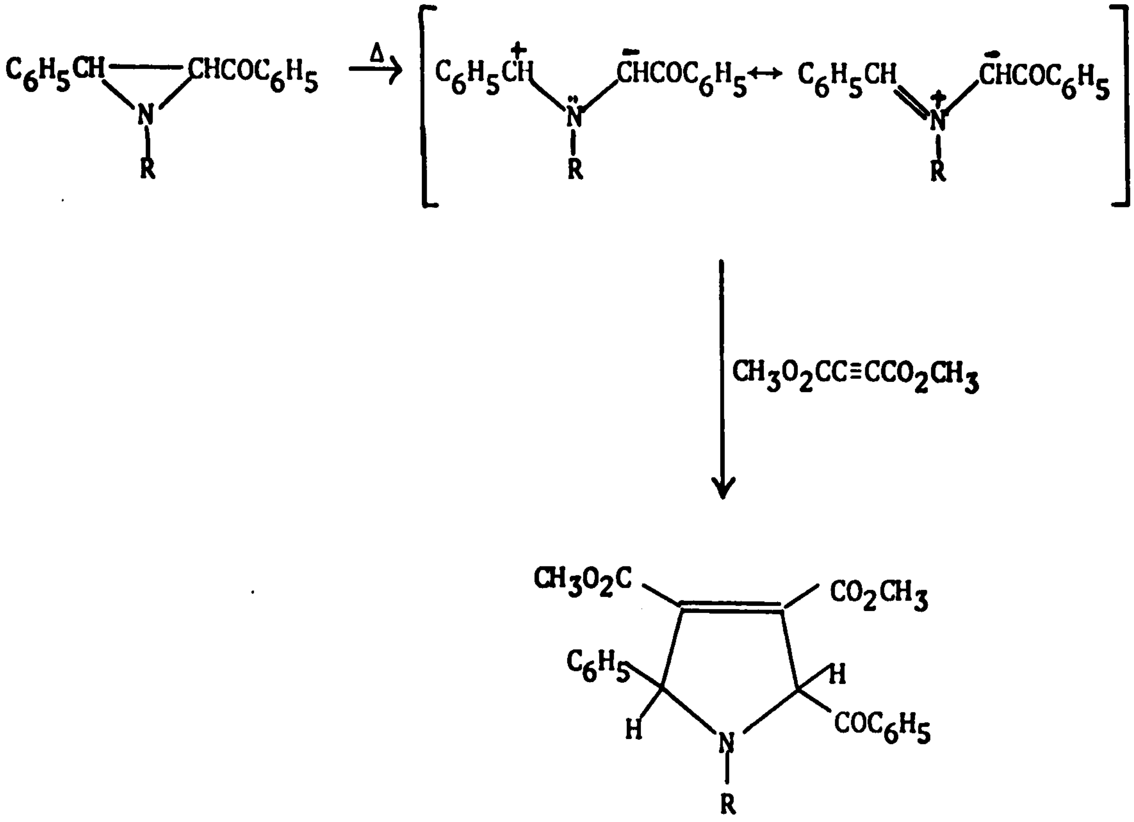
75% Ref. 143

On examination of the oxazolidine ring system it appeared feasible that such compounds might be readily synthesized by [2+3] cycloaddition reactions of substituted aziridines and certain carbonyl compounds, despite remarks by Huisgen[62] as to the low reactivity of the C=O bond as a dipolarophile in these reactions. This could proceed as in equation [71].

[71] 

R''-CH
CH-R'
N
R
+
O=C
R_4
R_5
R''
H
N
R
R_4
R_5
O
H
R'

Our interest was stimulated by the then recent reports of addition reactions of substituted aziridines involving cleavage of the 2-3 bond to an azomethine ylide, and subsequent [2+3] cycloaddition to activated acetylenes and olefins to produce pyrroles and pyrrolines,[66,101,102,103,105,106] equation [72].

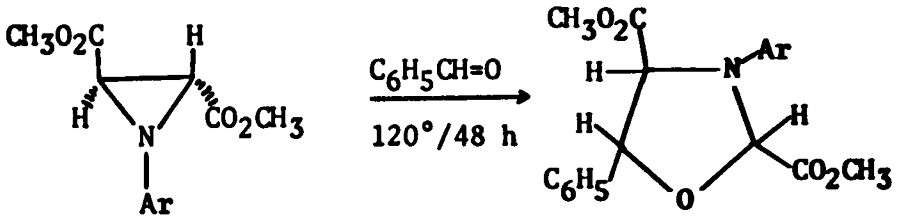


[72]

If this reaction were successful, it would provide a general synthesis of oxazolidines, since a variety of substituted aziridines and carbonyl compounds can be readily obtained. Besides establishing the gross structure of the product we intended to investigate the following points: i) the orientation of addition, ii) the stereochemical purity of the product, iii) the dependence of the reaction course on the stereochemistry of the aziridine, iv) any steric effects on the reaction arising from the dipolarophile structure. Answers to these questions would provide considerable insight as to the mechanism of the reaction.

It should be noted that after our work had been well advanced, an example of an oxazolidine synthesis by just such a [2+3] cycloaddition reaction was reported by Huisgen,[144] equation [73], which confirmed the validity of our approach.

[73]


CH3O2C
H
H
N
CO2CH3
Ar
C6H5CH=O
120°/48 h
CH3O2C
H
N
Ar
H
H
C6H5
O
CO2CH3

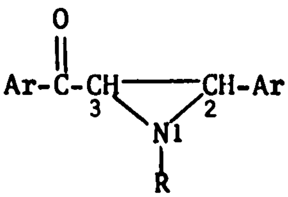
97% (3 stereoisomers)

RESULTS AND DISCUSSION

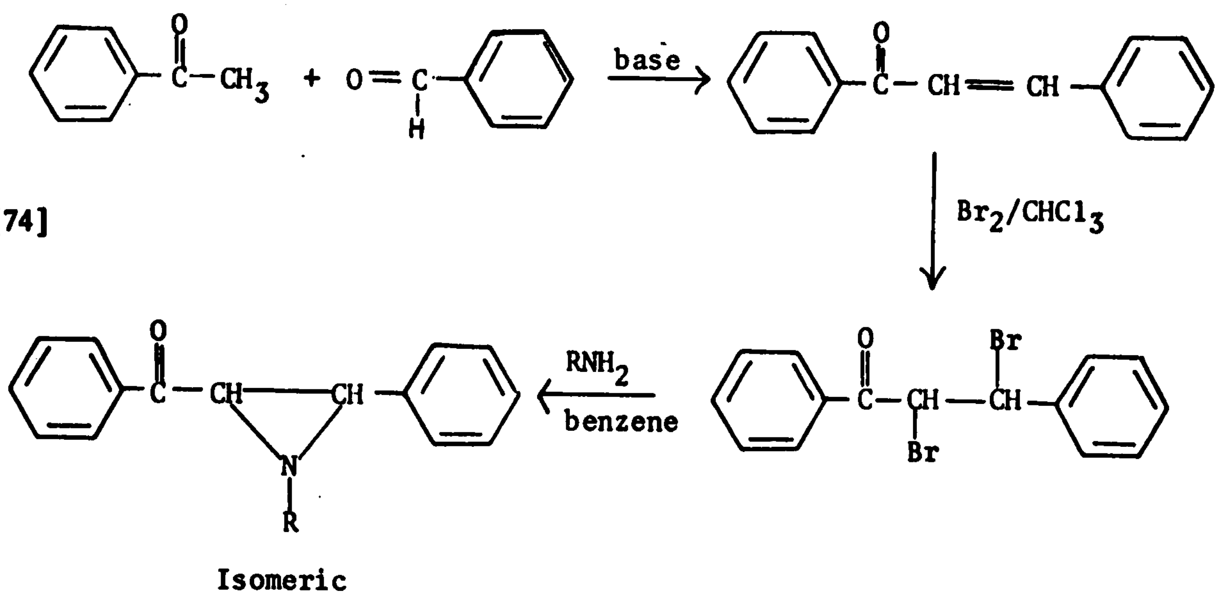
Synthesis of Model Aziridines for [2+3] Cycloaddition Reactions

Suitably substituted aziridines under thermal conditions had been proposed by Heine,[102] and verified by Huisgen,[103] to cleave across the 2-3 bond to form azomethine ylides, which could undergo [2+3] cycloaddition reactions with various dipolarophiles.

Since our proposed synthetic approach to oxazolidines involved the potentially sluggish carbonyl system as the dipolarophile,[62] it was necessary to choose aziridines whose substituents would render the intermediate azomethine ylide as stable as possible for a successful reaction to occur. Furthermore to permit an assignment of the orientation in the proposed cycloaddition, it was necessary that the 2- and 3-substituents on the aziridine ring be different. For these reasons the 3-aroyl-2-arylaziridine system was chosen, which had the further advantage of being readily prepared by established methods.[145]



The general procedure, outlined in equation [74], involved as the first step, the base catalyzed Claisen-Schmidt condensation of the aldehyde and ketone to form the α,β-unsaturated ketone, known as a chalcone. Addition of bromine readily afforded the corresponding dibromochalcone, which on treatment with at least three equivalents of a primary amine produced the desired aziridine.

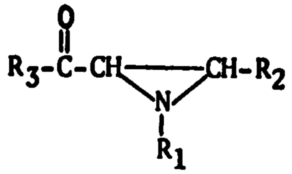


[74]

The yields of these reactions were generally good, and the *cis* and *trans* isomeric aziridines could frequently by separated by fractional crystallization or by chromatography. The stereochemistry of new isomeric aziridines was readily assigned by reference to published infrared and proton magnetic resonance spectra by Cromwell and coworkers.[146,147] The aziridines used in this study were prepared by the method described and are listed in Table XIII, in which new aziridines are indicated by an asterisk.

TABLE XIII

3-Aroyl-2-arylaziridines[†]

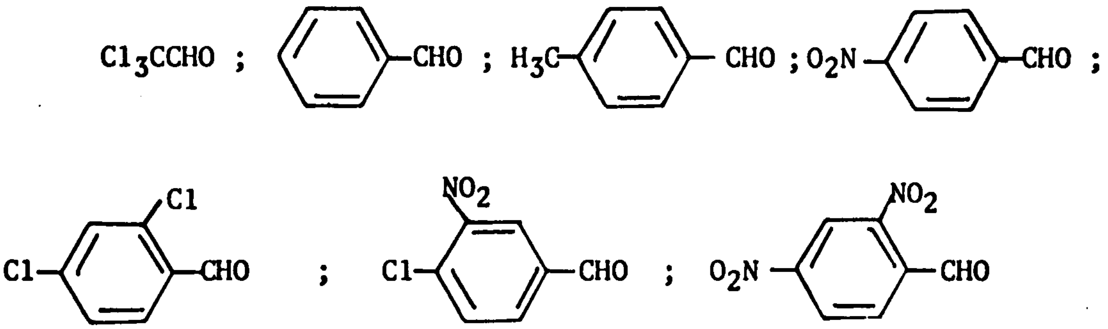


R_1	R_2	R_3	Yield %
$CH(CH_3)_2$	C_6H_5	C_6H_5	100*
$CH(CH_3)_2$	m-O_2N-C_6H_4	C_6H_5	95*
C_6H_{11}	p-O_2N-C_6H_4	C_6H_5	67
C_6H_{11}	m-O_2N-C_6H_4	C_6H_5	88*
C_6H_{11}	C_6H_5	C_6H_5	78
$CH_2C_6H_5$	C_6H_5	C_6H_4-p-CH_3	69
CH_3	C_6H_5	C_6H_5	80
C_6H_{11}	C_6H_5	C_6H_4-p-NO_2	76*

[†] Except where specified isomeric mixtures of aziridines were employed in oxazolidine synthesis.

Dipolarophiles

Aldehydes were chosen as the carbonyl system to function as the dipolarophile rather than ketones, due to their superior reactivity in cycloaddition reactions,[62] and also because the aldehyde proton which would form the C_5 proton of the product oxazolidine, would prove useful in assigning the stereochemistry of the oxazolidine at the 4- and 5-positions by proton magnetic resonance spectroscopy. The aldehydes chosen were chloral and substituted aromatic aldehydes of increasing steric bulk as shown below.

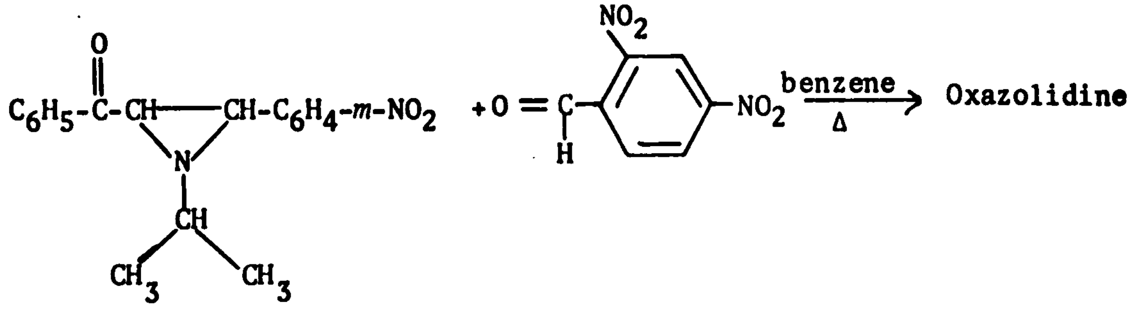


[2+3] Cycloaddition Reactions to form Oxazolidines

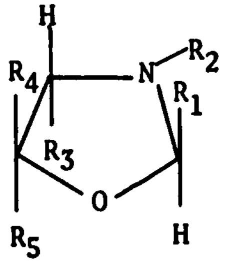
In general the 3-aroyl-2-arylaziridines listed in Table XIII were found to react smoothly with the above aldehydes in equimolar proportions, under conditions of benzene at reflux for periods of twelve to twenty-four hours, to produce in fair to good yields, products which analyzed for 1:1 adducts and which were assigned as oxazolidines.

In a typical reaction 3-benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine reacted with an equimolar quantity of 2,4-dinitrobenzaldehyde in benzene solution under reflux over a period of twenty-one hours to give after isolation, a pale yellow crystalline solid in 65% yield. The elemental analysis and mass spectrum of this pure compound indicated it to be a 1:1 adduct, equation [75].

[75]


O
C_6H_5-C-CH—CH-C_6H_4-m-NO_2
N
CH
CH_3
CH_3
+ O = C
H
NO_2
NO_2
benzene
Δ
Oxazolidine

From the results of a study of a series of like reactions between substituted aziridines and aldehydes, these products were termed oxazolidines and assigned the general structure and stereochemistry as shown in structure 1.


H
R_4
N
R_2
R_1
R_3
O
R_5
H

1

The analytical and spectral data on these new oxazolidines are summarized in Tables XIV, XV, XVI, and XVII.

TABLE XIV Oxazolidines

							Analysis (calc.)				Analysis (found)			
R_1	R_2	R_3	R_4	R_5	m.p.	Yield %	C	H	N	Cl	C	H	N	Cl
C_6H_5	C_3H_7*	COC_6H_5	CCl_3	H	oil	84	-	4.85	3.17	-	-	4.88	2.88	
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	CCl_3	H	111-113°	65	52.46	4.15	6.12	23.28	52.45	4.35	6.15	23.29
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	154-156°	78	55.48	4.62	5.63	21.41	55.44	4.70	5.71	21.70
C_6H_5	$CH_2C_6H_5$	$COC_6H_4pCH_3$	CCl_3	H	130-131°	38	63.22	4.64	2.95	22.45	63.18	4.65	2.96	22.58
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	128-130°	72	55.48	4.62	5.63	21.41	55.76	4.84	5.90	21.70
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_3ClNO_2$	H	118-120°	56	60.53	4.44	8.47	7.16	60.46	4.48	8.46	7.23
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3ClNO_2$	-		60.53	4.44	8.47	7.16	-	-	-	-
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_3ClNO_2$	H	138-140°	44	62.72	4.85	7.84	6.63	62.74	5.04	7.43	6.79
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	$C_6H_3ClNO_2$	-		62.72	4.85	7.84	6.63	-	-	-	-
C_6H_5	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	128-129°	21	72.11	5.77	6.73	-	72.31	5.89	6.72	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	133-135°	71	65.07	4.99	9.11	-	65.07	4.92	9.04	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_4pNO_2$	116-119°		65.07	4.99	9.11	-	65.01	4.90	9.18	-
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	156-158°	25	67.07	5.39	8.38	-	67.11	5.41	8.25	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3(NO_2)_2$	134-136°	65	59.28	4.35	11.07	-	59.28	4.40	10.97	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	C_6H_5	H	121-123°	48	72.11	5.77	6.73	-	72.47	5.74	7.05	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	C_6H_5										
C_6H_5	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	oil	45	73.67	6.14	6.14	-	-	6.13	6.03	-
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	C_6H_5	H	135-138°	44	73.67	6.14	6.14	-	-	6.15	6.43	-
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	C_6H_5										
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	128-131°	57	67.07	5.39	8.38	-	67.03	5.41	8.32	-
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	$C_6H_4pNO_2$										

*C_3H_7 refers to the $(CH_3)_2CH$ group.

TABLE XV Proton Magnetic Resonance Data on Oxazolidines

$\delta^{TMS}_{CHCl_3}$

								AB quartet		
R_1	R_2	R_3	R_4	R_5	Aryl protons	N-substituent	2 proton	4,5 protons *cis*	4,5 protons *trans*	Aryl subst.
C_6H_5	C_3H_7	COC_6H_5	CCl_3	H	7.2-8.4(10H)	$\left.\begin{matrix}0.92\\1.02\end{matrix}\right\}$ overlapping doublets J=7.2 Hz (6H) 2.70-3.24(1H)	5.84(s) 1H	-	5.09 4.83 J=5.7Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	CCl_3	H	7.45-8.69(9H)	0.96(3H,d,J=6.3Hz) 1.02(3H,d,J=6.4Hz) 2.74-3.25(1H)	6.34(s) 1H	-	5.30 4.92 J=4.4Hz	-
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	7.50-8.36(9H)	0.54-2.03(10H) 2.29-2.85(1H)	6.31(s) 1H	-	5.25 4.85 J=4.0Hz	-
C_6H_5	$CH_2C_6H_5$	$COC_6H_4pCH_3$	CCl_3	H	6.90-7.95(14H)	4.13 3.74 J=13.6Hz(2H) AB quartet	5.76(s) 1H	-	5.27 4.65 J=5.7Hz	2.39(s) 3H
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	7.20-8.80(9H)	0.50-2.04(10H) 2.26-2.85(1H)	6.33(s) 1H	-	5.28 4.86 J=4.1Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_3ClNO_2$	H	7.25-8.80(12H)	1.13(6H,d,J=6.5Hz) 2.95-3.51(1H)	6.19(s) 1H	-	5.50 4.58 J=7.2Hz	-
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_3ClNO_2$	H	7.25-8.60(12H)	0.66-2.15(10H) 2.42-3.06(1H)	6.24(s) 1H	-	5.45 4.67 J=6.85Hz	-

TABLE XV ...continued

R_1	R_2	R_3	R_4	R_5	Aryl protons	N-Substituent	2 proton	AB quartet		Aryl subst.
								4,5 protons *cis*	4,5 protons *trans*	
C_6H_5	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	7.00-8.30(14H)	1.03(6H,d,J=6.4Hz) 2.90-3.29(1H)	5.83(s) 1H	-	5.49 4.41 J=7.25Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	7.15-8.76(13H)	1.13(6H,d,J=6.6Hz) 2.92-3.53(1H)	6.23(s) 1H	-	5.59 4.66 J=7.45Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_4pNO_2$	7.08-8.36(13H)	0.79(3H,d,J=6.4Hz) 1.07(3H,d,J=6.4Hz) 3.00-3.66(1H)	6.28(s) 1H	5.77 5.56 J=5.8Hz	-	-
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	7.25-8.67(13H)	0.74-1.99(10H) 2.49-3.01(1H)	6.19(s) 1H	-	5.47 4.69 J=6.95Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3(NO_2)_2$	7.17-8.88(12H)	0.85(3H,d,J=6.5Hz) 1.12(3H,d,J=6.5Hz) 3.18-3.60(1H)	6.42(s) 1H	6.22 6.04 J=5.7Hz	-	-
C_6H_5	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	6.95-8.25(14H)	0.66-2.03(10H) 2.49-3.00(1H)	5.91(s) 1H	-	5.46 4.50 J=7.2Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	C_6H_5	H	7.80-8.66(14H)	0.94(6H,d,J=6.5Hz) 3.00-3.42(1H)	6.09(s) 1H	-	5.32 4.76 J=6.4Hz	-
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	C_6H_5	7.80-8.66(14H)	0.65(3H,d,J=6.3Hz) 0.97(3H,d,J=6.3Hz) 3.00-3.42(1H)	6.19(s) 1H	5.61 5.42 J=5.7Hz	-	-

TABLE XV ...continued

								AB quartet		
R_1	R_2	R_3	R_4	R_5	Aryl protons	N-Substituent	2 proton	4,5 protons *cis*	4,5 protons *trans*	Aryl subst.
$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	C_6H_5	H	6.85-8.62(14H)	0.50-1.89(10H) 2.60-3.15(1H)	6.12(s) 1H	-	5.31 4.91 J=5.9Hz	-
$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	C_6H_5	6.85-8.62(14H)	0.50-1.89(10H) 2.60-3.15(1H)	6.19(s) 1H	5.64 5.48 J=5.55Hz	-	-
$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	$C_6H_4 p NO_2$	7.00-8.60(13)	0.55-1.87(10H) 2.55-3.04(1H)	6.25(s) 1H	5.67 5.54 J=5.6Hz	-	-
$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4 p NO_2$	H	7.00-8.60(13H)	0.55-1.87(10H) 2.55-3.04(1H)	6.17(s) 1H	-	5.41 4.64 J=6.7Hz	-

TABLE XVI

Infrared and Mass Spectral Data on Oxazolidines

R_1	R_2	R_3	R_4	R_5	$CHCl_3$ $\nu_{max} cm^{-1}$	Calculated Mass spec - principal fragments	Measured
C_6H_5	C_3H_7	COC_6H_5	CCl_3	H	1680s(C=0)	306.0221($C_{13}H_{15}Cl_3NO$;M-C_6H_5CO)	306.0224
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	CCl_3	H	1688m }C=0 1678s 1528(NO_2)	310.1317($C_{18}H_{18}N_2O_3$;M-C_2HCl_3)	310.1321
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	1690m }C=0 1668s 1521(NO_2)	391.0383($C_{16}H_{18}Cl_3N_2O_3$;M-C_6H_5CO)	391.0390
C_6H_5	$CH_2C_6H_5$	$COC_6H_4pCH_3$	CCl_3	H	1678 (C=0)	354.0219($C_{17}H_{15}Cl_3NO$;M-$CH_3C_6H_4CO$)	354.0222
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	1690m }C=0 1675s 1530 (NO_2)	391.0383($C_{16}H_{18}Cl_3N_2O_3$;M-C_6H_5CO)	391.0390
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_3ClNO_2$	H	1685s(C=0)	184.9880($C_7H_4ClNO_3$;M-$C_{18}H_{18}N_2O_3$)	184.9882
					1531(NO_2)	310.1317($C_{18}H_{18}N_2O_3$;M-$C_7H_4ClNO_3$)	310.1318
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_3ClNO_2$	H	1680s(C=0) 1519(NO_2)	-	-
C_6H_5	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	1660(C=0) 1517(NO_2)	311.1396($C_{18}H_{19}N_2O_3$;M-C_6H_5CO)	311.1398
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	1684(C=0)	151.0269($C_7H_5NO_3$;M-$C_{18}H_{18}N_2O_3$)	151.0269
					1521(NO_2)	310.1317($C_{18}H_{18}N_2O_3$;M-$C_7H_5NO_3$)	310.1319

TABLE XVI ...continued

R_1	R_2	R_3	R_4	R_5	$CHCl_3$ $\nu_{max}cm^{-1}$	Calculated Mass spec - principal fragments	Measured
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_4pNO_2$	1683(C=O)	151.0269($C_7H_5NO_3$;M-$C_{18}H_{18}N_2O_3$)	151.0269
					1521(NO_2)	310.1317($C_{18}H_{18}N_2O_3$;M-$C_7H_5NO_3$)	310.1319
$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	1685s(C=O)	151.0269($C_7H_5NO_3$;M-$C_{21}H_{22}N_2O_3$)	151.0270
					1520(NO_2)	350.1630($C_{21}H_{22}N_2O_3$;M-$C_7H_5NO_3$)	350.1634
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3(NO_2)_2$	1678m(C=O)	196.0216($C_7H_4N_2O_5$;M-$C_{18}H_{18}N_2O_3$)	196.0213
					1528s(NO_2)	310.1317($C_{18}H_{18}N_2O_3$;M-$C_7H_4N_2O_5$)	310.1319
C_6H_5	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	1680(C=O)	151.0269($C_7H_5NO_3$;M-$C_{21}H_{23}NO$)	196.0213
					1516 (NO_2)	305. ($C_{21}H_{23}NO$;M-$C_7H_5NO_3$)	305.
$mO_2NC_6H_4$	C_3H_7	COC_6H_5	C_6H_5	H	1680s(C=O)	310.1317($C_{18}H_{18}N_2O_3$;M-C_7H_6O)	310.1321
			H	C_6H_5	1526(NO_2)	106.0419(C_7H_6O;M-$C_{18}H_{18}N_2O_3$)	106.0419
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	C_6H_5	H	1681s(C=O)	350.1630($C_{21}H_{22}N_2O_3$;M-C_7H_6O)	350.1634
			H	C_6H_5	1528s(NO_2)	106.0419(C_7H_6O;M-$C_{21}H_{22}N_2O_3$)	106.0418
$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	1678m(C=O)	151.0269($C_7H_5NO_3$;M-$C_{21}H_{22}N_2O_3$)	151.0270
			H	$C_6H_4pNO_2$	1528(NO_2)	350.1630($C_{21}H_{22}N_2O_3$;M-$C_7H_5NO_3$)	350.1634

TABLE XVII

					Proton Magnetic Resonance Spectrum $\delta_{CDCl_3}^{TMS}$			4,5 protons *cis*	4,5 protons *trans*
R_1	R_2	R_3	R_4	R_5	Aryl protons	N-Substituent	2 proton		
m$O_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3ClNO_2$	7.20-8.70(12H)	0.95-1.20(6H) 3.40-3.90(1H)	6.27(s)1H	5.72 J=5.4Hz 5.56	-
C_6H_5	C_3H_7	COC_6H_5	C_6H_5	H	6.90-8.33(15H)	0.98 (6H,d,J=6.6Hz) 2.90-3.20(1H)	5.79(1H)s	-	5.27 J=7.35Hz 4.56
C_6H_5	CH_3	COC_6H_5	C_6H_5	H	6.96-8.15(15H)	2.29(s,3H)	5.28(1H)s	-	5.57 J=7.90Hz 4.15
C_6H_5	C_6H_{11}	COC_6H_4*p*NO_2	C_6H_4*p*NO_2	H	7.33-8.55(14H)	0.83-2.00(10H) 2.20-2.56(1H)	5.94(1H)s	-	5.60 J=6.15Hz 4.38
C_6H_5	C_3H_7	COC_6H_5	C_6H_4*p*CH_3	H	6.60-7.91(14H) 2.09(3H, aryl CH_3)	0.79(6H,d,J=6.5Hz) 2.60-3.14(1H)	5.61(1H)s	-	5.13 J=7.35Hz 4.40

It should be noted that in preliminary reactions with 3-benzoyl-1-isopropyl-2-phenylaziridine and benzaldehyde, 4-methylbenzaldehyde, and 4-methoxybenzaldehyde, considerable difficulty was experienced in isolation of the intended product from the crude reaction mixture due to its lack of crystallinity. This obstacle was overcome by employing aziridines containing nitro groups on the aromatic rings, and afterwards little difficulty was encountered in obtaining crystalline products even with the above aldehydes.

Examination of Table XIV shows that about half of the reactions studied resulted in a single isomer for the product oxazolidine, while the remainder gave *cis,trans* mixtures, most of which could not be separated despite several efforts to this end. In the single case studied, 2,4-dichlorobenzaldehyde produced a mixture of several products which could not be identified, and was thereafter not further studied. The best yields were obtained from chloral which gave only one isomer in each case.

Table XV reveals that the oxazolidines obtained from aromatic aldehydes fall into two classes. The proton magnetic resonance spectra of the larger class exhibited a singlet for the oxazolidine 2 proton and a relatively widely spaced AB quartet (J = 7.45-5.90 Hz) for the 4 and 5 protons. The smaller group showed a singlet for the 2 proton and a much more closely spaced AB quartet with a consistently smaller coupling constant (J = 5.80-5.55 Hz). Furthermore for any particular pair of isomers considered, the compound with the larger coupling always showed the oxazolidine 2 proton at higher field. In cases where the nitrogen was substituted with an isopropyl group, a relatively widely spaced doublet of doublets was obtained for the isopropyl methyl groups (J = 6.5-6.3 Hz) in the smaller group of compounds mentioned above. The larger group showed either a singlet or overlapping doublets for these methyl groups.

The significance of these observations, which were consistent throughout the series, will be discussed later. As will also be shown, the larger group of oxazolidines from aromatic aldehydes have been assigned *trans*-1 stereochemistry (R_5=H), at the 4- and 5-positions, while to the smaller group the *cis*-1 stereochemistry has been given (R_4=H).

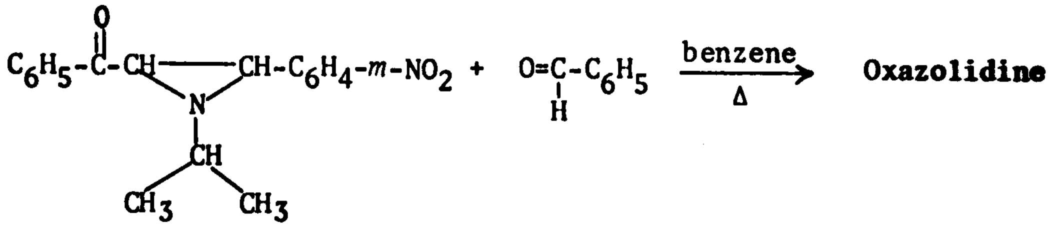
The additions of chloral were quite clean and produced exclusively *trans*-1 structures. It was also found that in the aromatic aldehyde series, benzaldehyde produced mixtures of about 60:40 *cis*-1 to *trans*-1, while 4-chloro-3-nitrobenzaldehyde gave 60:40 *trans*-1 to *cis*-1 isomeric oxazolidines. From 4-nitrobenzaldehyde, 50:50 mixtures were obtained, while in the example studied 2,4-dinitrobenzaldehyde produced exclusively *cis*-1.

The infrared spectra of these oxazolidines (Table XVI) showed a strong band at 1690-1675 cm^{-1}, indicative of aromatic ketones,[148] and in the relevant examples the intense band at 1530-1520 cm^{-1}, was characteristic of aromatic nitro groups.[148]

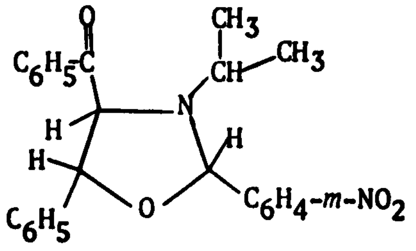
A feature of the mass spectra (Table XVI) was that with but two exceptions, no molecular ion was detected, though two principal fragments corresponding in total to the molecular ion were always observed. Two modes of cleavage were observed. The principal one involved cleavage of the oxazolidine along the $O-C_2$ and C_4-C_5 bonds respectively, while the minor mode of cleavage involved loss of the benzoyl group from the C_4 position of the oxazolidine ring.

Table XVII shows the proton magnetic resonance data on oxazolidine isomers which could not be isolated due to experimental difficulty.

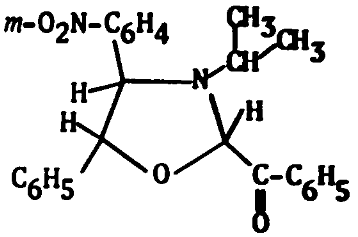
On the evidence presented in Tables XIV, XV, XVI, and XVII, three possible gross structures for the product oxazolidine could be envisaged that would fit the experimental findings. The structures, 2, 3, and 4 imply no stereochemistry at this point, and the reaction expressed by equation [76] will be used as an illustration.



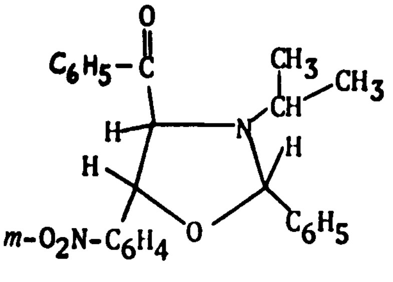
[76]



Class A 2



3 Class B

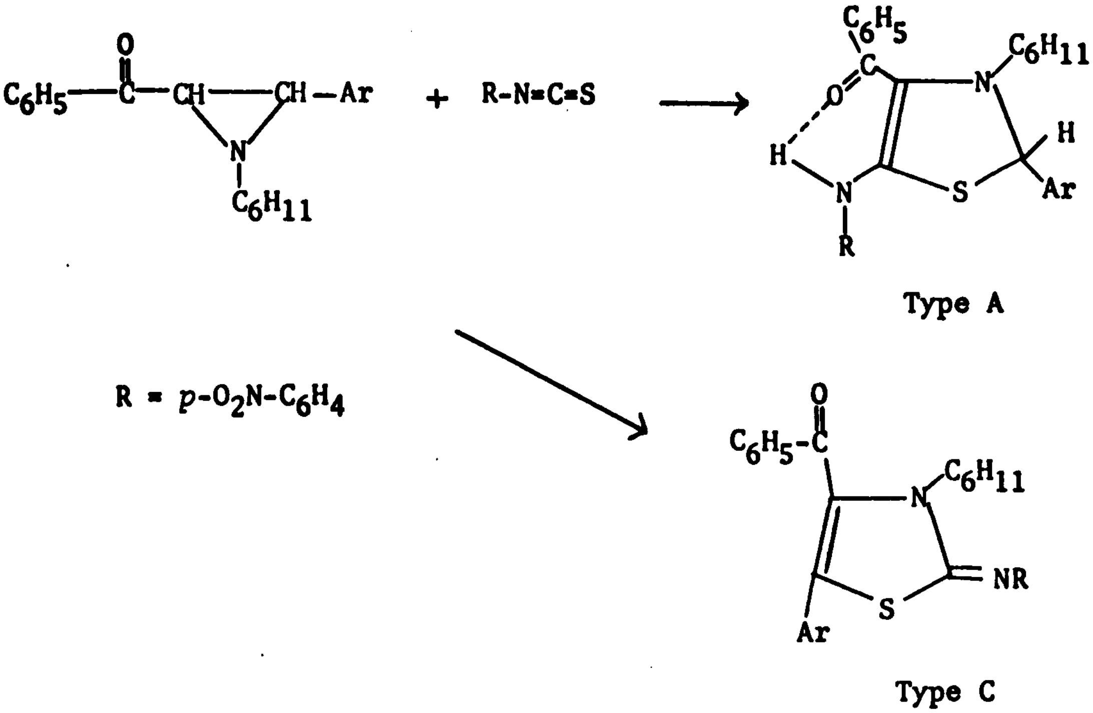


Class C 4

In the problem of unambiguous structure assignment to this product and those from other related reactions, several important factors must be taken into consideration. The first of these is the gross structure of the product, which may be one of the three classes of isomeric oxazolidines A, B, or C. Thermal cleavage of the aziridine ring to the intermediate azomethine ylide and [2+3] cycloaddition with the aldehyde would explain the products of class A and B. The third class, type C, could be envisaged as arising from a ring expansion reaction involving cleavage of the 1,2-bond of the aziridine ring. It is possible that this reaction might proceed by a nucleophilic attack at the more electrophilic 2-position of the aziridine ring,[149] followed by a ring expansion reaction. However in this discussion, a reaction of this type will be referred to as the "ring expansion" reaction in order that no unwarranted assumptions need be made about its mechanism.

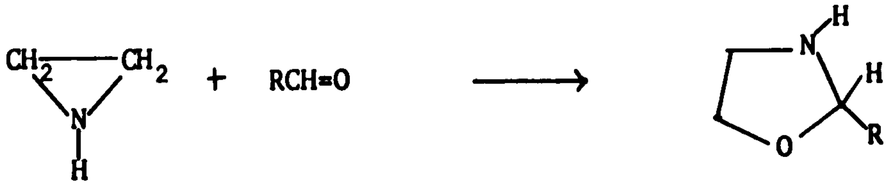
It was expected that products of several types might occur in this kind of reaction in view of the results obtained by Lown and coworkers in studies of 3-aroyl-2-arylaziridines with aryl isothiocyanates to form (a) 4-aroyl-5-arylamino-4-thiazolines (Type A) or (b) 2-arylimino-4-aroyl-4-thiazolines (Type C),[150] equation [77].

[77]



Similar results have very recently been obtained by Lown and Matsumoto in reactions of 3-aroyl-2-(2-thienyl)aziridines with aryl isothiocyanates,[151] and it appears that the size of the N-substituent controls the type of product obtained (Class A or C).[151,152] Furthermore the literature contained precedents for reactions which apparently led to oxazolidines of class C in instances where the aziridine ring contained no N-substituent,[153] equation [78].

[78]

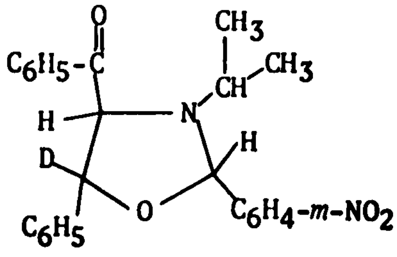


However the validity of this result has been questioned in recent years by Hillers and Lidaks.[154,155,156]

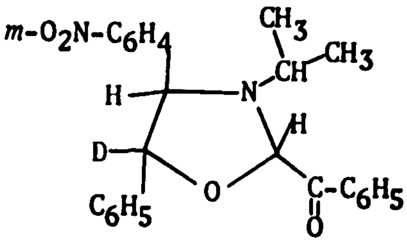
Distinction between [2+3] cycloaddition and ring expansion product oxazolidines.

3-Benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine and benzaldehyde were found to react in benzene solution under reflux to produce a mixture of approximately 60:40 isomeric oxazolidines as estimated by p.m.r. integration of the spectrum in Figure IVA. Examination of this p.m.r. spectrum of the products from equation [76], revealed that no clear cut distinction could be made between structures 2, 3, and 4 on this basis.

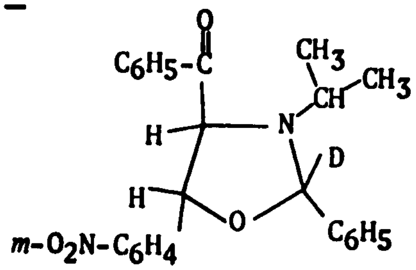
Accordingly when the reaction was repeated with α-D-benzaldehyde, (99.5% deuterium incorporation), a mixture of analogous deuterated oxazolidines was obtained in approximately the same proportions (67:33). Structures 5, 6, and 7 show the compositions of the possible products.


O
C_6H_5-C
CH_3
CH
CH_3
H
N
H
D
C_6H_5
O
C_6H_4-*m*-NO_2

5


m-O_2N-C_6H_4
CH_3
CH
CH_3
H
N
H
D
C_6H_5
O
C-C_6H_5
O

6

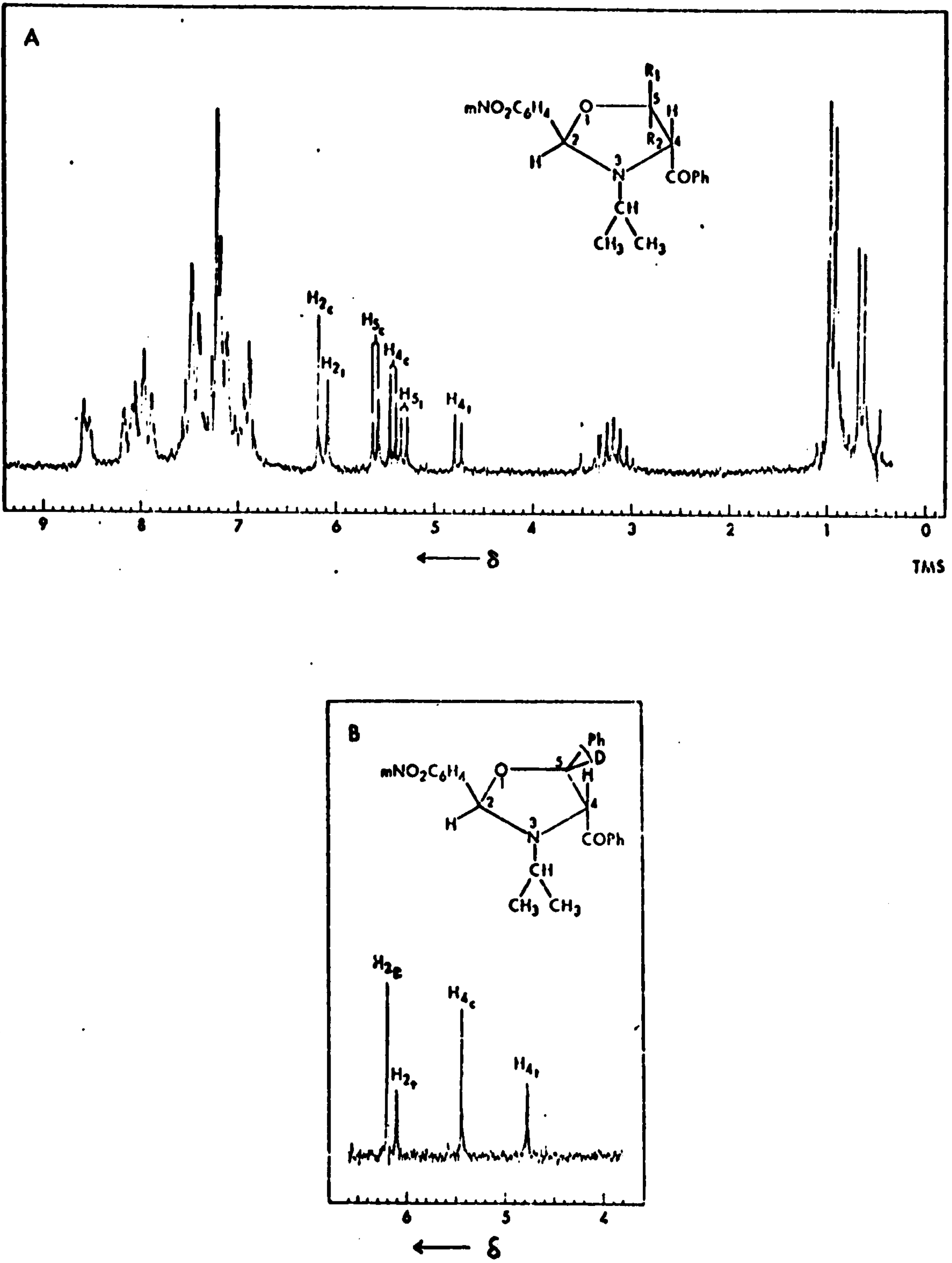

O
C_6H_5-C
CH_3
CH
CH_3
H
N
D
H
O
m-O_2N-C_6H_4
C_6H_5

7

The spectrum of the product (Figure IVA), showed that the two sharp singlets attributed to the 2 protons of the isomeric oxazolidines were undiminished, whereas the two AB quartets were now replaced by a pair of sharp singlets for the C_4 protons of isomeric oxazolidines. Since the deuterium incorporation was found to be almost 100% at the 5-positions, it is clear that the ring-expansion product structure 7 may be excluded from further consideration, since for this structure an unaffected AB quartet would be expected, and no singlet at all for the oxazolidine 2 proton.

On this basis structure 4 in the protium series can also be eliminated from consideration.

Figure IV



Proton magnetic resonance spectra at 100 MHz in $CDCl_3$ of (A) 4-benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine (B) methine protons of 4-benzoyl-5-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine.

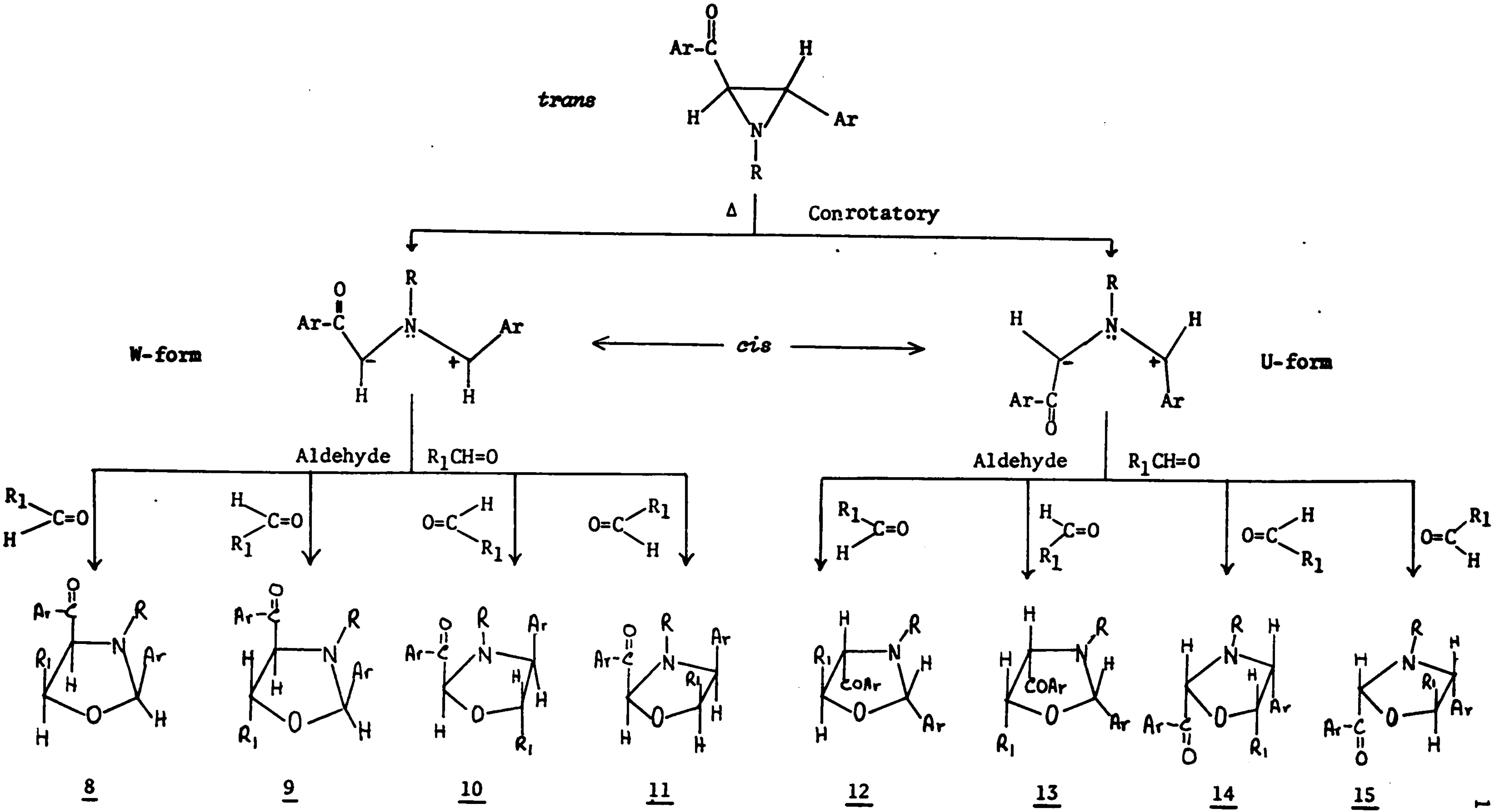
With this done, three possibilities still existed for the pair of isomeric oxazolidines from the deuterium labelling experiment. They could be *cis*- and *trans*-5, *cis*- and *trans*-6 or a pair of structural isomers from 5 and 6. The same possiblities existed for the protium compounds 2 and 3.

This problem was resolved by evidence derived from further critical deuterium labelling experiments described below, from which it was found that the above products were in fact *cis*- and *trans*-isomers of structures 2 and 5.

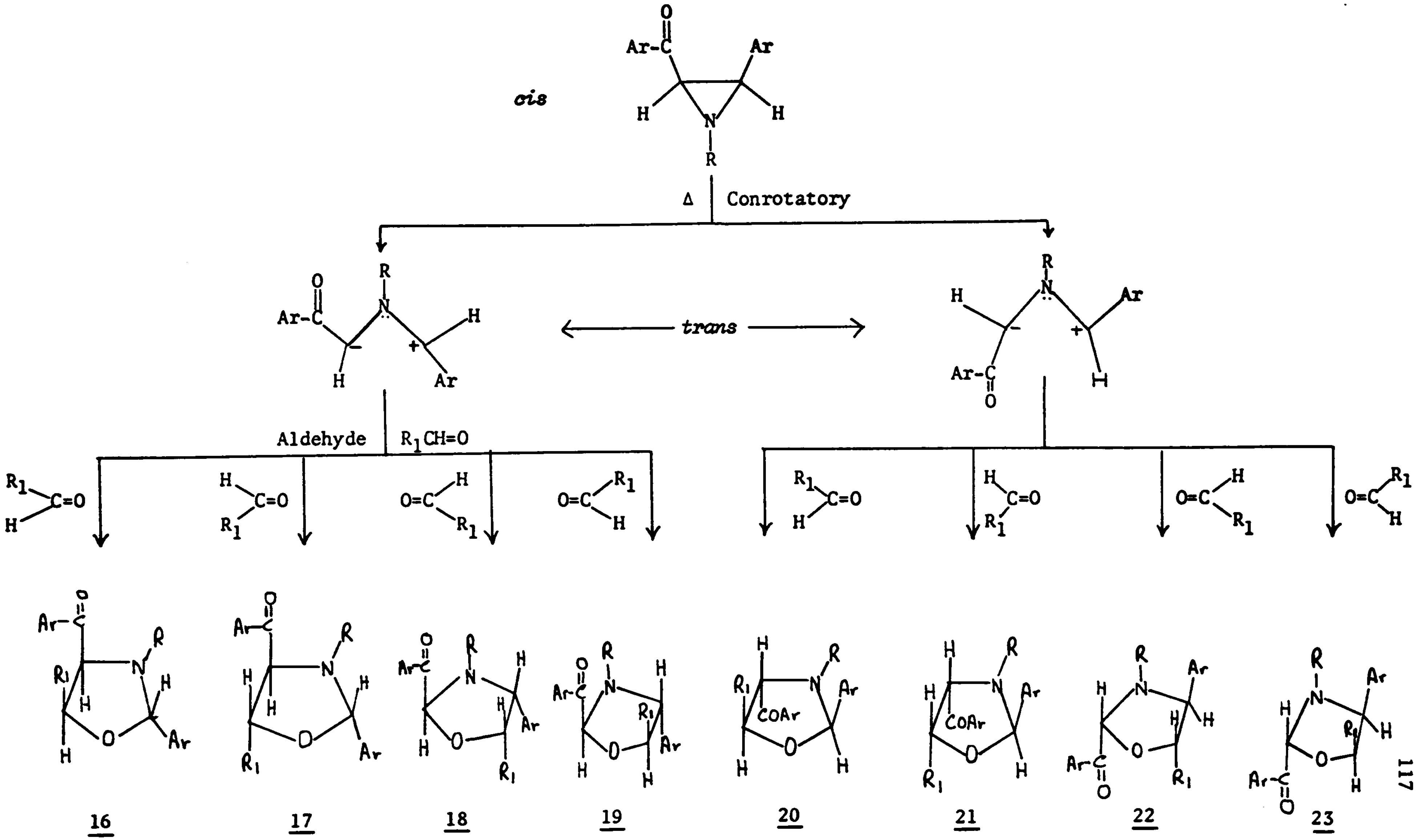
Orientation of the [2+3] cycloaddition reaction

The second important point to consider is the cycloaddition orientation with respect to the geometry of the aziridine and to the aldehyde dipolarophile. As will be shown this gives rise to, in principle, sixteen possible stereoisomeric oxazolidines representing eight racemic pairs.

It has been demonstrated by Huisgen and coworkers,[115] that under thermal conditions substituted aziridines cleave along the 2-3 bond in a conrotatory manner in accordance with the predictions of Woodward and Hoffmann[54] to form azomethine ylides. The *cis*-aziridine furnished the *trans*-ylide,while the *trans*-aziridine produced the *cis*-azomethine ylide. Furthermore since the aziridines used in this study possessed different substituents at the 2- and 3-positions, the *trans*-azomethine ylide could adopt two orientations, while for the *cis*-ylide the U (horse-shoe) and W forms[118] were possible. For each of these four azomethine ylides there existed four possible orientations of the aldehyde dipolarophile, giving a total of sixteen isomeric oxazolidines as shown below in Scheme I.


trans
Δ
Conrotatory
W-form
cis
U-form
Aldehyde
$R_1CH=O$
Aldehyde
$R_1CH=O$
8
9
10
11
12
13
14
15

Scheme I


cis
Δ
Conrotatory
trans
Aldehyde
R₁CH=O
16
17
18
19
20
21
22
23

Scheme I

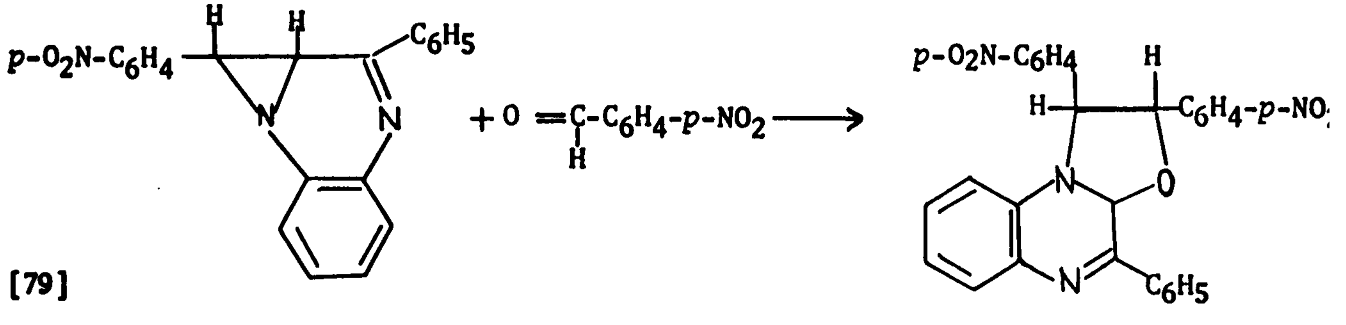
Examination of Scheme I shows that the racemic pairs of structures are 8 and 13, 9 and 12, 10 and 15, 11 and 14, for the oxazolidines from the *trans*-aziridine, and 16 and 21, 17 and 20, 18 and 23, 19 and 22 for the oxazolidines from the *cis*-aziridine.

Evidence will now be presented to show that from all these possible structures, only 16 and 17, (and 21 and 20) are in accordance with the experimental results.

As this work progressed, references appeared in the literature concerning this type of [2+3] cycloaddition reaction of aziridines and aldehydes. In a review by Huisgen in 1967,[144] an N-aroyl-*trans*-2,3-dicarbomethoxyaziridine was reported to have reacted with benzaldehyde to produce an oxazolidine in 97% yield, equation [73]. Since a symmetrical aziridine had been employed, there was no question regarding the orientation of the cycloaddition, though it was reported that three stereoisomers were obtained. The problem was apparently not further resolved.

In 1969, Heine and Henzel[108] studied the addition reaction of 4-nitrobenzaldehyde to a bicyclic aziridine, 1,1a-dihydro-1-(4-nitrophenyl)-2-phenylazirion[1,2-a]quinoxaline 24, to give 1,2-dihydro-1,2-di(4-nitrophenyl)-4-phenyl-3aH-oxazolo[3,2-a]quinoxaline, 25, equation [79].

[79]

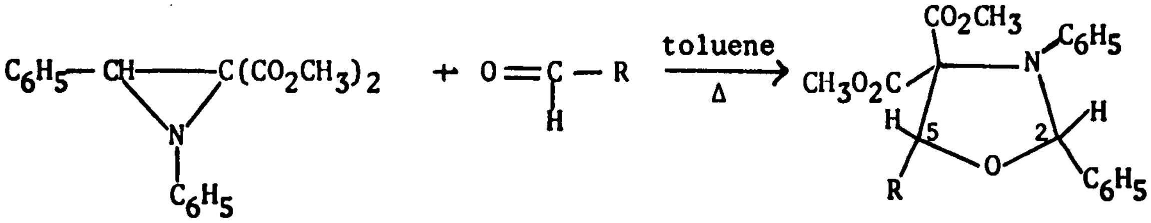

p-O2N-C6H4
H
H
C6H5
N
N
+ O =C-C6H4-p-NO2
H
p-O2N-C6H4
H
H
C6H4-p-NO
N
O
N
C6H5

24

25

The assignment by these workers of the orientation of addition was solely in the direction shown, but it should be noted that the assignment was based on proton magnetic resonance line positions and no attempt was made to study the stereochemistry of the reaction. This orientation of addition with the bicyclic aziridine is opposite to that assigned to the series of simpler aziridines in this work.

Texier and Carrie[157] have also reported a synthesis of oxazolidines by [2+3] cycloaddition reactions of an azomethine ylide with aliphatic and aromatic aldehydes, equation [80].


C6H5—CH——C(CO2CH3)2
N
C6H5
+ O=C—R
H
toluene
Δ
CO2CH3
CH3O2C
N
C6H5
H
5
2
H
O
R
C6H5

[80]

R = CH_3 26

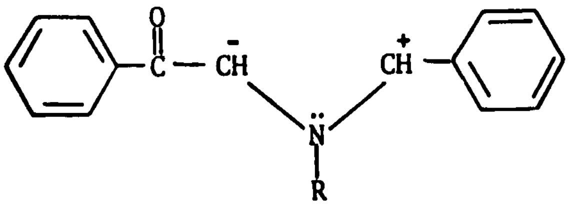
R = C_6H_5 27

R = C_6H_5-p-OCH_3 28

Their products, which were stable to attempted epimerization, were oriented solely in the direction shown in equation [80]. In some cases ($R=C_6H_5$), they obtained isomeric mixtures of oxazolidines which differed in the relative configurations at C_2 and C_5. The C_2 proton of their compounds was not coupled in the proton magnetic resonance spectrum and was always characterized by a singlet, independent of the nature of the R group.

Huisgen has stated[62] that the orientation of [2+3] cycloaddition reactions may not be safely predicted on the basis of an assumed assignment of nucleophilic and electrophilic centers in the 1,3-dipole. The results of Heine[108] and Texier[157] reported above would tend to support this statement, since their oxazolidines are oriented in the opposite directions.

Huisgen has also stated[62] that resonance formula with electron sextets, though they make at best a small contribution to the ground state of the 1,3-dipole, are capable of directing the course of reaction. The main sextet form of the azomethine ylides concerned in this work is given in structure 29.



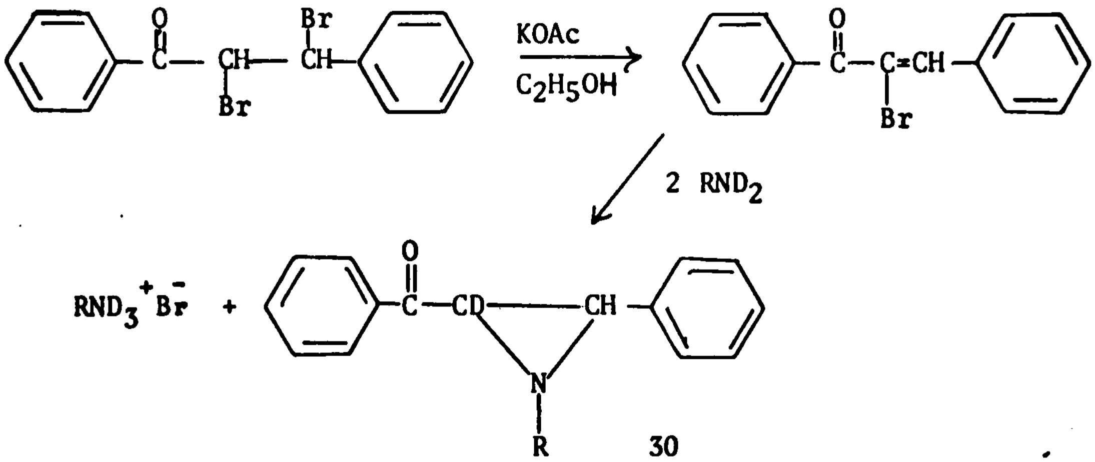
29

This might be expected, in the case of aldehyde dipolarophiles, to lead to products oriented in the fashion of the oxazolidines obtained by Texier and Carrie.[157]

Distinction between the two possible orientations of the [2+3] cycloaddition

A series of specifically 3-deuterated aziridines were prepared and reacted in [2+3] cycloadditions with the group of aldehydes previously mentioned to form deuterated oxazolidines in fair yields. The 3-deuterated aziridines were prepared by the general method of Lown, Moser, and Westwood[158] as shown in equation [81].

[81]



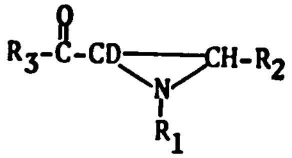
30

The readily available dibromochalcones were dehydrobrominated in good yields to the corresponding monobromochalcones using potassium acetate in ethanol solution. The carefully dried product was then treated in anhydrous ether with completely deuterated primary amines to afford the 3-deuterated aziridines. The extent of deuterium incorporation was determined by proton magnetic resonance spectroscopy.

A series of five such compounds were prepared and the yields and percentage deuterium incorporation are summarized in Table XVIII.

TABLE XVIII

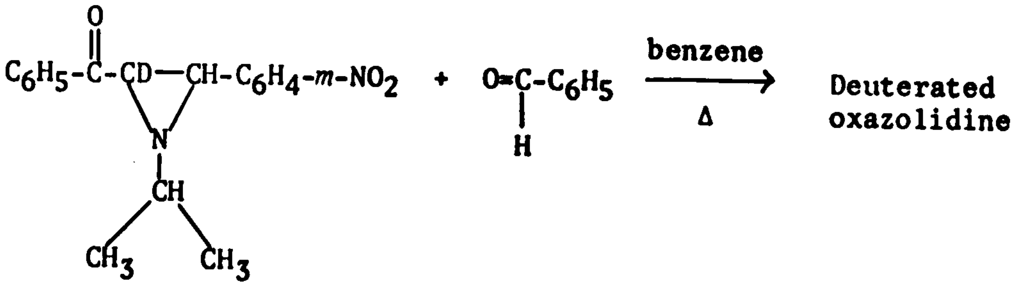
3-Deuteroaziridines


O
R3-C-CD
CH-R2
N
R1

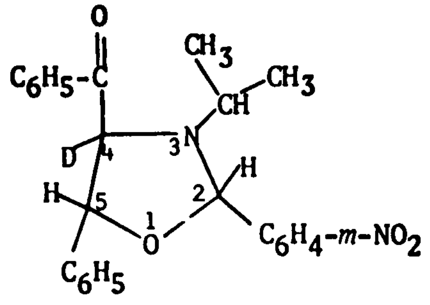
R_1	R_2	R_3	Yield %	D incorporation %
$CH_2C_6H_5$	C_6H_5	C_6H_4-*p*-CH_3	46	70
C_6H_{11}	C_6H_4-*p*-NO_2	C_6H_5	63	69
C_6H_{11}	C_6H_4-*m*-NO_2	C_6H_5	57	70
C_3H_7	C_6H_4-*m*-NO_2	C_6H_5	65	85
C_6H_{11}	C_6H_5	C_6H_4-*p*-NO_2	72	60

3-Benzoyl-3-deutero-1-isopropyl-2-(3-nitrophenyl)aziridine prepared in this manner (85% D incorporation), reacted with freshly distilled benzaldehyde to produce a pair of isomeric deuterated oxazolidines, equation [82].

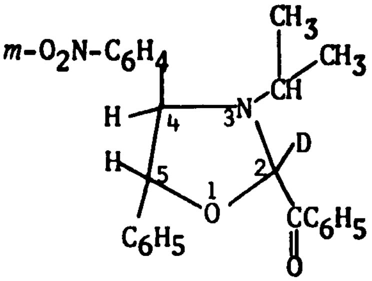
[82]


O
C6H5-C-CD—CH-C6H4-m-NO2
N
CH
CH3
CH3
+
O=C-C6H5
H
benzene
Δ
Deuterated
oxazolidine

Since the product of ring expansion had been excluded, two gross structures remained to be considered.



31



32

In the proton magnetic resonance spectrum, singlets for the 2 protons, and a diminished AB quartet for the 4 and 5 protons would be expected for structure 31. For structure 32, diminished singlets for the 2 protons, and unaffected AB quartets for the 4 and 5 protons would be expected for the isomeric product. One of the isomers was separated from the mixture and the p.m.r. spectrum of the compound showed a singlet at 6.10δ (1H) due to the 2 proton, and a diminished AB quartet centred at 4.76δ (0.3H) and 5.32 (1H) with J = 6.40 Hz (Figure VC). The remaining isomeric mixture contained a small quantity of the above isomer, plus the second isomer the p.m.r. spectrum of which showed a singlet at 6.20δ (1H) and a diminished AB quartet centred at 5.42δ (0.3H) and 5.61δ (1H) with J = 5.70 Hz (see Figure VC and D).

It is clear that both compounds were consistent with the gross structure 31 but not with 32, a conclusion which was later confirmed by acid hydrolysis experiments to be described. It is interesting to note that this unambiguous proof of the direction of orientation is in accordance with the results of Texier and Carrier,[157] and with recent work of Lown and coworkers,[150,151,158,159,160] and will receive further support in Chapter III of this thesis.

Having eliminated the ring expansion product and solved the mode of orientation it was concluded that the isomeric oxazolidines were *cis* and *trans* isomers of structures like 31. With this information the p.m.r. line positions of all three protons in each oxazolidine may be unambiguously assigned (see Tables XV and XVII).

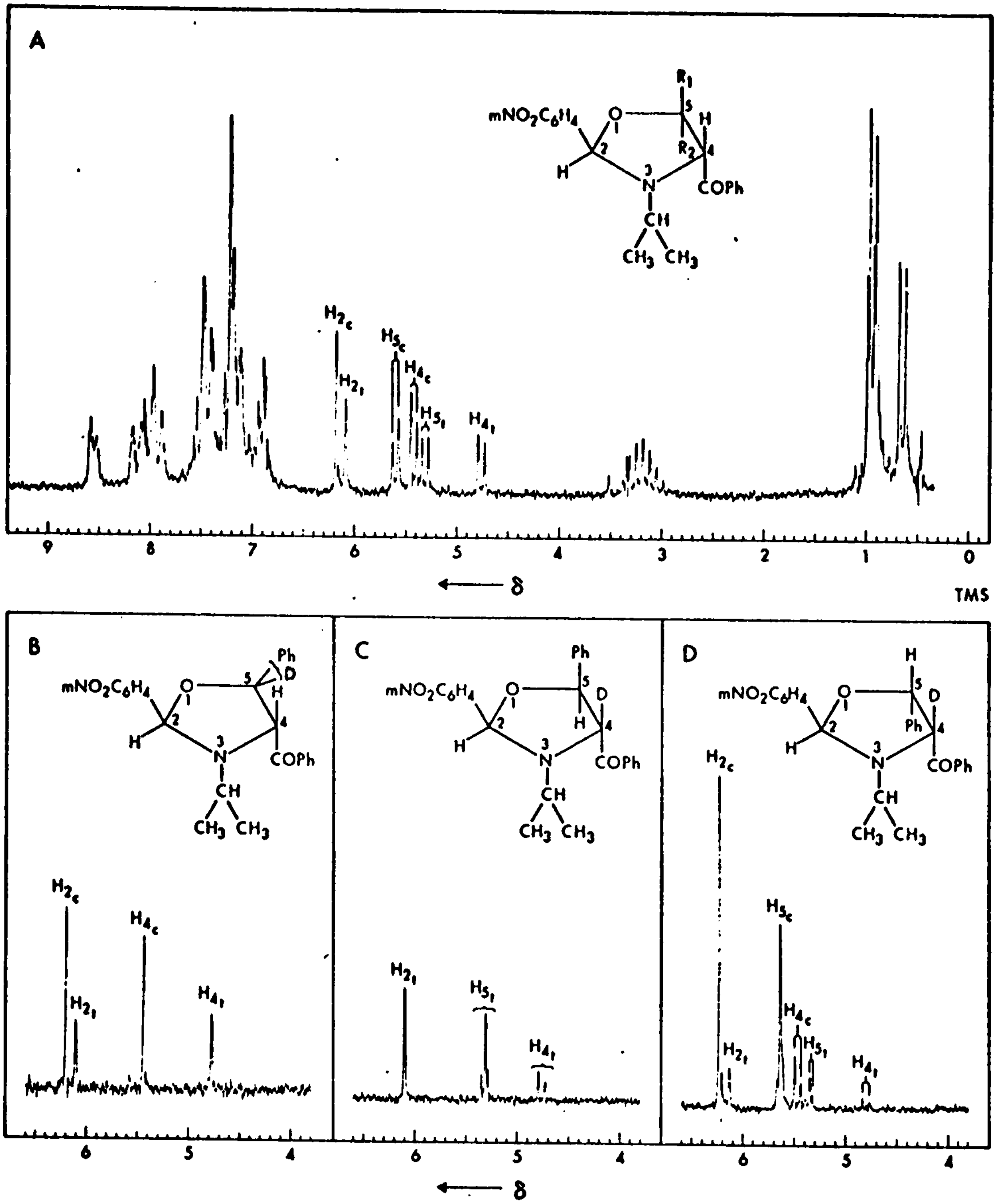


Figure V Nuclear magnetic resonance spectra at 100 MHz in $CDCl_3$ of (A) 4-benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine (B) methine protons of 4-benzoyl-5-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine (C) methine protons of 4,5-*trans*-4-benzoyl-4-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine (D) methine protons of 4,5-*cis*-4-benzoyl-4-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine.

The p.m.r. integration of the oxazolidine isomers in the experiment described indicated 68% incorporation of deuterium in the oxazolidine compared with 85% in the aziridine substrate (see Table XVIII). An analogous diminution of the extent of deuterium incorporation from aziridine to oxazolidine was observed in a series of related reactions. This should be contrasted with the cycloaddition of α-D-benzaldehyde, which gave virtually quantitative transfer of deuterium into the oxazolidine.

The loss of deuterium mentioned above has been attributed to leakage from the azomethine ylide intermediate, for independent experiments have shown that the oxazolidines are completely resistant to epimerization at the 4-position. This conclusion was supported by results from investigations of the stereochemistry of these cycloaddition reactions which will be described later. The leakage may be attributed to the relatively sluggish reactivity of the aldehyde as a dipolarophile, which enables the azomethine ylides to equilibrate and partially exchange prior to addition.

The above results were substantiated by analogous experiments with other specifically deuterated aziridines from Table XVIII to yield 4-D-oxazolidines, the proton magnetic resonance spectra and mass spectra of which are summarized in Tables XIX and XX.

TABLE XIX

4-D-Oxazolidines

Aziridine precursor % D incorp	Oxazolidine					$\delta_{CDCl_3}^{TMS}$			AB quartet			
	R_1	R_2	R_3	R_4	R_5	Aryl protons + aryl subst.	N-substituent	2 Proton	4 Proton	5 Proton	J (Hz)	% D incorp
69	$pO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	7.27-8.39 (9H)	0.66-2.00(10H) 2.33-2.74(1H)	6.34(s) (1H)	5.25 (0.32H)	4.86 (1H)	4.2	68
85	$mO_2NC_6H_4$	C_3H_7	COC_6H_5	CCl_3	H	7.40-8.80 (9H)	0.92 } over lapping dou- 0.98 } lets(6H) J=6.6Hz 2.91-3.19(1H)	6.31(s) (1H)	5.26 (0.32H)	4.88 (1H)	4.3	68
70	C_6H_5	$CH_2C_6H_5$	$COC_6H_4pCH_3$	CCl_3	H	7.0-7.86 (14H) 2.34(3H, s,CH_3)	4.04 3.75 J=13.7Hz(2H) benzyl CH_2	5.74(s) (1H)	4.64 (0.53H)	5.24 (1H)	5.65	47
70	C_6H_5	$CH_2C_6H_5$	$COC_6H_4pCH_3$	H	CCl_3	7.00-7.86 (14H) 2.24(3H, aryl CH_3)	3.70 3.44 J=14.0Hz(2H) benzyl CH_2	6.00(s) (1H)	5.07 (0.56H)	4.88 (1H)	3.4	46
70	$mO_2NC_6H_4$	C_6H_{11}	COC_6H_5	CCl_3	H	7.40-8.71 (9H)	0.60-2.00(10H) 2.38-2.78(1H)	6.35(s) (1H)	5.26 (0.46H)	4.85 (1H)	4.15	54
85	$mO_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_3(NO_2)_2$	7.14-8.70 (12H)	0.75(3H,d, J=6.35Hz) 1.03(3H,d, J=6.35Hz) 3.07-3.46(1H)	6.38(s) (1H)	5.98 (0.33H)	6.09 (1H)	5.7	67

TABLE XIX ... continued

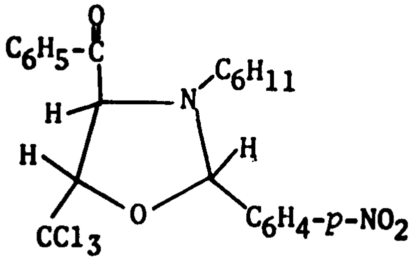
Aziridine precursor % D incorp	Oxazolidine					$\delta_{CDCl_3}^{TMS}$			AB quartet			
	R_1	R_2	R_3	R_4	R_5	Aryl protons + aryl subst.	N-Substituent	2 Proton	4 Proton	5 Proton	J (Hz)	% D Incorp
85	$m O_2NC_6H_4$	C_3H_7	COC_6H_5	$C_6H_4pNO_2$	H	7.05-8.60 (13H)	1.01(6H,d, J=6.5Hz) 2.92-3.38(1H)	6.12(s) (1H)	4.57 (0.31H)	5.46 (1H)	7.40	68
85	$m O_2NC_6H_4$	C_3H_7	COC_6H_5	H	$C_6H_4pNO_2$	7.05-8.60 (13H)	0.68(3H,d, J=6.2Hz 0.97(3H,d, J=6.2Hz) 2.92-3.38(1H)	6.22(s) (1H)	5.53 (0.34H)	5.68 (1H)	5.8	66
70	$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	$C_6H_4pNO_2$	H	7.06-8.60 (13H)	0.58-1.92(10H) 2.42-3.06(1H)	6.17(s) (1H)	4.64 (0.37H)	5.41 (1H)	6.7	64
70	$m O_2NC_6H_4$	C_6H_{11}	COC_6H_5	H	$C_6H_4pNO_2$	7.06-8.60 (13H)	0.58-1.92(10H) 2.42-3.06(1H)	6.25(s) (1H)	5.54 (0.37H)	5.67 (1H)	5.75	63
85	$m O_2NC_6H_4$	C_3H_7	COC_6H_5	C_6H_5	H	7.21-8.58 (14H)	0.95(3H,d, J=6.5Hz) 0.98(3H,d, J=6.5Hz) 2.97-3.28(1H)	6.09(s) (1H)	4.76 (0.30H)	5.30 (1H)	6.3	70
85	$m O_2NC_6H_4$	C_3H_7	COC_6H_5	H	C_6H_5	6.90-8.70 (14H)	0.69(3H,d, J=6.2Hz) 0.98(3H,d, J=6.2Hz) 3.09-3.44(1H)	6.23(s) (1H)	5.46 (0.26H)	5.63 (1H)	5.7	74

TABLE XX

4-D-Oxazolidines

R_1	R_2	R_3	R_4	R_5	Calculated Mass Spec - principal fragments	Measured
$p\mathrm{O_2NC_6H_4}$	C_6H_{11}	COC_6H_5	CCl_3	H	392.0463($C_{16}H_{17}DCl_3^{35}N_2O_3$;M-$C_6H_5CO$)	392.0470
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	CCl_3	H	352.0150($C_{13}H_{13}DCl_3^{35}N_2O_3$;M-$C_6H_5CO$)	352.0153
C_6H_5	$CH_2C_6H_5$	$COC_6H_4p\mathrm{CH_3}$	CCl_3	H	355.0299($C_{17}H_{14}DCl_3^{35}NO$;M-$CH_3C_6H_4CO$)	355.0299
C_6H_5	$CH_3C_6H_5$	$COC_6H_4p\mathrm{CH_3}$	H	CCl_3	355.0299($C_{17}H_{14}DCl_3^{35}NO$;M-$CH_3C_6H_4CO$)	355.0299
$m\mathrm{O_2NC_6H_4}$	C_6H_{11}	COC_6H_5	CCl_3	H	392.0463($C_{16}H_{17}DCl_3^{35}N_2O_3$;M-$C_6H_5CO$)	392.0462
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	H	$C_6H_3(NO_2)_2$	311.1396($C_{18}H_{17}DN_2O_3$;M-$C_7H_5N_2O_5$) 196.0126($C_7H_5N_2O_3$;M-$C_{18}H_{17}DN_2O_3$)	311.1398 196.0123
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	$C_6H_4p\mathrm{NO_2}$	H	357.1325($C_{18}H_{17}DN_2O_5$;M-C_6H_5CO)	357.1325
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	H	$C_6H_4p\mathrm{NO_2}$	357.1325($C_{18}H_{17}DN_2O_5$;M-C_6H_5CO)	357.1325
$m\mathrm{O_2NC_6H_4}$	C_6H_{11}	COC_6H_5	$C_6H_4p\mathrm{NO_2}$	H	351.1709($C_{21}H_{23}N_2O_3$;M-$C_7H_5NO_3$)	351.1705
$m\mathrm{O_2NC_6H_4}$	C_6H_{11}	COC_6H_5	H	$C_6H_4p\mathrm{NO_2}$	151.0269($C_7H_5NO_3$;M-$C_{21}H_{23}N_2O_3$)	151.0269
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	C_6H_5	H	311.1396($C_{18}H_{17}DN_2O_3$;M-C_6H_5CO)	311.1398
$m\mathrm{O_2NC_6H_4}$	C_3H_7	COC_6H_5	H	C_6H_5	311.1396($C_{18}H_{17}DN_2O_3$;M-C_6H_5CO)	311.1398

Table XIX shows that while aromatic aldehydes gave isomeric mixtures, the reactions with chloral as dipolarophile produced only one compound analogous to structure 31, e.g. 33.

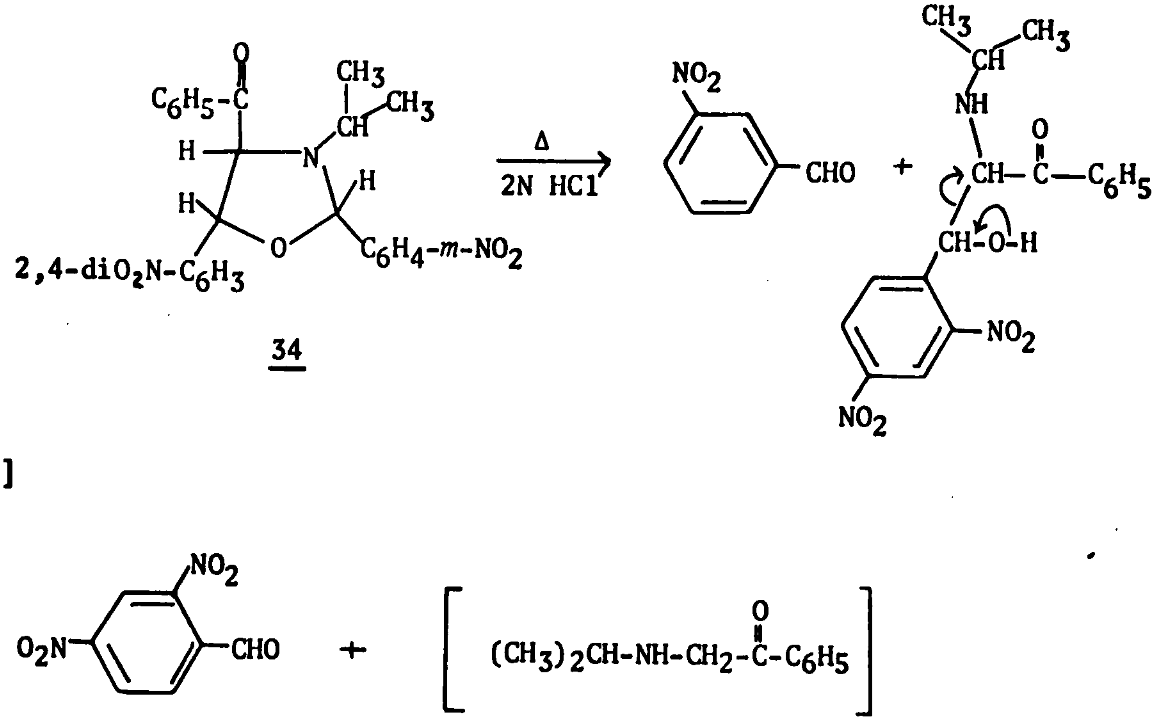


33

A new feature in these compounds was the powerful electron withdrawing effect of the 5-trichloromethyl group on the magnitude of the 4,5 proton-proton spin coupling constant, which was reduced to a value of (5.7-4.0 Hz) compared with the range of *trans* coupling of (7.45-5.90 Hz) in the oxazolidines derived from aryl aldehydes.

Chemical Proof of Oxazolidine Structure

It has been pointed out by Cornforth[12] that acid catalyzed hydrolysis of oxazolidines to give aldehydes is a characteristic reaction. Accordingly representative examples of the synthesized oxazolidines were subjected to acid catalyzed hydrolysis an example of which is shown in equation [83].



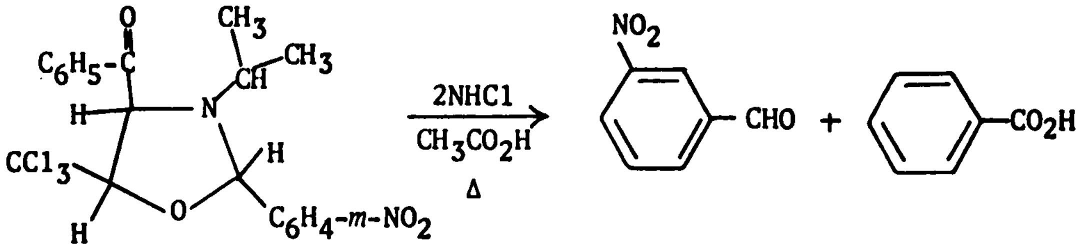
C_6H_5-C
O
H
H
CH_3
CH
CH_3
N
H
O
2,4-diO_2N-C_6H_3
C_6H_4-*m*-NO_2
34
Δ
2N HCl
NO_2
CHO
+
CH_3
CH_3
CH
NH
O
CH— C—C_6H_5
CH-O-H
NO_2
NO_2
NO_2
O_2N
CHO
+
$(CH_3)_2$CH-NH-CH_2-C-C_6H_5

[83]

Hydrolysis of 4-benzoyl-5-(2,4-dinitrophenyl)-3-isopropyl-2-(3-nitrophenyl)oxazolidine 34, in dilute hydrochloric acid produced 3-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde, which were isolated and characterized as their 2,4-dinitrophenylhydrazone derivatives. Similarly hydrolysis of 4-benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyloxazolidine 35, in glacial acetic acid containing hydrochloric acid afforded 3-nitrobenzaldehyde, characterized as its

2,4-dinitrophenylhydrazone, and benzoic acid, equation [84].

[84]



35

The benzoic acid probably was obtained from the oxazolidine 4-benzoyl group.

Thus the oxazolidines were in accordance with literature requirements for such compounds.

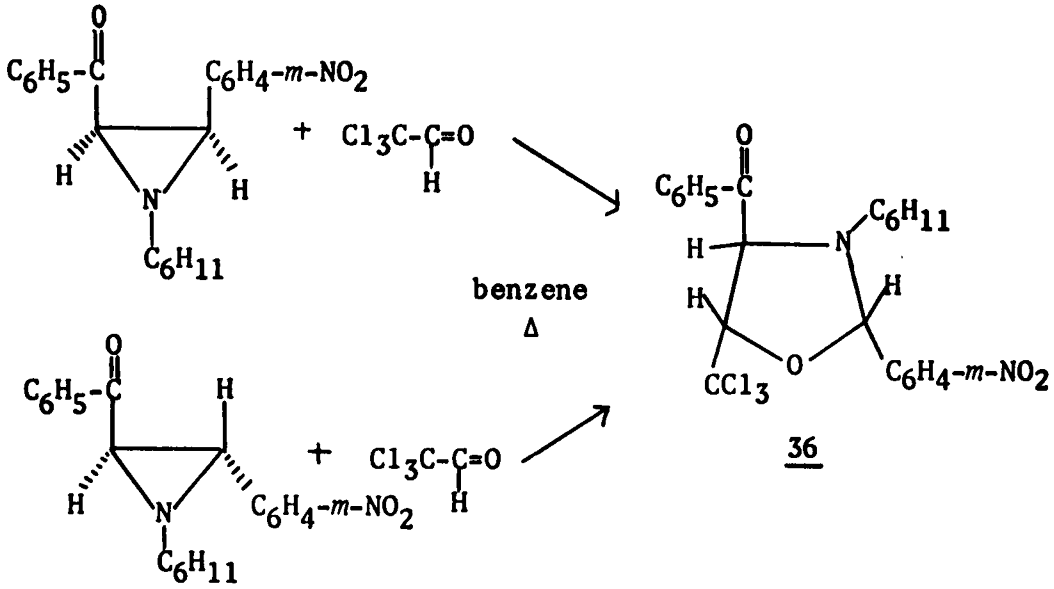
Attempts to effect epimerization of the oxazolidines at the 4-position by the action of bases like N-diisopropyl ethylamine and sodium methoxide were unsuccessful although some hydrolytic decomposition was observed. This effect has also been observed by Lown, Moser, and Westwood[158] in their work on imidazolidines. This result was of great importance in the assignment of the stereochemistry to the oxazolidines produced in the reactions under study, which is described in the next section.

In the examples studied the oxazolidines were found to be fairly stable under conditions of their formation.

Stereochemistry of the Cycloadditions

It was found that chloral reacted with stereoisomerically pure samples of *cis* and *trans*-3-benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine under the same conditions to give the identical oxazolidine in approximately the same yields. The gross structure and orientation of the product is shown in equation [85].

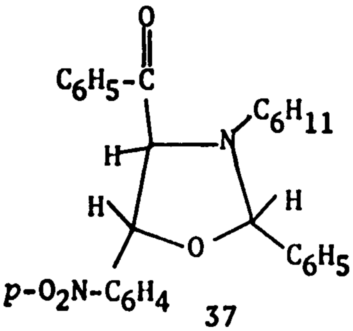
[85]



C_6H_5-C=O
C_6H_4-*m*-NO_2
H
N
C_6H_{11}
+ Cl_3C-CH=O
benzene
Δ
CCl_3
O

36

A similar representative reaction of 4-nitrobenzaldehyde to *cis* and *trans*-3-benzoyl-1-cyclohexyl-2-phenylaziridine also afforded only one stereoisomerically pure oxazolidine the gross structure of which is given by 37.

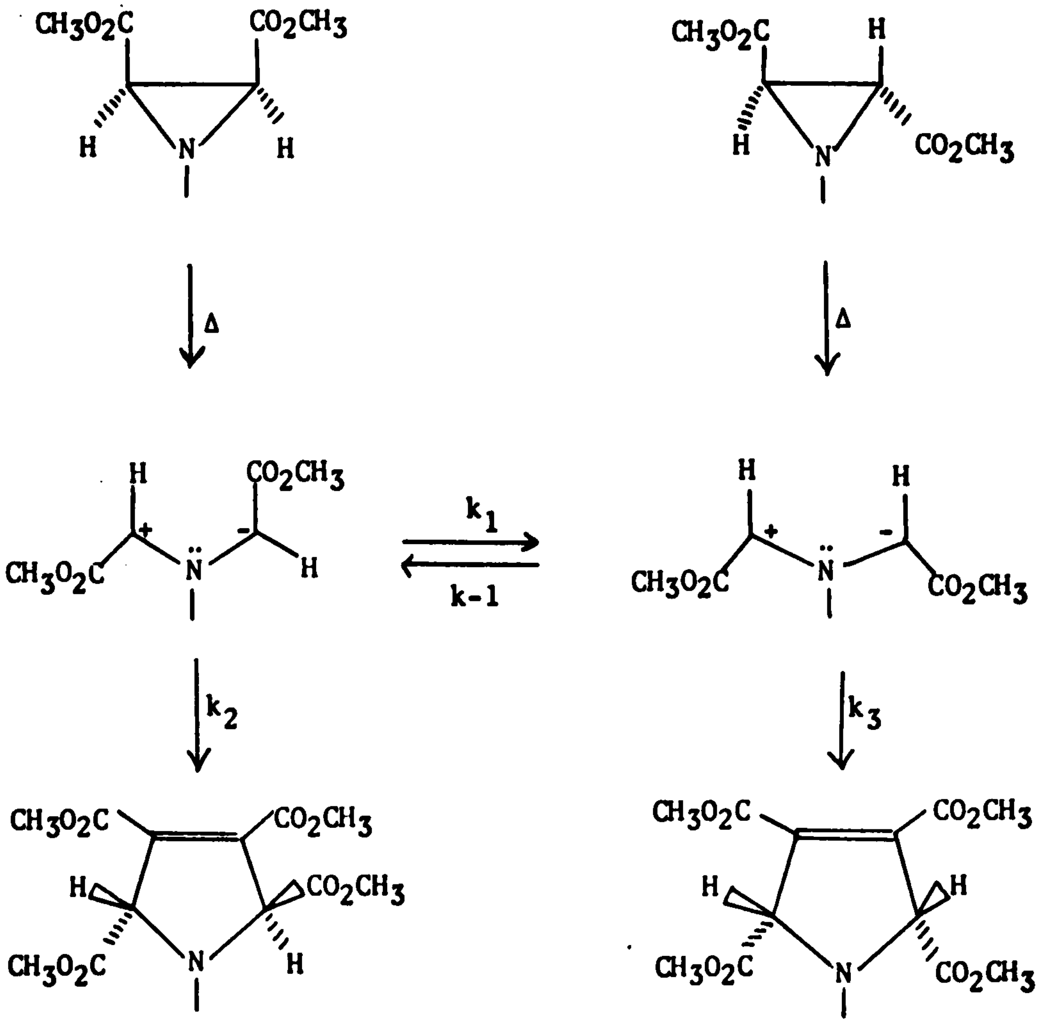


C_6H_5-C=O
H
N
C_6H_{11}
O
C_6H_5
p-O_2N-C_6H_4

37

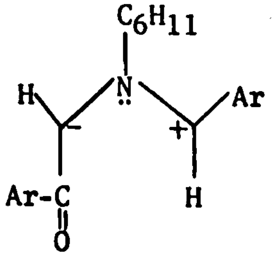
This showed that the cycloaddition was not stereospecific, and since it had been shown that there was no post isomerization of the oxazolidines, it was concluded that the reason must lie in the intermediate azomethine ylides. It has been demonstrated by Huisgen and coworkers (Chapter I), that aziridine 2,3-dicarboxylates under thermal conditions are subject to conrotatory ring cleavage, and that the resulting stereoisomeric azomethine ylides may frequently be trapped in a stereospecific manner, provided a sufficiently reactive dipolarophile is employed.[115,116,117,118] This is illustrated in Scheme II.

Scheme II


CH_3O_2C
CO_2CH_3
H
N
H
CH_3O_2C
H
H
N
CO_2CH_3
Δ
Δ
H
CO_2CH_3
+
-
CH_3O_2C
N
H
k_1
k_{-1}
H
H
+
-
CH_3O_2C
N
CO_2CH_3
k_2
k_3
CH_3O_2C
CO_2CH_3
H
CO_2CH_3
CH_3O_2C
N
H
CH_3O_2C
CO_2CH_3
H
H
CH_3O_2C
N
CO_2CH_3

In cases where less reactive dipolarophiles were used, the reaction with a *trans*-aziridine produced progressively less of the *cis*-adduct, and it was considered that the rate, symbolized by k_3, was sufficiently depressed to permit establishment of an equilibrium leading to reaction exclusively via the more stable *trans*-azomethine ylide.[117] The conclusion from this was that only a *trans* 1,3-dipolar cycloaddition product was to be anticipated from either the *cis*- or *trans*-aziridine under such conditions.

Since the carbonyl bond of aldehydes has been shown to be a sluggish dipolarophile,[62] it was concluded that in the present reactions the intermediate azomethine ylides derived from the thermal cleavage of the 2-3 bond of the 3-aroylaziridines equilibrate prior to addition, leading to the formation of oxazolidines exclusively through the more stable *trans*-azomethine ylide 38.

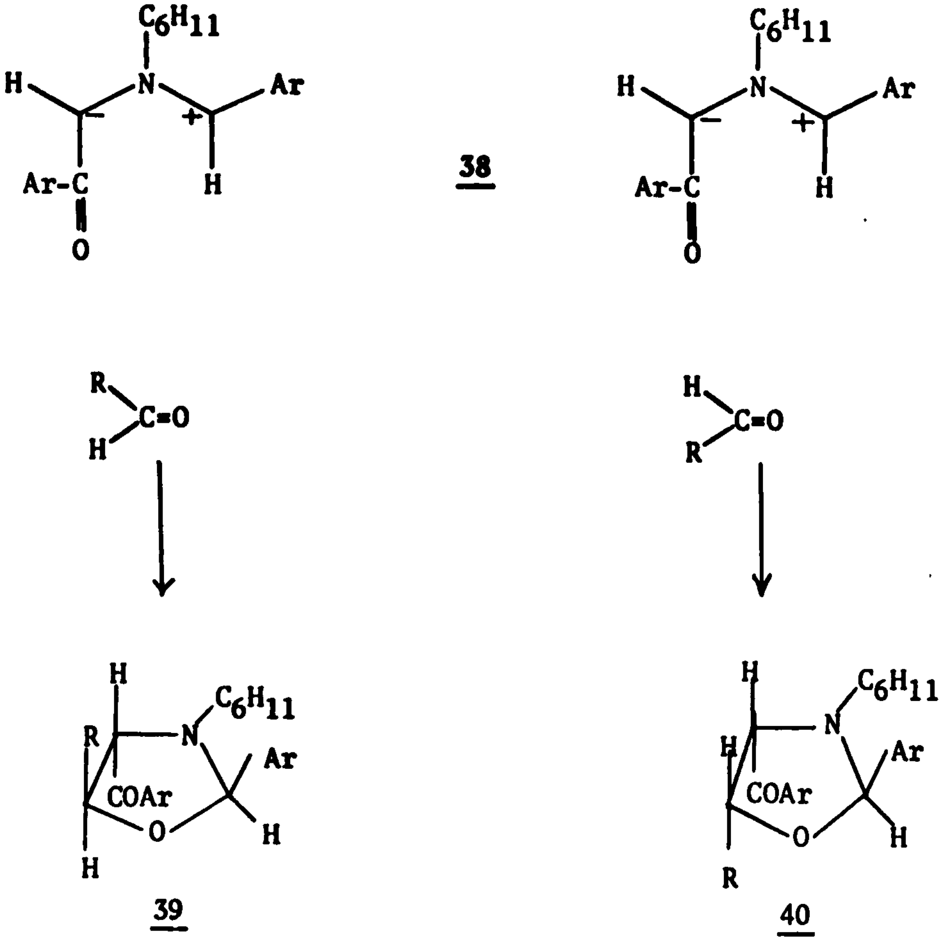


38

This therefore lowers the number of oxazolidines to be expected from eight racemic pairs to two such pairs (Scheme I).

The isolation of isomeric oxazolidines can now be accounted for by the two possible modes of addition for a constant orientation of the aldehyde as shown in Scheme III.

SCHEME III



38

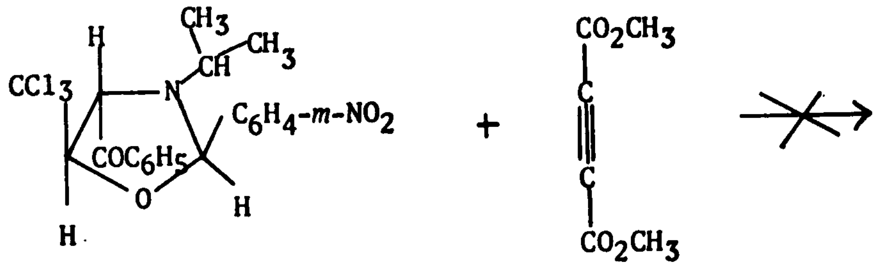
39 *trans*-4,5

40 *cis*-4,5

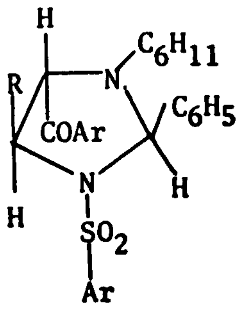
The *trans*-4,5-oxazolidine would be expected to be the more stable isomer and its mode of formation the favoured one, which indeed accounts for the majority of the products formed.

There existed however the possibility of an initial stereospecific addition to form the oxazolidine followed by a reverse electrocyclic cleavage back to the aldehyde and azomethine ylide. There was an analogy for this process in the cleavage of many of the oxazolidines in the mass spectrum (see Table XVI). Huisgen, Scheer, and Mader[116] have also considered this process in another example. This possibility was tested and found to be inoperative since an independent reaction of 4-benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine with dimethyl acetylenedicarboxylate, a much more powerful dipolarophile than an aldehyde,[117] produced no evidence of trans-3-pyrroline formation, giving only starting material, equation [86].

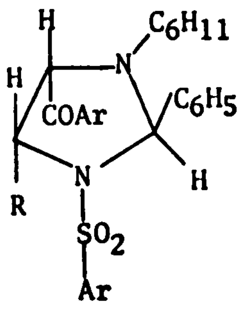
[86]


H
CH3
CH3
CH
CCl3
N
C6H4-m-NO2
COC6H5
O
H
H
+
CO2CH3
C
C
CO2CH3

The results from this work and the rationalization given in Scheme III are similar to those obtained by Lown, Moser, and Westwood[158] in the [2+3] cycloaddition reactions of sulfonylimines and 3-aroylaziridines, where the addition proceeded exclusively in the same direction as in the present work and gave predominantly *trans* 4,5-imidazolidines 41, and only occasionally *cis* 4,5-imidazolidines, 42.


H
C6H11
R
N
C6H5
COAr
N
H
H
SO2
Ar

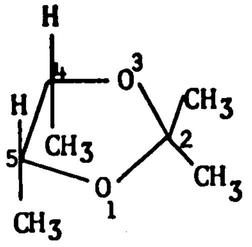
41


H
C6H11
H
N
COAr
C6H5
N
H
R
SO2
Ar

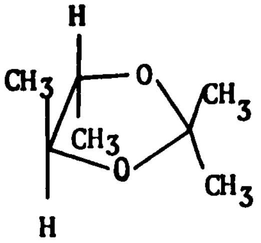
42

In six-membered ring systems, both homocyclic and heterocyclic, experience has shown that vicinal proton-proton spin coupling constants can be fairly reliably assigned to various configurations of the substituents in the molecule. However in five-membered ring compounds this is not necessarily the case, and vicinal proton coupling is notoriously variable in the degree of accuracy of correlation with molecular configuration.[161] With relatively rigid homocyclic and heterocyclic five-membered rings, the Karplus relationship of dihedral angle to coupling constant[162] can be applied, and leads to clear distinctions between couplings characteristic of *cis* and *trans* coupled protons.[102,103] However in other ring systems such as dioxolanes and the oxazolidines described in this work, examination of molecular models indicates a greater degree of flexibility of the heterocyclic ring, and this leads to smaller differences in the magnitude of the vicinal couplings thus rendering configurational assignment on this basis a hazardous process.[163,164,165,166] With the exception of line positions reported by Paukstelis and Hammaker[141] for a series of oxazolidine-Schiff base mixtures, no information on the p.m.r. spectra of oxazolidines has appeared in the literature to date. It was therefore necessary to seek analogous systems to obtain trends in the p.m.r. spectra vicinal coupling constants, and the dioxolane ring system was chosen as being as closely comparable to the oxazolidines as possible.

The closest analogy in the literature was the data on *cis* and *trans*-2,2,4,5-tetramethyldioxolane,[166] 43, 44.



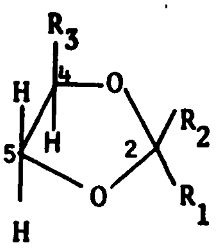
43 $J_{4,5}$ = 5.85 Hz



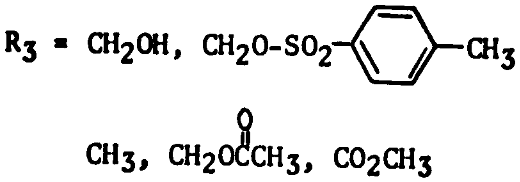
44 $J_{4,5}$ = 8.35 Hz

On the basis of the *trans* coupling constant in 44 being larger than the *cis* in 43, the oxazolidines described in this work with the larger coupling constants (7.45-5.90 Hz) were tentatively assigned the *trans* configuration, and the oxazolidines showing the smaller coupling (5.80-5.55 Hz) the tentative *cis* configuration at carbon atoms 4 and 5. Those oxazolidines from chloral have smaller coupling constants than either of the above cases (4.4-4.0 Hz), but have been tentatively assigned the *trans* oxazolidine structure. Examination of Dreiding models tends to support the above conclusions, and indeed the oxazolidines of *trans* configuration were the predominantly formed compounds.

However a very recent report by Inch and Williams[167] on the structural assignments of some 2,2,4-trisubstituted 1,3-dioxolanes, has opened to question the above basis for the oxazolidine configurational assignments, in that the magnitude of the *cis* and *trans* coupling constants at carbon atoms 4 and 5, appear to depend on the substituents at the 2-position of the 1,3-dioxolane ring, 45 (Table XXI).



45



$R_3 = CH_2OH,\ CH_2O\text{-}SO_2\text{-}C_6H_4\text{-}CH_3,\ CH_3,\ CH_2O\overset{O}{\overset{\|}{C}}CH_3,\ CO_2CH_3$

TABLE XXI

P.M.R. coupling constants of various 1,3-dioxolanes

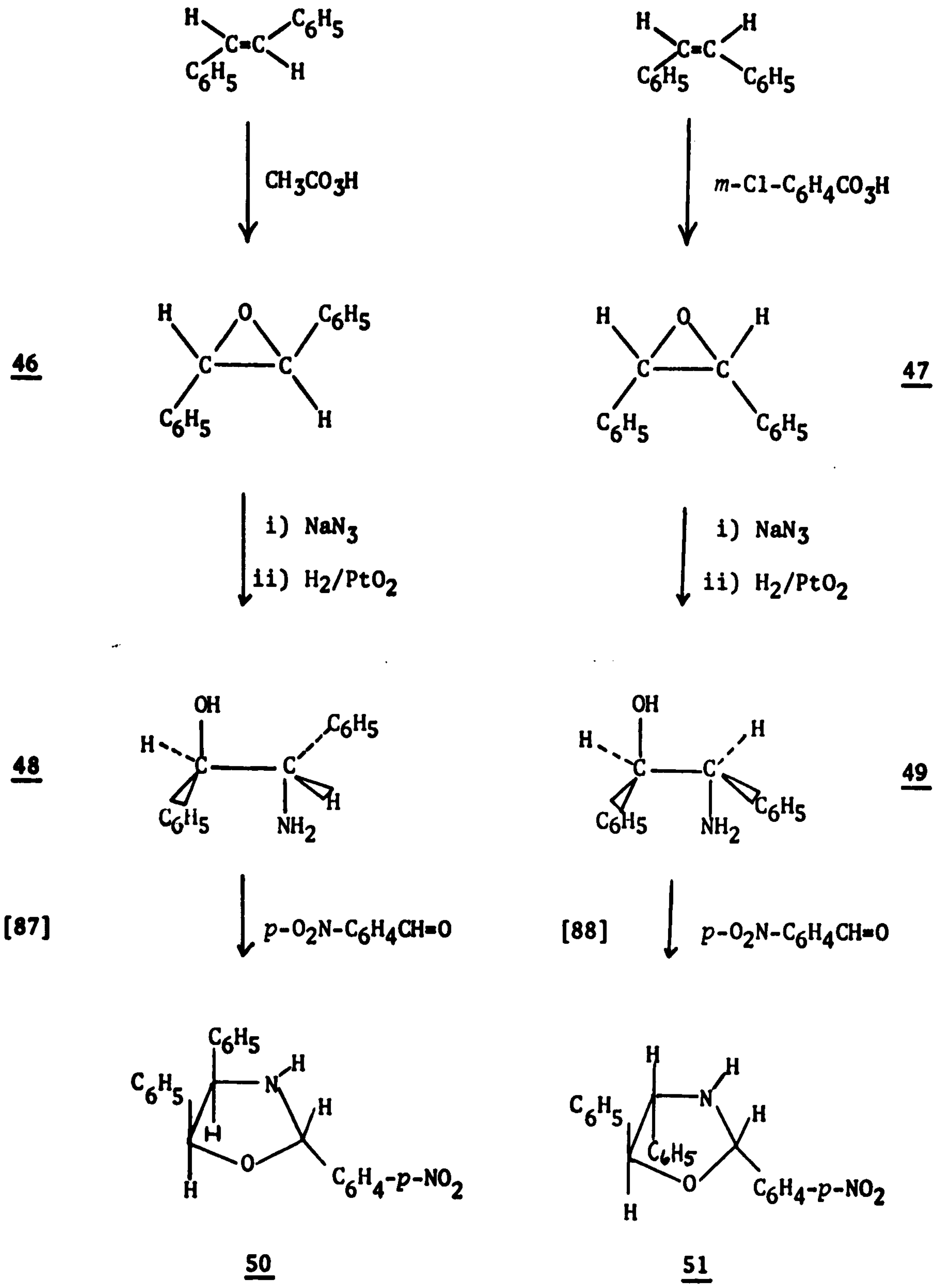
R_1	R_2	$J_{4,5}$ *(cis)*	$J_{4,5}$ *(trans)*
CH_3	H	$\sim$7.5	$\sim$6.2
C_6H_5	H	$\sim$7.2	$\sim$5.8
C_6H_5	CH_3	$\sim$4	$\sim$8
$CH_2C_6H_5$	CH_3	$\sim$5.2	$\sim$7.2

In keeping with the view that the oxazolidine reactions proceed via a *trans* azomethine ylide, only those 1,3-dioxolanes which had the larger substituents at the 2-and 4-positions in a *trans* configuration were considered. Table XXI shows that in the first two cases the *cis* 4,5 coupling constant is larger than the *trans* value, while for the latter two examples the reverse is the case. The latter pair are in agreement with the values of Anet,[166] while the former pair are in direct contrast.

These results when taken in conjunction with the failure to effect isomerization of the *cis* oxazolidines to *trans* oxazolidines or vice versa, indicated the need for an oxazolidine synthesis by an unambiguous stereocontrolled process.

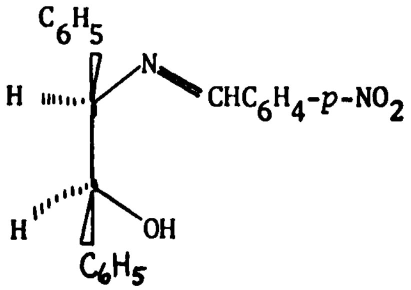
The following method, outlined in Scheme IV, was considered as a potential route to this end.

SCHEME IV


CH3CO3H
m-Cl-C6H4CO3H
46
47
i) NaN3
ii) H2/PtO2
i) NaN3
ii) H2/PtO2
48
49
[87]
[88]
p-O2N-C6H4CH=O
p-O2N-C6H4CH=O
C6H4-p-NO2
C6H4-p-NO2
50
51

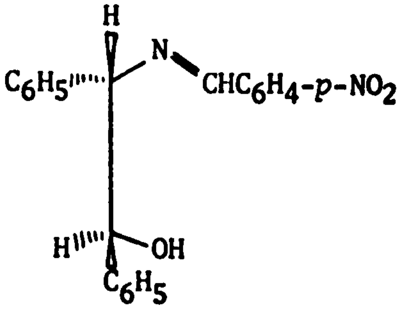
Although this method offered stereochemical control at carbons 4 and 5 throughout the synthesis, it suffered from the fact that no control could be exercised over the relative configuration of the substituents at the 2- and 4-positions of the ring. This was one of the major assets of the [2+3] cycloaddition method.

By the procedure of Foglia and Swern,[168] isomerically pure *trans*-stilbene was converted to the *erythro*-ethanolamine 48, via the *trans*-stilbene oxide 46.[169] By an analogous method *cis*-stilbene was transformed via the *cis*-stilbene oxide[170] 47, to the *threo*-ethanolamine 49.[168] The purified *erythro* and *threo*-ethanolamines were then reacted with 4-nitrobenzaldehyde in an attempt to prepare the *cis* and *trans*-4,5-oxazolidines 50 and 51, the p.m.r. spectra of which it was hoped would provide a solution to the stereochemical problem posed above. However instead of obtaining the *cis*- oxazolidine 50, a mixture consisting of the starting materials and the isomeric Schiff base 52, was isolated. No trace of the oxazolidine was observed in the product mixture, equation [87].



52

Conversely the reaction of the *threo*-ethanolamine with 4-nitrobenzaldehyde produced what appeared to be a mixture of oxazolidines and 4-nitrobenzaldehyde, although no clear product assignment could be made from the p.m.r. spectrum of the mixture. There appeared to be little of the Schiff base 53 present as judged from the infrared spectrum of the mixture.

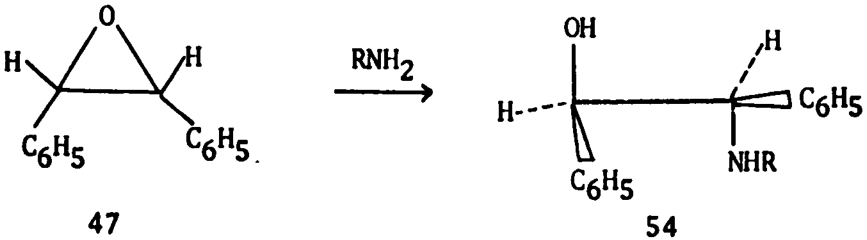

H
N
C_6H_5
CHC_6H_4-*p*-NO_2
H
OH
C_6H_5

53

This particular line of approach was therefore abandoned.

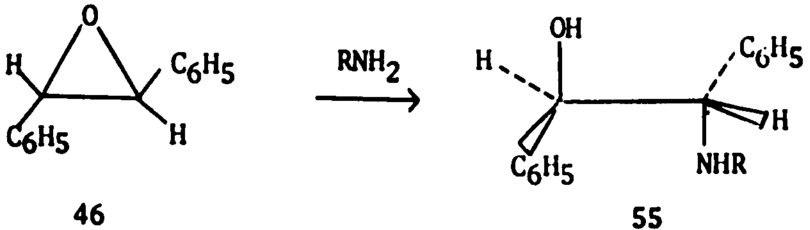
The problem of oxazolidine-Schiff base mixtures could probably be surmounted by employing *erythro* and *threo*-N-substituted ethanolamines, since there would be no possibility of the oxazolidine produced being in equilibrium with the Schiff base. The ethanolamines required could conceivably be obtained by the reaction of primary amines and *cis* and *trans*-stilbene oxide respectively, as shown in equations [89] and [90].

[89]


O
H
H
C_6H_5
C_6H_5
RNH_2
OH
H
H
C_6H_5
C_6H_5
NHR

47 54

[90]


O
H
C_6H_5
C_6H_5
H
RNH_2
OH
H
C_6H_5
H
C_6H_5
NHR

46 55

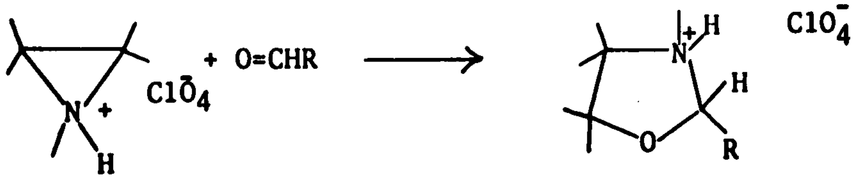
Preliminary studies in this direction were initiated but difficulty was encountered in the above stage, and lack of time prevented a more detailed study of the problem.

Thus the question of the relative stereochemistry of substituents at the 4-and 5-position of the oxazolidine ring was not settled unambiguously and though the majority of the available evidence appears to favour the assignments proposed, their tentative nature must be emphasized.

Summary

The [2+3] cycloaddition reactions of 3-aroyl-2-arylaziridines with aromatic aldehydes and chloral to form oxazolidines in fair to good yields have been demonstrated. The orientation of addition was established, and tentative assignments of the stereochemistry at positions 4 and 5 of the ring are proposed. An alternative ring expansion product structure was considered and discarded. It is of interest to note the work of Leonard and coworkers,[171] on the reactions of aziridinium salts with aldehydes, ketones, and nitriles in this context, for the products obtained, oxazolidinium, oxazolinium, and imidazolinium salts, all possessed structures of type C, equation [91].

[91]



An extension of this work to other compounds, containing active carbonyl groups, as dipolarophiles was initiated, and the novel reactions and products obtained from diphenylcyclopropenone are discussed in Chapter III.

EXPERIMENTAL

Throughout this work melting points were determined on a Fisher-Johns apparatus and along with boiling points are uncorrected.

Infrared spectra were recorded with a Perkin-Elmer model 421 spectrophotometer. The polystyrene 1601 cm^{-1}, band was used as a reference and only the principal well defined peaks are reported.

Absorption spectra were measured in 'spectro'-grade solvents on a Perkin-Elmer model 122 instrument.

Proton magnetic resonance spectra (p.m.r.) were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10-15% (w/v) solutions in appropriate deuterated solvents with tetramethylsilane as reference. Line positions are reported in parts per million from the reference.

Mass spectra were determined with an A.E.I. MS9 double-focusing high-resolution mass spectrometer. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000.

Thin-layer chromatography (t.l.c.) was performed with Kieselgel DF-5 (Camag. Switzerland) and Eastman-Kodak precoated silica and alumina sheets. Grade I B.D.H. alumina was used for column chromatography.

Elemental analysis were carried out by Dr. C. Daesslé Microanalysis Ltd., Montreal, Quebec, and by Mrs. D. Mahlow of this department.

In the work-up procedures reported for the various synthesis described, solvents were removed with a rotatory evaporator under reduced pressure unless otherwise stated.

For the stereochemical control experiments and wherever else it was necessary, dry benzene was prepared by heating commercial benzene over sodium and distilling from fresh sodium metal.

1. General Preparation of 3-Aroylaziridines

The substituted aziridines employed in this study were prepared by established methods involving Claisen-Schmidt condensations of appropriate aldehydes and ketones to form chalcones, then addition of bromine to afford the corresponding dibromochalcones, followed by treatment of the latter with primary amines to provide the 3-aroylaziridines. Full details of new aziridines are provided together with references to previously prepared compounds. The aziridines were generally obtained as *cis,trans* mixtures which were usually employed as such in the cycloaddition reactions unless otherwise stated.

1,3-Diphenylpropenone

This compound was prepared in 93% yield by the method of Kohler and Chadwell,[172] m.p. 53-56° (lit., m.p. 50-54°).

2,3-Dibromo-1,3-diphenylpropanone

This compound was prepared in 84% yield by the method of Weygand,[173] m.p. 160-161° (lit., m.p. 157°).

3-Benzoyl-1-isopropyl-2-phenylaziridine

Isopropylamine (24.0 g., 0.407 mole) was added in a dropwise manner to a stirred solution of 2,3-dibromo-1,3-diphenylpropanone

(50 g, 0.136 mole) in dry benzene (700 ml) at 0°, after which the solution was stirred for 1 h, at 0°, and then at room temperature for 23 h. The precipitated isopropylamine hydrobromide was collected by filtration (34 g, theoretical yield 34 g), and the yellow filtrate was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residual oil consisted of an approximately 1:1 mixture of *cis* and *trans* isomers of the desired aziridine (36 g, 100%), which partly crystallized on chilling. The isomers were separated by preparative thin-layer chromatography on silica with a 3:1 mixture of benzene and heptane, which afforded the pure *cis* isomer and slightly impure *trans*. The latter could be obtained isomerically pure by further chromatography on alumina with heptane as eluant. The stereochemistry was readily assigned by reference to published p.m.r. and infrared spectra.[146,147]

cis-Isomer: pale yellow crystals, m.p. 90-91° (heptane).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.51; h, 7.17; N, 5.28.

Found: C, 81.32; H, 7.20; N, 5.34.

Mass spectrum: Calcd. 265.1467 ($C_{18}H_{19}NO$). Found: 265.1468.

Infrared spectrum ν_{max} ($CHCl_3$): 1683 cm^{-1} (aryl C=O).

P.M.R. spectrum ($CDCl_3$): 1.22 (doublet, 6H; J = 5.70 Hz; isopropyl $C\underline{H}_3$), 1.86 (septet, 1H, isopropyl $C\underline{H}$), 3.18 (singlet, 2H, aziridine ring protons), 7.00-7.50 and 7.80-8.01 (multiplets, 10H, aryl protons).

trans-Isomer: low-melting yellow solid, m.p. <25°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28.

Found: C, 81.50; H, 7.39; N, 5.05.

Mass spectrum: Calcd. 265.1467 ($C_{18}H_{19}NO$). Found: 265.1468.

Infrared spectrum ν_{max} $(CHCl_3)$: 1662 cm^{-1} (aryl C=O).

P.M.R. spectrum $(CDCl_3)$: 0.91 (doublet, 3H; J = 6.0 Hz; isopropyl $C\underline{H}_3$), 1.18 (3H, doublet; J = 6.0 Hz; isopropyl CH_3), 2.19 (multiplet; 1H, isopropyl $C\underline{H}$), 3.46-3.66 (AB quartet, 2H, aziridine ring protons), 7.16-7.58 and 7.96-8.16 (multiplets, 10H, aryl protons).

1-(4-Nitrophenyl)-3-phenylpropenone.

This compound was prepared in 74% yield by the method of Pond, Maxwell, and Norman,[174] m.p. 145-147° (lit., m.p. 149-150°).

2,3-Dibromo-1-(4-nitrophenyl)-3-phenylpropanone

This compound was prepared in 85% yield by the method of Weygand,[175] m.p. 210°.

1-Cyclohexyl-3-(4-nitrobenzoyl)-2-phenylaziridine

A solution of cyclohexylamine (14.8 g, 0.15 mole) in benzene (50ml) was added to a stirred solution of 2,3-dibromo-1-(4-nitrophenyl)-3-phenylpropanone (20.4 g, 0.049 mole) in benzene (600 ml) at 0°, after which the suspension was stirred for 1 h, at 0°, and then at room temperature for 23 h. The precipitated cyclohexylamine hydrobromide was removed by filtration (17.3 g, theoretical yield 17.6 g), and the filtrate was washed with water (3 x 50 ml), dried $(MgSO_4)$, and the solution concentrated *in vacuo* to *ca.* 50 ml, and then chilled to give an isomeric mixture of the desired aziridine as an orange-brown solid (13 g, 76%) m.p. 96-99° (hexane).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 72.00; H, 6.29; N, 8.00.

Found: C, 72.10; H, 6.32; N, 7.94.

Mass spectrum: Calcd. 350.1630 $(C_{21}H_{22}N_2O_3)$. Found: 350.1634.

Infrared spectrum ν_{max} ($CHCl_3$): 1681, (C=O of *cis* isomer), 1656 cm^{-1} (C=O of *trans* aziridine).

P.M.R. spectrum ($CDCl_3$): 0.83-2.00 (multiplet, 10H, cyclohexyl C$\underline{H}_2$), 2.33-2.76 (multiplet, 1H, cyclohexyl C$\underline{H}$), 3.22 (singlet, 2H, *cis* aziridine ring protons), 3.57 (singlet, 2H, *trans* aziridine ring protons), 7.18-8.35 (multiplet, 9H, aryl protons).

3-(3-Nitrophenyl)-1-phenylpropenone

This compound was prepared in 100% yield by the method of Sorge,[176] m.p. 145-147° (lit., m.p. 145-146°).

2,3-Dibromo-3-(3-nitrophenyl)-1-phenylpropanone

This compound was prepared in 99% yield by the method of Sorge,[176] m.p. 187.5-190° (lit., m.p. 190°).

3-Benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine

A solution of isopropylamine (21.5 g, 0.364 mole) in dry benzene (100 ml) was added dropwise to 2,3-dibromo-3-(3-nitrophenyl)-1-phenylpropanone (50 g, 0.121 mole) in dry benzene (800 ml) stirred at 0°. The cloudy suspension was stirred at 0° for 1 h, and then at room temperature for 23 h. The precipitated isopropylamine hydrobromide was collected by filtration (23 g, theoretical yield 33.5 g), and the filtrate was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. The yellow oil obtained was dissolved in benzene (50 ml) and heptane (100 ml) was added and the mixture chilled to give as a white solid, the desired aziridine in the form of its *trans* isomer (35.6 g, 95%), m.p. 96-97° (methanol).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.84; N, 9.03.

Found: C, 69.94; H, 5.78; N, 9.08.

Mass spectrum: Calcd. 310.1310 ($C_{18}H_{18}N_2O_3$). Found: 310.1317.

Infrared spectrum ν_{max} ($CHCl_3$): 1665 cm^{-1} (C=O of *trans* aziridine).

P.M.R. spectrum ($CDCl_3$): 0.93 (doublet, 3H, isopropyl $C\underline{H}_3$), 1.19 (doublet, 3H, isopropyl $C\underline{H}_3$), 2.60-3.20 (multiplet, 1H, isopropyl $C\underline{H}$), 3.62 (singlet, 2H, *trans* aziridine ring protons), 7.20-8.30 (multiplet, 9H, aryl protons).

In later repeats of this reaction aziridine mixtures containing from 0-15% of the *cis* isomer were obtained but the latter was not isolated.

3-Benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine

A solution of cyclohexylamine (15.0 g, 0.152 mole) in benzene (50 ml) was added dropwise to 2,3-dibromo-3-(3-nitrophenyl)-1-phenylpropanone (20.65 g, 0.05 mole) in benzene (500 ml) stirred at 0°. The mixture was stirred at 0° for 1 h, and then at room temperature for 23 h. The precipitate cyclohexylamine hydrobromide was removed by filtration, and the filtrate was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo* to yield the desired isomeric aziridine as a yellow oil (15.5 g, 88%) which crystallized very slowly on chilling to give a white solid, m.p. 95° (methanol). The isomers were separated by fractional recrystallization from methanol.

cis-isomer: white solid, m.p. 124-126° (methanol).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 72.00; H, 6.29; N, 8.00.

Found: C, 71.70; H, 6.17; N, 8.02.

Mass spectrum: 350.1630 ($C_{21}H_{22}N_2O_3$). Found 350.1634.

Infrared spectrum ν_{max} ($CHCl_3$): 1681 cm^{-1} (C=O of *cis* aziridine).

P.M.R. spectrum ($CDCl_3$): 1.00-2.05 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.25-2.90 (multiplet, 1H, cyclohexyl $C\underline{H}$), 3.44 and 3.24 (AB quartet, 2H, aziridine ring protons, *cis* coupled, J = 7 Hz), 7.20-8.30 (multiplet, 9H, aromatic protons).

trans-isomer: white solid, m.p. 82-84° (methanol).

Anal. Found: C, 71.78; H, 6.11; N, 7.91.

Mass spectrum: Found, 350.1630.

Infrared spectrum ν_{max} ($CHCl_3$): 1663 cm^{-1} (C=O of *trans* aziridine).

P.M.R. spectrum ($CDCl_3$): 0.89-2.02 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.30-2.87 (multiplet, 1H, cyclohexyl $C\underline{H}$), 3.64 (singlet, 2H, aziridine ring protons, *trans* coupled). 7.30-8.30 (multiplet, 9H, aromatic protons).

3-Benzoyl-1-cyclohexyl-2-phenylaziridine

This aziridine was prepared in 70% yield by the method of Cromwell,[145] *cis* isomer m.p. 106-108° from methanol (lit., m.p. 107-109°; *trans* isomer m.p. 99-101.5° from methanol (lit., m.p. 99-101°).

3-Benzoyl-1-methyl-2-phenylaziridine

This aziridine was prepared in 80% yield as a *cis-trans* mixture m.p. 88-89° (methanol; lit., m.p. 85-87°) by the method of Cromwell and Caughlan.[177]

3-Benzoyl-1-cyclohexyl-2-(4-nitrophenyl)aziridine.

This aziridine was prepared in 67% yield by the general method of Cromwell and coworkers,[145] *cis* isomer m.p. 130-132° (methanol; lit., m.p. 127-128°)[178]; *trans* isomer m.p. 110-111° (methanol; lit., m.p. 107-109°).[178]

1-Benzyl-2-phenyl-3-(4-toluoyl)aziridine

This aziridine was prepared in 69% yield as a *cis-trans* mixture m.p. 113-114° (ethanol; lit., m.p. 116-118°) by the method of Cromwell Hoeksema.[179]

2. Preparation of Oxazolidines

The aldehydes used in the reactions described were commercial samples of highest available purity. Benzaldehyde was distilled prior to use though chloral was found to provide excellent results in commercial form.

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)oxazolidine

A solution of *trans*-3-benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine (3.50 g, 0.0113 mole) and 4-nitrobenzaldehyde (1.706 g, 0.0113 mole) in benzene (50 ml) was heated under reflux for 22 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting pale yellow oil on grade I alumina (BDH, 90g) with benzene as eluant, gave as the main fraction a pale yellow oil which crystallized on trituration with cold methanol to give as a pale yellow solid (3.7 g, 71%) m.p. 103-109°, a mixture (55:45 by p.m.r.) of the desired *cis* and *trans* oxazolidine. Each pure isomer was obtained by fractional crystallization from methanol.

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)-*trans* 4,5-oxazolidine

White needles, m.p. 133-135°.

Anal. Calcd. for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 4.99; N, 9.11.

Found: C, 65.07; H, 4.92; N, 9.04.

Mass spectrum: 310.1317 ($C_{18}H_{18}N_2O_3$; M-$C_7H_5NO_3$) and 151.0269 ($C_7H_5NO_3$; M-$C_{18}H_{18}N_2O_3$). Found: 310.1319 and 151.0269.

Infrared spectrum ν_{max} ($CHCl_3$): 1684 (C=O), 1521 cm^{-1} (aryl NO_2).

P.M.R. spectrum ($CDCl_3$): 1.13 (doublet, 6H, J = 6.6 Hz, isopropyl $C\underline{H}_3$), 2.92-3.53 (multiplet, 1H, isopropyl C$\underline{H}$), 5.59 and 4.66 (AB quartet, 2H, 4,5 ring protons *trans* coupled, J = 7.45 Hz), 6.23 (singlet, 1H, 2 proton), 7.15-8.76 (multiplet, 13H, aryl protons).

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)-*cis*-4,5-oxazolidine

White needles, m.p. 116-119°.

Anal. Found: C, 65.16; H, 4.94; N, 9.01.

Mass spectrum: 310.1319 and 151.0269.

Infrared spectrum ν_{max} ($CHCl_3$): 1683 (C=O) and 1521 cm^{-1} (aryl NO_2).

P.M.R. spectrum ($CDCl_3$): 0.79 (doublet, 3H, J = 6.4 Hz, isopropyl $C\underline{H}_3$), 1.07 (doublet, 3H, J = 6.4 Hz, isopropyl $C\underline{H}_3$), 3.00-3.66 (multiplet, 1H, isopropyl C$\underline{H}$), 5.77 and 5.56 (AB quartet, 2H, 4,5 ring protons, *cis* coupled, J = 5.8 Hz), 6.28 (singlet, 1H, 2 proton), 7.08-8.36 (multiplet, 13H, aryl protons).

4-Benzoyl-3-cyclohexyl-2-(4-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine.

A solution of 3-benzoyl-1-cyclohexyl-2-(4-nitrophenyl)aziridine (3.50 g, 0.01 mole) and chloral (1.475 g, 0.01 mole) in dry benzene (50 ml) was heated under reflux for 24 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting red oil on grade I alumina (BDH, 100 g) with benzene as eluant, gave as the main fraction a red syrup which crystallized on trituration with cold methanol to give the the *trans* oxazolidine (3.8 g, 78.4%), m.p. 154-156° (pale yellow needles from benzene and methanol).

Anal. Calcd. for $C_{23}H_{23}Cl_3N_2O_4$: C, 55.48; H, 4.62; N, 5.63; Cl, 21.41.
Found: C, 55.52; H, 4.59; N, 5.44; Cl, 21.45.

Mass spectrum: 391.0383 ($C_{16}H_{18}{}^{35}Cl_3N_2O_3$; M-$C_6H_5CO$). Found: 391.0390.

Infrared spectrum ν_{max} ($CHCl_3$): 1689w, 1677s (C=O), 1519s cm^{-1} (aryl NO_2).

P.M.R. spectrum ($CDCl_3$): 0.54-2.03 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.29-2.85 (multiplet, 1H, cyclohexyl $C\underline{H}$), 5.25 and 4.85 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 4.0 Hz), 6.31 (singlet, 1H, 2 proton), 7.50-8.36 (multiplet, 9H, aryl protons).

4-Benzoyl-5-(4-chloro-3-nitrophenyl)-3-isopropyl-2-(3-nitrophenyl)oxazolidine

A solution of 3-benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine (1.55 g, 0.005 mole) and 4-chloro-3-nitrobenzaldehyde (0.928 g, 0.005 mole) in benzene (30 ml) was heated under reflux for 22 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting yellow-brown oil on grade I alumina (BDH, 60 g) with benzene as eluant, gave as the main fraction a yellow oil which crystallized on trituration with cold methanol to give as a yellow solid (1.382 g, 55.8%), m.p. 82-92°, a mixture (39:61, *cis:trans* by p.m.r.) of the desired oxazolidine. By recrystallization from ethyl acetate and ethanol, the *trans* isomer was obtained in pure form, m.p. 118-119.5°.

Anal. Calcd. for $C_{25}H_{22}ClN_3O_6$: C, 60.53, H, 4.44; N, 8.47; Cl, 7.16.
Found: C, 60.46; H, 4.48, N, 8.46; Cl, 7.23.
Mass spectrum: 310.1317 ($C_{18}H_{18}N_2O_3$; M-$C_7H_4ClNO_3$) and 184.9880 ($C_7H_4ClNO_3$; M-$C_{18}H_{18}N_2O_3$). Found: 310.1318 and 184.9882.
Infrared spectrum ν_{max} ($CHCl_3$): 1683 (C=O) and 1528 cm^{-1} (aryl NO_2).
P.M.R. spectrum ($CDCl_3$): 1.13 (doublet, 6H, J = 6.5 Hz, isopropyl $C\underline{H}_3$), 2.95-3.51 (multiplet, 1H, isopropyl C$\underline{H}$), 5.50 and 4.58 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 7.20 Hz), 6.19 (singlet, 1H, 2 proton), 7.25-8.80 (multiplet, 12H, aryl protons).

The *cis* isomer could not be isolated but was characterized by its presence in the p.m.r. spectrum of the *cis*,*trans* mixture, δ($CDCl_3$): 0.95-1.20 (6H, isopropyl $C\underline{H}_3$), 3.40-3.90 (multiplet, 1H, isopropyl C$\underline{H}$), 5.72 and 5.56 (AB quartet, 2H, 4,5 ring protons, *cis* coupled, J = 5.4 Hz), 6.27 (singlet, 1H, 2 proton), 7.20-8.70 (multiplet, 12H, aryl protons).

By the above general procedure the following series of oxazolidines were prepared. Their analytical and spectral data are summarized in Tables XIV, XV and XVI.

4-Benzoyl-3-isopropyl-2-phenyl-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared as an oil in 84% yield.

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 65% yield, m.p. 111-113° (methanol).

4-Benzoyl-3-cyclohexyl-2-(4-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 78% yield, m.p. 154-156° (benzene-methanol).

3-Benzyl-2-phenyl-4-(4-toluoyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 38% yield, m.p. 130-131° (methanol).

4-Benzoyl-3-cyclohexyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 72% yield, m.p. 128-130° (methanol).

4-Benzoyl-5-(4-chloro-3-nitrophenyl)-3-isopropyl-2-(3-nitrophenyl)-oxazolidine was prepared in 56% yield as a 39:61 mixture of *cis:trans*; isomers; m.p. 80-92°, *trans* isomer, m.p. 118-120° (ethyl acetateethanol).

4-Benzoyl-5-(4-chloro-3-nitrophenyl)-3-cyclohexyl-2-(4-nitrophenyl)-oxazolidine was prepared in 44% yield as a 25:75 mixture of *cis* and *trans* isomers m.p. 128-132°, *trans* isomer, m.p. 138-140° (hexane-benzene).

4-Benzoyl-3-isopropyl-5-(4-nitrophenyl)-2-phenyl-*trans*-4,5-oxazolidine was prepared in 21% yield, m.p. 128-129° (methanol).

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)oxazolidine was prepared in 71% yield as a 55:45 mixture of *cis* and *trans* isomers; *cis* isomer m.p. 116-119° (methanol), *trans* isomer 133-135° (methanol).

4-Benzoyl-3-cyclohexyl-2,4-di-(4-nitrophenyl)-*trans*-4,5-oxazolidine was prepared in 25% yield, m.p. 156-158° (ethyl acetate-methanol).

4-Benzoyl-5-(2,4-dinitrophenyl)-3-isopropyl-2-(3-nitrophenyl)-*cis*-4,5-oxazolidine was prepared in 65% yield, m.p. 134-136° (ethyl acetate-methanol).

4-Benzoyl-3-isopropyl-2(3-nitrophenyl)-5-phenyloxazolidine was prepared in 48% yield as a 64:36 mixture of *cis* and *trans* isomers,m.p. 121-123° (methanol).

4-Benzoyl-3-cyclohexyl-5-(4-nitrophenyl)-2-phenyl-*trans*-4,5-oxazolidine was prepared in *ca.* 45% yield as an oil.

4-Benzoyl-3-cyclohexyl-2-(3-nitrophenyl)-5-phenyloxazolidine was prepared in 44% yield as a 58:42 mixture of *cis* and *trans* isomers, m.p. 135-138° (ethylacetate-ethanol).

4-Benzoyl-3-cyclohexyl-2-(3-nitrophenyl)-5-(4-nitrophenyl) oxazolidine was prepared in 57% yield as a 68:32 mixture of *cis* and *trans* isomers m.p. 128-131° (methanol).

By the above general method several other oxazolidines were prepared, but due to experimental difficulties they could not be isolated from the reaction mixtures. Their p.m.r. data are listed in Table XVII.

Attempted Reaction of 1-Benzyl-2-phenyl-3-(4-toluoyl)aziridine with 2,4-Dichlorobenzaldehyde

A solution of 1-benzyl-2-phenyl-3-(4-toluoyl)aziridine (3.27 g, 0.01 mole) and 2,4-dichlorobenzaldehyde (1.75 g, 0.01 mole) in dry benzene (40 ml) was heated under reflux for 20 h. Work-up of the solution as above produced a yellow-brown oil (1.8 g) which could not be identified.

3. Deuterium Labelling Experiments

A. Reaction of 3-Benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine with α-D-Benzaldehyde

A solution of 3-benzoyl-1-isopropyl-2-(3-nitrophenyl)aziridine (1.55 g, 0.005 mole) and freshly distilled α-D-benzaldehyde (0.535 g, 0.005 mole, 99.5%D incorporation Merck, Sharp and Dohme, Montreal, Canada) in dry benzene (35 ml), was heated under reflux for 24 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting dark red oil on grade I alumina (BDH, 60 g) with benzene as eluant, gave as the main fraction a yellow oil which crystallized on trituration with cold methanol to give as a yellow solid (0.768 g, 36.8%), a mixture (67:33 by p.m.r.) of *cis* and *trans*-4-benzoyl-5-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine m.p. 118-121° (methanol). Mass spectrum: 310.1317 ($C_{18}H_{18}N_2O_3$; M-C_6H_5CDO) and 107.0497 (C_6H_5CDO; M-$C_{18}H_{18}N_2O_3$). Found: 310.1319 and 107.0497.
Infrared spectrum ν_{max} ($CHCl_3$): 1678s (C=O), 1526s cm^{-1} (aromatic NO_2).

Although no isomer separation was achieved, both the *cis* and *trans* isomers were characterized by their p.m.r. spectra.

4-Benzoyl-5-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyl-*cis*-4,5-oxazolidine

δ($CDCl_3$): 0.69 (doublet, 3H, J = 6.4 Hz, isopropyl $C\underline{H}_3$), 1.02 (doublet, 3H, J = 6.4 Hz, isopropyl $C\underline{H}_3$), 3.06-3.41 (multiplet, 1H, isopropyl $C\underline{H}$), 5.43 (singlet, 1H, 4 proton), 6.20 (singlet, 1H, 2 proton), 6.88-8.67 (multiplet, 14H, aryl protons).

4-Benzoyl-5-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyl-*trans*-4,5-oxazolidine

δ($CDCl_3$): 0.97 (doublet, 6H, J = 6.6 Hz, isopropyl C$\underline{H}_3$), 3.06-3.41 (multiplet, 1H, isopropyl C$\underline{H}$), 4.77 (singlet, 1H, 4 proton), 6.10 (singlet, 1H, 2 proton), 6.88-8.67 (multiplet, 14H, aryl protons).

B. Preparation of 3-Deuteroaziridines

These compounds were prepared by the general method of Lown, Moser, and Westwood.[156] All new compounds are reported in full, with references being given to previously prepared products.

2-Bromo-3-(3-nitrophenyl)-1-phenylpropenone

A slurry of 2,3-dibromo-3-(3-nitrophenyl)-1-phenylpropanone (22.0 g, 0.053 mole) and potassium acetate (5.194 g, 0.053 mole) in 95% ethanol (600 ml) was heated under reflux for 12 h. The resulting pale yellow solution was evaporated to *ca.* 50 ml, poured into cold water (350 ml) and the organic material extracted with ether. The combined ether extract was dried ($MgSO_4$), and evaporated *in vacuo*, to give a pale yellow oil which solidified on cooling. Crystallization from methanol gave the desired product (12.5 g, 71%), m.p. 94-96°.

Anal. Calcd. for $C_{15}H_{10}BrNO_3$: C, 54.23; H, 3.01; N, 4.22; Br, 24.10.

Found: C, 54.15; H, 2.96; N, 4.16; Br, 24.03.

Mass spectrum: 330.9844 ($C_{15}H_{10}{}^{79}BrNO_3$). Found: 330.9842.

Infrared spectrum ν_{max} ($CHCl_3$): 1667 (α,β-unsaturated ketone), 1615 (C=C), 1528 cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 7.28-8.83 (multiplets, 10H, aryl protons and vinyl proton).

2-Bromo-3-(4-nitrophenyl)-1-phenylpropenone

This compound was prepared in 78% yield by the method of Weygand, m.p. 106° (lit., m.p. 106°).[175]

2-Bromo-1-(4-nitrophenyl)-3-phenylpropenone

This compound was prepared in 78% yield by the method of Weygand,[175] m.p. 104-106° (lit., m.p. 108°).[180]

2-Bromo-1-(4-toluoyl)-3-phenylpropenone

This compound was prepared in 92% yield by the method of Weygand, m.p. 66° (lit., m.p. 66-67°).[175]

Cyclohexylamine-ND_2 was prepared from cyclohexylamine by the method of Denny and Greenbaum.[180] Isopropylamine-ND_2 and benzylamine-ND_2 were prepared by this method though in the former case the ethereal solution was used as such in the preparation of the deuterated aziridines, owing to the volatility of the isopropylamine-ND_2

3-Benzoyl-3-deutero-1-isopropyl-2-(3-nitrophenyl)aziridine

To a stirred solution of 2-bromo-3-(3-nitrophenyl)-1-phenylpropenone (14.3 g, 0.043 mole) in dry ether (300 ml) was added an estimated five-fold excess of isopropylamine-ND_2 in dry ether solution at a rapid rate at room temperature, and the resulting mixture stirred for 24 h. The precipitated deuterobromide salt was removed by filtration, and the filtrate was concentrated *in vacuo*, and subjected to chromatography on grade I alumina (BDH, 120 g) with benzene as eluant. In this manner a pale yellow oil was obtained which crystallized on chilling and trituration with cold ethanol to give as

a white solid the required aziridine (8.69 g, 65%) m.p. 90-92°.
Mass spectrum: 311.1396 ($C_{18}H_{18}DN_2O_3$). Found: 311.1394.
P.M.R. spectrum ($CDCl_3$): 0.92 (doublet, 3H, J = 6.2 Hz, isopropyl C$\underline{H}_3$), 1.18 (doublet, 3H, J = 6.2 Hz, isopropyl C$\underline{H}_3$), 2.67-3.20 (septet, 1H, isopropyl C$\underline{H}$) 3.64 (1.15H, singlet, aziridine ring protons), 7.42-8.40 (multiplet, 9H, aryl protons).

This corresponds to approximately 85% incorporation of deuterium at the 3-position.

1-Benzyl-3-deutero-2-phenyl-3-(4-toluoyl)aziridine

A solution of benzylamine-ND_2 (7.64 g, 0.07 mole) in dry ether (70 ml) was added dropwise over 1 h, to a stirred solution of 2-bromo-1-(4-toluoyl)-3-phenylpropenone (4.3 g, 0.014 mole) in dry ether (200 ml) at 0°. The resulting mixture was then stirred at room temperature for 23 h, when the precipitated white deuterobromide salt was collected. The filtrate was washed with water and dried ($MgSO_4$). Removal of the ether *in vacuo* gave a yellow oil, which was dissolved in benzene (10 ml) and heptane (20 ml) was added and the mixture chilled to give the required deuterated aziridine (2.11 g, 45%), m.p. 109°.
Infrared spectrum ν_{max} ($CHCl_3$): 1682 cm^{-1} (C=O).
P.M.R. spectrum ($CDCl_3$): 2.30 (singlet, 3H, aryl C$\underline{H}_3$), 3.30 (1.3 H, broad based singlet, aziridine ring protons), 4.05 and 3.73 (AB quartet, 2H, benzyl C$\underline{H}_2$, J = 14.05 Hz), 7.0-8.0 (multiplet, 14H, aryl protons).
This corresponds to about 70% deuterium incorporation at the 3-position.

3-Benzoyl-1-cyclohexyl-3-deutero-2-(4-nitrophenyl)aziridine was prepared in 63.3% yield by the above methods with a deuterium incorporation of 69%.

3-Benzoyl-1-cyclohexyl-3-deutero-2-(3-nitrophenyl)aziridine was prepared in 57% yield as above with a deuterium incorporation of 70%.

1-Cyclohexyl-3-deutero-3-(4-nitrobenzoyl)-2-phenylaziridine was prepared by the method of Lown, Moser, and Westwood[156] in 72% yield containing 60% of deuterium at the 3-position. These results are summarized in Table XVIII.

C. Preparation of Oxazolidines Containing Deuterium at the 4-Position

4-Benzoyl-3-cyclohexyl-4-deutero-2-(4-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine

A solution of 3-benzoyl-1-cyclohexyl-3-deutero-2-(4-nitrophenyl)aziridine (1.93 g, 0.0055 mole, 69% D incorporation) and chloral (0.806 g, 0.0055 mole) in dry benzene (35 ml), was heated under reflux for 24 h. Concentration of the cooled solution *in vacuo* and chromatography of the resulting red-brown oil on grade I alumina (BDH, 100 g) with benzene as eluant, gave as the main fraction an oil which crystallized on trituration with cold methanol to give the required oxazolidine (1.965 g, 71.8%), m.p. 153-155° (pale yellow needles from methanol).

Mass spectrum: 392.0463 ($C_{16}H_{17}DCl^{35}_3N_2O_3$; M-$C_6H_5$CO). Found: 392.0470.
Infrared spectrum ν_{max} ($CHCl_3$): 1690w, 1675s (C=O), 1523 cm^{-1}, (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.66-2.00 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 2.33-2.74 (multiplet, 1H, cyclohexyl $C\underline{H}$), AB quartet centered at 5.25 (0.32 H, 4 proton) and 4.86 (1H, 5 proton), J = 4.2 Hz, *trans* coupling; 6.34 (singlet, 1H, 2 proton), 7.27-8.39 (multiplet, 9H aryl protons).

This integration corresponded to 68% incorporation of deuterium into the oxazolidine.

4-Benzoyl-4-deutero-5-(2,4-dinitrophenyl)-3-isopropyl-2-(3-nitrophenyl)-*cis*-4,5-oxazolidine

A solution of 3-benzoyl-3-deutero-1-isopropyl-2-(3-nitrophenyl)aziridine (1.04 g, 0.0033 mole, 85% D incorporation) and 2,4-dinitrobenzaldehyde (0.653 g, 0.0033 mole) in dry benzene (35 ml), was heated under reflux for 18 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting orange-brown oil on grade I alumina (BDH, 80 g) with benzene as eluant, gave as the main fraction a yellow oil which rapidly crystallized on trituration with cold methanol to give the required oxazolidine (1.046 g, 61.8%), m.p. 134-136° (methanol).

Mass spectrum: 311.1396 ($C_{18}H_{17}DN_2O_3$; $M-C_7H_4N_2O_5$) and 196.0126 ($C_7H_4N_2O_5$; $M-C_{18}H_{17}DN_2O_3$). Found: 311.1398 and 196.0123.

Infrared spectrum ν_{max} ($CHCl_3$): 1678 (C=O), 1533 cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.75 (doublet, 3H, J = 6.35 Hz, isopropyl $C\underline{H_3}$), 1.03 (doublet, 3H, J = 6.35 Hz, isopropyl $C\underline{H_3}$), 3.07-3.46 (multiplet, 1H, isopropyl $C\underline{H}$), AB quartet centered at 6.09 (1H, 5 proton) and 5.98 (0.33 H, 4 proton), J = 5.7 Hz, *cis* coupling; 6.38 (singlet, 1H, 2 proton), 7.14-8.70 (multiplet, 12H, aryl protons). This corresponds to

67% incorporation of deuterium into the oxazolidine.

By the general method outlined above the following series of oxazolidines specifically deuterated in the 4-position were prepared. Their spectral data are summarized in Tables XIX and XX.

4-Benzoyl-4-deutero-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 48% yield as a very pale yellow solid m.p. 110-111° (methanol).

3-Benzyl-4-deutero-2-phenyl-4-(4-toluoyl)-5-trichloromethyloxazolidine was prepared in 43% yield as a 18:82 mixture of *cis* and *trans* isomers m.p. 118-122°. Recrystallization from methanol gave *trans* isomer m.p. 129-130°.

4-Benzoyl-3-cyclohexyl-4-deutero-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine was prepared in 64.7% yield m.p. 127-129° (methanol).

4-Benzoyl-4-deutero-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)oxazolidine was prepared in 54.9% yield as a 58:42 mixture of *cis* and *trans* isomers m.p. 116-119° (methanol).

4-Benzoyl-3-cyclohexyl-4-deutero-2-(3-nitrophenyl)-5-(4-nitrophenyl)oxazolidine was prepared in 57% yield as a 68:32 mixture of *cis* and *trans* isomers m.p. 128-131° (methanol).

4-Benzoyl-4-deutero-3-isopropyl-2-(3-nitrophenyl)-5-phenyloxazolidine was prepared in 20.2 % yield as a *cis-trans* mixture. Careful chromatography (alumina/benzene) enabled the pure *trans* isomer to be isolated, m.p. 135-137° (see Figure II).

4. Acid Hydrolysis of Oxazolidines.

4-Benzoyl-5-(2,4-dinitrophenyl)-3-isopropyl-2-(3-nitrophenyl)-*cis*-4,5-oxazolidine

The title oxazolidine (0.506 g, 0.001 mole) was heated under reflux in 2N hydrochloric acid (25 ml) for 3 h. The yellow solution was cooled and extracted with portions of ether, after which the combined organic extracts were dried ($MgSO_4$). Removal of the ether *in vacuo* yielded a red-brown light oil (0.309 g).
Infrared spectrum ν_{max} (film): 1685 (aromatic C=O), 1530 cm^{-1}, (aromatic NO_2). T.L.C. (silica/benzene) showed the oil to be a 2 component mixture. Examination of the 2,4-dinitrophenylhydrazone derivative of this oil (m.p. 270-280°) by mass spectrum showed parent ions corresponding to those of the 2,4-dinitrophenylhydrazones of 3-nitrobenzaldehyde [331.0553 ($C_{13}H_9N_5O_6$). Found: 331.0549], and 2,4-dinitrobenzaldehyde [376.0404 ($C_{13}H_8N_6O_8$). Found: 376.0404]. This mixture proved to be insoluble in common solvents and hence no separation was achieved.

4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine

The title oxazolidine (0.92 g, 0.0021 mole) was heated under reflux in glacial acetic acid (35 ml) containing 2N hydrochloric acid (0.5 ml) for 3 h. The yellow solution was cooled, diluted with water

(30 ml) and extracted with chloroform. The combined organic extract was then washed with water and dried ($MgSO_4$). Removal of the chloroform *in vacuo* yielded an orange oil (0.295 g), t.l.c. (silica/benzene) of which showed one major component and a trace of a minor component. This major compound was shown to be 3-nitrobenzaldehyde on the following basis:
Mass spectrum: 151.0269 ($C_7H_5NO_3$). Found 151.0270.
Infrared spectrum ν_{max} ($CHCl_3$): 1688 (aromatic C=O), 1515 cm^{-1} (aromatic NO_2).

A 2,4-dinitrophenylhydrazone derivative was prepared m.p. 291-292° (lit., m.p. 293°).[181]

Mass spectrum: 331.0553 ($C_{13}H_9N_5O_6$). Found: 331.0552.

The aqueous layer was neutralized with potassium carbonate whereupon a yellow oil separated and was extracted with chloroform and dried ($MgSO_4$). Removal of the chloroform *in vacuo* yielded a yellow oil (0.19 g), t.l.c. of which showed a major component together with trace contaminants. This major component was found to be benzoic acid on the basis of its infrared and mass spectral data. 122.0367 ($C_7H_6O_2$) Found: 122.0368.

3-Benzyl-2-phenyl-4-(4-toluoyl)-5-trichloromethyl-*trans*-4,5-oxazolidine

The title oxazolidine (0.311 g, 0.006 mole) was heated under reflux in glacial acetic acid (25 ml) containing 2N hydrochloric acid (0.5 ml) for 3 h. The yellow solution was cooled, diluted with water (25 ml) and extracted with portions of chloroform. The combined organic extract was then washed with water and dried ($MgSO_4$). Removal of the chloroform *in vacuo* yielded a yellow oil which partly solidified on cooling (0.070 g). This was shown to consist of a mixture of benzoic acid and 4-toluic acid on the basis of its infrared and mass spectral data.

Infrared spectrum ν_{max} ($CHCl_3$): 3440-2500 br (bonded OH of acid), 1690 br cm^{-1} (aromatic C=O).

Mass spectrum: 122.0368 ($C_7H_6O_2$, benzoic acid). Found: 122.0365.
136.0524 ($C_8H_8O_2$, 4-toluic acid). Found: 136.0522.

Examination of the aqueous extract by first neutralization (NaOH) and then chloroform extraction revealed only traces of both acids.

5. Attempted Decomposition of 4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyloxazolidine.

The title compound (0.20 g) was heated under reflux in benzene (35 ml) for a period of 24 h. The cooled solution was evaporated to yield a yellow oil which crystallized on trituration with cold methanol to give the starting oxazolidine (0.135 g, 68% recovery). Infrared, p.m.r. and mass spectra comparison with that of authentic material confirmed this result.

6. Attempted Epimerization of Oxazolidines

A. 4-Benzoyl-5-(2,4-dinitrophenyl)-3-isopropyl-2-(3-nitrophenyl)-*cis*-4,5-oxazolidine

a) The title oxazolidine (0.07 g, 0.00014 mole) and sodium methoxide (0.003 g, 0.00005 mole) were heated under reflux in a mixture of methanol (10 ml) and tetrahydrofuran (10 ml) for 40 min. Removal of the solvent *in vacuo* from the cooled solution, gave a brown oil, which was dissolved in chloroform and washed with water, dried ($MgSO_4$), and the solvent evaporated to give a brown gum, p.m.r. examination of which indicated complete decomposition of the oxazolidine ring.

b) A solution of the title compound (0.253 g, 0.0005 mole) and N-diisopropyl ethylamine (0.065 g, 0.0005 mole) in ethyl acetate (20 ml) was heated under reflux for 5 h. Removal of the solvent *in vacuo* gave a yellow-brown oil, which crystallized on trituration with cold methanol to give the starting *cis*-oxazolidine (0.04 g, 15% recovery), m.p. 125-128°. Comparison of spectral properties with those of the authentic material confirmed this result.

c) A solution of the title compound (0.253 g, 0.0005 mole) and sodium methoxide (0.009 g, 0.00017 mole) in 1,2-dimethoxyethane (25 ml) was stirred at room temperature for 2 h. Removal of the solvent *in vacuo* gave an orange oil which was dissolved in chloroform, washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo* to yield an oil which crystallized on trituration with methanol to give the title oxazolidine (0.10 g, 39.5% recovery), m.p. 130-133°.

B. 4-Benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-(4-nitrophenyl)-*trans*-4,5-oxazolidine

The title compound (0.056 g) and sodium methoxide (0.003 g) were heated under reflux in methanol (20 ml) for 30 min. Work-up as above gave the title oxazolidine as a pale yellow solid (0.026 g, 46.5% recovery) m.p. 128-131°. Spectral comparison with that of authentic material confirmed the result.

C. 4-Benzoyl-3-cyclohexyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine

The title compound (0.30 g, 0.0006 mole) and sodium methoxide (0.0065 g, 0.00012 mole) were heated under reflux in methanol (20 ml) for 60 min. Work-up as before produced a yellow oil which did not crystallize and whose p.m.r. spectrum showed only the title compound.

7. Stereochemistry Control Experiments

A. Reaction of *trans*-3-benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine with Chloral

A solution of *trans*-3-benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine (3.50 g, 0.01 mole) and chloral (1.475 g, 0.01 mole) in dry benzene (50 ml) was heated under reflux for 24 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting orange oil on grade I alumina (BDH, 100 g) with benzene as eluant, gave as the main fraction a yellow oil which crystallized on trituration with cold methanol to give 4-benzoyl-3-cyclohexyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine (3.60 g, 72.3%), m.p. 128-130° (methanol).

Anal. Calcd. for $C_{23}H_{23}Cl_2N_2O_4$: C, 55.48; H, 4.62; N, 5.63; Cl, 21.41

Found: C, 55.44; H, 4.70; N, 5.71; Cl, 21.70.

Mass spectrum: 391.0384 ($C_{16}H_{18}Cl_3N_2O_3$; M-C_6H_5CO). Found: 391.0390.

Infrared spectrum ν_{max} ($CHCl_3$): 1690w, 1675 (C=O), 1530s cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.50-2.04 (multiplet, 10H, cyclohexyl CH_2), 2.26-2.85 (multiplet, 1H, cyclohexyl CH), 5.28 and 4.86 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 4.1 Hz), 6.33 (singlet, 1H, 2 proton), 7.20-8.80 (multiplet, 9H, aryl protons).

Reaction of *cis*-3-Benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine with Chloral

A solution of *cis*-3-benzoyl-1-cyclohexyl-2-(3-nitrophenyl)aziridine (1.30 g, 0.0037 mole) and chloral (0.546 g, 0.0037 mole) in dry benzene (30 ml) was heated under reflux for 24 h. Work-up of the product under the above conditions gave the identical oxazolidine as a pale yellow solid (1.11 g, 60%), m.p. 126-128° (methanol).

Anal. Found: C, 55.76; H, 4.84; N, 5.90; Cl, 21.70.

Mass spectrum: Found, 391.0390 ($C_{16}H_{18}Cl_3N_2O_3$; M-C_6H_5CO).

Infrared spectrum ν_{max} ($CHCl_3$): 1688w, 1675 (C=O), 1528 cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.50-2.17 (multiplet, 10H, cyclohexyl CH$_2$), 2.33-2.93 (multiplet, 1H, cyclohexyl CH), 5.28 and 4.85 (AB quartet, 2H, 4,5 ring protons; *trans* coupled, J = 4.1 Hz), 6.32 (singlet, 1H, 2 proton), 7.25-8.42 (multiplet, 9H, aryl protons).

Reaction of *trans*-3-Benzoyl-1-cyclohexyl-2-phenylaziridine with 4-Nitrobenzaldehyde

A solution of *trans*-3-benzoyl-1-cyclohexyl-2-phenylaziridine (3.35 g, 0.011 mole) and 4-nitrobenzaldehyde (1.66 g, 0.011 mole) in dry benzene (100 ml) was heated under reflux for 11 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting orange-brown oil on Fisher alumina (80-200 mesh, 150 g) with benzene as eluant, gave as the main fraction a brown oil (4.2 g), which was found by t.l.c. to be a 2-component mixture consisting mainly of 4-benzoyl-3-cyclohexyl-5-(4-nitrophenyl)-2-phenyl-*trans*-4,5-oxazolidine.

Anal. Calcd. for $C_{28}H_{28}N_2O_4$: H, 6.14; N, 6.14.

Found: H, 6.13; N, 6.03.

Mass spectrum: 305 ($C_{21}H_{23}NO$; M-$C_7H_5NO_3$) and 151.0269 ($C_7H_5NO_3$; M-$C_{21}H_{23}NO$). Found: 305 and 151.0267.

Infrared spectrum ν_{max} ($CHCl_3$): 1678 (C=O), 1513 cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.66-2.03 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 2.49-3.00 (multiplet, 1H, cyclohexyl $C\underline{H}$), 5.46 and 4.50 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 7.2 Hz), 5.91 (singlet, 1H, 2 proton), 6.95-8.25 (multiplet, 14H, aryl protons).

From the p.m.r. and infrared spectra, the contaminant appeared to be unreacted 4-nitrobenzaldehyde.

Reaction of *cis*-3-Benzoyl-1-cyclohexyl-2-phenylaziridine

A solution of *cis*-3-benzoyl-1-cyclohexyl-2-phenylaziridine (2.0 g, 0.007 mole) and 4-nitrobenzaldehyde (1.06 g, 0.007 mole) in dry benzene (70 ml) was heated under reflux for 12 h. Work-up of the solution as described above, gave a red-brown oil (1.4 g) which was shown by t.l.c. to be the same two component mixture as in the above case.

Anal. Calcd. for $C_{28}H_{28}N_2O_4$: H, 6.14; N, 6.14.

Found: H, 6.12; N, 6.05.

Mass spectrum: 305 ($C_{21}H_{23}NO$; M-$C_7H_5NO_3$) and 151 ($C_7H_5NO_3$; M-$C_{21}H_{23}NO$).

Infrared spectrum ν_{max} ($CHCl_3$): 1680 (C=O), 1516 cm^{-1} (aromatic NO_2).

P.M.R. spectrum ($CDCl_3$): 0.50-2.08 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.39-3.03 (multiplet, 1H, cyclohexyl $C\underline{H}$), 5.44 and 4.49 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 7.1 Hz), 5.90 (singlet, 1H, 2 proton), 6.70-8.21 (multiplet, 14H, aryl protons).

B. Attempted Reverse Electrocyclic Cleavage Reactions

A solution of 4-benzoyl-3-isopropyl-2-(3-nitrophenyl)-5-trichloromethyl-*trans*-4,5-oxazolidine (0.46 g, 0.003 mole) and dimethyl acetylenedicarboxylate (0.42 g, 0.003 mole) in benzene (35 ml) was heated under reflux for 24 h. Concentration of the cooled, pale yellow solution *in vacuo*, and chromatography of the resulting oil on grade I alumina (BDH, 40 g) with a 1:1 mixture of heptane and benzene as eluant, gave a yellow oil which crystallized on trituration with cold 95% ethanol to give the starting *trans*-oxazolidine (0.349 g, 75.9% recovery), m.p. 103°. Comparison of the infrared, p.m.r. and mass spectra with that of the authentic material confirmed this result.

A repeat of this above reaction in toluene (35 ml) as solvent caused complete decomposition of the starting oxazolidine.

8. Attempted Synthesis of Oxazolidines by an Unambiguous Stereocontrolled Method

trans-Stilbene Oxide

This compound was prepared in 70% yield from *trans*-stilbene by the method of Reif and House,[169] m.p. 67-68° (lit., m.p. 68-69°).

erythro-1,2-Diphenylaminoethanol

This compound was prepared in 45% yield from *trans*-stilbene oxide by the method of Foglia and Swern,[168] m.p. 166-168° (lit., m.p.

165-166°).

Reaction of *erythro*-1,2-Diphenylaminoethanol and 4-Nitrobenzaldehyde

A solution of *erythro*-1,2-diphenylaminoethanol (0.70 g, 0.0033 mole) and 4-nitrobenzaldehyde (0.495 g, 0.0033 mole) in toluene (40 ml) was heated under reflux in a Dean-Stark apparatus for 22 h. The solvent was removed *in vacuo* to yield a yellow gum (1.10 g) which did not crystallize. Thin-layer chromatography indicated a mixture of at least three components, which were deduced from the infrared and p.m.r. spectra of the mixture to be the starting materials and the Schiff-base 52.

cis-Stilbene Oxide

This compound was prepared by a modification of the method of Curtin and Kellum.[170] A solution of 3-chloroperbenzoic acid (8.301 g, 0.048 mole) in dry benzene (180 ml) was added to a solution of *cis*-stilbene oxide (8.225 g, 0.046 mole) in dry benzene (35 ml), and the resulting solution stirred overnight at room temperature. The precipitated 3-chlorobenzoic acid was removed by filtration, and the filtrate was washed with 5% sodium bicarbonate solution, then with water and finally dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a pale yellow sticky solid which was washed with hexane and crystallized from 95% ethanol to give the product as white needles (3.16 g, 35%), m.p. 36-38° (lit., m.p. 37-37.5°).[170]

threo-1,2-Diphenylaminoethanol

This compound was prepared in 50% yield from *cis*-stilbene oxide by the method of Foglia and Swern,[168] m.p. 123-125° (lit., m.p. 127-128°).

Reaction of *threo*-1,2-Diphenylaminoethanol and 4-Nitrobenzaldehyde

A solution of *threo*-1,2-diphenylaminoethanol (1.20 g, 0.0056 mole) and 4-nitrobenzaldehyde (0.85 g, 0.0056 mole) in toluene (40 ml) was heated under reflux in a Dean-Stark apparatus for 22 h. The solvent was removed *in vacuo* to yield a yellow gum (1.90 g) which could not be crystallized. Thin-layer chromatography indicated a mixture of several components, one of which was shown by infrared spectroscopy to be 4-nitrobenzaldehyde [ν_{max} 1704 cm^{-1} (C=O)]. The major component was a 1:1 adduct as judged from the mass spectrum [347.1521 ($C_{21}H_{18}N_2O_3$). Found: 347.1530], but no clear assignment of its structure could be made from the p.m.r. spectrum of the mixture.

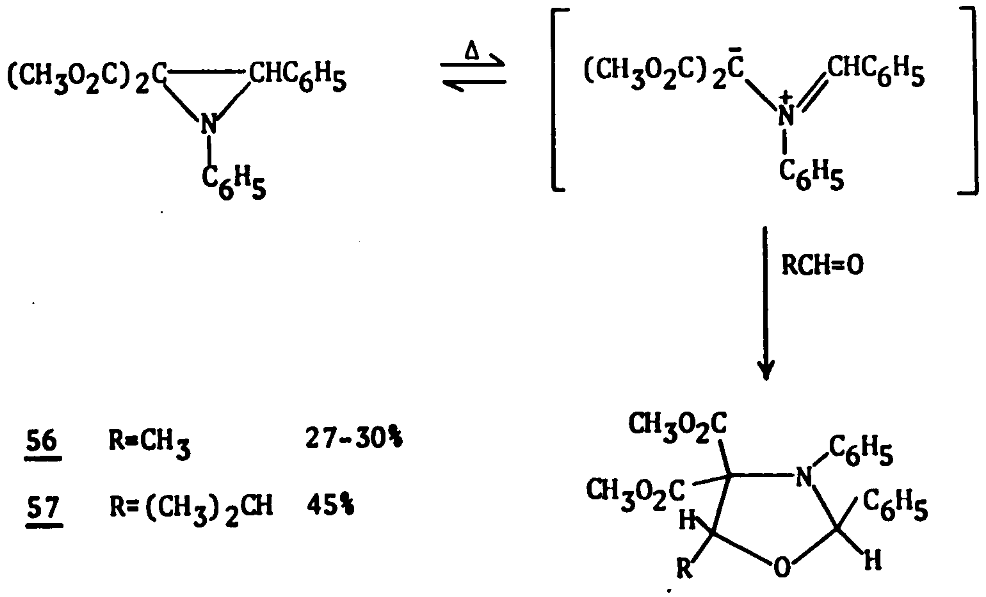
CHAPTER III

[2+3] CYCLOADDITION REACTIONS OF SUBSTITUTED AZIRIDINES WITH DIPHENYLCYCLOPROPENONE

In the work described in Chapter II it was found that 3-aroyl-2-arylaziridines reacted readily with a variety of aromatic aldehydes and chloral to form oxazolidines in good yields. This was seen to proceed by thermal cleavage of the aziridines to intermediate azomethine ylides followed by [2+3] cycloaddition reactions in a manner in which the stereochemistry could be predicted with some certainty. The most reactive carbonyl group was that of chloral, which was found to react cleanly to give a single product in 70-80% yield.

Texier and Carrie [157] have demonstrated that simple aliphatic aldehydes also react to form oxazolidines in fair yields with 1,2-diaryl-3-dicarboalkoxyaziridines as shown in equation [92].

[92]

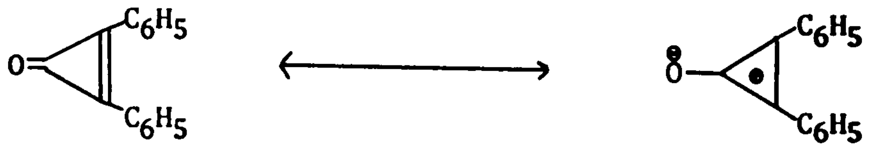

$(CH_3O_2C)_2C$
CHC_6H_5
N
C_6H_5
Δ
$(CH_3O_2C)_2\bar{C}$
CHC_6H_5
$\overset{+}{N}$
C_6H_5
RCH=O
CH_3O_2C
CH_3O_2C
N
C_6H_5
C_6H_5
H
R
O
H

56	R=CH_3	27-30%
57	R=$(CH_3)_2CH$	45%

In view of the known sluggish nature of the carbonyl group as a dipolarophile,[62] these results emphasize the high reactivity of the intermediate azomethine ylide employed by Texier and Carrie.

Conversely it was found by Lown and coworkers[182] that aliphatic aldehydes were insufficiently reactive to participate in [2+3] cycloaddition reactions with azomethine ylides derived from 3-aroyl-2-arylaziridines.

In a further search for other reactive carbonyl compounds to participate as dipolarophiles in [2+3] cycloaddition reactions, it appeared that diphenylcyclopropenone might prove particularly useful, since the carbonyl group was known to be highly polarizable due to resonance of the type shown.[183]

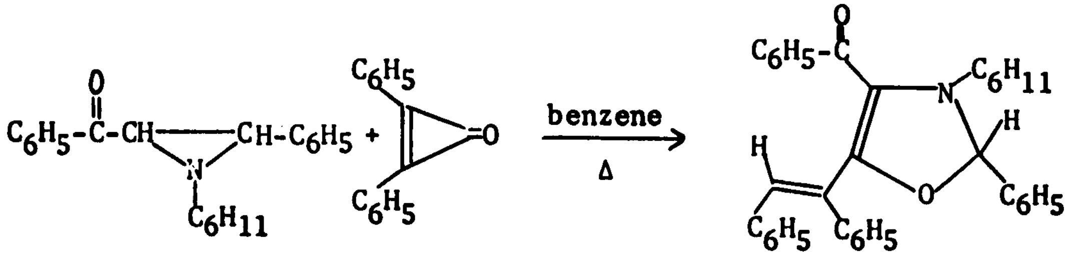


Even before its preparation, Hückel Molecular Orbital calculations by Roberts and Manatt[184] had predicted the stability of diphenylcyclopropenone (DPP), due to resonance of the above type, the energy of which was sufficient to overcome the considerable strain in the molecule.

It was thought that this resonance contribution would enhance the dipolarophilic nature of the compound, and lead to improved reactions with substituted aziridines. This represented therefore the first step in a logical extension of the work described in Chapter II.

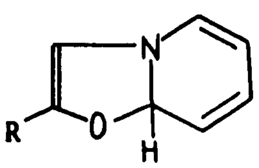
The products obtained from the reactions of diphenylcyclopropenone with 3-aroyl-2-arylaziridines have been tentatively formulated as 4-oxazolines. A whole series of such compounds have been conveniently prepared in fair to good yields by this method, an example of which is the reaction of 3-benzoyl-1-cyclohexyl-2-phenylaziridine with diphenylcyclopropenone to form 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline in 65% yield, as shown in equation [93].

[93]

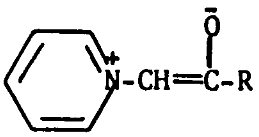


58

The first report of such a ring system in the literature appeared in 1933, when Krollpfeiffer and Müller[185] proposed a 4-oxazoline structure 59, for a pyridinium ylide, but this was later rejected in favor of the enol betaine structure[186] 60.



59

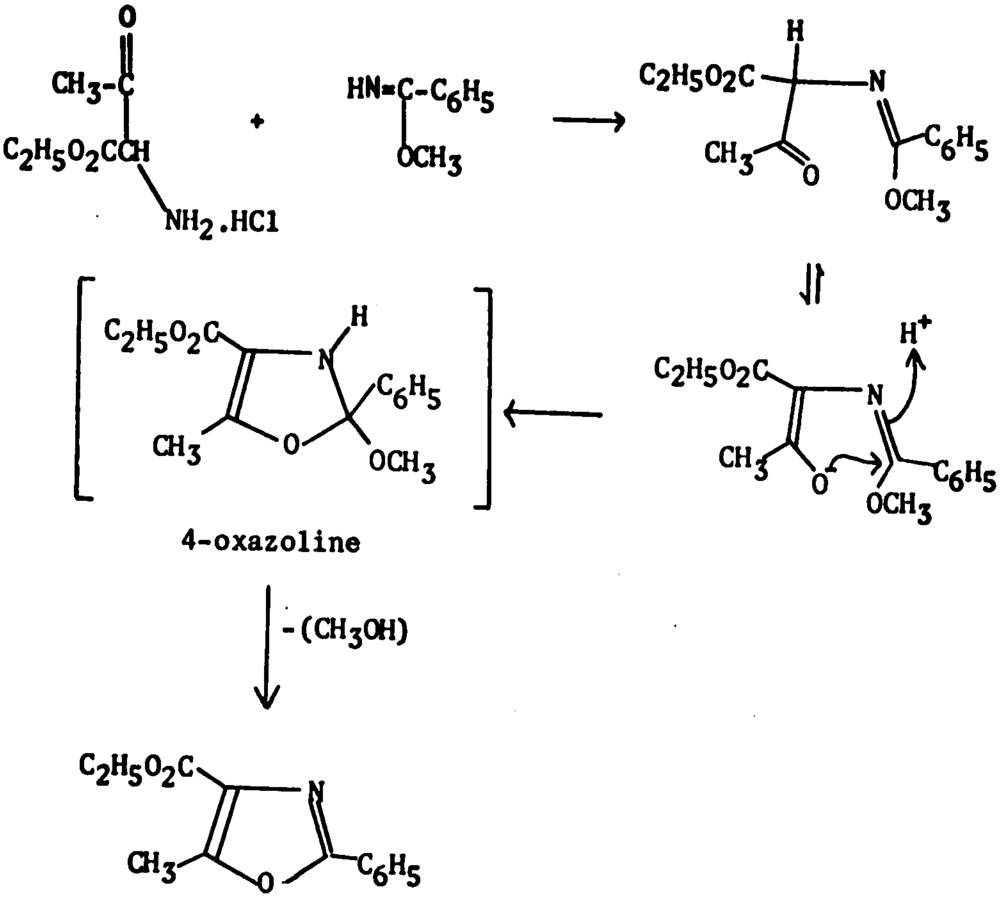


60

$R=C_6H_3(SC_2H_5)_2CH_3$

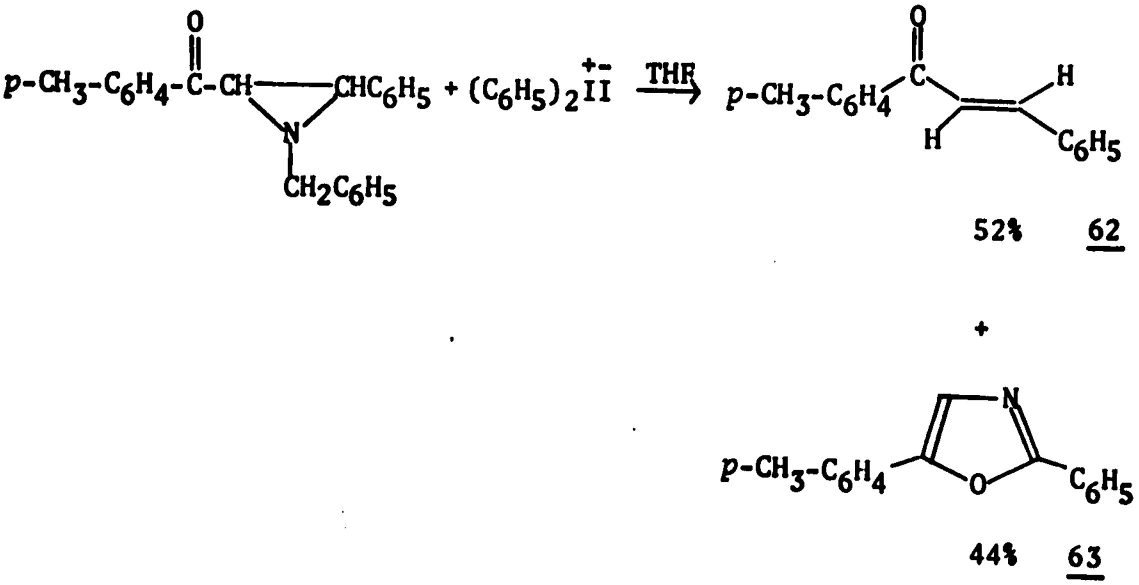
Although 2- and 3-oxazolines have been known for some time, the 4-oxazolines represent a completely unexamined heterocyclic system, though they have been postulated as intermediates in reactions leading to the formation of oxazoles as shown in equations [94][13] and [95].[24,187]

[94]

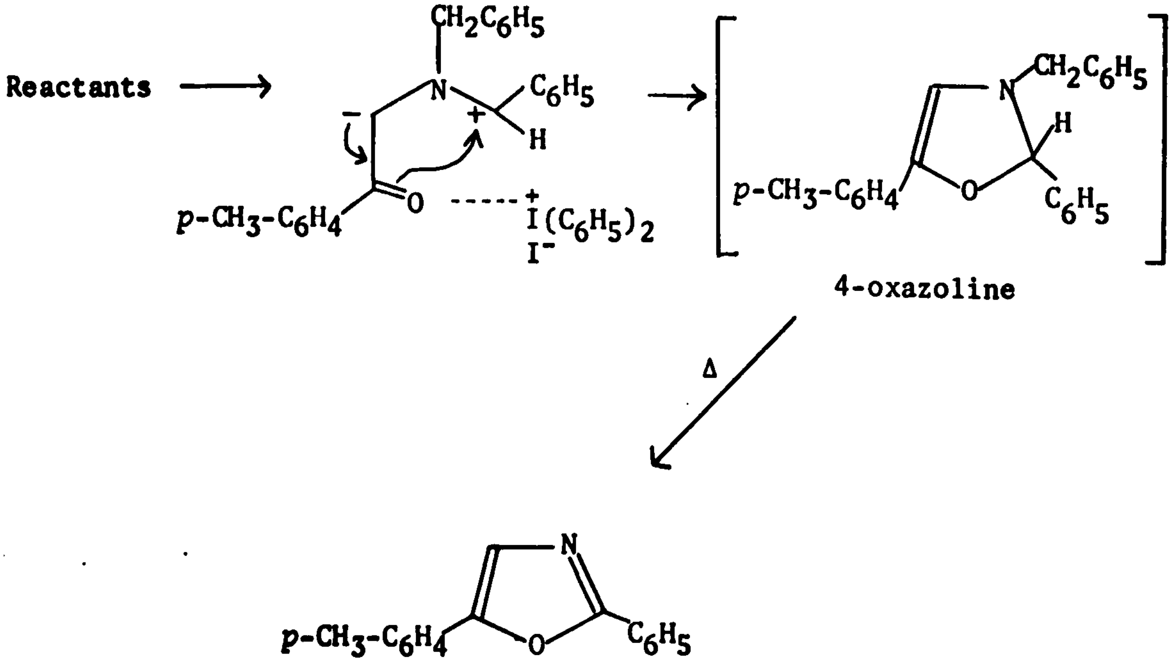

4-oxazoline
-(CH$_3$OH)

61 Ref. 13

[95]


THF
52% 62
+
44% 63

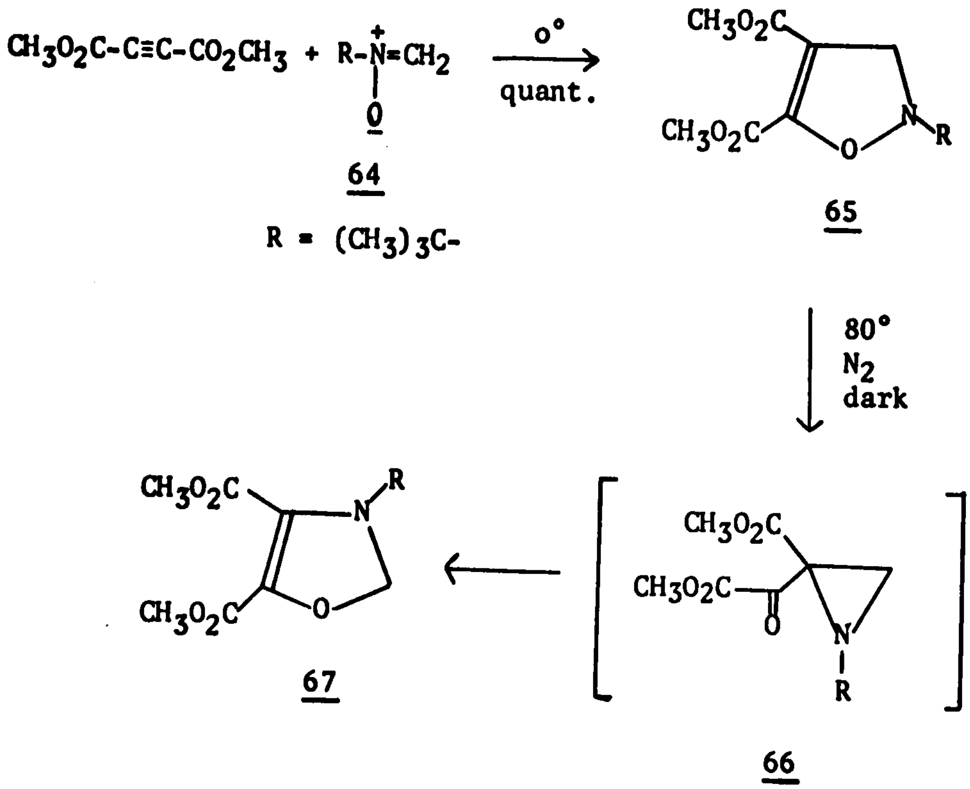
The mechanism of formation of the oxazole is given as follows:[24,187]


Reactants
$CH_2C_6H_5$
N
C_6H_5
H
p-CH_3-C_6H_4
O
$\overset{+}{I}(C_6H_5)_2$
I^-
4-oxazoline
Δ
N
O

63

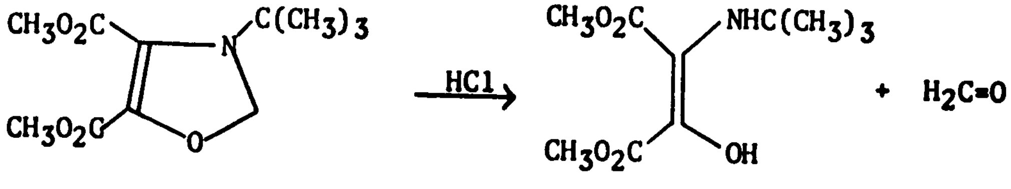
The first successful preparation of the 4-oxazoline system was reported by Baldwin, Pudussery, Qureshi, and Sklarz[188] in 1968, who demonstrated the facile thermal valence rearrangement of 4-isoxazolines via 2-acylaziridines to 4-oxazolines as shown in Scheme V.

SCHEME V


CH3O2C-C≡C-CO2CH3 + R-N=CH2
O
64
R = (CH3)3C-
0°
quant.
CH3O2C
CH3O2C
N
R
O
65
80°
N2
dark
CH3O2C
CH3O2C
O
N
R
66
CH3O2C
CH3O2C
N
R
O
67

The 4-isoxazolines required were readily prepared by the cycloaddition reactions of nitrones and dimethyl acetylenedicarboxylate. Compound 65 proved thermally very labile and readily isomerized to the 4-oxazoline 67, the structure of which was readily proved by acid hydrolysis, equation (96].

[96]


CH3O2C
CH3O2C
N
C(CH3)3
O
HCl
CH3O2C
CH3O2C
NHC(CH3)3
OH
+ H2C=O

68

When the tertiary butyl group on the nitrone was replaced by the

2,4,6-trimethylphenyl moiety, the reaction with dimethyl acetylenedicarboxylate rapidly gave the aziridine at room temperature, which was independently isomerized to the 4-oxazoline by heating in toluene solution. The latter compound was found to be very labile and readily hydrolyzed to formaldehyde and the appropriate enol.

In Scheme V it is probable that the 3,3-disubstituted aziridine opens to an azomethine ylide which subsequently ring closes on the adjacent carbonyl group to produce the 4-oxazoline. The fact that Baldwin obtained the 4-oxazolines from 4-isoxazolines via the aziridine intermediate, and that no reversal of this process was observed, proved invaluable in the assignment of structure to the products described in this work. However the 4-oxazolines prepared by Baldwin and coworkers did not appear to possess the novel properties nor the stability of the 4-oxazolines to be described in this chapter.

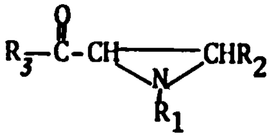
RESULTS AND DISCUSSION

Aziridine Precursors

The 3-aroyl-2-arylaziridines employed in the [2+3] cycloaddition reactions leading to 4-oxazolines were obtained by the standard procedures outlined in Chapter II, and are listed in Table XXII. It was found that 3-acyl-2-arylaziridines also reacted in good yield with diphenylcyclopropenone to form 4-acyl-4-oxazolines. The aziridines were in general employed as isomeric mixtures although where necessary pure isomers were used. In such cases the assignment of *cis* and *trans* isomers was based on the infrared and p.m.r. data of Cromwell and coworkers.[146,147]

TABLE XXII

3-Aroyl and 3-Acyl-2-Arylaziridines*



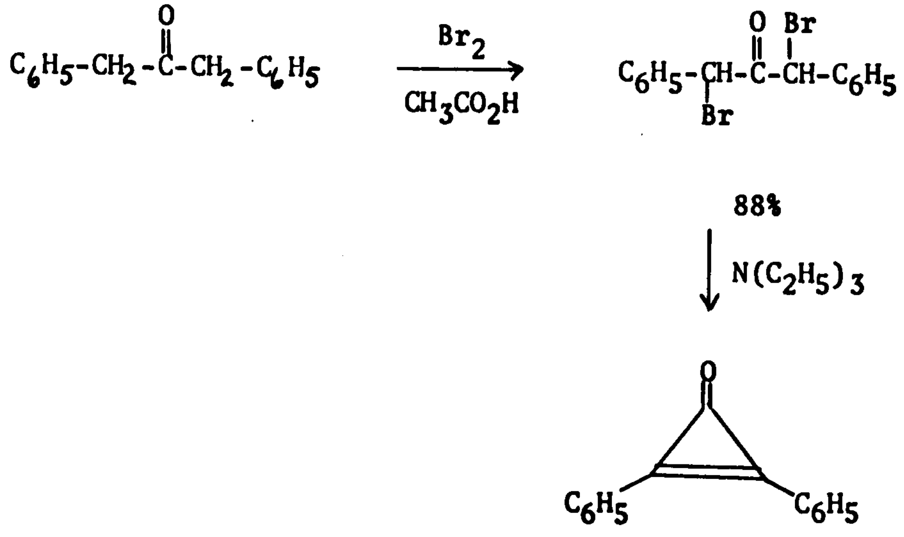
R_1	R_2	R_3	Yield %
C_6H_{11}	C_6H_5	C_6H_5	70
C_6H_{11}	C_6H_5	C_6H_4-*p*-NO_2	76*
C_6H_{11}	*m*-O_2N-C_6H_4	C_6H_5	88*
C_6H_{11}	*p*-O_2N-C_6H_4	C_6H_5	67
C_6H_{11}	*p*-CH_3O-C_6H_4	C_6H_5	80
C_6H_{11}	C_6H_5	C_6H_4-*p*-OCH_3	75*
C_6H_{11}	C_6H_5	CH_3	85*
C_6H_{11}	C_6H_5	C_6H_4-*p*-CH_3	72
$(CH_3)_2CH$	C_6H_5	C_6H_5	100*
$(CH_3)_2CH$	C_6H_5	C_6H_4-*p*-CH_3	77

*Indicates new compound.

Diphenylcyclopropenone (DPP)

This compound was first prepared in 1959 by the independent methods of Breslow and coworkers,[189] and Vol'pin and coworkers.[190] Since these preliminary publications, Breslow and coworkers have shown that diphenylcyclopropenone can be conveniently prepared by a modified Favorski reaction in which an α,α'-dibromoketone is treated with a tertiary amine,[183] equation [97].

[97]


O
$C_6H_5-CH_2-C-CH_2-C_6H_5$
Br_2
CH_3CO_2H
O Br
$C_6H_5-CH-C-CH-C_6H_5$
Br
88%
$N(C_2H_5)_3$
O
C_6H_5
C_6H_5

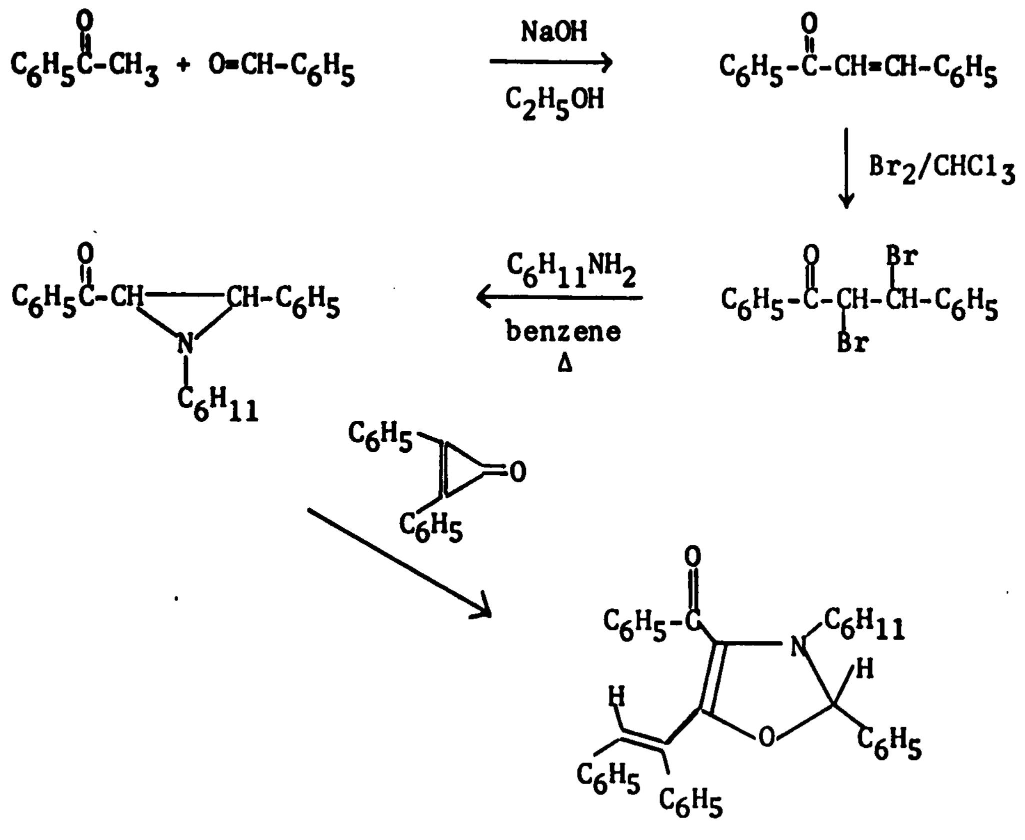
69 45%

Because of its convenience this latter method was used to prepare diphenylcyclopropenone throughout this work.

4-Oxazolines

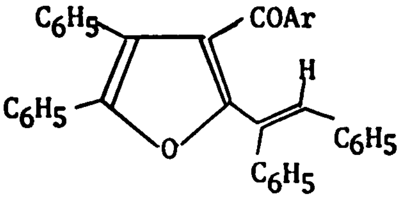
An outline of the synthesis of 4-oxazolines employing a particular example is shown in Scheme VI.

SCHEME VI



65%

The 4-oxazolines were obtained by the reaction of either *cis* or *trans*-3-aroyl-2-arylaziridines with diphenylcyclopropenone in benzene solution under reflux for periods of twenty to twenty-four hours, followed by chromatographic separation on alumina.[182] Initially equimolar ratios of the reactants were used, but it was subsequently found that a 4:3 ratio of the aziridine to diphenylcyclopropenone produced much improved yields of 4-oxazolines, and eliminated a contaminating side product, *vide infra.* In these reactions it is essential that both reactants and especially the aziridine be of high purity, for it was observed that contamination of the aziridine with traces of amine hydrobromide, or the monobromochalcone, caused either complete failure of the reaction or production of the side product mentioned above, which was shown to be a tetrasubstituted furan of general structure.

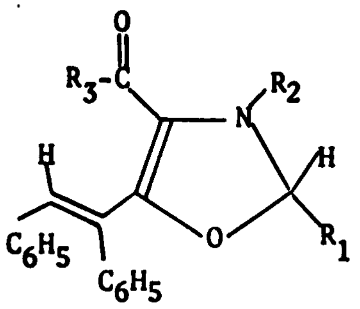


An excess of diphenylcyclopropenone also led to this product to the exclusion of the 4-oxazoline. This finding will be explained in Chapter IV of this thesis.

The choice of solvent was found to be of extreme importance in this reaction and the following solvents were examined: a) benzene, b) acetonitrile,[182] c) methylene chloride,[182] d) ethanol, e) toluene. Solvents (a) and (b) allowed the production of 4-oxazolines in good yield while with ethanol,[191] and equimolar quantities of reactants, only the tetrasubstituted furan was obtained. The boiling point of methylene chloride, 37°, was found to be insufficient to cause thermal cleavage of the 2-3 bond of the aziridine and hence the starting materials were returned in slightly reduced yield. Toluene produced only the tetrasubstituted furan. The conclusion reached from these observations was that the boiling point of the chosen solvent should be about 80°, for it was found that in toluene (b.p. 113°), the 4-oxazolines were decomposed. Benzene was the most convenient solvent tested, and was employed in all subsequent 4-oxazoline syntheses.

Since it had been demonstrated that both *cis* and *trans* 3-aroyl-2-arylaziridines upon reaction with diphenylcyclopropenone gave rise to an identical product,[182] isomeric mixtures of aziridines were subsequently employed in the general procedure.

The analytical and spectral data on the 4-oxazolines prepared by this method are summarized in Tables XXIII, XXIV, XXV and XXVI which exemplify the scope of the reaction. The numbering of the substituents in the tables refers to the general structure 70.



70

TABLE XXIII

4-Oxazolines

No.	R_1	R_2	R_3	m.p.	Yield %	Analysis (calc) % C	H	N	mol.ion	Analysis (found) % C	H	N	mol.ion (meas)
A	C_6H_5	C_6H_{11}	C_6H_5	163°	65	84.54	6.46	2.74	511.2511	84.26	6.40	2.65	511.2510
B	C_6H_5	C_6H_{11}	C_6H_4-*p*-NO_2	191-192.5°	23	77.70	5.76	5.04	556.2362	77.56	6.03	4.76	556.2373
C	*m*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	165-166°	27*	77.70	5.76	5.04	556.2362	77.65	6.03	4.79	556.2362
D	*p*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	180-182°	64	77.70	5.76	5.04	556.2362	77.46	5.75	5.19	no mol. ion.
E	*p*-CH_3O-C_6H_4	C_6H_{11}	C_6H_5	158-160°	23*	82.07	6.47	2.59	541.2616	82.02	6.45	2.62	no mol. ion.
F	C_6H_5	C_6H_{11}	C_6H_4-*p*-OCH_3	175-176.5°	79	82.07	6.47	2.59	541.2616	82.27	6.49	2.50	541.2614
G	C_6H_5	C_6H_{11}	CH_3	80-82°	84	82.85	6.90	3.12	499.2355	82.65	7.04	3.03	449.2353
H	C_6H_5	C_6H_{11}	C_6H_4-*p*-CH_3	176-178°	20*	84.53	6.72	2.67	525.2668	84.50	6.60	2.40	525.2665
J	C_6H_5	$(CH_3)_2CH$	C_6H_5	175°	24*	82.05	6.20	2.97	471.2198	84.15	6.35	3.45	471.2192
K	C_6H_5	$(CH_3)_2CH$	C_6H_4-*p*-CH_3	165-166°	31*	84.13	6.44	2.89	485.2355	84.00	6.85	3.10	485.2358

*Indicates made by 1:1 aziridine:DPP; otherwise by 4:3 aziridine:DPP.

TABLE XXIV

Spectroscopic Data of 4-Oxazolines

					Proton Magnetic Resonance* (δ)($CDCl_3$)				
No	R_1	R_2	R_3	ν(C=O) cm^{-1} ($CHCl_3$)	2 proton	Cyclohexyl CH_2 or $(C\underline{H_3})_2CH$	Cyclohexyl $\underline{CH}$, or $(CH_3)_2C\underline{H}$	Aryl + vinyl protons	Aryl substituent and acetyl protons
A	C_6H_5	C_6H_{11}	C_6H_5	1698	4.95(1)s	0.35-1.75(10)m	2.72-3.05(1)m	6.8-8.0(21)m	-
B	C_6H_5	C_6H_{11}	C_6H_4-*p*-NO_2	1699	5.05(1)s	0.65-1.80(10)m	2.54-2.94(1)m	6.75-8.06(19)m 8.16(1)s	-
C	*m*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	1696	4.96(1)s	0.50-1.78(10)m	2.67-3.24(1)m	6.82-8.12(20)m	-
D	*p*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	1696	5.03(1)s	0.42-1.73(10)m	2.70-3.15(1)m	6.84-8.25(20)m	-
E	*p*-CH_3O-C_6H_4	C_6H_{11}	C_6H_5	1695	4.90(1)s	0.50-1.66(10)m	2.70-3.17(1)m	6.75-8.08(20)m	3.78(3)s,OCH_3
F	C_6H_5	C_6H_{11}	C_6H_4-*p*-OCH_3	1700	4.95(1)s	0.38-1.95(10)m	2.55-3.15(1)m	6.78-8.10(20)m	3.85(3)s,OCH_3
G	C_6H_5	C_6H_{11}	CH_3	1703	5.14(1)s	0.66-2.15(10)m	3.10-3.56(1)m	7.32-8.50(16)m	2.02(3)s,CH_3
H	C_6H_5	C_6H_{11}	C_6H_4-*p*-CH_3	1695	4.96(1)s	0.50-1.75(10)m	2.65-3.0(1)m	6.70-8.05(20)m	2.42(3)s,CH_3
J	C_6H_5	$(CH_3)_2CH$	C_6H_5	1700	4.95(1)s	0.73(3)d, J = 6.5 Hz 0.81(3)d, J = 6.5 Hz	3.43(1)m	6.75-8.15(21)m	-
K	C_6H_5	$(CH_3)_2CH$	C_6H_4-*p*-CH_3	1695	4.91(1)s	0.72(3)d, J = 6.5 Hz 0.80(3)d, J = 6.5 Hz	3.39(1)m	6.80-8.10(20)m	2.42(3)s,CH_3

*s = singlet; d = doublet; m = multiplet.

TABLE XXV

Ultraviolet Absorption Spectra of 4-Aroyl-4-oxazolines and Their Visible Absorption on Addition of *p*-Toluenesulfonic Acid

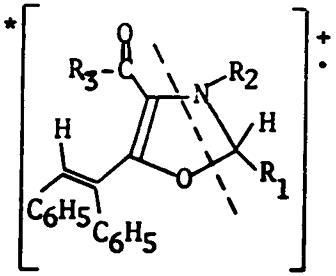
No	R_1	R_2	R_3	Absorption spectrum		Acid added*	
				λ_{max} (CH_3CN) mμ	log ε	λ_{max}	λ_{max} (visible)
A	C_6H_5	C_6H_{11}	C_6H_5	227 267	4.19 3.82	232 277 311	527
B	C_6H_5	C_6H_{11}	C_6H_4-*p*-NO_2	228 273	4.24 4.19	228 276 350	532
C	*m*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	231 268	4.29 4.14	229 268	524
D	*p*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	229 276	4.21 4.09	229 282	530
E	*p*-CH_3O-C_6H_4	C_6H_{11}	C_6H_5	230 275	4.29 3.76	229 266 316	525
F	C_6H_5	C_6H_{11}	C_6H_4-*p*-OCH_3	233 274	4.16 3.87	229 275 326	534
K	C_6H_5	$(CH_3)_2CH$	C_6H_4-*p*-CH_3	232 265	4.16 3.80	228 275 317	528

*Trace quantity of *p*-toluenesulfonic acid added, log ε was not determined since concentration of colored species was unknown.

TABLE XXVI

Principal Fragmentations in the High Resolution Mass Spectra of 4-Aroyl-4-oxazolines*

No	R_1	R_2	R_3	Molecular ion *m/e*	Relative abundance %	Anil *m/e*	Relative abundance %	M^+-Anil *m/e*	Relative abundance %
A	C_6H_5	C_6H_{11}	C_6H_5	511	5	187	100	324	75
B	C_6H_5	C_6H_{11}	C_6H_4-*p*-NO_2	556	6	187	85	369	39
C	*m*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	556	1	232	19	324	100
D	*p*-O_2N-C_6H_4	C_6H_{11}	C_6H_5	556	-	232	91	324	20
E	*p*-CH_3O-C_6H_4	C_6H_{11}	C_6H_5	541	-	217	100	324	16
F	C_6H_5	C_6H_{11}	C_6H_4-*p*-OCH_3	541	1	187	100	354	19
G	C_6H_5	C_6H_{11}	CH_3	449	19	187	12	262	100

*

The dotted lines show the principal cleavage

Table XXIII shows the scope of the synthesis to extend to aroyl or acyl groups at the 4-position, aryl groups containing both electron withdrawing and donating groups at the 2-position, and cyclohexyl and isopropyl groups at the 3-position. The main feature of this table is the striking increase in yield observed when the ratio of the reactants was changed from 1:1 to 4:3 of the aziridine and diphenylcyclopropenone. For instance a yield increase from 36% to 64% was observed in the preparation of compound 70D when the 4:3 ratio of reactants was employed, and a five-fold increase in yield in the case of compound 70B.

Table XXIV shows the characteristic aryl ketone absorption at 1695-1700 cm^{-1} in the infrared spectra. In the p.m.r. spectra, a singlet was consistently observed at about 5δ and assigned to the 2 proton. As was occasionally observed with the oxazolidines of Chapter II, the 4-oxazolines containing an isopropyl group at the 3-position showed non-equivalent methyl groups, indicating proximity to an asymmetric center in accordance with the proposed structure.

The ultraviolet spectra of Table XXV were consistent with the assigned structures and were dominated by two intense absorption bands in the regions of (227-232) and (265-276) mμ.

Tables XXIII and XXVI show the high resolution mass spectra of these 4-oxazolines. The observed mode of cleavage involved scission of the 4-oxazoline to the anil, as shown in the footnote of Table XXVI.

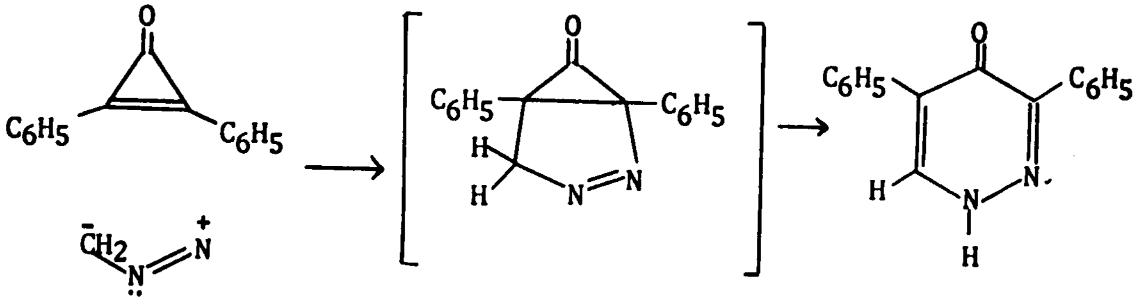
As will be discussed later these 4-oxazolines possess unusual physical and chemical properties, and have been found to undergo a variety of cycloaddition reactions with activated multiple bond systems.

Discussion of possible structures for the reaction product of 3-aroyl-2-arylaziridines and diphenylcyclopropenone.

The potential reaction of diphenylcyclopropenone with aziridines was of considerable interest, since in the former there existed two possible sites for cycloaddition to occur with the intermediate azomethine ylide, a) at the C=C bond of the ring, or b) at the C=O bond. The literature contained precedents for both modes of addition.

Izzo and Kende[192] had shown that diphenylcyclopropenone reacts with diazomethane (a diazoalkane) at the C=C bond of the ring, followed by subsequent ring expansion and no decarbonylation to give a pyridazone as shown in equation [98].

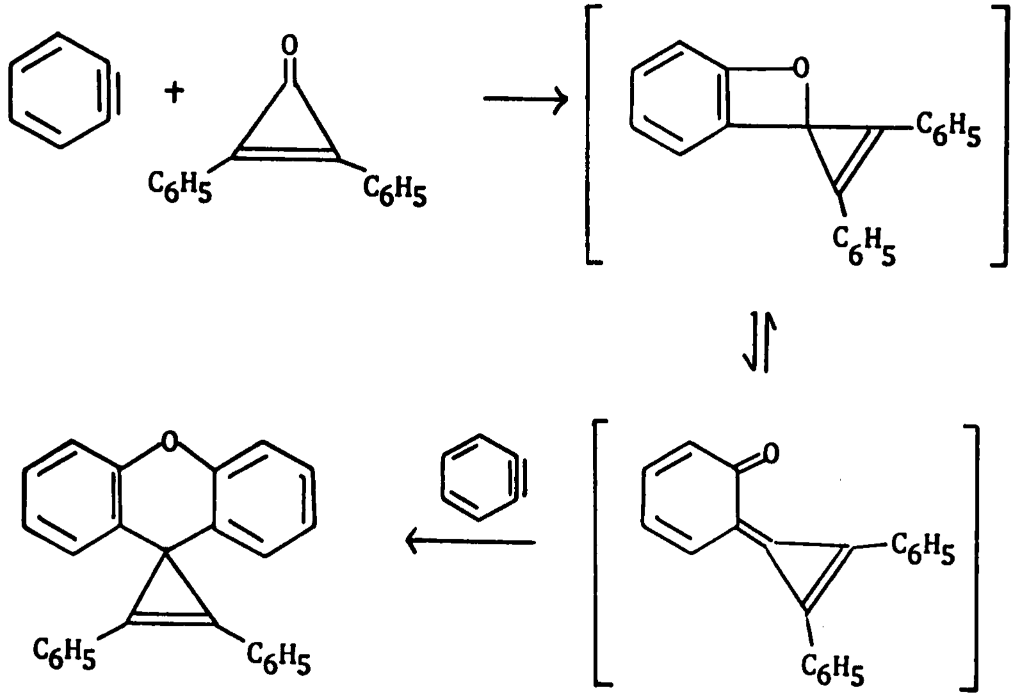
[98]



71

Various structures arising from the reaction of 3-aroyl-2-arylaziridines with diphenylcyclopropenone at the C=C bond were considered and rejected on the basis of the analytical and spectral data in Tables XIII to XXVI. This was necessary not only from the above result of Izzo and Kende, but also in view of the fact that 3-carboalkoxy-2-arylaziridines do react with diphenylcyclopropenone in this mode to yield *trans*-3-pyrrolines.[193]

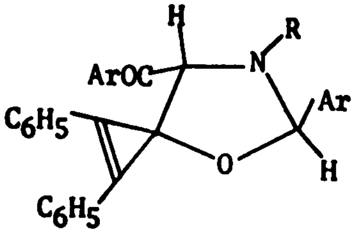
The available evidence pointed to the reaction having proceeded at the carbonyl group of diphenylcyclopropenone. A literature survey revealed an analogy for this in the reaction of diphenylcyclopropenone with benzyne,[194] equation [99].



[99]

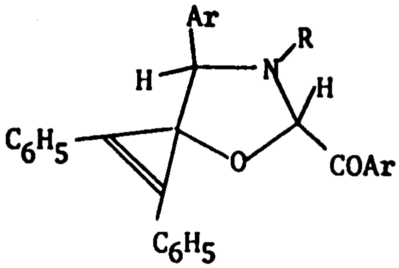
72

In view of the results described in Chapter II it was anticipated that the reaction of aziridines and diphenylcyclopropenone would take place at the carbonyl group of the latter to produce, initially at least, spiro-oxazolidines. As before, three classes of product were considered, two from [2+3] cycloaddition (A and B), and one (C) from ring expansion of the aziridine.



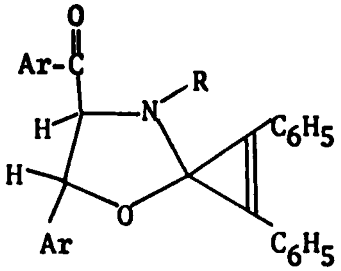
73

Type A



74

Type B

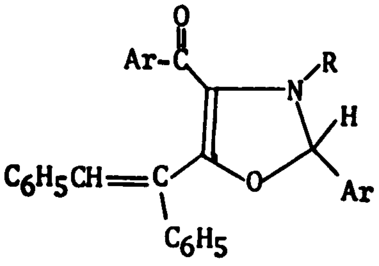


75

Type C

On the basis of the deuterium labelling experiments described in Chapter II, structure 73 was the predicted initial product.

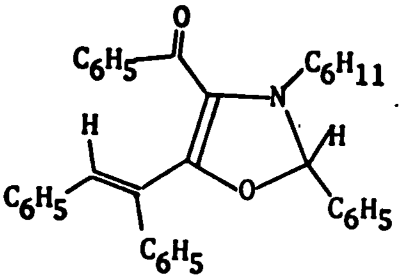
It became immediately clear from consideration of the p.m.r. spectra of the products from these reactions, that they were not oxazolidines. The lack of an AB quartet eliminated structure 75, and 73 and 74 were rejected since there was no signal corresponding to the 4 proton of the oxazolidine ring. The mode of cleavage in the mass spectra was also considerably different from that observed in the oxazolidines previously studied. However the fact that they corresponded to 1:1 adducts indicated that they were structural isomers of oxazolidines, which possessed only one distinguishable isolated proton as shown by the singlet at 5δ in the p.m.r. spectra. Furthermore this singlet was not diminished in an attempted deuterium exchange reaction under base catalyzed conditions.[182] On this basis the 4-oxazoline structure was proposed for these products.



76

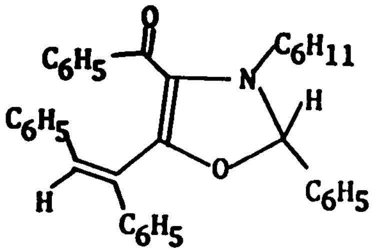
A careful study of the p.m.r. spectra of the products bearing no substituents on the aromatic rings revealed the presence of a one proton singlet at about 8.2δ, which could be attributed to the vinyl proton of structure 76. This was later confirmed by parallel reactions with specifically labelled 3-deuteroaziridines.

Several structures were considered for the product of these reactions. Those 4-oxazoline structures considered were based in the main on the three classes of oxazolidines previously mentioned. To clarify matters the product from the reaction of 3-benzoyl-1-cyclohexyl-2-phenylaziridine and diphenylcyclopropenone will be used for illustrative purposes. The possible structures are as shown below.

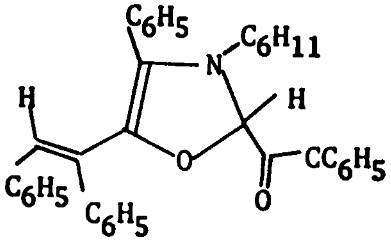


Type A

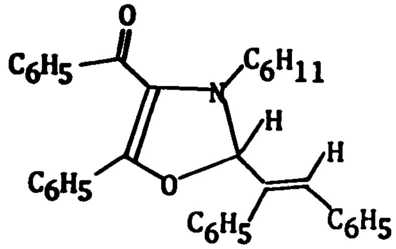
70A



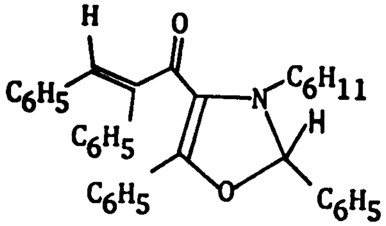
77



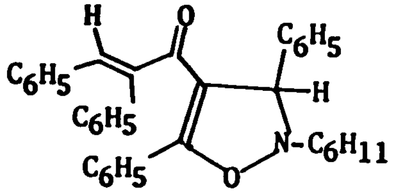
78 Type B



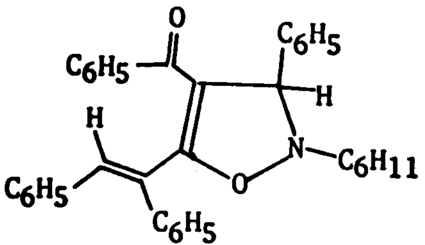
79 Type C



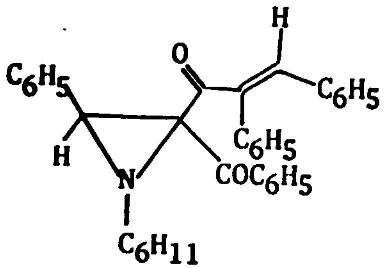
80



81



82



83

In view of the work of Baldwin and coworkers, structures 81, 82, and 83, had to be taken into consideration for the product from the above reaction. The p.m.r. spectra of these products show a one proton singlet at about 5δ (Table XXIV), which is inconsistent with structure

83, for which a value of 3-4δ would be expected.[147] Furthermore the infrared spectra exhibit only a single band for the carbonyl group stretching frequency. Table XXIV shows that this strong band occurs at 1695 cm^{-1}, which is consistent with that of an aromatic ketone.[195a] On this basis the 4-isoxazoline 81 and the 4-oxazoline 80 were rejected, for in both of these structures the 4-substituent is an α,β-unsaturated ketone which would be expected to show carbonyl absorption in the region 1685-1665 cm^{-1}.[195b] Furthermore in such systems the C=C stretching frequency at 1650-1600,[196] is of comparable intensity to that of the C=O group, whereas no such band existed in the spectrum of the product. Structures 70A, 77, and 82 are consistent with these findings since examination of space filling models has shown[182] that steric hindrance would prevent conjugation of the carbonyl group with the ring double bond.

In the mass spectrum, the molecule was shown to cleave cleanly into two principal fragments (see Table XXVI), corresponding to the anil 84 (*m/e* 187) and its accompanying fragment (*m/e* 324).

$$C_6H_5\text{-}CH\text{=}N\text{-}C_6H_{11}$$

84

This is clearly inconsistent with structure 79 and an unlikely mode of cleavage for 78 but satisfies structures 70A, 77, and 82. This cleavage of the anil moiety was found to be a direct counterpart of the thermal cleavage involved in the reactions of the 4-oxazolines to be described. For these reasons, the work in Chapter II on deuterium labelling, and the fact that Smalley[182] had shown that the isolated ring proton could not be exchanged by deuterium under basic conditions, structures 78 and 79 were rejected.

Structure 77 was eliminated on the basis of the known chemistry of diphenylcyclopropenone for Breslow and coworkers[183] have shown nucleophile catalyzed ring opening to proceed in a *cis* fashion. This was confirmed by a specific deuterium labelling experiment to be later described.

Structures 70A and 82 were in accordance with all the spectral data. The 4-oxazoline 70A was considered the more likely possibility since it is formed under equilibrium conditions, and in view of the findings of Baldwin and coworkers,[188] who showed that 4-isoxazolines could be readily isomerized thermally to 4-oxazolines, but the reverse process was not detected. Just such a process would be necessary for formation of 82 from the initially formed 70A. There was also the possibility that the 4-isoxazoline 82, might be susceptible to base catalyzed deuterium exchange at the 3-position. Furthermore the products from the cycloaddition reactions undergone by these compounds were more readily explainable in terms of the 4-oxazoline structure.

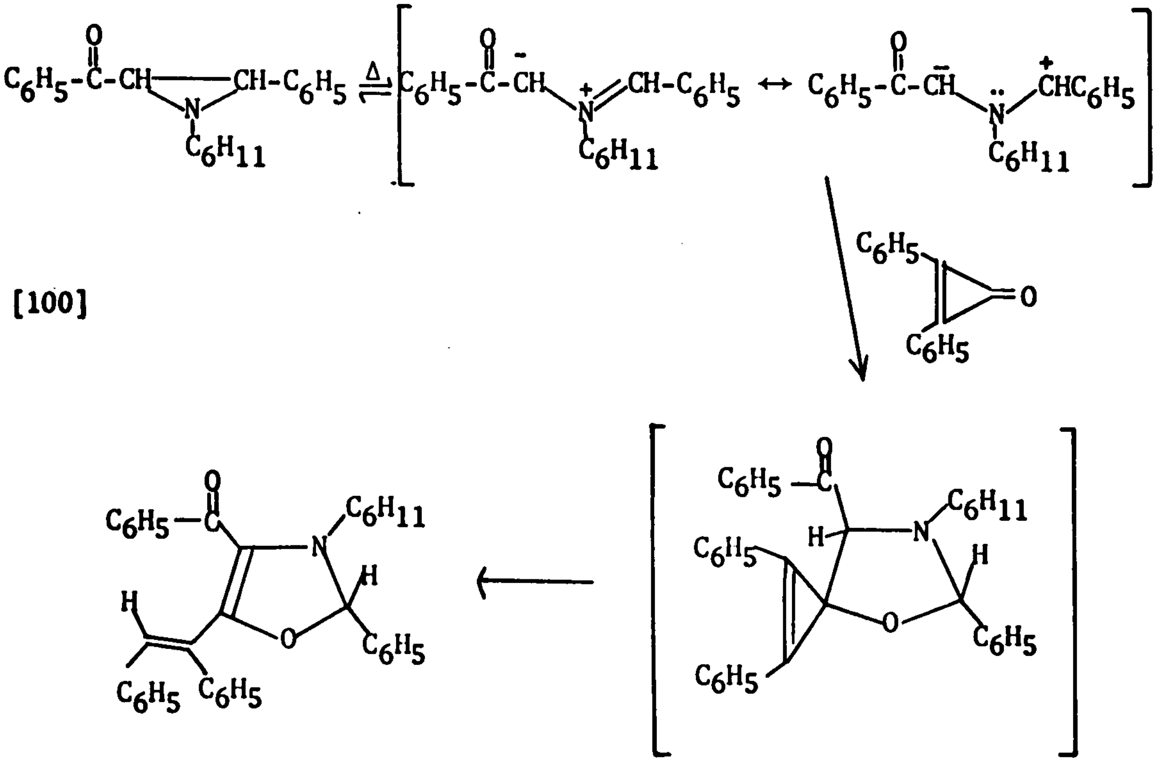
Thus in the absence of further concrete evidence, structure 70A was tentatively formulated for the product from the above reaction.

It appears that only a direct synthesis or an unambiguous X-ray crystallographic determination on a suitable heavy atom derivative will provide a direct answer to the problem.

Mechanism of Formation of 4-Oxazolines

These reactions may be plausibly interpreted as proceeding by an initial [2+3] cycloaddition of an azomethine ylide, derived from thermal conrotatory cleavage of the aziridine, to the carbonyl group of diphenylcyclopropenone, to produce a spiro oxazolidine which then rearranges to the 4-oxazoline as shown in equation [100].

[100]

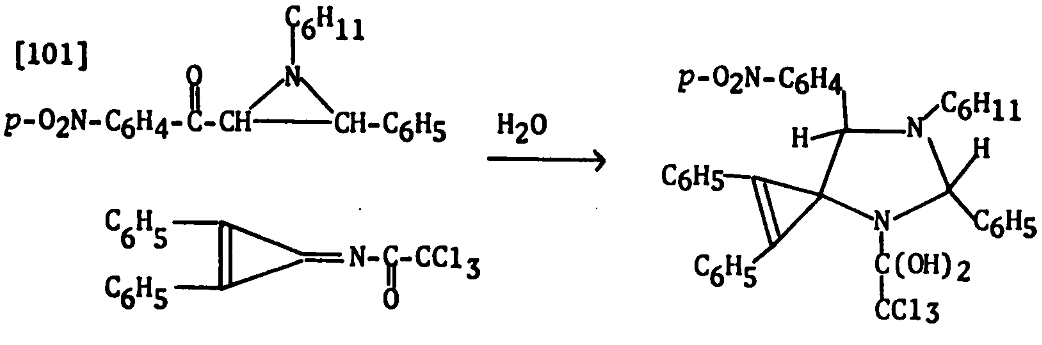


70A 73

The observed lack of dependence on the stereochemistry of the aziridine is understandable in terms of the product structure, though it is possible that the *cis* azomethine ylide (in W form) isomerizes to the *trans* form prior to cycloaddition with diphenylcyclopropenone.

No trace of the proposed oxazolidine intermediate 73 was ever found. However good evidence for such a species has since been obtained by Lown, Westwood, and Moser[197] from a parallel reaction of 1-cyclohexyl-3-(4-nitrobenzoyl)-2-phenylaziridine and N-trichloroacetyl-diphenylcyclopropenimine,[198] where the intermediate [2+3] cycloaddition product was isolated directly as shown in equation [101].

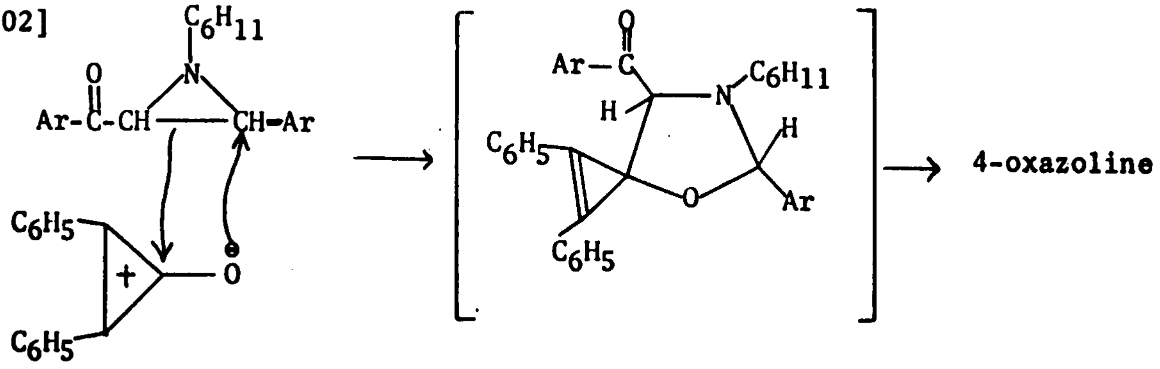
[101]



85, 50%

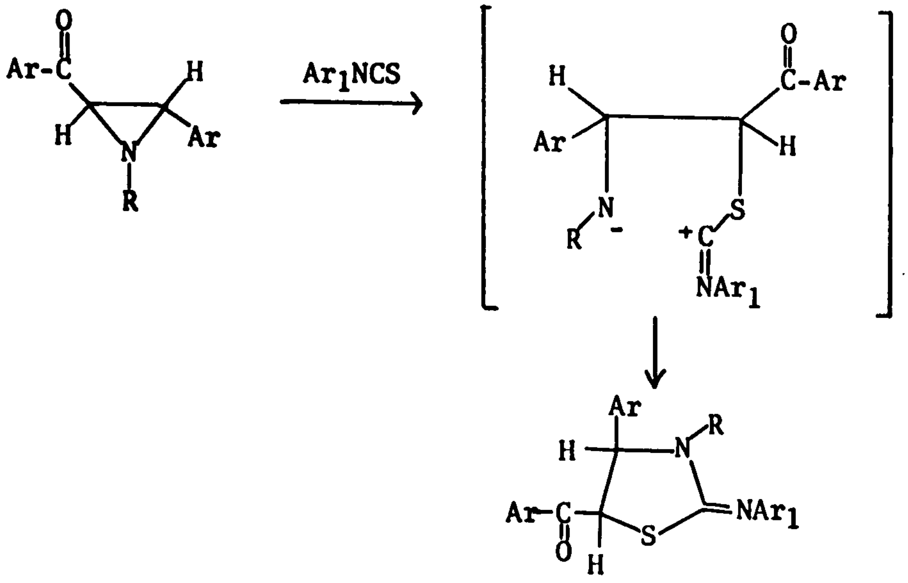
When the resonance structures of diphenylcyclopropenone are examined,it could be considered that the initial reaction proceeded by an attack by diphenylcyclopropenone as an O-nucleophile at the 2-position of the aziridine ring, equation [102].

[102]



A one or two-step mechanism could be postulated for the first stage of this process. This mechanism seems very unlikely however in view of the established nucleophilic ring cleavage of aziridines at the 1,2 or 1,3 positions.[153,199,200] Particularly pertinent are the reactions of aziridines and known good nucleophilic species such as aryl isothiocyanates,[150,151] where products arising from cleavage of the aziridine 1,2 bond rather than the 2,3 bond were obtained, along with products of normal [2+3] cycloaddition as shown in equation [103].

[103]

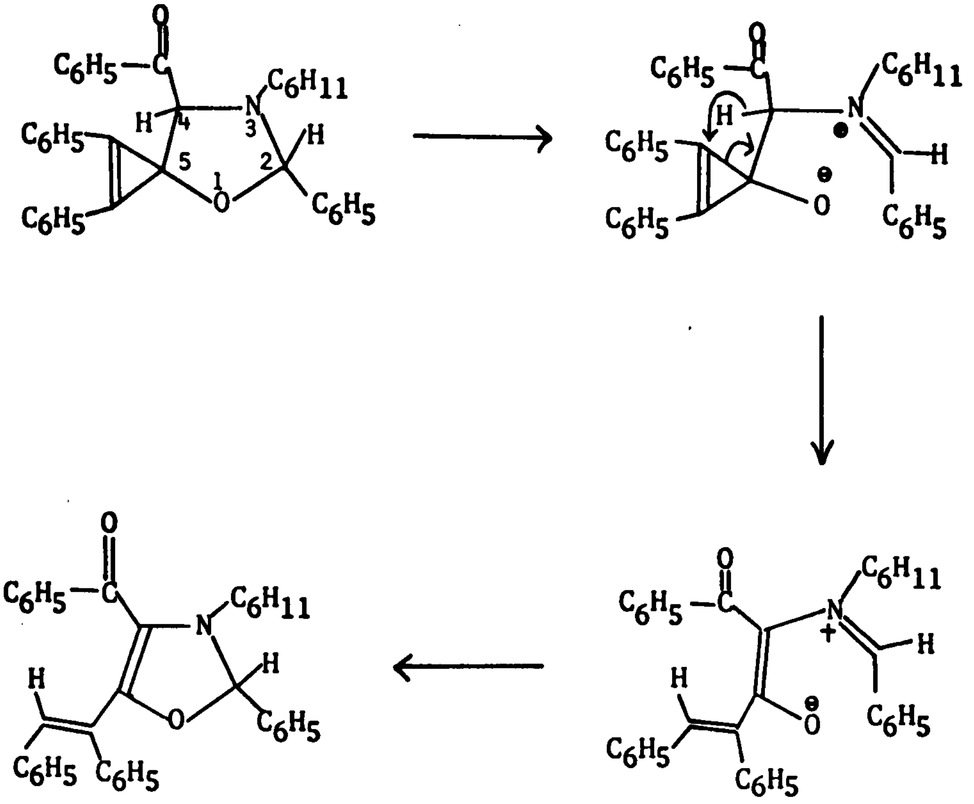


86

No such products were obtained in the reactions involving diphenylcyclopropenone with similar aziridines.

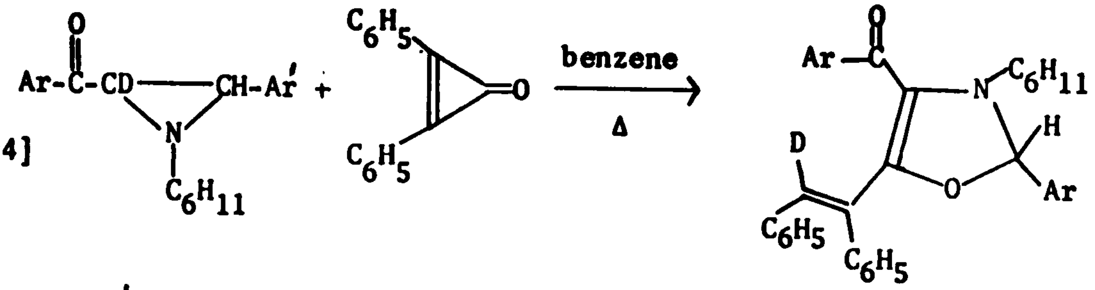
The mechanism of the rearrangement of the proposed spiro-oxazolidine to the 4-oxazoline is a matter of conjecture and a possible pathway is outlined below in Scheme VII.

SCHEME VII



It was suspected from the results of Breslow and coworkers,[183] that the opening of the spiro-cyclopropene ring might be concerted and intramolecular with the hydrogen atom at the 4-position of the hypothetical oxazolidine appearing on the diphenylvinyl moiety of the 4-oxazoline. That this was indeed the case was shown by reaction of diphenylcyclopropenone with specifically 3-deuterated aziridines, where it was found that the deuterium was incorporated in good yield into the 1,2-diphenylvinyl group of the 4-oxazoline as shown in equation [104].

[104]

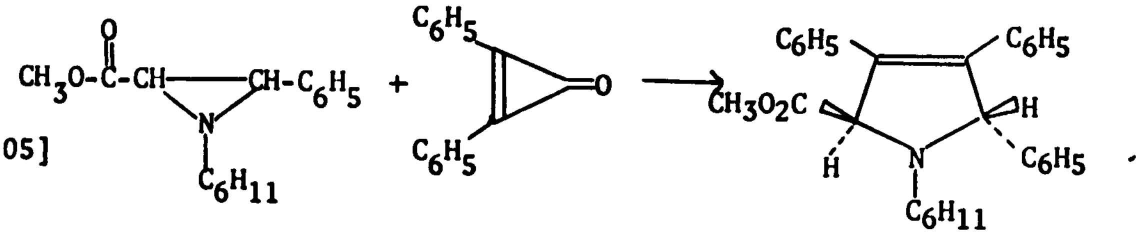


$Ar' = p\text{-}O_2N\text{-}C_6H_4$

87

This 4-oxazoline synthesis appears to be confined to aziridines containing acyl or aroyl groups at the 3-position. It has been shown that when these groups were replaced by carboalkoxy groups, reaction with diphenylcyclopropenone proceeded at the C=C bond to furnish *trans*-3-pyrrolines,[193,201] instead of producing 4-oxazolines, equation [105].

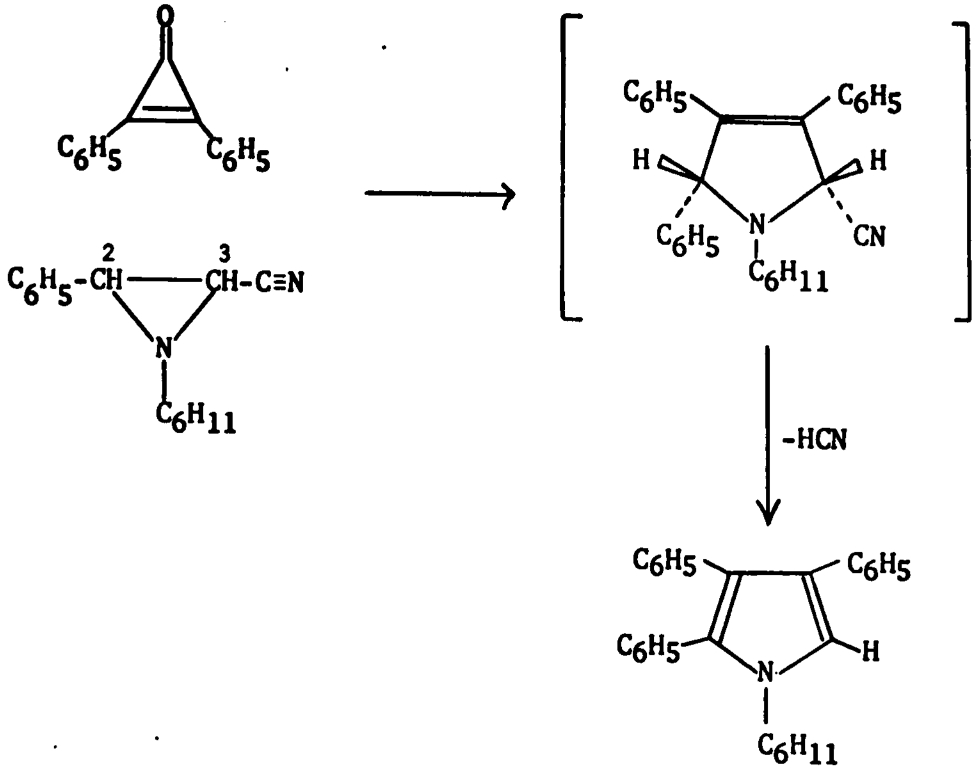
[105]



88 86%

In an attempt to investigate this phenomenon a potentially more reactive aziridine, 3-cyano-1-cyclohexyl-2-phenylaziridine, was synthesized by the method previously described and treated with diphenylcyclopropenone. This reaction was also observed to proceed at the C=C bond and produced only the pyrrole 89, as shown in equation [106].

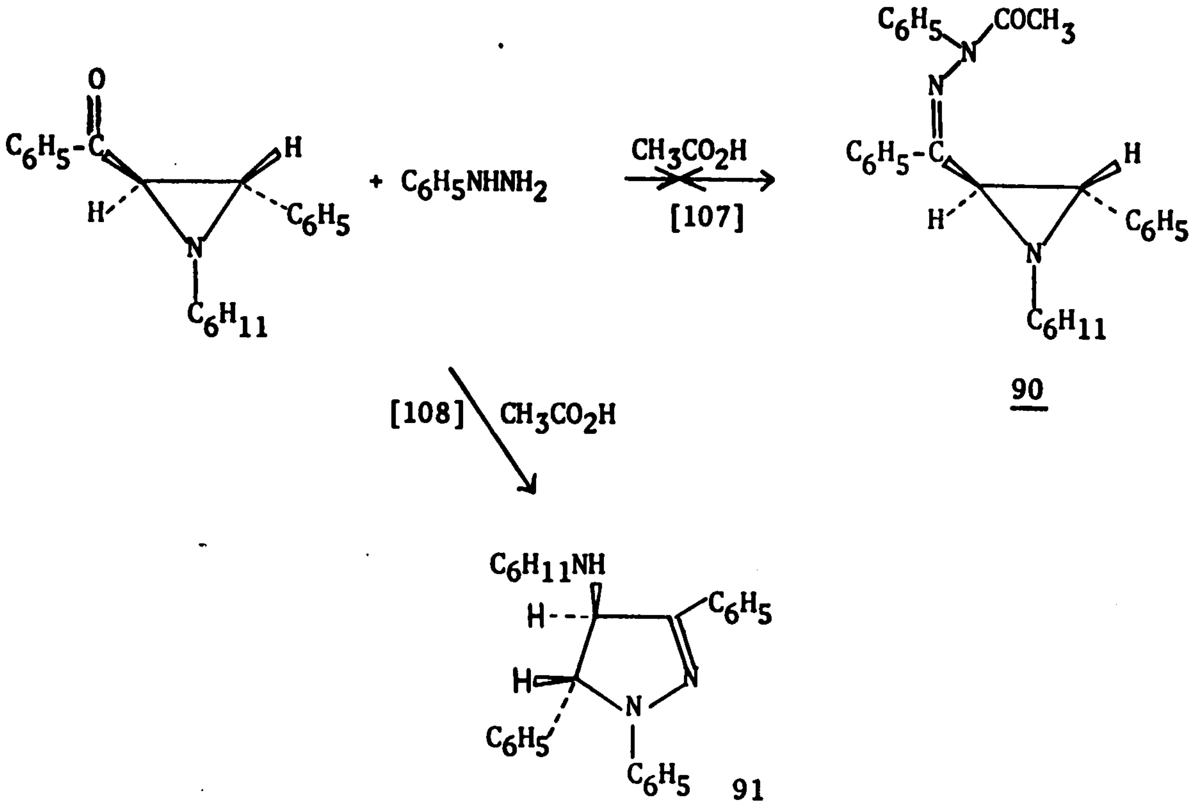
[106]



89 73%

Further work on this subject was restricted due to difficulties encountered in the synthesis of suitably active 3-substituted aziridines.

An attempt was made to surmount this problem by masking the carbonyl group of *trans*-3-benzoyl-1-cyclohexyl-2-phenylaziridine with phenylhydrazine, under the conditions of Cromwell and Hoeksema[202] to produce compound 90, equation [107]. However the product obtained was the 2-pyrazoline 91, which probably resulted from isomerization of the initially formed hydrazone adduct as shown in equation [108].



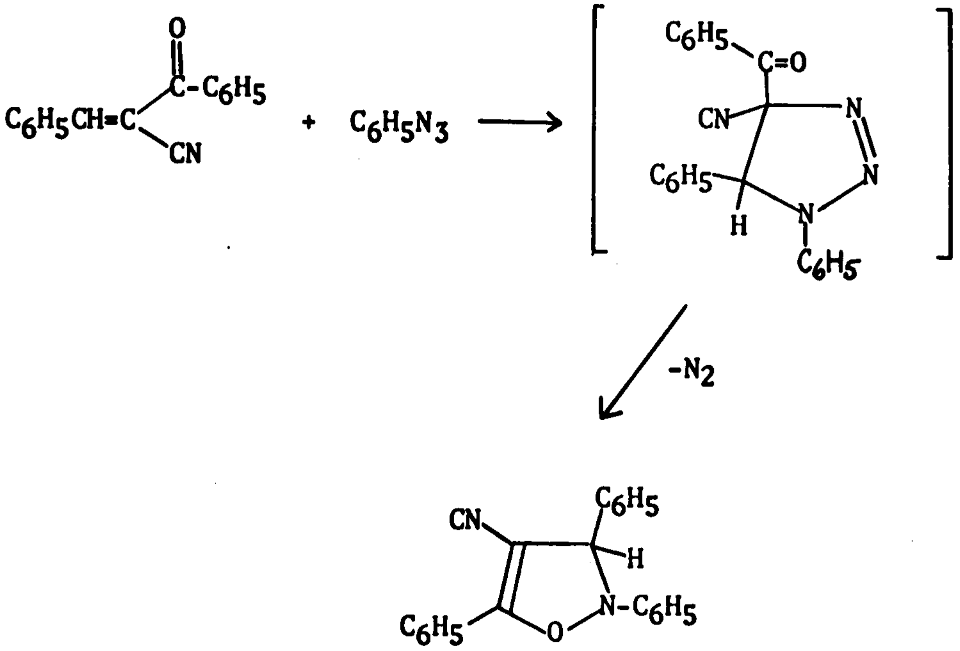
90

91

While the effect of the nature of the aziridine 2-substituent on the course of the reaction has not been critically examined, it appears as though aryl groups are necessary for successful formation of 4-oxazolines.

It is of interest to note that in no instance was a mixture of products resulting from reaction at both the C=C and C=O bonds of diphenylcyclopropenone ever isolated, either in the course of this work or that of Maloney.[201] There seems little difference in the various types of azomethine ylides employed, and the course of the cycloaddition to diphenylcyclopropenone may depend upon a delicate interplay of steric and electronic factors, which are all too little understood at present. Furthermore the compounds prepared in this work were shown to be stable at normal temperatures in direct contrast to those reported by Baldwin and coworkers,[188] and Texier and Carrie.[203] These latter workers found that the reaction of α-benzoylcinnamonitrile and phenylazide produced a 4-isoxazoline, which was found to be very unstable and could only be isolated at low temperature and under a nitrogen atmosphere.

[109]



92 15%

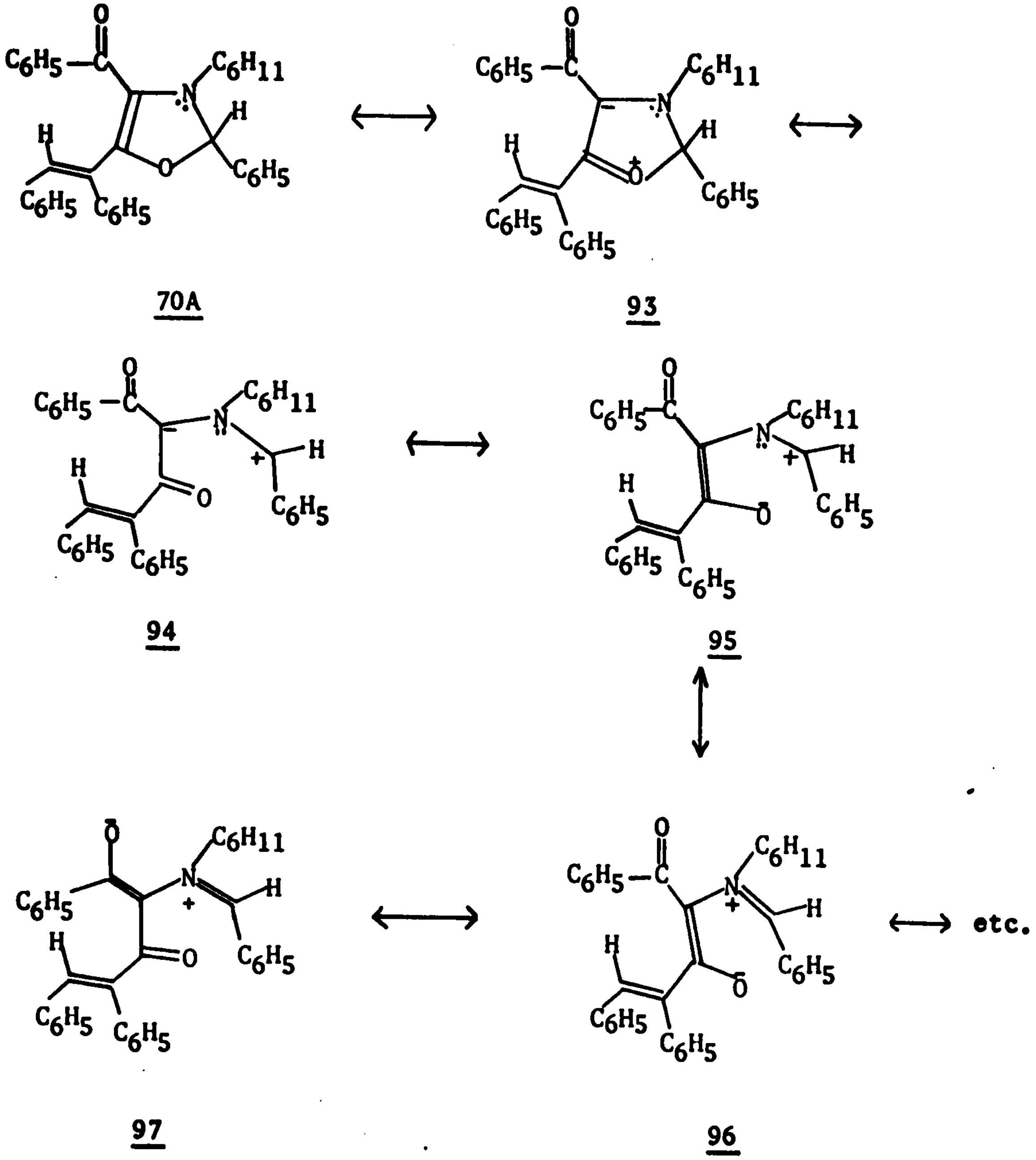
No comment was made in this publication about any possible rearrangement product of this compound in the manner of that found by Baldwin and coworkers.[188] However the instability of these 4-isoxazolines would tend to support the preference for the 4-oxazoline structure 70A over that of the isomeric 4-isoxazoline 82.

Properties of 4-Oxazolines

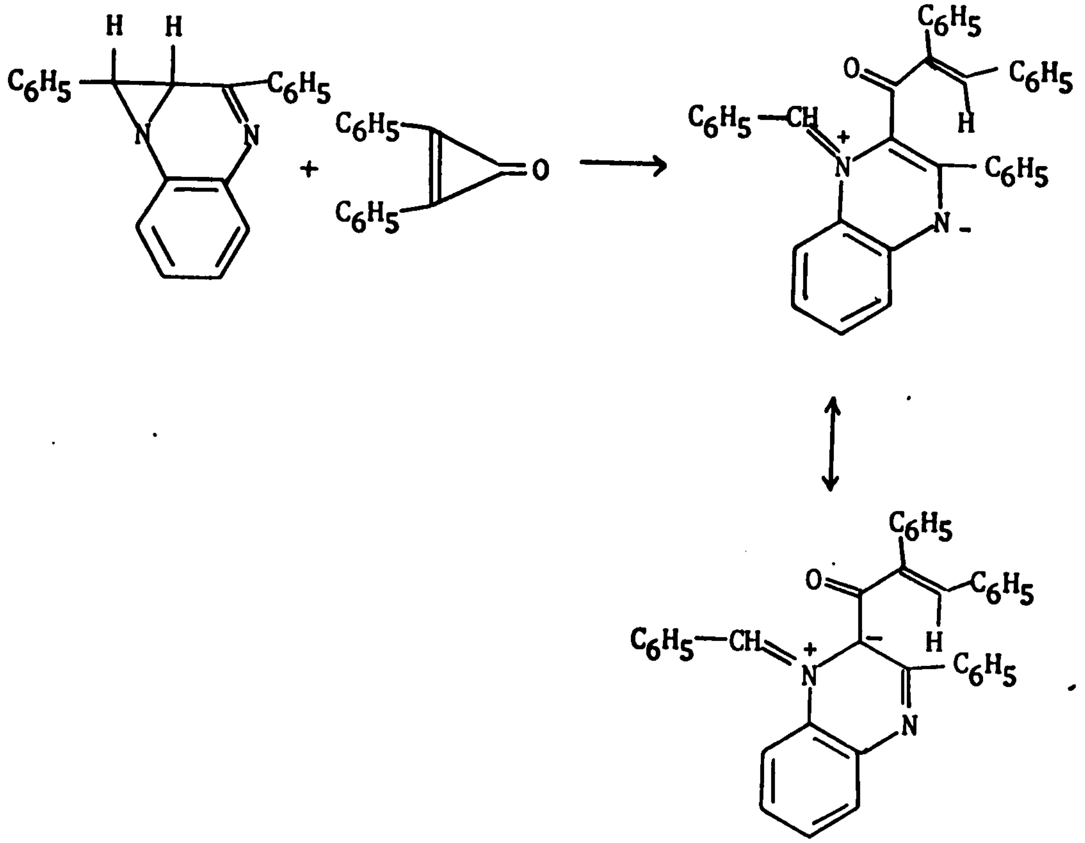
The spectral properties of the 4-oxazolines are summarized in Tables XXIII, XXIV, XXV and XXVI.

However the most characteristic properties of these compounds are their photochromism and thermochromism. When freshly prepared, many of the oxazolines are white or cream coloured solids, which turn an orange-pink color on exposure to light and tend to revert towards their original hue when kept in the dark. This phenomenon is reversible and no detectable decomposition has been observed to occur. A more important effect is that all the 4-oxazolines give blood red melts, and in solution in hot benzene, toluene, and xylene, impart a wine-red coloration to the solution. In the solid this color change sets in at temperatures above 90°C. These phenomena have been attributed to contributions from the following dipolar species which are reminiscent of the mesoionic oxazolone[110] and sydnone systems,[109] (Scheme VIII).

SCHEME VIII


70A
93
94
95
97
96
etc.

In the limit, substantial contributions from the canonical forms 94, 95, 96 and 97, are equivalent to photochemical or thermal ring-chain valence isomerization to a new azomethine ylide. Just this kind of situation has since been found to exist in the case of the product from the reaction of diphenylcyclopropenone and a bicyclic aziridine, as shown in equation [110].[182]


H
H
C_6H_5
C_6H_5
N
N
+
C_6H_5
C_6H_5
O
C_6H_5
O
C_6H_5
C_6H_5—CH
+
N
H
C_6H_5
N -
C_6H_5
O
C_6H_5
C_6H_5—CH
+
N
−
H
C_6H_5
N

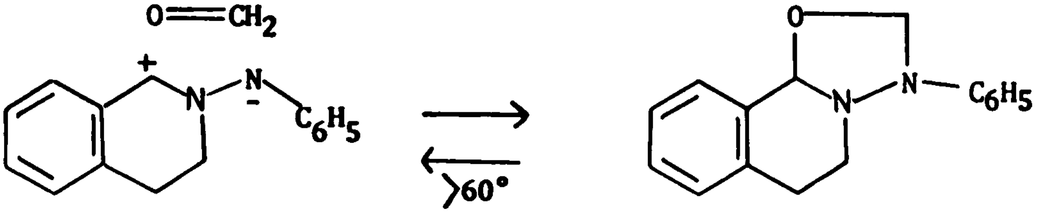
[110]

98

The product, which was blood red in colour, behaved like a typically highly polar substance and was accordingly assigned the zwitterionic ylide structure shown.

Further analogies for the above behaviour are displayed by some [2+3] cycloaddition products of azomethine imines,[204] as shown in equation [111].

[111]

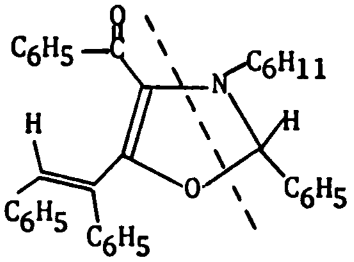


99

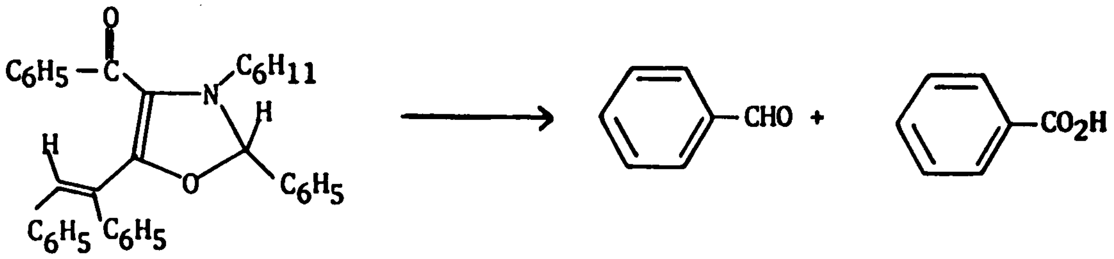
Huisgen has found that reversible thermochromism of the 1,3,4-oxadiazolidine 99 occurs at temperatures above 60°, and has remarked on the truly astonishing mobility of this equilibrium.

Direct support for the above proposals has been found from the facile ring opening and [2+3] cycloaddition reactions that these 4-oxazolines undergo. This work will be described in Chapter IV of this thesis.

The appearance of the characteristic red colour in solutions of 4-oxazolines was enhanced by the addition of catalytic quantities of acids, especially Lewis acids, and occurred at lower temperatures and often at room temperature. Treatment of a benzene solution of a 4-oxazoline with a trace, (often one crystal), of *p*-toluenesulfonic acid at room temperature with swirling, quickly imparted a pink-red colour to the solution which deepened with time or as the temperature was increased. At room temperature, a strong visible absorption band at about 530 mμ (see Table XXV) was observed, and this method proved to be valuable in substantially reducing the reaction times of a variety of [2+3] cycloadditions of 4-oxazolines. At room temperature in a control reaction, 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline 70A, was recovered in 80% yield from treatment with *p*-toluenesulfonic acid. It was not possible to assign the position of protonation on the 4-oxazolines (C, O, or N) with any confidence since addition of sufficient acid to affect the p.m.r. spectrum resulted in decomposition of the compound. However with Lewis acids [$AlCl_3$, $SnCl_4$, $(C_6H_5)_2II$] the position of coordination would most likely be to the oxygen atom since the nitrogen atom is trisubstituted. Whatever the position of protonation or coordination, this procedure evidently assists in the separation of the anil moiety, just as in the cleavage pattern in the mass spectra of these compounds (see Table XXVI).

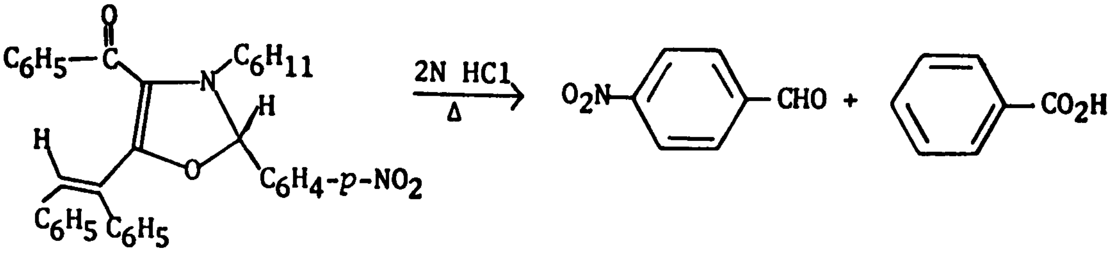


As was observed with oxazolidines in Chapter II, 4-oxazolines can be decomposed under controlled hydrolytic conditions. Treatment of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline 70A, with 50% sulfuric acid produced benzaldehyde, characterized as its 2,4-dinitrophenylhydrazone derivative, and benzoic acid as shown in equation [112].



[112] 70A

In a similar manner 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline (70D) yielded 4-nitrobenzaldehyde and benzoic acid on hydrolysis in dilute hydrochloric acid as in equation [113].

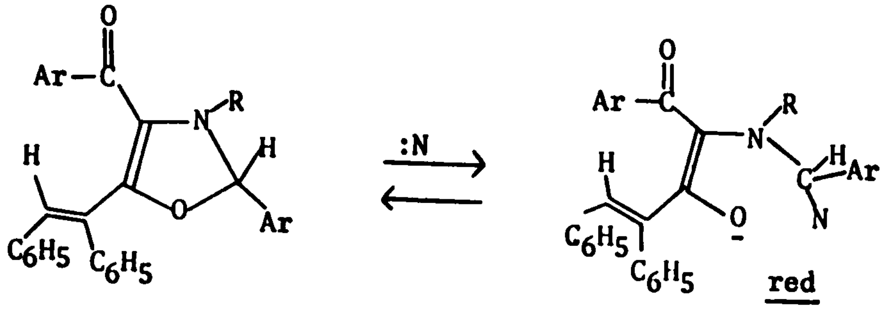


O
C6H5
C
N
C6H11
H
H
O
C6H4-p-NO2
C6H5
C6H5
2N HCl
Δ
O2N
CHO +
CO2H

70D

These results directly parallel those of Baldwin and coworkers[188] (equation [97]), on hydrolysis of 4-oxazolines prepared from 4-isoxazolines.

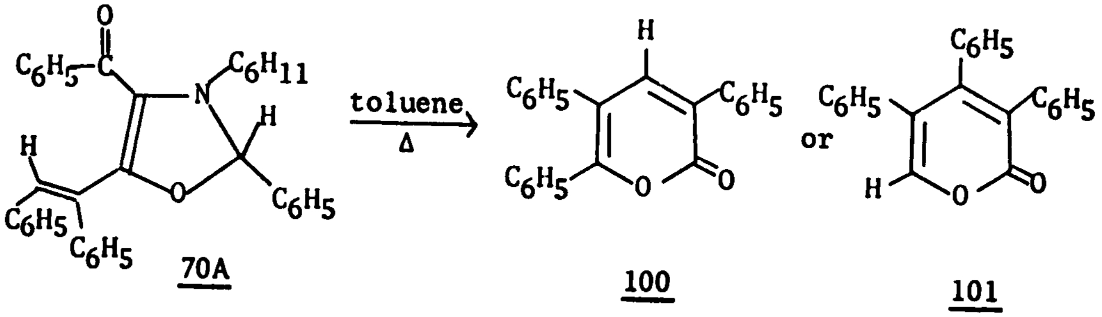
4-Aroyl-4-oxazolines have been shown to be stable to alkali and to nucleophiles.[182] The compound 70A was recovered in good yield (>80%) from heating under reflux with a) potassium thiocyanate in acetone, b) sodium iodide in acetone, c) potassium carbonate in aqueous tetrahydrofuran. It was also found to be stable under conditions of dimethyl sulfoxide in benzene solution under reflux. The red colour imparted to the hot solutions may be tentatively attributed to a reversible nucleophile catalyzed ring opening at the 2-position of the oxazoline.



O
Ar
C
N
R
H
H
O
Ar
C6H5
C6H5
:N
O
Ar
C
N
R
H
C
H
Ar
O
N
C6H5
C6H5
red

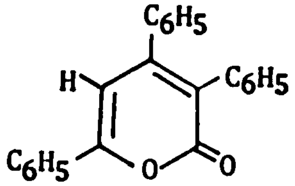
The results of these and related studies[193,201] suggested that for photochromism, thermochromism, and facile ring cleavage of 4-oxazolines to occur, a 2-aryl group and a 4-aroyl or acyl-substituent must be present in the molecule. The 4-oxazolines prepared by Baldwin and and coworkers[188] lacked a 2-substituent and possessed carbomethoxy groups at positions 4 and 5, and although the oxazolines were reported to be unstable,no mention was made of any of the above effects nor the tendency to undergo [2+3] cycloaddition reactions.

Although they are stable in benzene solution at 78° and in toluene solution under reflux for short periods (<60 min), 4-oxazolines were found to undergo thermal decomposition over longer periods in toluene or n-butanol solution (1-2 days). The decomposition in toluene afforded three crystalline products, the major one of which was assigned to an α-pyrone on the basis of the compatibility of its spectral properties with those of the known α-pyrone 102.[205] This is shown in equation [114].



70A 100 101

[114]



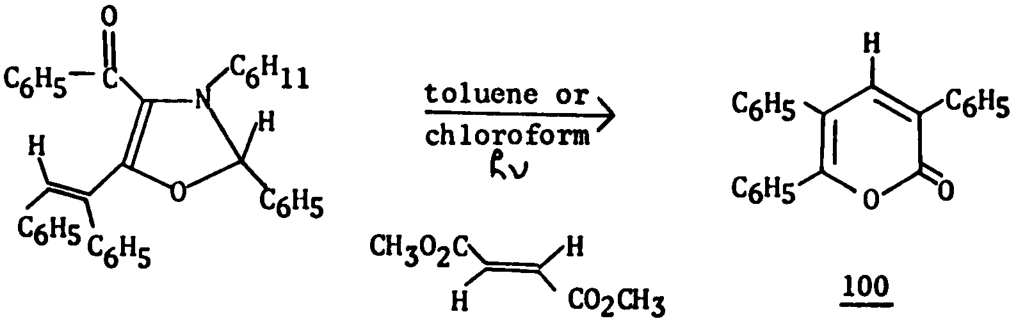
102

The other two products could not be identified.

The above thermal decomposition was repeated in n-butanol (b.p. 118°) to attempt to gain information as to the nature of the intermediates in the process by trapping any reactive species with the protic solvent. However the sole product from this reaction was the same α-pyrone as was obtained from the decomposition in toluene. This indicated that the initial product of decomposition, which corresponded in mass to the loss of the anil from the 4-oxazoline, had internally cyclized before it could be trapped by the solvent. This α-pyrone did not exhibit any red colour even in boiling xylene (b.p. 135°).

The identical α-pyrone was also obtained in about 10% yield from photolytic reactions of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline 70A in chloroform, and in toluene solution, where the very reactive dipolarophile dimethyl fumarate had been added as a trapping agent. No red colour was imparted to the solution in these trial reactions which were conducted at room temperature as shown in equation [115].

[115]



70A

100

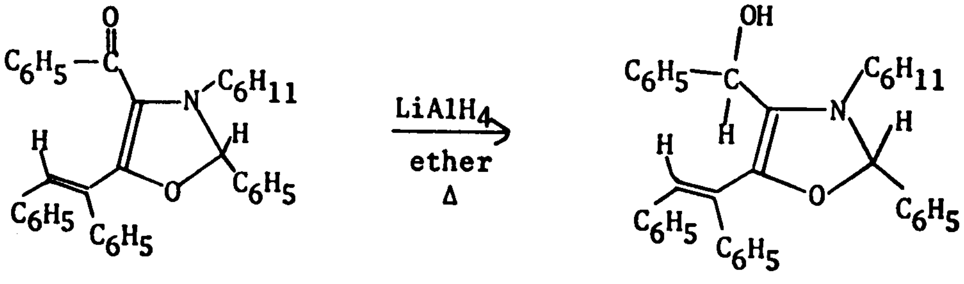
No trace of the anil moiety was ever obtained from these thermal decompositions.

That no extensive accumulation of radicals occurred in room temperature photolysis of 4-oxazolines was shown by an e.p.r. experiment where 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline 70D in the solid state gave no signal nor produced any change in colour during the experiment.

A systematic study of the chemical properties and reactions of a representative of the 4-oxazoline series was undertaken to determine the reactivity at various points in the molecule. As mentioned these compounds were stable to base and selected nucleophiles, but were hydrolyzed in hot dilute mineral acid. Bromine was observed to be incorporated but the product obtained was a gum which could not be identified. Attempts were made to cleave the *cis*-1,2-diphenylvinyl group with a) ozone, b) potassium permanganate-sodium periodate, but were unsuccessful. The carbonyl group proved to be extremely hindered and failed to react with a) 2,4-dinitrophenylhydrazine, b) semicarbazide hydrochloride c) hydroxylamine, d) hydrazine. In reaction (a) the 2,4-dinitrophenylhydrazone derivative of benzaldehyde was obtained in keeping with previous observations. It had previously been shown by Smalley[206] that the C=C bond of the 4-oxazoline ring and the 1,2-diphenylvinyl group were resistant to catalytic hydrogenation.

The carbonyl group was reduced by employing lithium aluminum hydride in ether solution under reflux for periods of 40 h. Reactions at room temperature produced little reduction of the carbonyl group and these findings indicate just how hindered this carbonyl group is to attack by nucleophilic reagents. A representative reaction is shown in equation [116].

[116]



70A   103

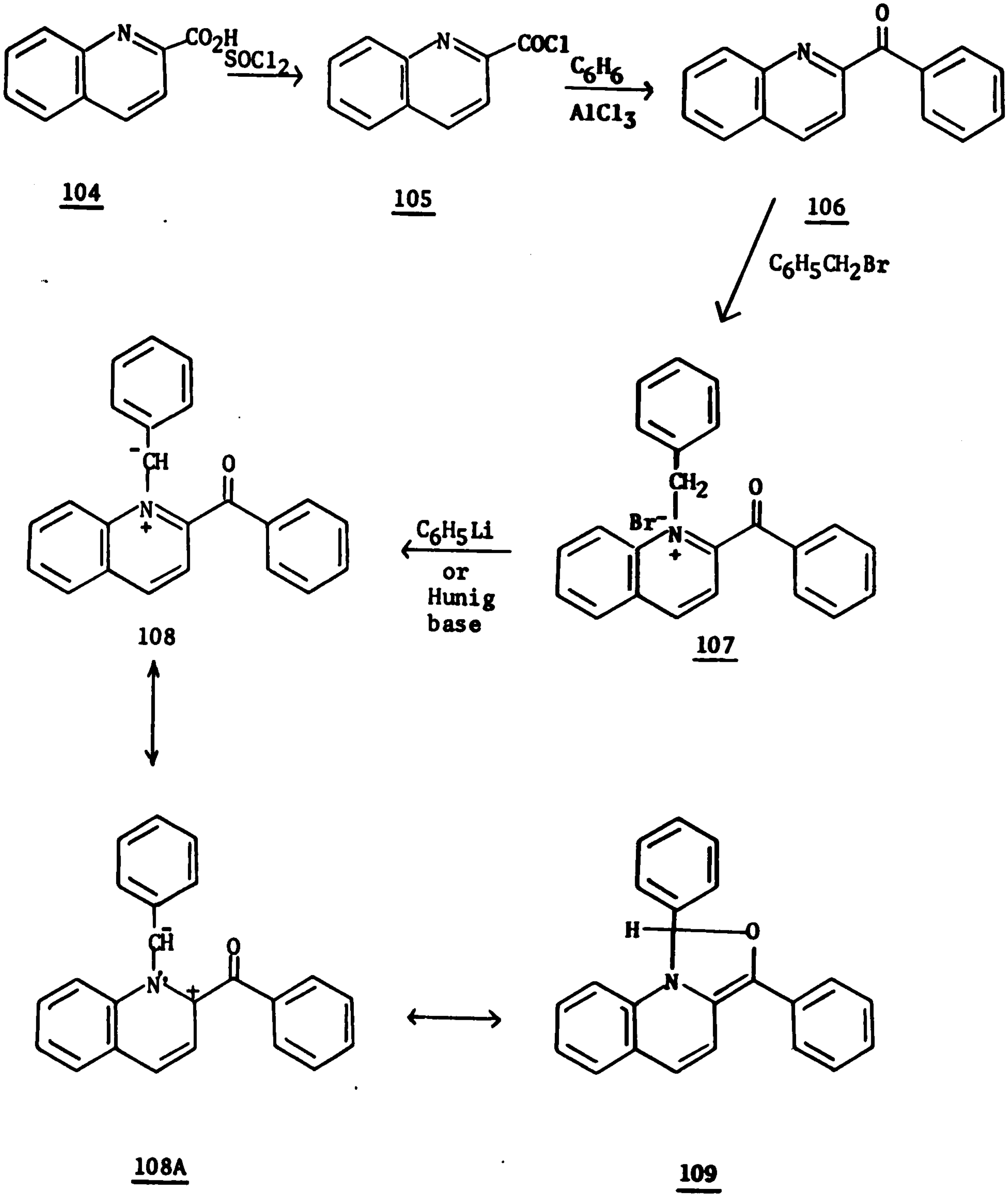
Creation of a second asymmetric center in the molecule produced, as expected, a pair of diastereoisomers which were not separated. Structure 103 satisfied the spectral data of the product and was thus assigned to the reduced 4-oxazoline. The complete loss of the carbonyl group in the infrared spectrum of the product and the single band for the hydroxyl group finally disposes of the aziridine structure 83 which was initially considered as a possible structure for the product obtained from the reaction of diphenylcyclopropenone and 3-aroyl-2-arylaziridines.

These reduced 4-oxazolines gave pink melts which tended to intensify when heated to temperatures above 200°.

Attempted Independent Synthesis of 4-Oxazolines

Because of the unusual nature of the *cis*-1,2-diphenylvinyl substituent at the 5-position of the 4-oxazoline ring, an independent synthesis of this particular series of compounds (70A-70K) was deemed unlikely. Attempts were made however to prepare the 4-oxazoline ring system by a variety of independent schemes which are outlined below.

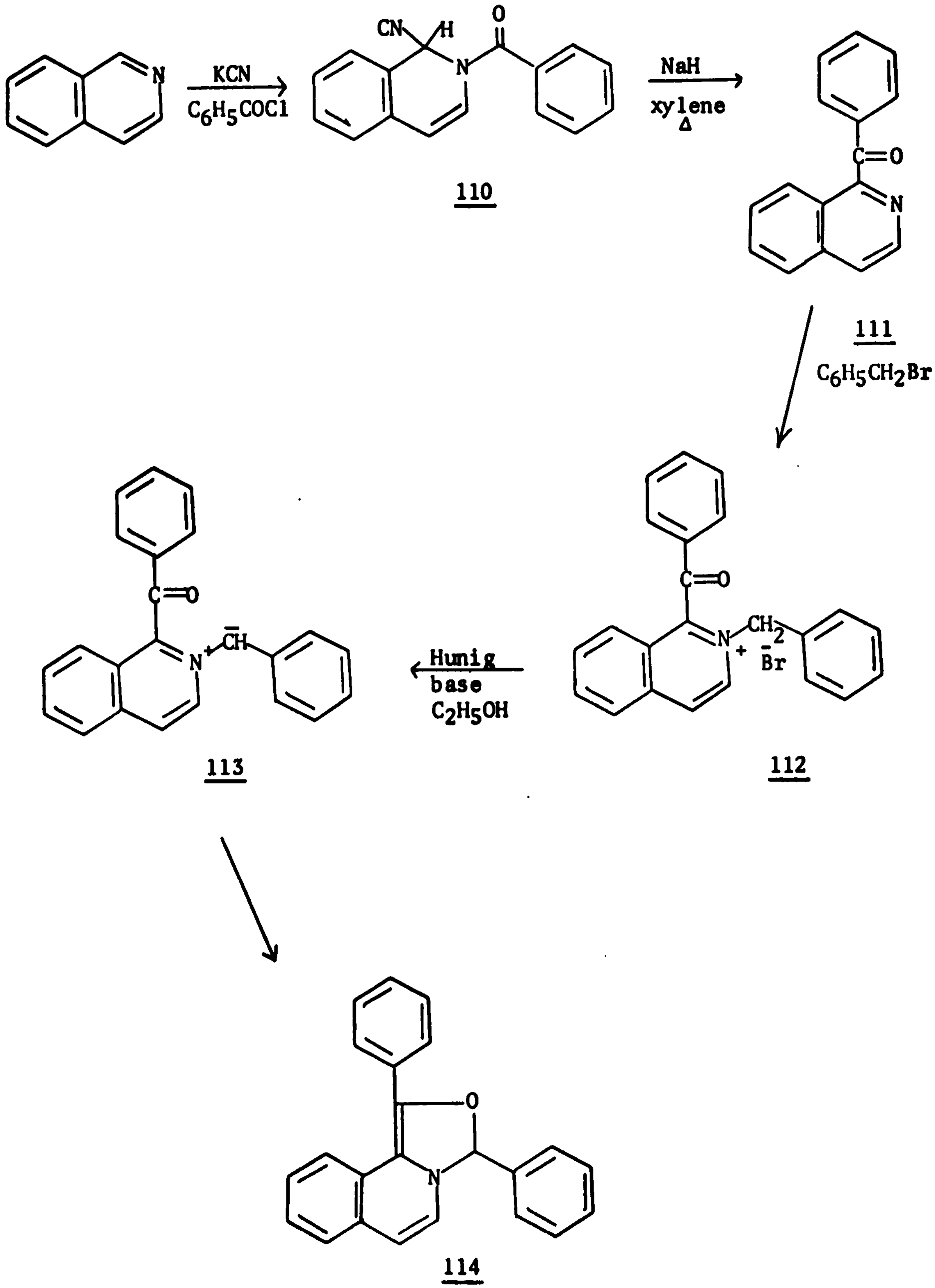
SCHEME IX


CO2H
SOCl2
COCl
C6H6
AlCl3
O
104
105
106
C6H5CH2Br
CH2
Br−
C6H5Li
or
Hunig
base
107
108
108A
109
H
O
N

In Scheme IX it was envisaged that a powerful base like phenyl lithium would remove a proton from compound 107 to yield 108 which might spontaneously cyclize to the 4-oxazoline 109. Quinaldic acid 104 was converted to its acid chloride in good yield,[207] which readily underwent a Friedel-Crafts acylation to produce compound 106.[208] However the attempted quaternization step was unsuccessful probably due to steric hindrance of the nitrogen atom to approach of the benzyl bromide.

Examination of the literature revealed the corresponding isoquinoline compound had been successfully quaternized[211] and thus led to the second attempted synthesis (Scheme X).

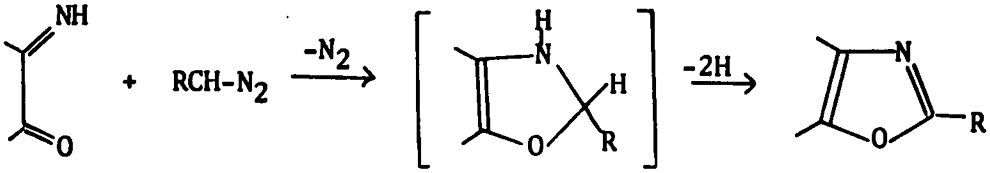
SCHEME X


KCN
C6H5COCl
CN
H
O
N
110
NaH
xylene
Δ
C=O
N
111
C6H5CH2Br
C=O
N+
CH2
Br-
112
Hunig base
C2H5OH
C=O
N+
CH-
113
O
N
114

Isoquinoline under Reissert conditions[209] readily produced the cyanoketone 110, which on treatment with sodium hydride in boiling xylene gave 1-benzoylisoquinoline,[210] quaternization of which was achieved by the method of Bradsher and Solomons.[211] However on treatment of this salt with diisopropylethylamine (Hunig's base) an intractable brown oil was obtained which could not be identified. No further work was done on this line of approach to the problem.

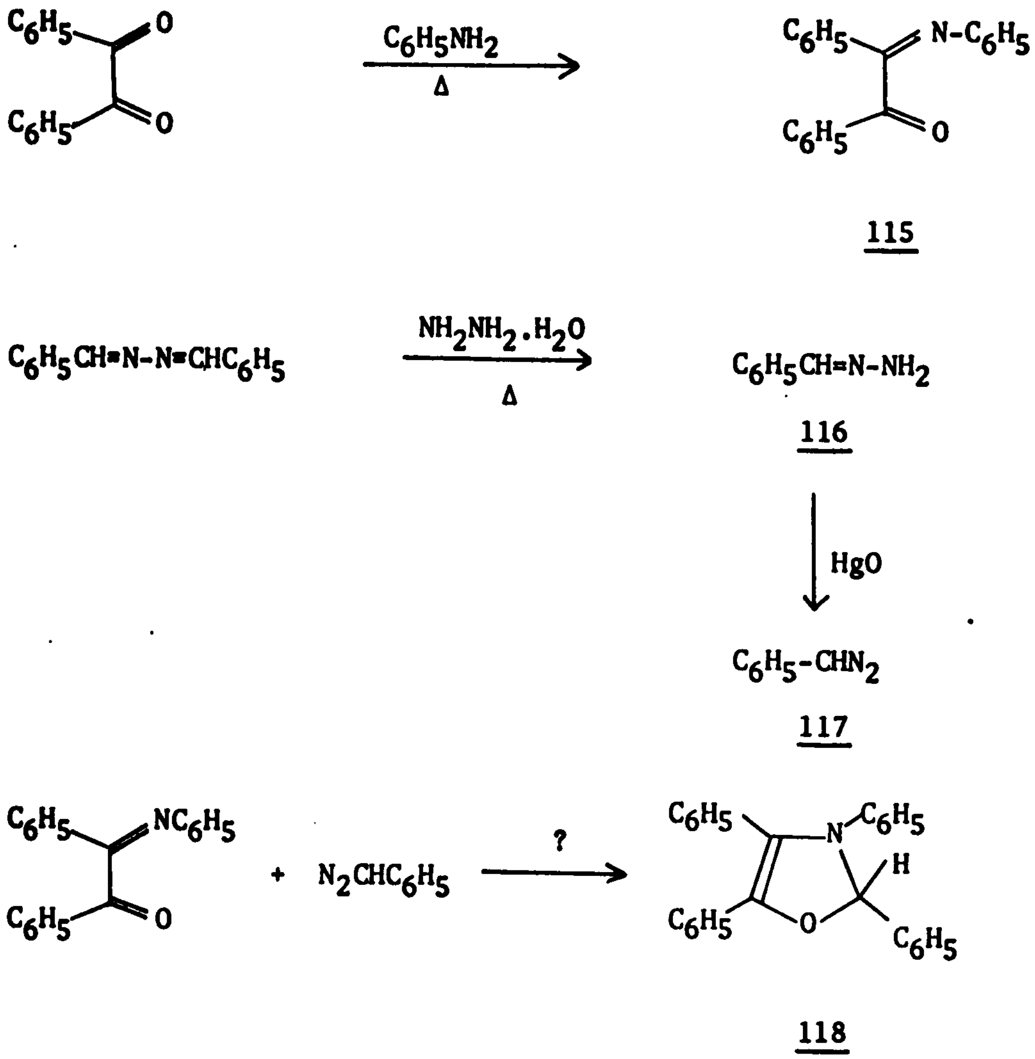
In 1947, Schönberg and Awad[212] reported that oxazoles could be obtained by the action of diazocompounds on the monoimines of 1,2-diketones as shown in equation [117].

[117]



Though the mechanism has not been established the reaction is thought to proceed via the intermediate 4-oxazoline.[213] It was envisaged that were the hydrogen of the monoimine replaced by an alkyl or aryl group, the intermediate 4-oxazoline might be stable enough to be isolated. The reaction scheme investigated is shown in Scheme XI.

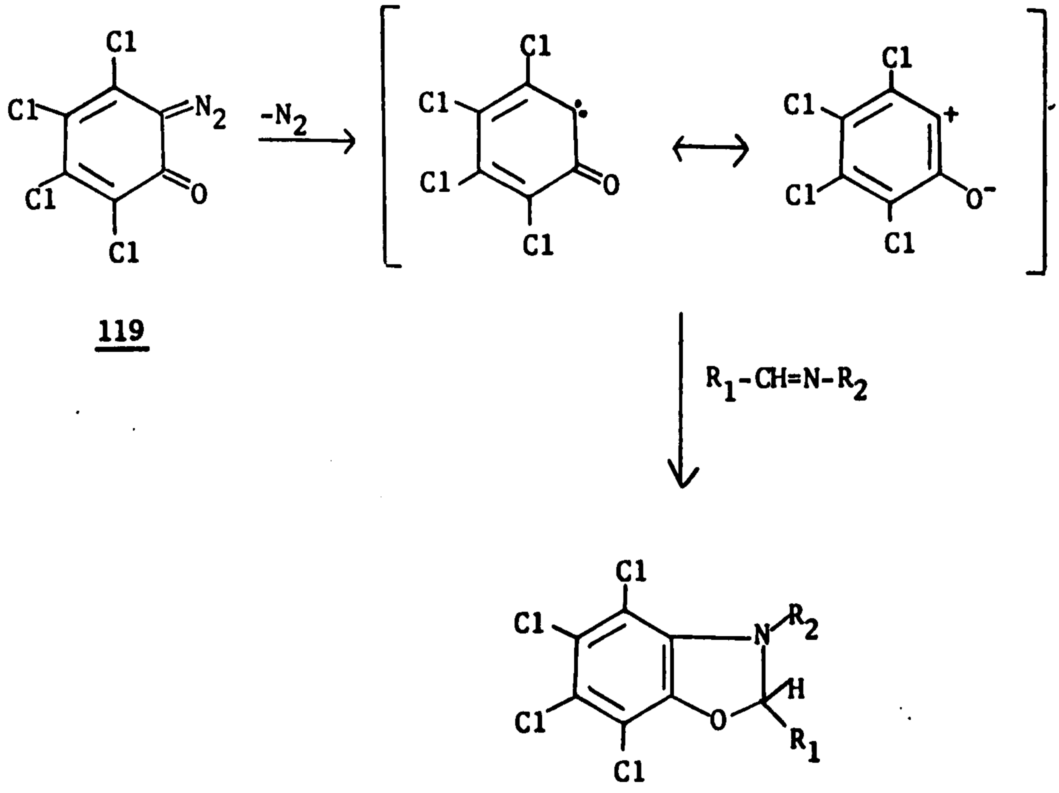
SCHEME XI


$C_6H_5NH_2$
Δ
115
$NH_2NH_2.H_2O$
Δ
$C_6H_5CH{=}N{-}N{=}CHC_6H_5$
$C_6H_5CH{=}N{-}NH_2$
116
HgO
$C_6H_5{-}CHN_2$
117
+ $N_2CHC_6H_5$
?
118

Benzil was readily converted to its phenylimino derivative 115 in 91% yield by the method of Blitz.[214] Phenyldiazomethane 117 was prepared from benzalazine by standard methods as shown above.[215,216] Generation of phenylcarbene from phenyldiazomethane in the presence of compound 115 was attempted by the following methods: a) thermally in chloroform at reflux while under a nitrogen atmosphere, b) photochemically in benzene solution under nitrogen first at room temperature,and then at 78°, c) under copper sulfate catalysis in chloroform solution at room temperature and in nitrogen atmosphere. In cases (a) and (c) phenylcarbene was generated in 3-5 h, as judged by the disappearance of the red colour of the solution,but no addition occurred in either case and the substrate 115 was recovered in good yield. In case (b) despite radiation for 24 h, little or no carbene was generated. When the reaction temperature was raised to 78° decomposition of phenyldiazomethane occurred in 4 h, but as before no addition of phenylcarbene to the substrate 115 took place. This method was therefore abandoned.

Another approach involving a carbene moiety was devised as shown in equation [118].

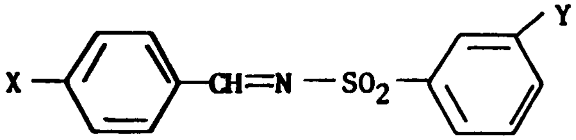
[118]



119

120

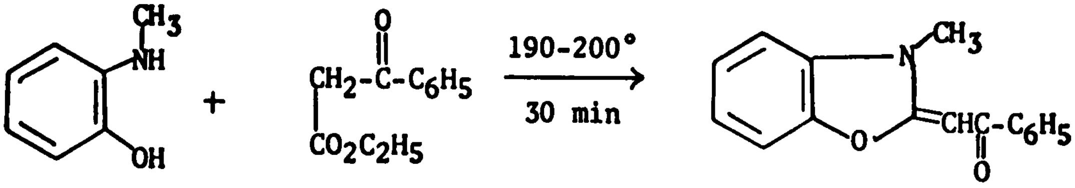
Huisgen[62] has demonstrated the synthetic utility of the ketocarbene intermediate obtained from the diazoketone 119 in [2+3] cycloaddition reactions with various dipolarophiles. One major disadvantage of this procedure is that the dipolarophile must be present as the solvent for any appreciable reaction to take place. This naturally seriously limits the choice of dipolarophilic species available. Lown, Westwood, and Moser[158] had shown N-sulfonyl anils to react smoothly and in good yield with azomethine ylides derived from 3-aroyl-2-arylaziridines to produce imidazolidines. Less active anils (or imines) led to poorer results or did not react at all. However the anils employed were solids of general structure 121.



121 $X = NO_2, Cl$; $Y = NO_2$

Attempts were made to prepare liquid N-sulfonylanils by replacing the phenyl groups of 121 by alkyl moieties but without success.

Very recently an example of a synthesis of the 4-oxazoline ring system has been reported by Ciurdaru and Denes,[217] and involves the condensation of *o*-hydroxy-N-methylaniline and benzoylacetic ester in equimolar proportions under thermal conditions. No details of the product other than its melting point were reported. The reaction is shown in equation [119].

[119] 

122 m.p. 231°

Summary

The [2+3] cycloaddition reactions of 3-aroyl-2-arylaziridines to carbonyl groups as dipolarophiles has been successfully extended to diphenylcyclopropeneone. The available evidence points to a rearrangement under the reaction conditions of the initially formed spiro-oxazolidine cycloadducts to form compounds the spectral data of which can be satisfactorily represented by the 4-oxazoline structure. Alternative structures have been considered and rejected either on direct experimental evidence or by relevant comparison with other published work. The main characteristic of the 4-oxazolines was their thermochromism and photochromism which were explained by contributions from various resonance hybrids.

These 4-oxazolines were found to undergo a variety of novel cycloaddition reactions with various dipolarophilic species which are described in Chapter IV of this thesis.

Experimental

1. General Preparation of Aziridines

The substituted aziridines employed in this study were prepared by the established methods described in Chapter II of this thesis. Full details of all new aziridines not previously reported in Chapter II are provided, together with references to literature preparations. The aziridines were employed in general as *cis,trans* mixtures except where otherwise stated.

1-(4-Anisyl)-3-phenylpropenone

This compound was prepared in 90% yield by the method of Stockhausen and Gattermann,[218] m.p. 106-107° (lit., m.p. 106-107°).

1-(4-Anisyl)-2,3-dibromo-3-phenylpropanone

This compound was prepared in 90% yield by the method of Stockhausen and Gattermann,[218] m.p. 155-157° (lit., m.p. 158-159°).

3-(4-Anisoyl)-1-cyclohexyl-2-phenylaziridine

A solution of cyclohexylamine (14.8 g, 0.15 mole) in benzene (50 ml) was added to a stirred solution of 1-(4-anisyl)-2,3-dibromo-3-phenylpropanone (19.9 g, 0.05 mole) in benzene (500 ml) at 0°, after which the solution was stirred for 1 h, at 0°, and then at room temperature for 23 h. The precipitated cyclohexylamine hydrobromide was removed by filtration, and the filtrate was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*, to yield a yellow oil which was triturated with hexene and chilled to give the desired isomeric aziridine as a pale yellow solid (12.57 g, 75%), m.p. 103-109°.

Recrystallization from hexane produced the pure *trans* isomer as a white crystalline solid, m.p. 126-127°.

Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.81; H, 7.46; N, 4.18.

Found: C, 78.76; H, 7.36; N, 4.10.

Mass spectrum: 335.1885 ($C_{22}H_{25}NO_2$). Found: 335.1888.

Infrared spectrum ν_{max} ($CHCl_3$): 1658 cm^{-1} (C=O of *trans* aziridine).

P.m.r. spectrum ($CDCl_3$): 0.85-2.00 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.36-2.77 (multiplet, 1H, cyclohexyl $C\underline{H}$), 3.53 (singlet, 2H, aziridine ring protons, *trans* coupled), 3.83 (singlet, 3H, methoxyl protons), 6.83-8.14 (multiplet, 9H, aryl protons).

2,3-Dibromo-1-methyl-3-phenylpropanone

This compound was prepared from 1-methyl-3-phenylpropenone in 99% yield by the method of Claisen and Claparède,[219] m.p. 122-124° (lit., m.p. 124-125°).

3-Acetyl-1-cyclohexyl-2-phenylaziridine

A solution of cyclohexylamine (36.0 g, 0.364 mole) was added dropwise to a stirred solution of 2,3-dibromo-1-methyl-3-phenylpropanone (36.0 g, 0.118 mole) at 0°, and the mixture stirred at 0° for 1 h, then at room temperature for 23 h. The precipitated cyclohexylamine hydrobromide was collected, and the red filtrate washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, to yield a red oil which was purified by chromatography on alumina (BDH, 150 g). In this manner the desired isomeric aziridine was obtained as a red oil (24.5 g, 85%).

Anal. Calcd. for $C_{16}H_{21}NO$: C, 79.01; H, 8.71; N, 5.72.

Found: C, 78.90; H, 8.83; N, 5.75.

Mass spectrum: 243.1623 ($C_{16}H_{21}NO$). Found: 243.1623.

Infrared spectrum ν_{max} ($CHCl_3$): 1699 cm^{-1} (C=O).

P.m.r. spectrum ($CDCl_3$): 1.00-2.00 (multiplet, 10H, cyclohexyl $\underline{CH_2}$), 2.15-2.75 (multiplet, 1H, cyclohexyl $\underline{CH}$), 2.83-2.88 (2H, aziridine ring protons, *cis* coupled), 2.24-3.36 (2H, aziridine ring protons, *trans* coupled), 2.27 (singlet, 3H, acetyl $\underline{CH_3}$), 7.26-7.46 (multiplet, 5H, aryl protons).

2-(4-Anisyl)-3-benzoyl-1-cyclohexylaziridine

This compound was prepared in 80% yield by the method of Cromwell, Bambury and Adelfang,[220] m.p. 82-96° (lit., m.p. 75-100°).

1-Cyclohexyl-2-phenyl-3-(4-toluoyl)aziridine

This compound was prepared in 72% yield by the method of Cromwell and coworkers,[145] *cis*-isomer m.p. 111-113° (lit., m.p. 111-112°), *trans* isomer m.p. 86-87° (lit., m.p. 89-90°).

1-Isopropyl-2-phenyl-3-(4-toluoyl)aziridine

This compound was prepared in 77% yield as an oily mixture of *cis* and *trans* isomers.

Anal. Calcd. for $C_{19}H_{21}NO$: N, 5.02.

Found: N, 4.80.

Mass spectrum: 279 ($C_{19}H_{21}NO$).

Infrared spectrum ν_{max} ($CHCl_3$): 1680 sh (C=O of *cis* aziridine), 1660 cm^{-1} (C=O of *trans* aziridine).

P.m.r. spectrum ($CDCl_3$) of *trans* isomer: 0.90 (doublet, 3H, J = 6 Hz, isopropyl $\underline{CH_3}$) 1.21 (doublet, 3H, J = 6 Hz, isopropyl $\underline{CH_3}$), 2.38

(singlet, 3H, toluoyl $C\underline{H}_3$), 3.52 and 3.61 (AB quartet, 2H, aziridine ring protons, *trans* coupled J = 2.4 Hz), 7.00-8.21 (multiplet, 9H, aryl protons).

cis isomer: 1.24 (doublet, 6H, J = 5.85 Hz, isopropyl $C\underline{H}_3$), 1.66-2.04 (multiplet, 1H, isopropyl $C\underline{H}$), 2.34 (singlet, 3H, toluoyl $C\underline{H}_3$), 3.18 (singlet, 2H, *cis* aziridine ring protons), 7.00-8.21 (multiplet, 9H, aryl protons).

The other aziridines employed in this work are shown in Table XXII and were prepared as described in Chapter II.

2. Diphenylcyclopropenone

This compound was prepared in 40-45% according to the procedure of Breslow, Eicher, Krebs, Peterson, and Posner[183] with the following slight modification. The crude product was purified by Soxhlet extraction using cyclohexane as solvent. Diphenylcyclopropenone crystallized from cyclohexane as white needles, m.p. 123-124°, (lit., 119-120°).

3. Preparation of 4-Oxazolines

The control experiments between diphenylcyclopropenone and isomerically pure samples of *cis* and *trans*-3-aroyl-2-arylaziridines employing an equimolar ratio have been described elsewhere.[182] In the reactions described here *cis,trans* mixtures of aziridines were employed throughout. Representative reactions using a) the 1:1 and b) 4:3 methods are described in detail after which the 4-oxazolines are listed and referred to Tables XXIII, XXIV, XXV and XXVI.

a) Reaction of 1-Cyclohexyl-2-phenyl-3-(4-toluoyl)aziridine with Diphenylcyclopropenone

A solution of 1-cyclohexyl-2-phenyl-3-(4-toluoyl)aziridine (1.6 g, 0.005 mole) and diphenylcyclopropenone (1.03 g, 0.005 mole) in dry benzene (60 ml) was heated under reflux for 16 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting oil on alumina (BDH, 120 g) with benzene as eluant, gave on evaporation, an orange oil which when dissolved in heptane (20 ml) and chilled yielded 4,5-diphenyl-2-(*cis*-1,2-diphenylvinyl)-3-(4-toluoyl)furan (0.3 g, 12%), m.p. 186-187° (ethanol).

Anal. Calcd. for $C_{38}H_{28}O_2$: C, 88.34; H, 5.46.

Found: C, 88.50; H, 5.39.

Mass spectrum: 516.2089 ($C_{38}H_{28}O_2$). Found: 516.2089.

Infrared spectrum ν_{max} ($CHCl_3$): 1693 cm^{-1} (aryl C=O).

P.m.r. spectrum ($CDCl_3$): 2.35 (singlet, 3H, toluoyl $\underline{H_3}$), 6.70-7.80 (multiplet, 24H, aryl protons), 8.05 (singlet, 1H, vinyl proton).

Concentration and further chilling of the heptane filtrate gave as a pink solid 3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-(4-toluoyl)-4-oxazoline (70H), (0.65 g, 20%), m.p. 175-176° (ethanol). These pink crystals slowly became colorless on standing in the dark.

Anal. Calcd. for $C_{37}H_{35}NO_2$: C, 84.53; H, 6.72; N, 2.67.

Found: C, 84.47; H, 6.69; N, 2.60.

Mass spectrum: 525.2668 ($C_{37}H_{35}NO_2$). Found: 525.2665.

Infrared spectrum ν_{max} ($CHCl_3$): 1695 cm^{-1} (aryl C=O).

P.m.r. spectrum ($CDCl_3$): 0.40-1.81 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 2.65-3.00 (multiplet, 1H, cyclohexyl C$\underline{H}$), 2.42 (singlet, 3H, toluoyl $C\underline{H_3}$), 4.96 (singlet, 1H, 2 proton), 6.70-8.05 (multiplet, 20H, aryl protons and vinyl proton).

By this procedure the following 4-oxazolines listed in Table XXIII and indicated by an asterisk were prepared.

4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(3-nitrophenyl)-4-oxazoline (70C), was prepared in 27% yield, m.p. 165-166° (ethanol).

2-(4-Anisyl)-4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-4-oxazoline (70E), was prepared as above in 23% yield, m.p. 158-160° (ethanol).

4-Benzoyl-5-(*cis*-1,2-diphenylvinyl)-3-isopropyl-2-phenyl-4-oxazoline (70J), was prepared as above in 24% yield, m.p. 175° (ethanol).

5-(*cis*-1,2-Diphenylvinyl)-3-isopropyl-2-phenyl-4-(4-toluoyl)-4-oxazoline (70K), was prepared in 31% yield by the above method, m.p. 165-166° (ethanol).

b) 4-Oxazolines prepared by the 4:3 method

4-Anisoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70F)

A solution of isomeric 3-anisoyl-1-cyclohexyl-2-phenylaziridine (0.62 g, 0.00185 mole) and diphenylcyclopropenone (0.29 g, 0.0014 mole) in benzene (30 ml) was heated under reflux for 24 h. The deep red solution was cooled, and the solvent removed *in vacuo* to yield a red oil, which was subjected to chromatography on grade 1 alumina (BDH, 40 g). Elution with a 4:1 mixture of benzene and hexane afforded a red oil which crystallized on trituration with ethanol to give the desired 4-oxazoline (0.60 g, 79%), m.p. 175-176.5° (ethanol).

Anal. Calcd. for $C_{37}H_{35}NO_3$: C, 82.07; H, 6.47; N, 2.59.

Found: C, 82.27; H, 6.49; N, 2.50.

Mass spectrum: 541.2616 ($C_{37}H_{35}NO_3$). Found: 541.2614.

Infrared spectrum ν_{max} ($CHCl_3$): 2850 (OCH_3), 1700 (aryl C=O), 832 cm^{-1} (1,4-disubst. ring).

Ultraviolet spectrum λ_{max} (CH_3CN): 233.5 (log ε 4.16), 274 mμ (log ε 3.87).

P.m.r. spectrum ($CDCl_3$): 0.38-1.95 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.55-3.15 (multiplet, 1H, cyclohexyl $C\underline{H}$), 3.85 (singlet, 3H, toluoyl $C\underline{H}_3$), 4.95 (singlet, 1H, 2 proton), 6.78-8.10 (multiplet, 20H, aryl protons plus vinyl proton).

4-Acetyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70G)

A solution of 3-acetyl-1-cyclohexyl-2-phenylaziridine (3.24 g, 0.013 mole) and diphenylcyclopropenone (2.06 g, 0.01 mole) in benzene (80 ml) was heated under reflux for 23 h. Concentration of the cooled red solution *in vacuo*, and chromatography of the resulting red oil on grade 1 alumina (BDH, 80 g) with a 1:1 mixture of benzene and hexane as eluant, gave as the main fraction a red oil which slowly crystallized on trituration with a hexane-ethanol mixture to yield the required 4-oxazoline (3.75 g, 84%), m.p. 80-82° (ethanol). On heating the melt >140° the characteristic red colour was imparted to the melt.

Anal. Calcd. for $C_{31}H_{31}NO_2$: C, 82.85; H, 6.90; N, 3.12.

Found: C, 82.65; H, 7.04; N, 3.03.

Mass spectrum: 449.2355 ($C_{31}H_{31}NO_2$). Found: 449.2353.

Infrared spectrum ν_{max} ($CHCl_3$): 1703 cm^{-1} (acetyl C=O).

P.m.r. spectrum ($CDCl_3$): 0.66-2.15 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 3.10-3.56 (multiplet, 1H, cyclohexyl $C\underline{H}$), 2.02 (singlet, 3H, acetyl $C\underline{H}_3$), 5.14 (singlet, 1H, 2 proton), 7.32-8.50 (multiplet, 16H, aryl protons and vinyl proton).

4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70A)

A solution of 3-benzoyl-1-cyclohexyl-2-phenylaziridine (6.10 g, 0.02 mole) and diphenylcyclopropenone (3.09 g, 0.015 mole) in benzene (200 ml) was heated under reflux for 24 h. Concentration of the cooled dark red solution *in vacuo*, and chromatography of the resulting red oil on grade 1 alumina (BDH, 140 g) with benzene as eluant, gave as the main fraction a yellow-orange oil which crystallized on trituration with heptane containing a little 95% ethanol and chilling, to yield the title compound as an orange-pink solid (4.98 g, 65%), m.p. 162-163° (ethanol).

Anal. Calcd. for $C_{36}H_{33}NO_2$: C, 84.54; H, 6.46; N, 2.74.

Found: C, 84.26; H, 6.40; N, 2.65.

Mass spectrum: 511.2511 ($C_{36}H_{33}NO_2$). Found: 511.2510.

Infrared spectrum λ_{max} ($CHCl_3$): 1695 cm^{-1} (aryl C=O).

Ultraviolet spectrum λ_{max} (CH_3CN): 227 (log ε 4.19), 267 mμ (log ε 3.82).

P.m.r. spectrum ($CDCl_3$): 0.35-1.75 (multiplet, 10H, cyclohexyl $C\underline{H}_2$), 2.70-3.05 (multiplet, 1H, cyclohexyl $C\underline{H}$), 4.95 (singlet, 1H, 2 proton), 6.80-8.02 (multiplet, 21H, aryl protons and vinyl proton).

By the above procedure the following 4-oxazolines were prepared, the analytical and spectral data of which are listed in Tables XXIII to XXVI.

3-Cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-4-(4-nitrobenzoyl)-2-phenyl-4-oxazoline (70B) was prepared in 23% yield, m.p. 191-192.5° (ethanol).

4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline (70D) was obtained in 64% yield by the above method, m.p. 180-182° (ethanol).

4. Addition Reactions Employing Other Solvents with 1:1 Molar Ratios of 3-Aroylaziridines and Diphenylcyclopropenone

A solution of 3-benzoyl-1-cyclohexyl-2-phenylaziridine (3.05 g, 0.01 mole) and diphenylcyclopropenone (2.06 g, 0.01 mole) in dry toluene (80 ml) was heated under reflux for 24 h. Removal of the solvent *in vacuo*, and chromatographic separation of the resulting oil on grade 1 alumina (BDH, 200 g) with benzene as eluant, caused the rapid separation of a yellow band which was collected in (3x50 ml) fractions. Removal of the solvent afforded a yellow oil which on trituration with heptane gave 3-benzoyl-4,5-diphenyl-2-(*cis*-1,2-diphenylvinyl)furan as a pale yellow solid, (1.45 g, 29%), m.p. 195-196° (ethanol).

Anal. Calcd. for $C_{37}H_{26}O_2$: C, 88.41; H, 5.21.

Found: C, 88.31; H, 5.18.

Mass spectrum: 502.1933 ($C_{37}H_{26}O_2$). Found: 502.1935.

Infrared spectrum ν_{max} ($CHCl_3$): 1695 cm^{-1} (aryl C=O).

P.m.r. spectrum ($CDCl_3$): 6.70-8.00 (multiplet, 25H, aryl protons), 7.99 (singlet, 1H, vinyl proton).

Further elution with benzene yielded an oil containing benzaldehyde and unreacted 3-benzoyl-1-cyclohexyl-2-phenylaziridine. Continued elution with chloroform, and then ethanol, gave unreacted diphenylcyclopropenone.

5. Deuterium Labelling Experiments.

These reactions involved the specifically labelled 3-aroyl-3-deuteroaziridines which were prepared by the method outlined in Chapter II.

Reaction of 3-Benzoyl-1-cyclohexyl-3-deutero-2-(4-nitrophenyl)aziridine and Diphenylcyclopropenone

A solution of 3-benzoyl-1-cyclohexyl-3-deutero-2-(4-nitrophenyl)aziridine (1.70 g, 0.0049 mole; 85% D incorporation) and diphenylcyclopropenone (0.75 g, 0.0037 mole) in dry benzene (70 ml) was heated under reflux for 22 h. Concentration of the cooled solution *in vacuo*, and chromatography of the yellow gum obtained on grade 1 alumina (BDH, 40 g) with benzene as eluant, afforded a yellow syrup which on chilling and trituration with 95% ethanol produced a yellow-pink solid (1.45 g, 59%) m.p. 173-175°. Mass spectrum : 557.2425 ($C_{36}H_{31}DN_2O_4$). Found 557.2431. Because of the effect of the nitro group in spreading the aromatic proton resonance signals in the p.m.r. spectrum, the extent of deuterium incorporation could not be determined from this experiment. However subsequent [2+3] cycloaddition reactions of this product with acetylenic dipolarophiles produced tetrasubstituted furans containing about 60% deuterium incorporation in the *cis*-1,2-diphenylvinyl group. These experiments will be described in detail in Chapter IV of this thesis.

6. Investigation of Scope of 4-Oxazoline Synthesis

1,2-Dibromo-1-cyano-2-phenylethane

This compound was prepared in 85% yield from 1-cyano-2-phenylethylene by the method of Birks and Wright[221] as a sharp smelling yellow-brown solid, m.p. 89-90° (lit., m.p. 92-83°).

3-Cyano-1-cyclohexyl-2-phenylaziridine

To a solution of 1,2-dibromo-1-cyano-2-phenylethane (2.89 g, 0.01 mole) in benzene (150 ml) with stirring at 0°, was added dropwise a solution of cyclohexylamine (9.0 g, 0.09 mole) in benzene (30 ml). The resulting solution was then stirred at room temperature for 14 days, when the theoretical quantity of cyclohexylamine hydrobromide (3.6 g) was collected. The yellow filtrate was concentrated *in vacuo*, and subjected to chromatography on grade 1 alumina (BDH, 120 g) with benzene as eluant. Removal of the solvent gave the title compound as a buff colored solid (2.07 g, 92%), m.p. 108.5-110.5° (heptane).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.64; H, 7.96; N, 12.39.

Found: C, 79.42; H, 8.00; N, 12.44.

Mass spectrum: 226.1470 ($C_{15}H_{18}N_2$). Found: 226.1470.

Infrared spectrum ν_{max} ($CHCl_3$): 2253 (C≡N), 2200 cm^{-1} (C≡N).

P.m.r. spectrum ($CDCl_3$): 1.00-2.08 (multiplet, 11H, cyclohexyl $C\underline{H}_2$ and $C\underline{H}$), 2.90 and 2.31 (AB quartet, 2H, aziridine ring protons, J = 6.3 Hz), 7.27-7.58 (multiplet, 5H, aryl protons).

Reaction of 3-Cyano-1-cyclohexyl-2-phenylaziridine with Diphenylcyclopropenone

A solution of 3-cyano-1-cyclohexyl-2-phenylaziridine (0.452 g, 0.002 mole) and diphenylcyclopropenone (0.406 g, 0.002 mole) in *o*-xylene (35 ml) was heated under reflux for 24 h. The yellow solution was cooled and the xylene removed *in vacuo*, giving a yellow oil which solidified on cooling. Recrystallization from ethanol gave 1-cyclohexyl-2,3,4-triphenylpyrrole (89), as white crystals (0.55 g, 73%), m.p. 165-166°.

Anal. Calcd. for $C_{28}H_{27}N$: C, 89.12; H, 7.16; N, 3.71.

Found: C, 89.17; H, 7.34; N, 3.78.

Mass spectrum: 377.2143 ($C_{28}H_{27}N$). Found: 377.2144.

Infrared spectrum ν_{max} ($CHCl_3$): 1602 cm^{-1} (aromatic C=C) (there was *no* C≡N stretching frequency present in the spectrum).

Ultraviolet spectrum λ_{max} ($CHCl_3$): 247 (log ε 4.38), 253 (log ε 4.37), 286 mμ (log ε 4.10).

P.m.r. spectrum ($CDCl_3$): 0.83-2.28 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 3.57-4.13 (multiplet, 1H, cyclohexyl $C\underline{H}$), 7.00-7.42 (multiplet, 16H, aryl protons and ring C_5 proton).

This same pyrrole was also obtained in 61% yield, m.p. 164-165° by heating under reflux for 24 h, a solution of 3-cyano-1-cyclohexyl-2-phenylaziridine (0.226 g, 0.001 mole) and diphenylcyclopropenone (0.206 g, 0.001 mole) in toluene (25 ml). The product was isolated in the manner described above, and was identical in all respects with the above mentioned pyrrole.

Reaction of *trans*-3-Benzoyl-1-cyclohexyl-2-phenylaziridine with Phenylhydrazine

Phenylhydrazine (1.296 g, 0.012 mole) was added to a solution of *trans*-3-benzoyl-1-cyclohexyl-2-phenylaziridine (2.44 g, 0.008 mole) in glacial acetic acid (14 ml) and the mixture heated to 50° for a few minutes, cooled to room temperature, and allowed to stand for 24 h. The yellow solution obtained was cooled to 0°, when a yellow solid settled out of solution and was collected by filtration (1.18 g). The filtrate was diluted with an equal volume of water[202] whereupon a second yellow solid precipitated from the mixture and was isolated (1.93 g). The solids were found to be identical and to be 4-(N-cyclohexyl)-1,3,5-triphenyl *trans* 4,5-pyrazoline (3.11 g) contaminated with some acetic acid. Recrystallized from benzene-ethanol, m.p. 143-145°.

Anal. Calcd. for $C_{27}H_{29}N_3$: C, 82.02; H, 7.34; N, 10.63.

Found: C, 81.95; H, 7.35; N, 10.57.

Mass spectrum: 395.2362 ($C_{27}H_{29}N_3$). Found: 395.2362.

Infrared spectrum ν_{max} ($CHCl_3$): 3505 cm^{-1} (NH).

P.m.r. spectrum ($CDCl_3$): 1.00-2.07 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 2.73-3.10 (multiplet, 1H, cyclohexyl $C\underline{H}$), 4.42 and 5.11 (AB quartet, 2H, ring 4,5 protons, *trans* coupled, J = 2.5 Hz).[84] 7.06-8.00 (multiplet, 15H, aryl protons).

7. Chemical Properties of 4-Oxazolines

Control Attempted Reaction of 4-Oxazolines with Lewis Acids

4-Toluenesulfonic acid (0.001-0.002 g) was added to a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.10 g) in benzene (30 ml). The flask was shaken for a few minutes and a red coloration was imparted to the solution which darkened with time. The flask was kept in the dark at room temperature for 16 h, after which the solvent was removed *in vacuo* and the residual oil passed down a short column of grade 1 alumina (BDH, 20 g) with benzene as eluant. In this manner a yellow oil was obtained which crystallized on trituration with heptane to give the starting 4-oxazoline (0.070 g, 70% recovery), m.p. 158-160°.

Comparison of the spectra of this compound with that of the authentic material confirmed the identical nature of the compounds.

In a later experiment over a period of 4-5 h, an 80% recovery of the 4-oxazoline was obtained.

Acid Hydrolysis of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline (70D)

The title 4-oxazoline (0.30 g, 0.00054 mole) was heated under reflux in 2N hydrochloric acid (25 ml) for a period of 3½ h. On cooling the orange mixture, a yellow residue appeared in the flask, while a white sublimate was observed in the condenser and was isolated. The mixture was then extracted with ether (3x20 ml) to give an organic layer, an aqueous layer, and an insoluble yellow residue.

a) White sublimate: this was found to be benzoic acid (0.007 g), m.p. 116-118°, and was identified by spectral comparison with authentic material.

b) Ether extract: this was dried ($MgSO_4$) and the ether removed *in vacuo* to yield a yellow oil (0.035 g) which partly crystallized on standing. This was found to be 4-nitrobenzaldehyde on the basis of its compatibility in infrared and p.m.r. spectra with authentic material, and by its 2,4-dinitrophenylhydrazine derivative, m.p. 317-318° (lit., m.p. 320°),[222] having an identical infrared spectrum and undepressed mixed melting point with the same derivative of authentic 4-nitrobenzaldehyde.

c) Yellow residue: no structure could be assigned to this semi-solid (0.02 g), which possessed a carbonyl stretching frequency in the infrared spectrum (Nujol) of 1754 cm^{-1} and from the mass spectrum was seen to correspond to *m/e* 324 (parent 4-oxazoline-anil moiety).

d) Aqueous solution: this contained only cyclohexylamine hydrochloride.

Acid Hydrolysis of 3-Cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-4-(4-nitrobenzoyl)-2-phenyl-4-oxazoline (70B)

The title 4-oxazoline (0.40 g, 0.00072 mole) was heated under reflux in 2N hydrochloric acid (25 ml) for a period of 3½ h. From this reaction four products were isolated in the manner described above. The white sublimate (0.008 g) and the ether extract (0.050 g) were found to consist of benzoic acid (m.p. 119-120.5°), while the aqueous layer contained cyclohexylamine hydrochloride. As before, no structural assignment could be given to the brown residue (0.12 g, m.p. 85°) the physical data of which was as follows.

Mass spectrum: 369 (parent 4-oxazoline-anil moiety).

Infrared spectrum ν_{max} ($CHCl_3$): 1766 (C=O), 1695 cm^{-1} (C=O).

P.m.r. spectrum ($CDCl_3$): 6.70-8.50 (multiplet, aryl protons).

Acid Hydrolysis of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70A)

The title 4-oxazoline (0.20 g, 0.00039 mole) was heated under reflux in 50% (w/w) sulfuric acid (25 ml) for a period of 3 h. As in the procedure described above, benzoic acid was sublimed out in the condenser and benzaldehyde was obtained from the ether extract which was characterized as its 2,4-dinitrophenylhydrazine derivative.

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-Oxazoline (70A) with Dimethyl Sulfoxide

A solution of the title 4-oxazoline (0.511 g, 0.001 mole) and dimethyl sulfoxide (0.234 g, 0.003 mole) in benzene (30 ml) was heated under reflux for 24 h. Removal of the solvent *in vacuo* and chromatography of the resulting red oil on Fisher alumina (30 g) with a 1:1 mixture of heptane and benzene as eluant, gave as the main fraction an oil which crystallized on trituration with ethanol to give as a yellow-pink solid the title 4-oxazoline (0.408 g, 80% recovery), m.p. 157-159°. Comparison of spectral properties with those of the authentic material confirmed this result.

A repeat of this reaction in neat dimethyl sulfoxide caused decomposition of the 4-oxazoline.

With Sodium Hydroxide

4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(3-nitrophenyl)-4-oxazoline (0.25) was heated under reflux in 10% sodium hydroxide solution (20 ml) for 4 h. Filtration of the reaction mixture gave the above starting 4-oxazoline (0.185 g, 74% recovery), m.p. 158-160°.

Thermal Decomposition of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvonyl)-2-phenyl-4-oxazoline (70A) in Toluene

A solution of the title 4-oxazoline (0.767 g, 0.0015 mole) in toluene (60 ml) was heated under reflux for 48 h. The deep red solution was allowed to cool overnight by which time the colour had faded to yellow. The solution was concentrated *in vacuo* and the residue taken up in a small volume of benzene from which a white solid precipitated and was collected (0.02 g). The benzene solution was again concentrated and subjected to chromatography on grade 1 alumina (BDH, 50 g) with benzene as eluant, to produce a yellow oil which solidified on standing. Recrystallization from ethanol gave a white solid (0.065 g), and a yellow filtrate which on further concentration and cooling afforded a bright yellow solid (0.07 g), m.p. 144-146° (ethanol). These compounds were:

a) White insoluble compound: no structure could be assigned with confidence to this highly insoluble product the physical and spectral data of which are tabulated below.

M.p. 278-280°. Anal. Found: C, 80.96; H, 5.14; N, 0.00. This gives an empirical formula of C_8H_6O or $C_{15}H_{12}O_2$.

Mass spectrum principal fragments *m/e*: 235, 105 (C_6H_5CO).

Infrared spectrum ν_{max} (Nujol): 3083 (sharp C=CH), 1752, 1748 cm^{-1} (C=O).

No suitable solvent for p.m.r. spectroscopy could be found.

b) White compound from column: as before no structure could be assigned to this compound whose physical and spectral data are as follows.

M.p. 180-181°. Anal. Found: C, 80.30; H, 4.76; N, 0.00 (empirical formula C_7H_5O). Osmometric molecular wt. 329.

Mass spectrum principal fragments *m/e*: 235, 178 and 105.

Infrared spectrum ν_{max} ($CHCl_3$): 1819, 1817, 1795 (C=O), 1680 cm^{-1}.

P.m.r. spectrum ($CDCl_3$): 6.34 (broad based singlet), 7.10-7.94 (multiplet, aryl protons), ratio $\sim$ 1:19.

c) Yellow compound: this product was assigned as an α-pyrone on the basis of the compatibility of its physical and spectral properties with those of known α-pyrones.

M.p. 144-146°. Anal. Calcd. for $C_{23}H_{16}O_2$: C, 85.19; H, 4.49.

Found: C, 84.81; H, 5.01.

Mass spectrum: 324.1150 ($C_{23}H_{16}O_2$). Found: 324.1157.

Infrared spectrum ν_{max} ($CHCl_3$): 1719 (C=O of α-pyrone), 1701 cm^{-1} (shoulder, C=O).

Ultraviolet spectrum λ_{max} ($CHCl_3$): 243 (log ε 4.07), 265 sh (log ε 3.99), 361 mμ (log ε 4.09).

P.m.r. spectrum ($CDCl_3$): 7.08-7.92 (multiplet, aryl protons and ring proton).

If this reaction was stopped after 45 min, and worked up as described previously, the title 4-oxazoline was recovered in 80% yield.

Thermal Decomposition of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70A) in n-Butanol

A solution of the title 4-oxazoline (0.256 g, 0.0005 mole) in n-butanol (20 ml) was heated under reflux for 48 h. The cooled red solution was concentrated *in vacuo* and the residual red oil subjected to chromatography on grade 1 alumina (BDH, 25 g) with benzene as eluant. The main fraction, which on removal of the solvent and trituration of the resulting yellow oil with heptane, gave a yellow solid (0.029 g), m.p. 143-145° (ethanol). This product was found to be identical in all respects (superimposable i.r. spectrum, mass spectrum, and undepressed mixed melting point) with the α-pyrone obtained from the decomposition of the same 4-oxazoline in toluene solution. No other products were obtained from this reaction.

Photochemical Decomposition of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline in the Presence of Dimethyl Fumarate

A solution of the title 4-oxazoline (0.102 g, 0.0002 mole) and dimethyl fumarate (0.029 g, 0.0002 mole) in chloroform (10 ml) was subjected to photolysis for 1 h, at room temperature using a Hanovia medium pressure mercury lamp (450W) with a Vicor 7910 filter (>2150Å), and a quartz tube. At no time during the reaction did any red colour appear in the solution. The reaction was monitored by following the disappearance of the 4-oxazoline carbonyl stretching frequency. The solvent was removed *in vacuo* and the yellow oil produced was subjected to chromatography on grade 1 alumina (BDH, 25 g) with benzene as eluant. Removal of the solvent gave a yellow oil which crystallized on standing.

This was a two-component mixture (t.l.c.) which was separated by crystallization from ethanol to give a yellow solid (0.005 g), m.p. 141-142°, and a white solid which was found to be dimethylfumarate. The yellow compound possessed identical spectral properties to the α-pyrone obtained from the thermal decomposition of the 4-oxazoline and was concluded that both compounds were identical.

Lithium Aluminum Hydride Reduction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70A)

A solution of the title 4-oxazoline (0.511 g, 0.001 mole) in dry ether (50 ml) was added in a rapid dropwise manner to a solution of lithium aluminum hydride (0.038 g, 0.001 mole) in dry ether (20 ml) and the mixture was heated under reflux for 40 h. The steel grey coloured mixture was cooled and extracted with aqueous ether (25 ml), water (5 ml), dilute sodium hydroxide (5 ml) and water (5 ml). The final mixture was filtered and the organic layer separated and dried ($MgSO_4$). The ether was removed *in vacuo* to yield a white sticky solid which crystallized on trituration with 95% ethanol to give as a diastereoisomeric pair 3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-4-hydroxybenzyl-2-phenyl-4-oxazoline 103, (0.35 g, 68.2%), m.p. 190-192° (ethanol).

Anal. Calcd. for $C_{36}H_{35}NO_2$: C, 84.21; H, 6.82; N, 2.73.

Found: C, 84.26; H, 6.61; N, 2.65.

Mass spectrum: 513.2668 ($C_{36}H_{35}NO_2$). Found: 513.2662.

Infrared spectrum ν_{max} ($CHCl_3$): 3550 cm^{-1} (OH). No trace of the carbonyl group of the substrate at 1695 cm^{-1} was present.

P.m.r. spectrum ($CDCl_3$): 0.40-1.80 (multiplet, 10H, cyclohexyl $\underline{CH_2}$), 2.50-3.00 (multiplet, 1H, cyclohexyl CH), 4.85 (singlet, 1H, 2 proton), 5.06 and 5.25 (broad based singlets, 1H, hydroxyl proton of diastereoisomeric pair), 6.49 and 6.52 (singlets, 1H, allylic protons of diastereoisomeric pair), 7.10-8.14 (multiplet, 21H, aryl protons and vinyl proton).

Attempted Synthesis of the 4-Oxazoline Ring System

Method I (see Scheme IX)

Quinaldoyl Chloride (105)

This compound was prepared from quinaldic acid in 65% yield by the method of Besthorn and Ibele,[206] m.p. 92-94° (lit. m.p. 97°).

2-Benzoylquinoline (106)

This compound was prepared from quinaldoyl chloride in 61% yield by a Friedel-Crafts acylation employing the method of Besthorn,[207] m.p. 108-109° (lit. m.p. 110-111°).

Attempted Quaternization of 2-Benzoylquinoline with Benzyl Bromide

A solution of 2-benzoylquinoline (1.0 g, 0.0043 mole) and benzyl bromide (1.1 g, 0.0064 mole) in dry ether (50 ml) was allowed to stand at room temperature for 14 days. The solvent was allowed to evaporate giving a pale yellow crystalline compound which was found to be 2-benzoylquinoline (1.0 g), m.p. 108-110°.

This reaction was repeated in dry acetone (40 ml) and heated under reflux for 24 h. Removal of the solvent gave only 2-benzoylquinoline, m.p. 108-109°.

This procedure was then abandoned.

Method II (see Scheme X)

2-Benzoyl-1-cyanoisoquinoline (110)

This compound was prepared in 37% yield from isoquinoline by the method of Reissert,[208] m.p. 124-126° (lit. m.p. 125-126°).

1-Benzoylisoquinoline (111)

This compound was prepared from 2-benzoyl-1-cyanoisoquinoline in 62% yield by the method of Boekelheide and Weinstock,[209] m.p. 73-75° (lit. m.p. 76°).

1-Benzoyl-2-benzylisoquinolinium bromide (112).

This reaction was carried out following the method of Bradsher and Solomons.[210]

1-Benzoylisoquinoline (2.0 g, 0.0086 mole) and benzyl bromide (2.0 g, 0.012 mole) were allowed to react for 12 days at room temperature. The brown oil obtained was crystallized by trituration with ethyl acetate to give the title compound as a yellow powder (1.56 g, 89.7%), m.p. 168-170° (lit. m.p. 172°).

Attempted cyclization of 1-benzoyl-2-benzylisoquinolinium bromide to the corresponding 4-oxazoline

A solution of diisopropylethylamine (0.774 g, 0.006 mole) in 98% ethanol (10 ml) was added to a solution of 1-benzoyl-2-benzylisoquinolinium bromide (1.20 g, 0.003 mole) in 98% ethanol (40 ml) and the resulting brown solution stirred at room temperature for 30 h. Removal of the solvent *in vacuo* gave a brown oil which could not be identified.

Lack of time prevented further work on this subject.

Method III (see Scheme XI).

C-Benzoylbenzylideneaniline (115)

A mixture of benzil (21.0 g, 0.1 mole) and redistilled aniline (93.0 g, 1.0 mole) was heated at 150° in a pressure bottle for 5½ h. The dark brown solution was cooled and the excess aniline removed *in vacuo* to give a dark brown oil which was taken up in 95% ethanol and chilled to give the title compound as a pale yellow solid (26.0 g, 92.2%), m.p. 95-96°. Recrystallization from ethanol gave pale yellow needles, m.p. 103-104° (lit. m.p. 105°).[213]

Benzylidenehydrazine (116)

This compound was prepared in 56% yield from benzalazine by the method of Curtius and Franzen,[214] b.p. 88° at 1.5 mm (lit. b.p. 140° at 14 mm).

Phenyldiazomethane (117)

Yellow mercuric oxide (11 g) was added to a cooled suspension of benzylidenehydrazine (6.6 g, 0.055 mole) in hexane (40 ml) and the mixture stirred for 45 min, during which the colour of the hexane changed to red-brown. The mixture was decanted and the hexane removed *in vacuo* at <25° to yield phenyldiazomethane (5.0 g, 77%) as a red oil which was stored at 0-10° in a tightly stoppered vessel. This compound could be purified by distillation, b.p. 90-93°/10 mm, but some loss due to decomposition was encountered.

Infrared spectrum ν_{max} ($CHCl_3$): 2078 cm^{-1} ($N\equiv N$).

Attempted reaction of phenyldiazomethane and C-benzoylbenzylideneaniline

a) Thermally in chloroform

A solution of C-benzoybenzylideneaniline (2.85 g, 0.01 mole) and phenyldiazomethane (3.54 g, 0.03 mole) in chloroform (50 ml) was heated under reflux in a nitrogen atmosphere for 3½ h, when the red colour of the solution had faded to pale yellow. Heating was continued for a further 30 min, after which the solution was cooled and the chloroform removed *in vacuo* to give a yellow-orange oil which was shown by t.l.c. to be a two-component mixture. Heptane (15 ml) was added and the mixture chilled to give a yellow solid (2.26 g), m.p. 95-128°. This was shown by spectral evidence to consist mainly of the starting material, C-benzoylbenzylideneaniline and a minor product which appeared to be a polymeric product of phenylcarbene (*m/e* 360) but which was not identified.

b) Catalytically in chloroform

A solution of C-benzoylbenzylideneaniline (0.884 g, 0.031 mole) and phenyldiazomethane (1.10 g, 0.0093 mole) in chloroform (40 ml) containing copper sulfate (0.050 g, 0.00031 mole) was stirred at room temperature under nitrogen for a period of 10 h. The yellow solution was filtered to remove the suspended copper salts, and concentrated *in vacuo* to give a yellow oil which crystallized on trituration with cold heptane to produce as a yellow solid C-benzoylbenzylideneaniline (0.76 g, 86% recovery), m.p. 103-106°.

c) Photochemically in benzene

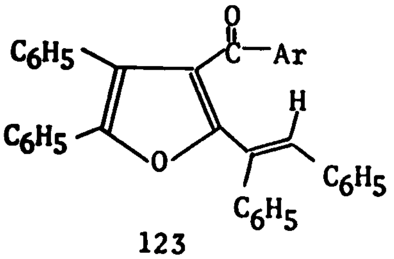
A solution of C-benzoylbenzylideneaniline (0.95 g, 0.0033 mole) and phenyldiazomethane (1.18 g, 0.01 mole) in benzene (40 ml) under nitrogen was irradiated at room temperature using a Hanovia medium pressure mercury lamp (450W). The light was unfiltered and the reaction vessel was Pyrex. After 21 h, no loss of colour was observed and the i.r. spectrum of an alliquot still showed the characteristic $\nu(N{\equiv}N)$ at 2080 cm^{-1}.

The irradiation was continued for 4 h at 78° by which time the red solution had faded to a pale yellow hue. Work-up of the solution as before produced only C-benzoylbenzylideneaniline (0.70 g, 73.7% recovery).

CHAPTER IV

[2+3] CYCLOADDITION REACTIONS OF 4-OXAZOLINES

As mentioned in Chapter III when 4-oxazolines were prepared by the 1:1 aziridine to diphenylcyclopropenone method, common side products were yellow crystalline compounds which were assigned as tetrasubstituted furans of general structure 123.

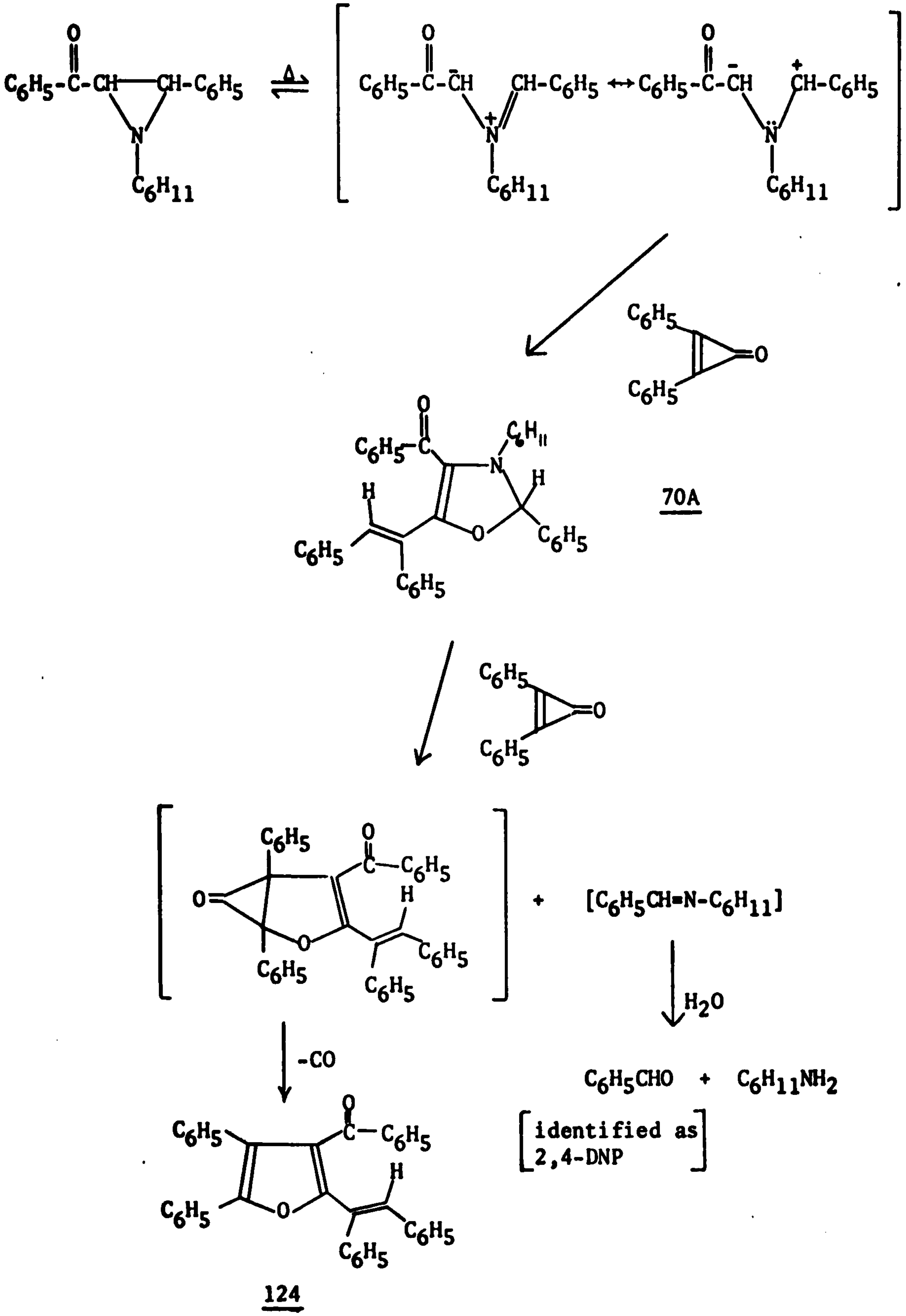


123

Indeed when diphenylcyclopropenone was present in excess, or when higher temperatures were used, the furans were the sole product from the reactions. These furans, once characterized, were of considerable significance in substantiating the proposed structure of the 4-oxazolines and the cleavage of the latter in appropriate solvents, and further provided the key to an extremely fruitful field of study in dihydrofuran chemistry.

A plausible rationalization for the formation of the tetrasubstituted furans is shown in Scheme XII.

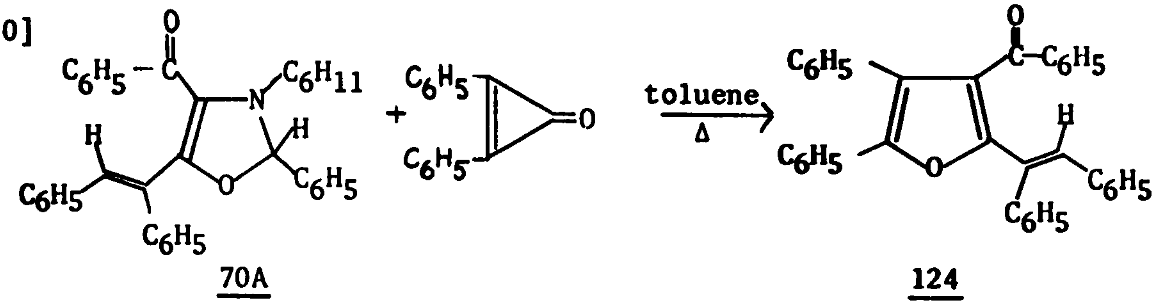
SCHEME XII


Δ
70A
-CO
H_2O
$[C_6H_5CH=N-C_6H_{11}]$
C_6H_5CHO + $C_6H_{11}NH_2$
identified as 2,4-DNP
124

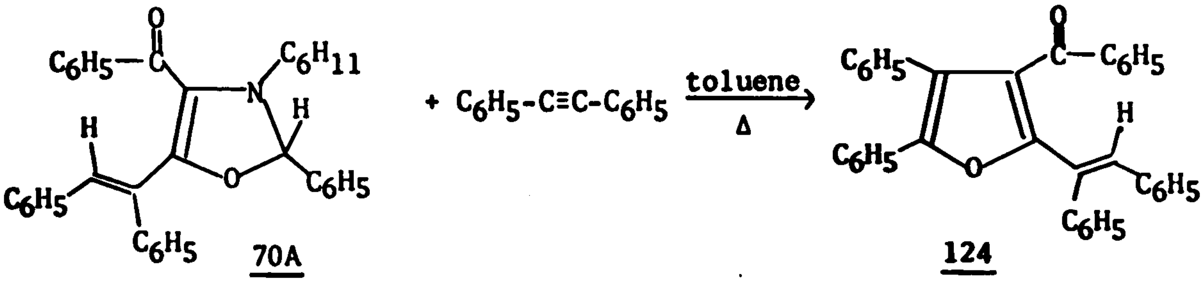
In Scheme XII it is postulated that the initially formed 4-oxazoline reacts with diphenylcyclopropeneone in a [2+3] cycloaddition reaction at the C=C bond of the latter to produce the intermediate shown, which then decarbonylates to yield the furan 124. The extruded anil moiety was almost invariably hydrolyzed in the isolation procedure to the corresponding aldehyde and cyclohexylamine.

This rationalization has been supported by the following experimental evidence. Lown and Smalley[182] have found that treatment of the 4-oxazoline (70A) with one equivalent of diphenylcyclopropenone in toluene solution under reflux produced the furan 124 as shown in equation [120].

[120]


C6H5
C6H11
H
C6H5
C6H5
+
C6H5
C6H5
toluene
Δ
C6H5
C6H5
H
C6H5
C6H5
70A
124

The identical furan was also obtained in 76% yield from a separate reaction of the 4-oxazoline 70A and diphenylacetylene as shown in equation [121].[182]


C6H5
C6H11
H
H
C6H5
C6H5
C6H5
70A
+ C6H5-C≡C-C6H5
toluene
Δ
C6H5
C6H5
C6H5
H
C6H5
C6H5
124

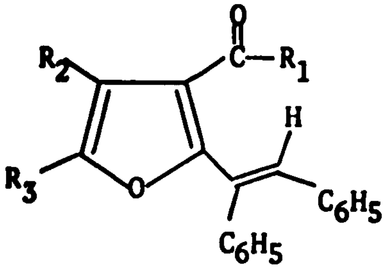
[121]

The possibility of decarbonylation of diphenylcyclopropenone to diphenylacetylene prior to cycloaddition with the 4-oxazoline was eliminated by a control reaction in which diphenylcyclopropenone was recovered in good yield from boiling toluene (b.p. 113°) containing cyclohexylamine over a period of 24 h. Also Breslow and coworkers[183] have shown that decarbonylation of diphenylcyclopropenone occurs only at temperatures around 160°.

The conclusion from these results was that the cycloaddition of 3-aroyl-2-arylaziridines to diphenylcyclopropenone involved competing 1:1 and 1:2 reactions to produce 4-oxazolines and tetrasubstituted furans respectively. This latter reaction was successfully suppressed by altering the ratio of the reactants to 4:3 in favour of the aziridine, and thus only the 4-oxazolines were produced in increased yield.

Another interesting observation from Chapter III was that higher reaction temperatures favoured the exclusive formation of furans. By employing this fact a series of substituted furans were prepared by the reaction of 4-oxazolines with various acetylenic dipolarophiles by heating in toluene or xylene solution for periods of twenty-four to forty-eight hours. Usually the acetylenic species was employed in a slight excess, and the reaction run till the initial deep red colour had changed to a translucent pale yellow. This colour change provided an excellent visual means of following the progress of the reaction. Alternative monitoring by t.l.c. produced the same result.

These furans were stable compounds and exhibited no red coloured melts. The compounds prepared and their analytical and spectral properties are listed in Tables XXVII and XXVIII and refer to the general structure 125.

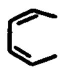
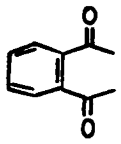


O
C
R1
R2
R3
O
H
C6H5
C6H5

125

TABLE XXVII

3-Aroylfurans

No	R_1	R_2 and R_3		M.p.	Yield %	Calculated C	Calculated H	Calculated Molecular ion	Found C	Found H	Found Molecular ion
A	C_6H_5	CO_2CH_3	CO_2CH_3	134-136°	43	74.68	4.72	466.1416	74.55	4.59	466.1415
B	C_6H_5	CO_2CH_3	C_6H_5	178-180°	59	81.79	4.99	484.1675	81.84	4.89	484.1678
C	C_6H_5	CO_2CH_3	H	176-178°	78†	79.39	4.90	408.1361	78.99	4.82	408.1363
D	C_6H_5	C_6H_5	H	163-165°	56	87.32	5.16	426.1620	87.06	5.41	426.1624
E	C_6H_5	C_6H_5	C_6H_5	195-196°	29*	88.41	5.21	502.1933	88.31	5.18	502.1935
F	C_6H_4-*p*-CH_3	C_6H_5	C_6H_5	186-187°	12*	88.34	5.46	516.2089	88.50	5.39	516.2089
G	C_6H_5			83-85°	30	87.00	5.00	400.1463	86.51	5.12	400.1470
H	C_6H_5			118-120°	60†	82.50	4.17	480.1362	82.20	4.37	480.1358

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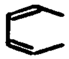
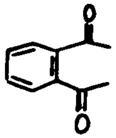
*Prepared by reaction of aziridines and DPP.
†Reaction run in benzene solution under acid catalysis.

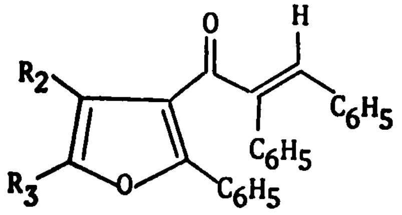
TABLE XXVIII

Spectroscopic Data on 3-Aroylfurans

No	R_1	R_2 and R_3		Infrared $cm^{-1}(CHCl_3)$	Proton Magnetic Resonance δ_{TMS} $(CDCl_3)$*		
					Aryl protons and ring proton	Vinyl proton	Tolyl CH_3 and ester
A	C_6H_5	CO_2CH_3	CO_2CH_3	1744-1710 (C=0)	7.18-7.78(15H)M	7.86(1H)S	3.56(3H)S ester $C\underline{H_3}$ 3.61(3H)S ester $C\underline{H_3}$
B	C_6H_5	CO_2CH_3	C_6H_5	1730 (C=0) 1690 (C=0)	7.0-7.90(20H)M	8.15(1H)S	3.47(3H)S ester $C\underline{H_3}$
C	C_6H_5	CO_2CH_3	H	1728 (C=0) 1706 (C=0)	7.12-7.66(16H)M	7.93(1H)S	3.54(3H)S ester $C\underline{H_3}$
D	C_6H_5	C_6H_5	H	1698 (C=0)	6.93-7.82(20H)M 6.80(1H)S	8.17(1H)S	-
E	C_6H_5	C_6H_5	C_6H_5	1695 (C=0)	6.80-8.00(25H)M	7.99(1H)S	-
F	C_6H_4-p-CH_3	C_6H_5	C_6H_5	1693 (C=0)	6.80-7.80(24H)M	8.05(1H)S	2.35(3H)S tolyl $C\underline{H_3}$
G	C_6H_5			1705 (C=0)	7.00-7.75(19H)M	7.84(1H)S	-
H	C_6H_5			1707 (C=0) 1670 (C=0)	7.00-8.25(19H)M	8.00(1H)S	-

*s = singlet; d = doublet; q = quartet; t = triplet.

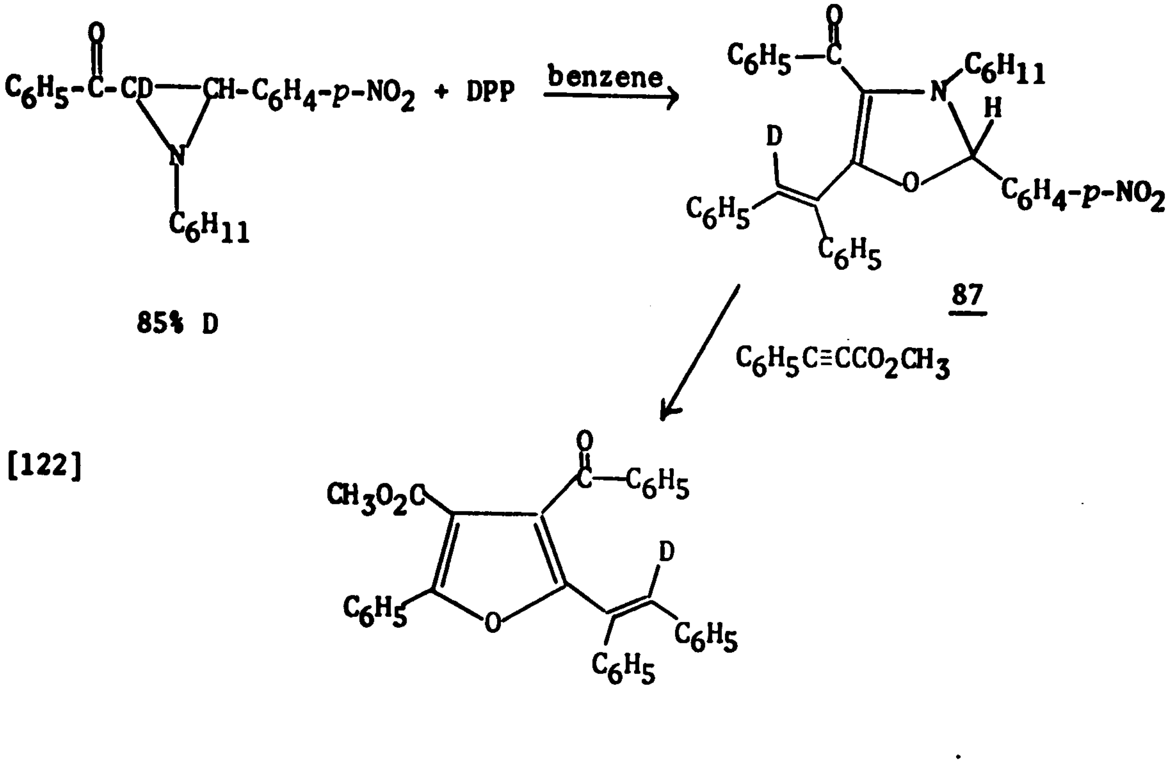
These reactions proceeded smoothly and in fair to good yields to give the furans, the structure assignment of which rests on spectral evidence and on the structure of the 4-oxazoline precursors. The mass spectra of several of the furans were characterized by the loss of the aroyl ion from the molecular ion. This taken together with the carbonyl stretching frequencies in the infrared spectra would tend to eliminate an alternative structure 126.



126

The assignment of these groups is therefore the same as in the parent 4-oxazolines, and this finding was observed to apply to all the [2+3] cycloaddition products reported in this chapter.

It was also shown, that the original 3 proton of the aroylaziridine ring,which was found in Chapter III to become the vinyl proton of the 4-oxazoline,is also the vinyl proton of the 2-substituent on the furan ring as shown in equation [122].



85% D

87

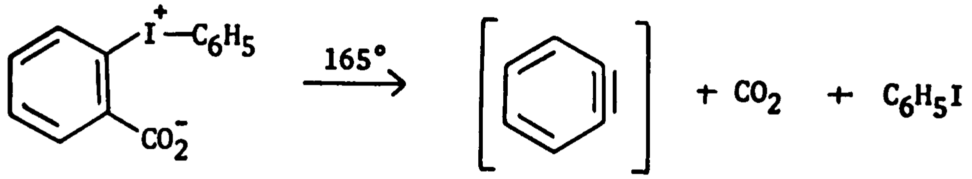
[122]

127 57%D

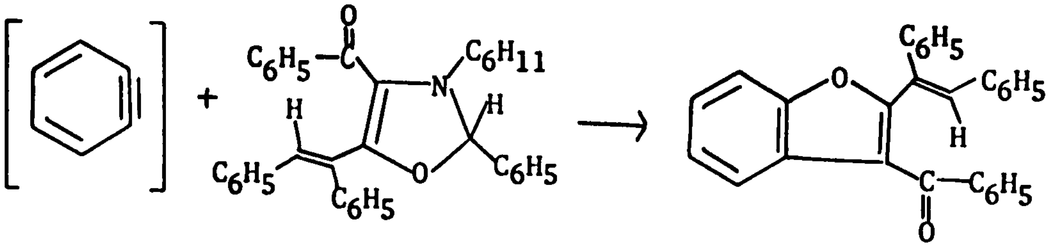
The loss of deuterium label can be attributed to leakage from the intermediate azomethine ylide in the first stage of the reaction.

In the case of products 125B, C, and D, where the original dipolarophilic species was unsymmetrical, it was not possible to assign a particular orientation with confidence, and the numbering of the ring substituents in the experimental section must be regarded as tentative. No mixtures were ever obtained from these reactions.

Of particular interest was the very rapid reaction (20 min) of the 4-oxazoline (70A) with benzyne, which was generated *in situ* from diphenyliodonium carboxylate[223] as shown in equation [123].

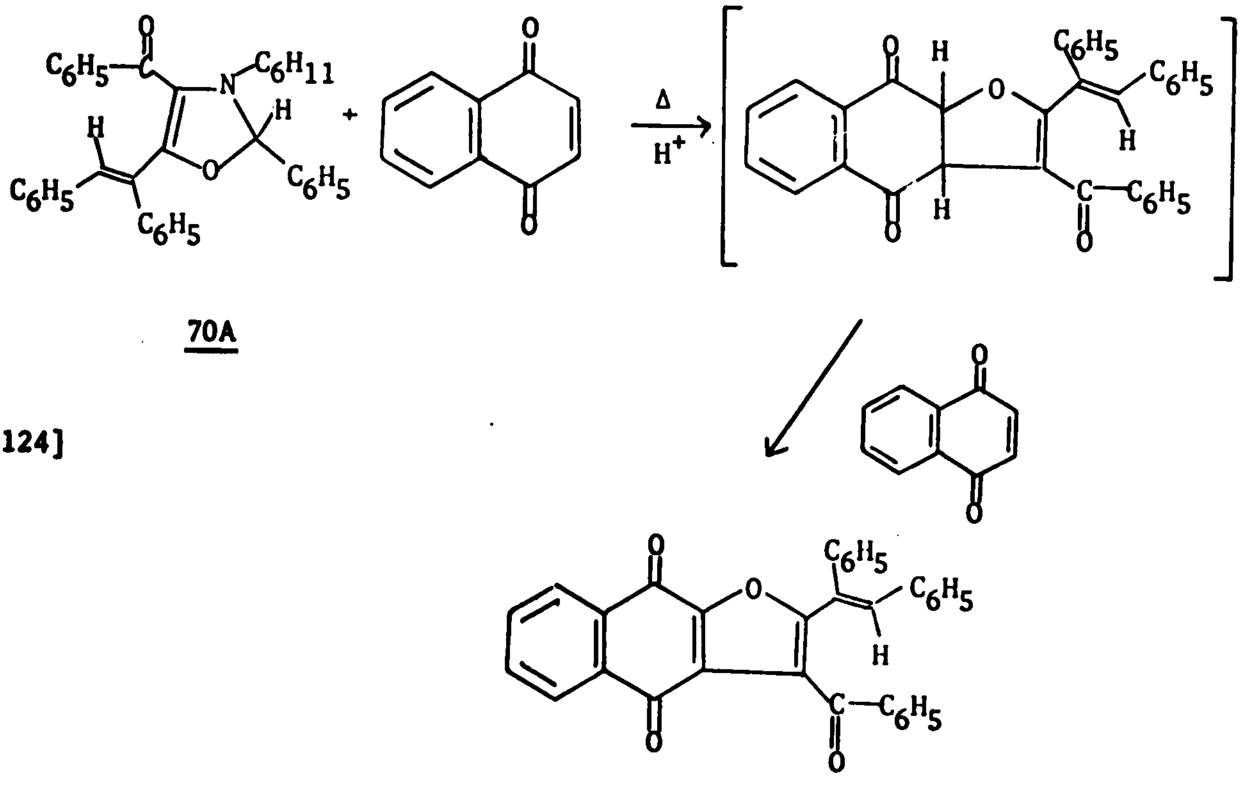


[123]



70A 125G

Furan 125H was obtained by the reaction of the 4-oxazoline 70A with 1,4-naphthoquinone and the initial dihydrofuran produced by the [2+3] cycloaddition was probably dehydrogenated *in situ* by unreacted quinone as shown in equation [124].



70A

[124]

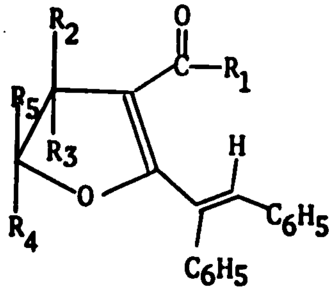
125H 60%

It was found that the addition of a catalytic quantity of 4-toluenesulfonic acid to the reaction mixture had an accelerating effect on the rate of reaction, and as mentioned in Chapter III probably assists in the removal of the anil moiety. No reduction in product yield was found to accompany this process. This finding was observed to have wider implications as will be described later.

As a logical extension of the reactions of 4-oxazolines with acetylenic dipolarophiles, attention was turned to their olefinic counterparts which Huisgen has shown to be no less reactive in [2+3] cycloaddition reactions.[62,79] By employing the more numerous olefinic dipolarophiles the scope of the reaction would be greatly expanded, and furthermore there existed the possibility of obtaining information on the orientation of the addition and on the reaction stereospecificity. Also a literature survey revealed just how little work had been done on the chemistry of dihydrofurans of any complexity, and they did not appear to be readily attainable by standard synthetic procedures.[224]

It was found that many olefinic dipolarophiles reacted smoothly with the 4-oxazolines to produce dihydrofurans, the yields of which were related to the reactivity of the dipolarophilic species. A slight excess of the olefin was generally employed and the reactions were conducted in either a) toluene or xylene under reflux, or b) in benzene solution with acid catalysis. The progress of the reaction could be followed by t.l.c. or visually, as the formation of the product was accompanied by a gradual change in the colour of the solution from deep red to pale yellow. Furthermore, when *cis* and *trans* olefinic dipolarophiles were employed, complete stereospecificity was observed in the product dihydrofurans with the exception of two readily explainable cases where stereoselective reactions occurred.

The dihydrofurans thus prepared and their analytical and spectral data are listed in Tables XXIX and XXX in which the numbering of the substituents refers to the general structure 128.



128

TABLE XXIX

3-Acyl and 3-Aroyl-4,5-dihydrofurans

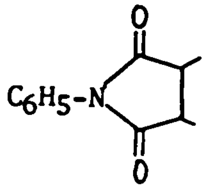
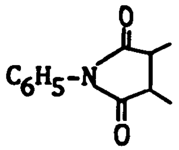
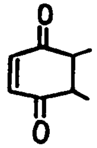
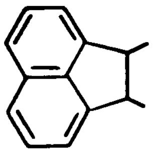
No	R_1	R_2	R_3	R_4	R_5	M.p.	Yield %	Calculated				Found			
								%			Molecular ion	%			Molecular ion
								C	H	N		C	H	N	
A	C_6H_5	H	CO_2CH_3	H	CO_2CH_3	188-190°	73	74.36	5.13	-	468.1572	74.24	5.16	-	468.1570
B	C_6H_5	H	CO_2CH_3	CO_2CH_3	H	159-177°	66	74.36	5.13	-	468.1572	74.32	5.13	-	468.1570
C	C_6H_5	H	$CO_2C_2H_5$	H	$CO_2C_2H_5$	114-115°	39	75.00	5.65	-	496.1886	74.86	5.68	-	496.1822
D	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	H	141-142°	60	75.00	5.65	-	496.1886	74.70	5.70	-	496.1883
E	CH_3	H	CO_2CH_3	H	CO_2CH_3	144-145°	25	70.92	5.46	-	406.1416	70.80	5.38	-	406.1416
F	C_6H_5	H	$CO_2C_2H_5$	H	CO_2CH_3	163-164°	46	74.69	5.39	-	482.1729	74.47	5.41	-	482.1724
G	C_6H_5	H	CN	H	H	184-186°	28	82.76	5.04	3.71	377.1416	82.61	5.05	4.00	377.1417
H	C_6H_5	H	COC_6H_5	H	COC_6H_5	125-128°	16	83.57	5.00	-	324.1150* 236.0837	83.46	5.05	-	324.1151 236.0839
J	C_6H_5	H	COC_6H_5	COC_6H_5	H	189-191°	31	83.57	5.00	-	324.1150* 236.0837	83.78	5.16	-	324.1154 236.0839
K	C_6H_5	H	CO_2CH_3	H	H	150-152°	59	78.98	5.37	-	410.1518	78.63	5.39	-	410.1528
L	C_6H_5	H	C_6H_5	H	NO_2	197-199°	10	78.65	4.86	2.96	473.1698	78.42	4.69	3.07	473.1698
M	C_6H_5	H			H	222-224°	66	79.64	4.85	2.81	497.1627	79.29	4.60	3.02	497.1621

TABLE XXIX

3-Acyl and 3-Aroyl-4,5-dihydrofurans

No	R_1	R_2	R_3	R_4	R_5	M.p.	Yield %	Calculated % C	Calculated % H	Calculated % N	Calculated Molecular ion	Found % C	Found % H	Found % N	Found Molecular ion
N	C_6H_5-*p*-CH_3	H			H	155-158°	65	79.84	4.89	2.74	511.1784	79.63	4.93	2.60	511.1783
P	C_6H_5	H			H	190-193°	10	80.56	4.63	-	432.1367	80.72	4.72	-	432.1362
Q	C_6H_5	H			H	210-212°	75	88.24	5.04	-	476.1775	88.20	5.17	-	476.1776

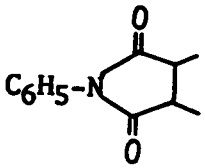
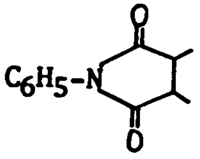
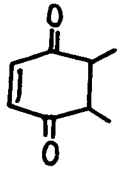
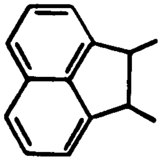
[*] Principal fragments measured; molecular ion too small to measure.

TABLE XXX

Spectroscopic Data on 3-Aroyl-4,5-dihydrofurans

No	R_1	R_2	R_3	R_4	R_5	$>$=O Infrared cm^{-1} ($CHCl_3$)	Proton Magnetic Resonance δ_{TMS} ($CDCl_3$)* Aryl + vinyl protons	Ring protons		4,5 Substituents + acetyl CH_3
A	C_6H_5	H	CO_2CH_3	H	CO_2CH_3	1736 1701	7.18-7.90(16H)M	4.07 4.25	J=3.7Hz	3.02(3H)S 3.64(3H)S
B	C_6H_5	H	CO_2CH_3	CO_2CH_3	H	1742 1699	7.17-7.83(16H)M	3.69 4.10	J=11.5Hz	3.57(6H)S
C	C_6H_5	H	$CO_2C_2H_5$	H	$CO_2C_2H_5$	1735 1699	7.18-7.94(16H)M	3.97 4.12	J=3.7Hz	0.64(3H)t, 3.48(2H)q 1.09(3H)t, 4.07(2H)q
D	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	H	1735 1698	7.12-7.97(16H)M	3.74 4.14	J=11.5Hz	1.06-1.30(6H)t 3.90-4.24(4H)q
E	CH_3	H	CO_2CH_3	H	CO_2CH_3	1730 1695	7.26-7.82(11H)M	3.72 4.21	J=3.8Hz	1.60(3H)S 3.64(3H)S, 3.72(3H)S
F	C_6H_5	H	$CO_2C_2H_5$	H	CO_2CH_3	1732 1701	7.20-7.93(16H)M	4.03 4.22	J=3.5Hz	0.75(3H)t, 3.52(2H)q 3.71(3H)S
G	C_6H_5	H	CN	H	H	1704	7.23-7.80(16H)M	3.68 3.10 2.89	J_{AB}=9.0Hz J_{BC}=12.5Hz J_{AC}=4.5Hz	-
H	C_6H_5	H	COC_6H_5	H	COC_6H_5	1705 1676	6.92-7.84(26H)M	4.89 5.42	J=4.75Hz	-
J	C_6H_5	H	COC_6H_5	COC_6H_5	H	1706 1685	6.90-7.88(26H)M	4.87 5.23	J=7.1Hz	-

TABLE XXX - continued

No	R_1	R_2	R_3	R_4	R_5	$>$=O Infrared cm^{-1} (CHCl$_3$)	Proton Magnetic Resonance δ_{TMS} (CDCl$_3$)*		
							Aryl + vinyl protons	Ring protons	4,5 Substituents + acetyl CH$_3$
K	C_6H_5	H	CO_2CH_3	H	H	1732 1698	7.20-7.88(16H)M	3.60 J_{AB}=9.4Hz 2.96 J_{BC}=14.9Hz 2.73 J_{AC}=4.1Hz	3.02(3H)s
L	C_6H_5	H	C_6H_5	H	NO_2	1701	6.86-7.95(21H)M	4.53 5.48 J=5.2Hz	-
M	C_6H_5	H			H	1780 1725-1695	6.80-8.10(21H)M	4.05 4.16 J=9.2Hz	-
N	C_6H_4-*p*-CH_3	H			H	1780 1725 1705	6.81-8.00(20H)M	4.05 4.09 J=9.25Hz	2.38(3H)s
P	C_6H_5	H			H	1705 1665 1643	6.40-7.90(18H)M	3.75-4.08(2H)	-
Q	C_6H_5	H			H	1695	6.91-7.89(21H)M 8.00(1H)s	4.58 4.68 J=6.4Hz	-

*s = singlet; d = doublet; t = triplet; q = quartet.

Table XXIX shows the scope of the reaction and illustrates how the yields of products vary with dipolarophilic reactivity. It is interesting to note that with the exception of acenaphthalene the trend as expressed by these results closely parallels that obtained by Huisgen in his study of the reactions of dipolarophiles with diphenylnitrile imine (Table VII).[83]

A variety of other olefins were screened in reactions with the 4-oxazolines but failed to produce dihydrofurans for a variety of reasons, some of which are offered below. One difficulty arose from the temperature required to initiate the cycloaddition reaction in solvents like toluene (b.p. 113°) and xylene (135-140°), for it had been found that at lesser temperatures the reaction did not occur. Highly active dipolarophiles such as acrolein were found to polymerize under such conditions before addition to the reactive intermediate from the 4-oxazoline could take place. When the temperature of the reaction was lowered to 78° (benzene), acid catalysis was necessary to effect cycloaddition, but under such conditions another potentially active dipolarophile, acrylamide, failed to react. Other species (*trans*-stilbene) were too sluggish for any cycloaddition to proceed. Several substituted quinones (*o*-chloranil, *p*-chloranil, 2,3-dichloro-5,6-dicyanobenzoquinone) were screened but failed to react due probably to the steric requirements of the reaction.

As with the furans of Table XXVII, the reaction of olefins and 4-oxazolines proceeded in one direction only and no mixtures of structural isomers were ever obtained. However in this case it was possible to determine the orientation of addition to many unsymmetrical olefinic dipolarophiles from p.m.r. line positions as will be described later.

The assignment of the geometry of the 4 and 5 protons of the dihydrofuran ring was based on the work of Heine, Peavy, and Durbetaki.[102]

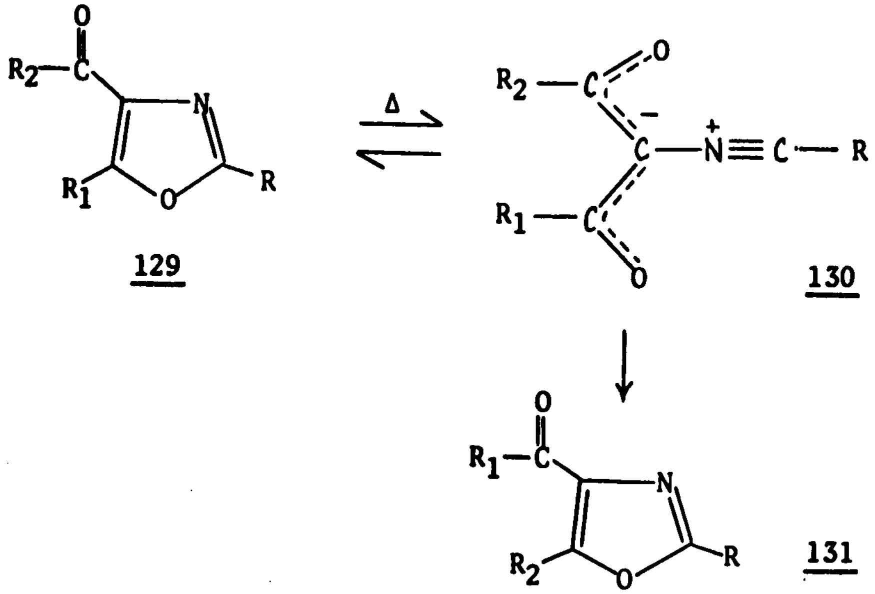
These dihydrofurans prepared by [2+3] cycloaddition reactions gave red melts when heated to >185° and were found to themselves undergo [2+3] cycloaddition reactions with suitable dipolarophiles (*vide infra*).

It also appears that the presence of a carbonyl group at the 4-position of the oxazoline ring is necessary for successful [2+3] cycloaddition reaction to occur, for when this group was reduced to a hydroxyl function no such reaction took place with N-phenylmaleimide.

Mechanism of Formation of 3-Aroylfurans and 3-Aroyl-4,5-dihydrofurans

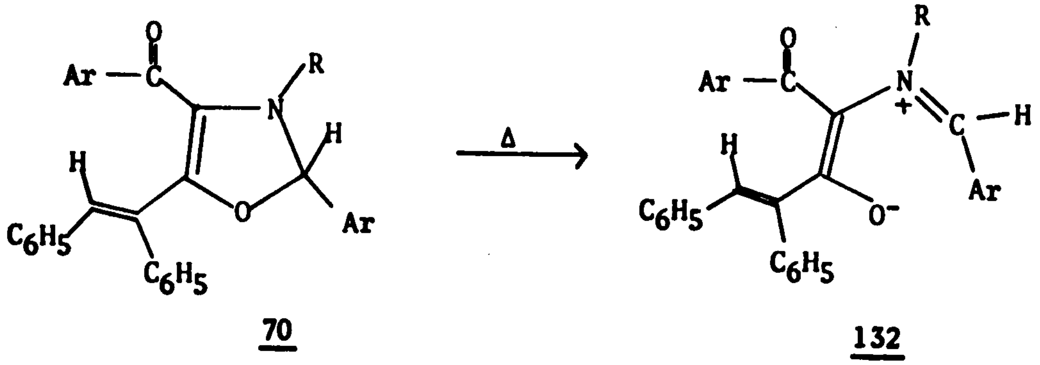
It has been shown by Cornforth[12] that 4-aroyloxazoles can undergo thermal isomerization, and this rearrangement was interpreted by Dewar[225] in terms of an "open-chain zwitterionic" species (a nitrogen ylide) as shown in Scheme XIII.

SCHEME XIII



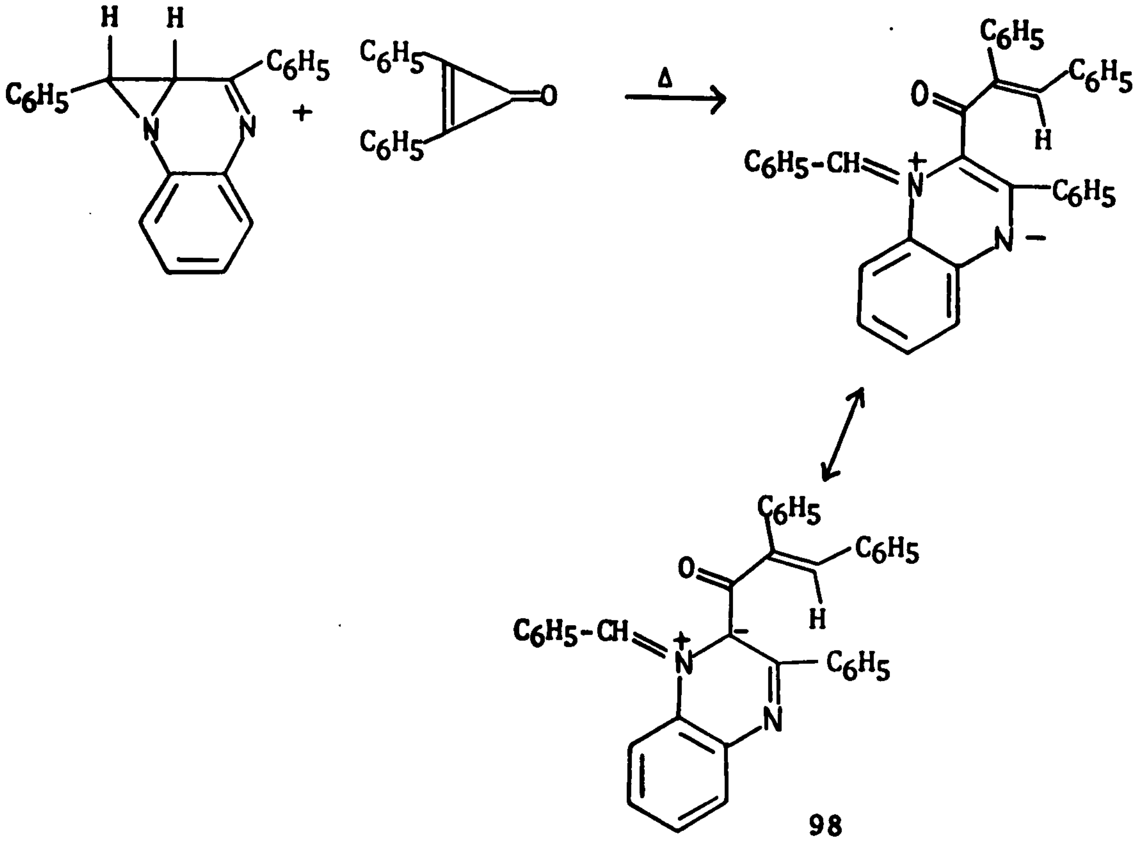
The 4-aroyl-4-oxazolines described in this work bear a close structural resemblance to Cornforth's 4-aroyloxazoles, and by analogy could conceivably cleave along the O-C_2 bond upon heating to produce another open chain zwitterionic species as shown in equation [125].

[125]



This ring opening to an ylide structure,and the red colour associated with the thermal process has received support from the isolation of a stable red crystalline 4-oxazoline in the open chain form from a reaction in the quinoxaline series as shown in equation [126].[182]

[126]

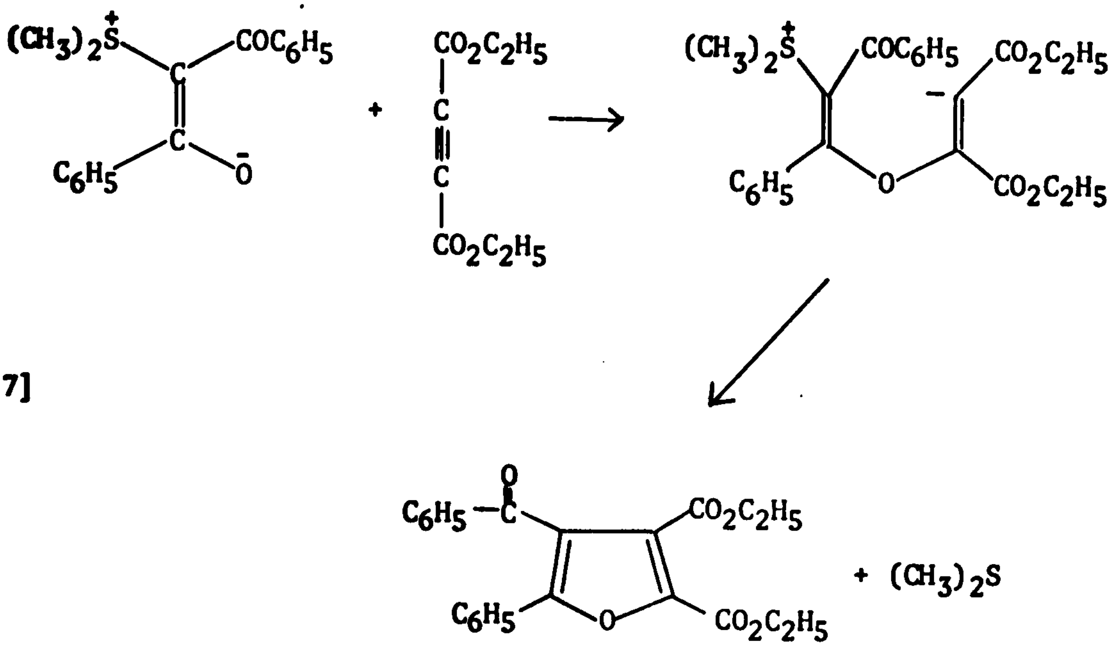


H
H
C_6H_5
C_6H_5
N
N
+
C_6H_5
C_6H_5
O
Δ
C_6H_5
C_6H_5
O
H
C_6H_5-CH
+
N
C_6H_5
N
−
C_6H_5
C_6H_5
O
H
C_6H_5-CH
+
N
−
C_6H_5
N

98

A direct analogy for the synthesis of furans by reaction of 4-aroyl-4-oxazolines with diphenylacetylene[182] has recently been provided by Takaku, Hayasi, and Nozaki[226] in the reaction of dimethylsulfonium dibenzoyl methylide with diethyl acetylenedicarboxylate as shown in equation [127].

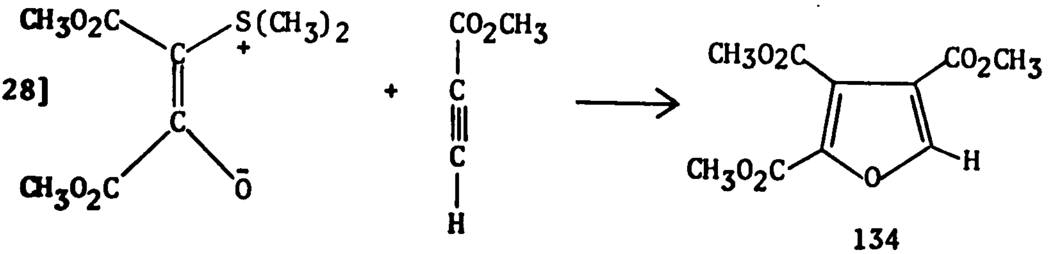
[127]



133

Another furan synthesis from an ylide intermediate analogous to that of the Japanese workers is shown in equation [128].[227]

[128]

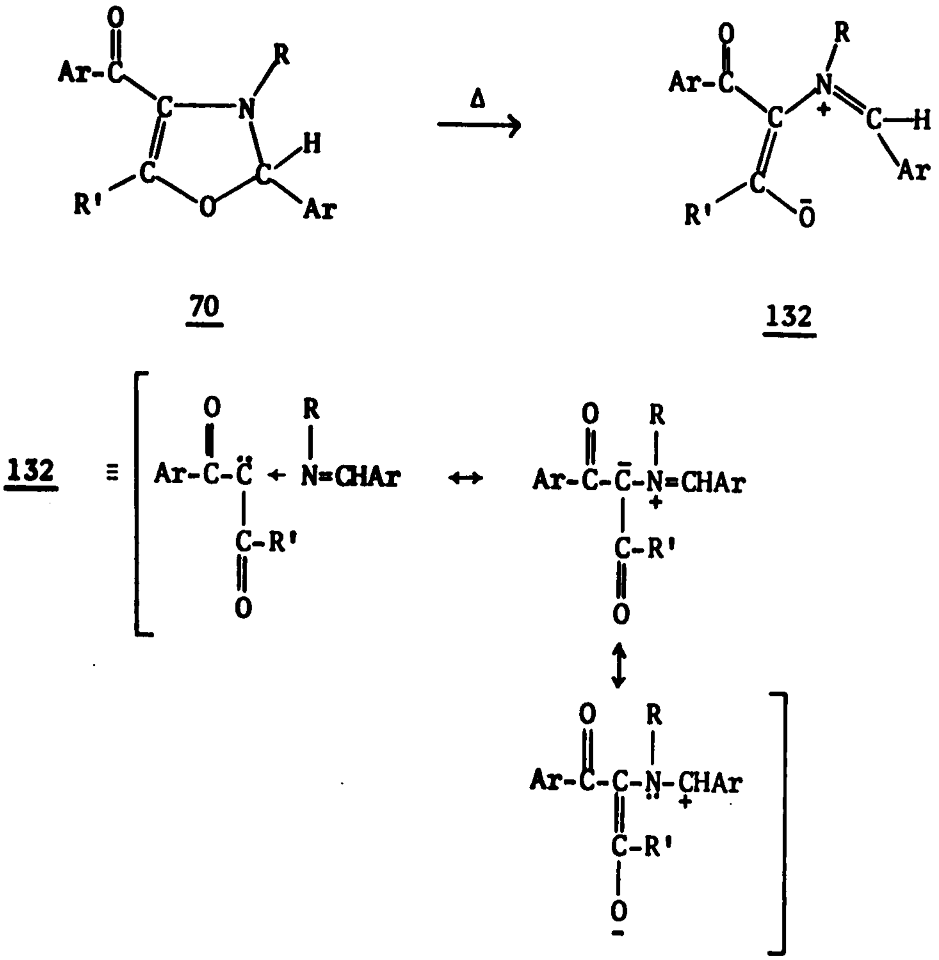


134

A survey of the literature has revealed that information on the properties of diarylammonium ylides and other similar ylide structures is virtually nonexistent, and is probably due to the very poor nucleophilicity of the species.[186,201,226] However the ylide structure 132 obtained from the postulated thermally induced ring cleavage of the 4-oxazoline 70 was of special interest since such species could conceivably react as a) C-nucleophiles, b) O-nucleophiles, or c)

1,3-dipoles with external octet stabilization provided by the anil moiety as shown in Scheme XIV.

SCHEME XIV



Examination of Scheme XIV shows that if the 1,3-dipolar interpretation were correct, then the open-chain forms of the 4-aroyl-4-oxazolines such as 132 could be regarded as masked ketocarbenes, and would be expected to undergo concerted [2+3] cycloaddition reactions with suitably reactive dipolarophiles followed by expulsion of the anil moiety.

It is noteworthy that this mechanism would only satisfy a

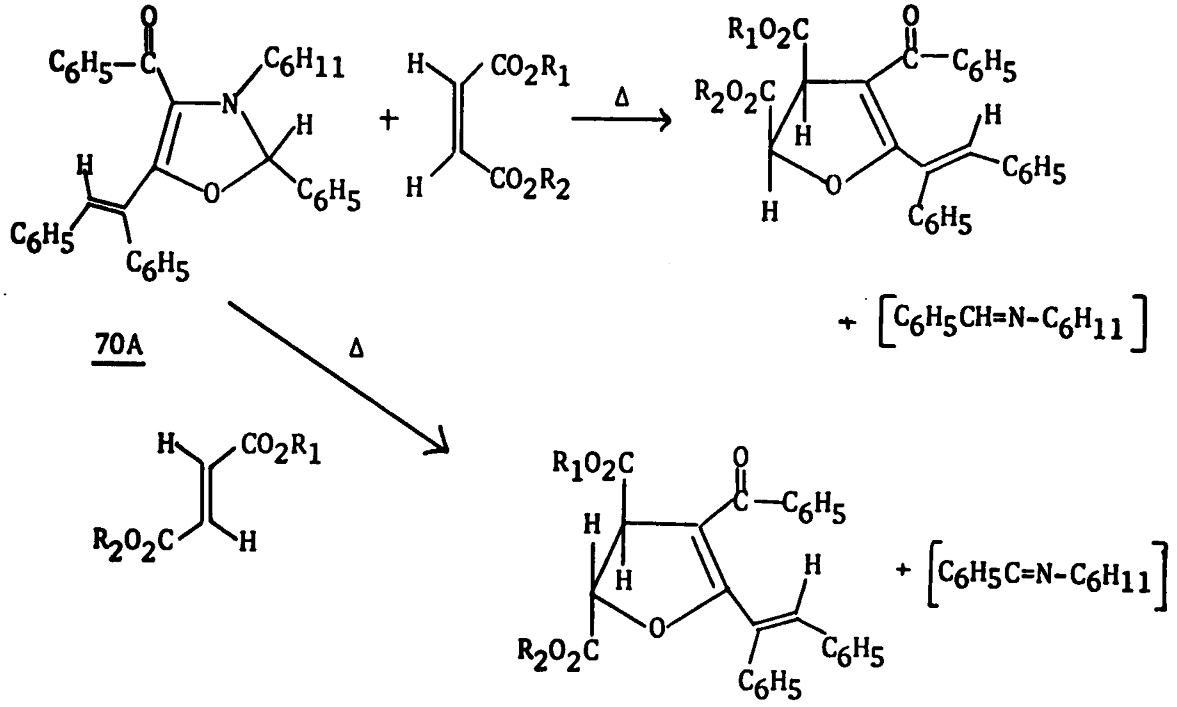
4-isoxazoline structure if an initial rearrangement to the 4-oxazoline was first postulated, and this is unlikely in view of Baldwin's results, and the fact that the compounds called 4-oxazolines in this work were formed under equilibrium conditions.

The observed formation of furans by the reaction of 4-oxazolines and acetylenes fails to distinguish between the mode of reaction of the postulated open-chain species 132 as an O-nucleophile or a 1,3-dipole. Since *cis*-stereospecificity is regarded as one of the main criteria of concerted cycloaddition reactions,[79,81] the reaction of 4-oxazolines with isomeric olefinic dipolarophiles was regarded as a suitable means of distinction between the two modes of reaction.

[2+3] Cycloaddition reactions of 4-Aroyl-4-oxazolines to olefinic dipolarophiles

4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline 70A reacted smoothly with one equivalent of diethyl maleate in toluene under reflux for twenty-four hours, to produce after isolation, a 51% yield of exclusively 3-benzoyl-4,5-dicarboethoxy-2-(*cis*-1,2-diphenylvinyl)-*cis*-4,5-dihydrofuran 128D. The *cis* configuration was assigned because of the observed AB quartet (J = 11.5 Hz) in the p.m.r. spectrum.[102] A parallel reaction with diethyl fumarate gave exclusively the *trans*-4,5-dihydrofuran in 39% yield, and similar stereospecific addition of the 4-oxazoline 70A to dimethyl maleate and dimethyl fumarate was observed as shown in Tables XXIX and XXX and are summarized in Scheme XV. In none of these four cases was the extruded anil moiety isolated.

SCHEME XV



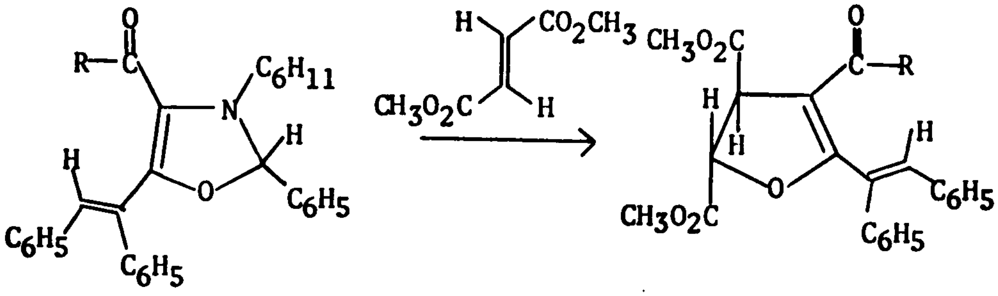
128A $R_1 = R_2 = CH_3$ 128C $R_1 = R_2 = C_2H_5$
128B $R_1 = R_2 = CH_3$ 128D $R_1 = R_2 = C_2H_5$

The reaction with dimethyl maleate in fact produced a 78:22 mixture of *cis* and *trans*-dihydrofurans and seemed to indicate a stereoselective rather than a stereospecific reaction. However in a control reaction, dimethyl maleate under the above reaction conditions was partially isomerized to dimethyl fumarate, the net result being a 84:16 mixture of *cis* and *trans* isomers, which was to a good approximation the extent of isomerization observed in the reaction with the 4-oxazoline. This finding had been previously observed by Huisgen and coworkers[68] in reactions of dimethyl maleate and ketocarbenes, though in their work complete isomerization of the dipolarophile occurred prior to addition.

A similar situation occurred in the reaction of the 4-oxazoline 70A with *trans*-1,2-dibenzoylethylene where an isomeric mixture of dihydrofurans was obtained (128H and 128J). However Kuwajima and Mukaiyama[288] had demonstrated the susceptibility of 1,2-dibenzoylethylene to base addition, and a separate control reaction with cyclohexylamine confirmed this finding.

The generality of the observed stereospecificity in these reactions is illustrated by the reactions of 4-acetyl and 4-aroyl-4-oxazolines with dimethyl fumarate in which the product dihydrofurans (128A and 128E) possessed exclusively the *trans* configuration as shown in equation [129].

[129]



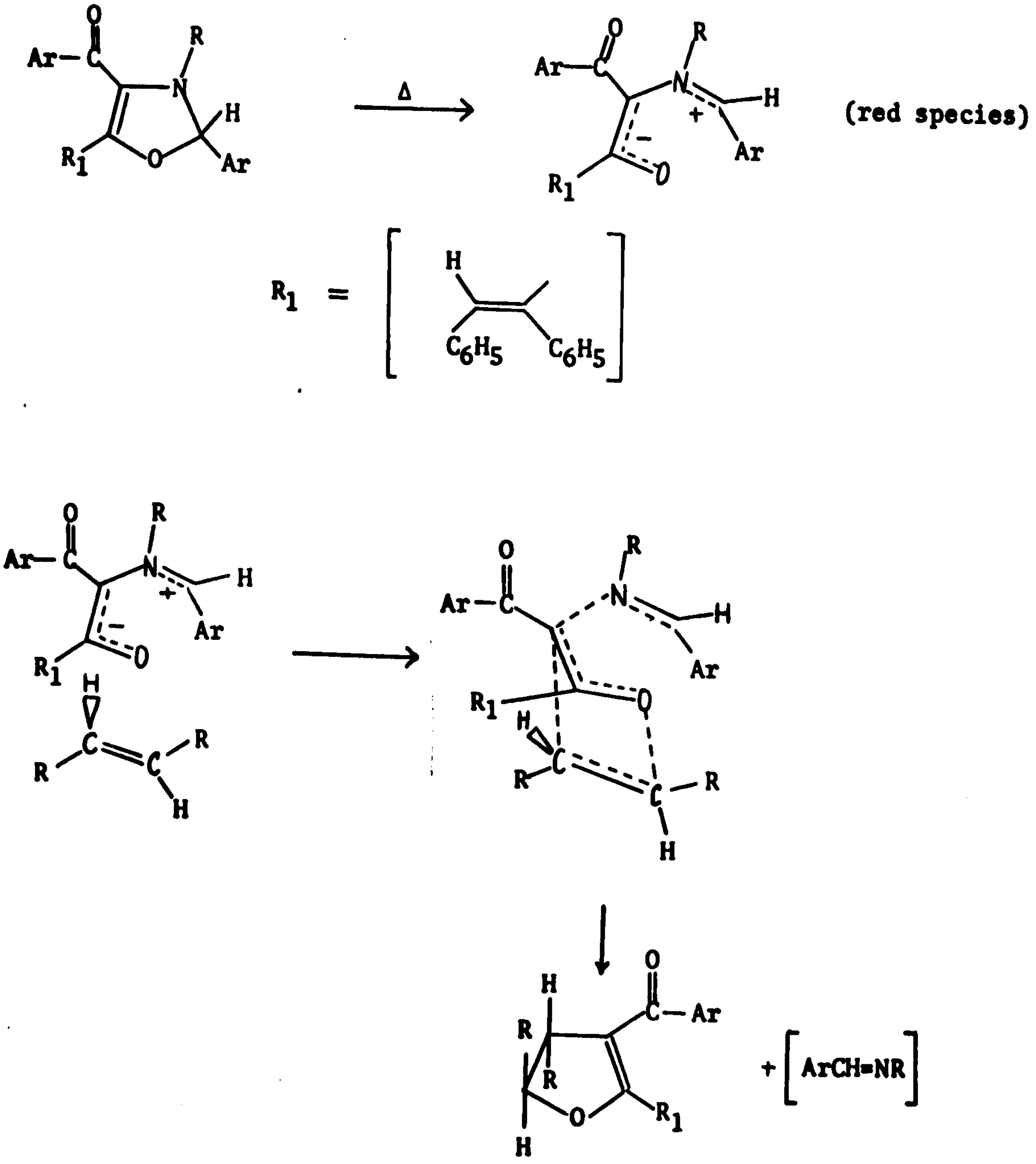
R = C_6H_5 70A
= CH_3 70G

R = C_6H_5 128A
= CH_3 128E

With N-phenylmaleimide and the other cyclic dipolarophiles, the product dihydrofurans all possessed the expected *cis* configuration at the 4- and 5-positions.

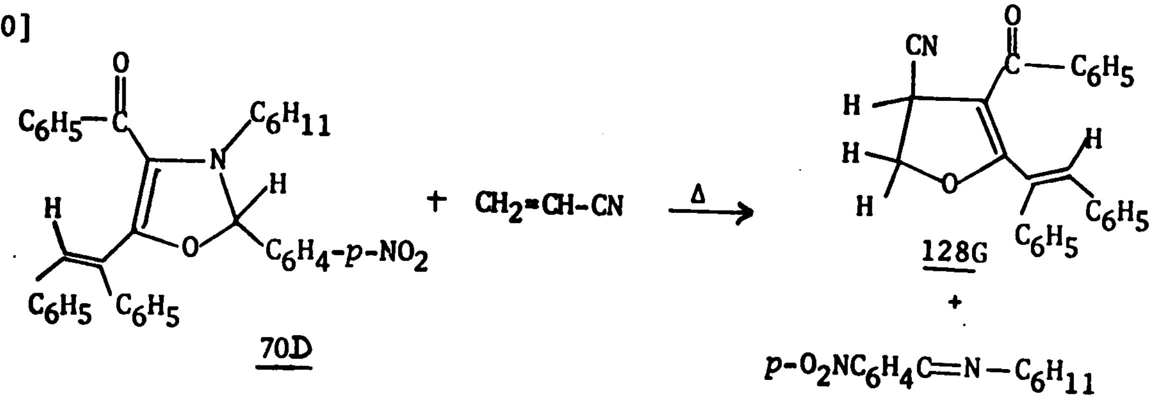
It was concluded from the experimental evidence presented above that 4-aroyl-4-oxazolines cleave thermally to produce dipolar species which do not behave as oxygen nucleophiles. The observed stereospecificity of the reaction with olefinic dipolarophiles demands that the dipolar species behave as externally stabilized ketocarbenes and consequently undergo concerted and stereospecific [2+3] cycloadditions to olefinic species as shown in Scheme XVI. These conclusions present a good case against the 4-isoxazoline structure for the products from the reactions of aziridines and diphenylcyclopropenone.

SCHEME XVI


Ar
R
H
R_1
O
Δ
(red species)
R_1 =
C_6H_5
C_6H_5
+
ArCH=NR

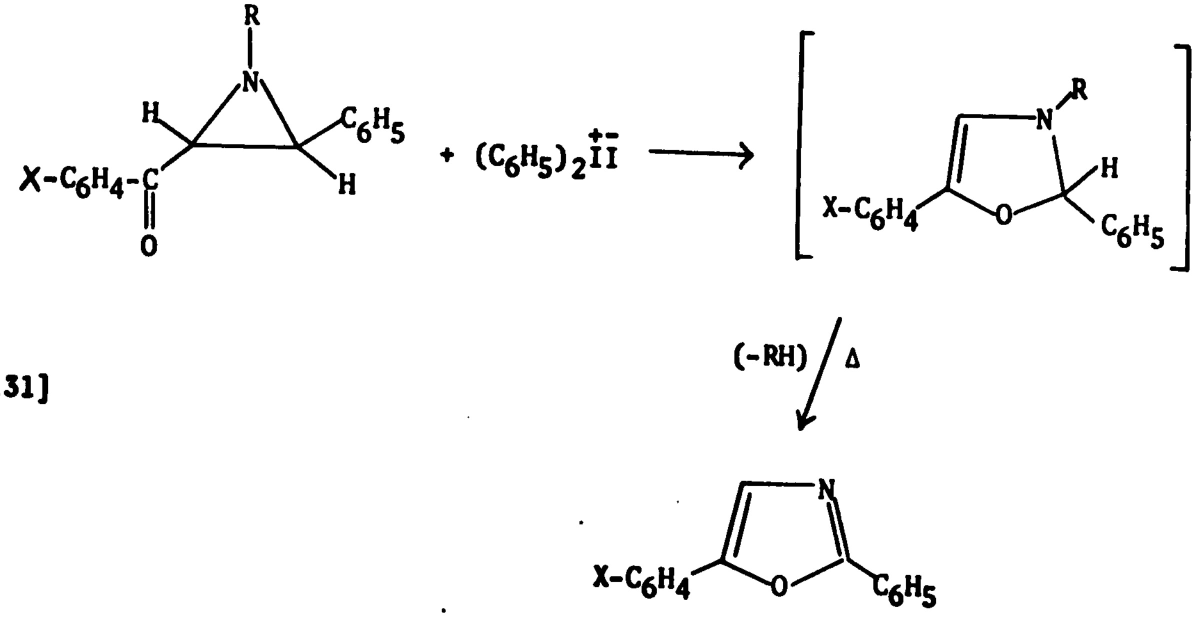
In only one case, that of vinyl cyanide, was the anil isolated intact and this was no doubt due to the stabilizing influence of the 4-nitro group, equation [130].

[130]



Alternative Mechanism for the Reactions of 4-Aroyl-4-oxazolines with Olefins and Acetylenes

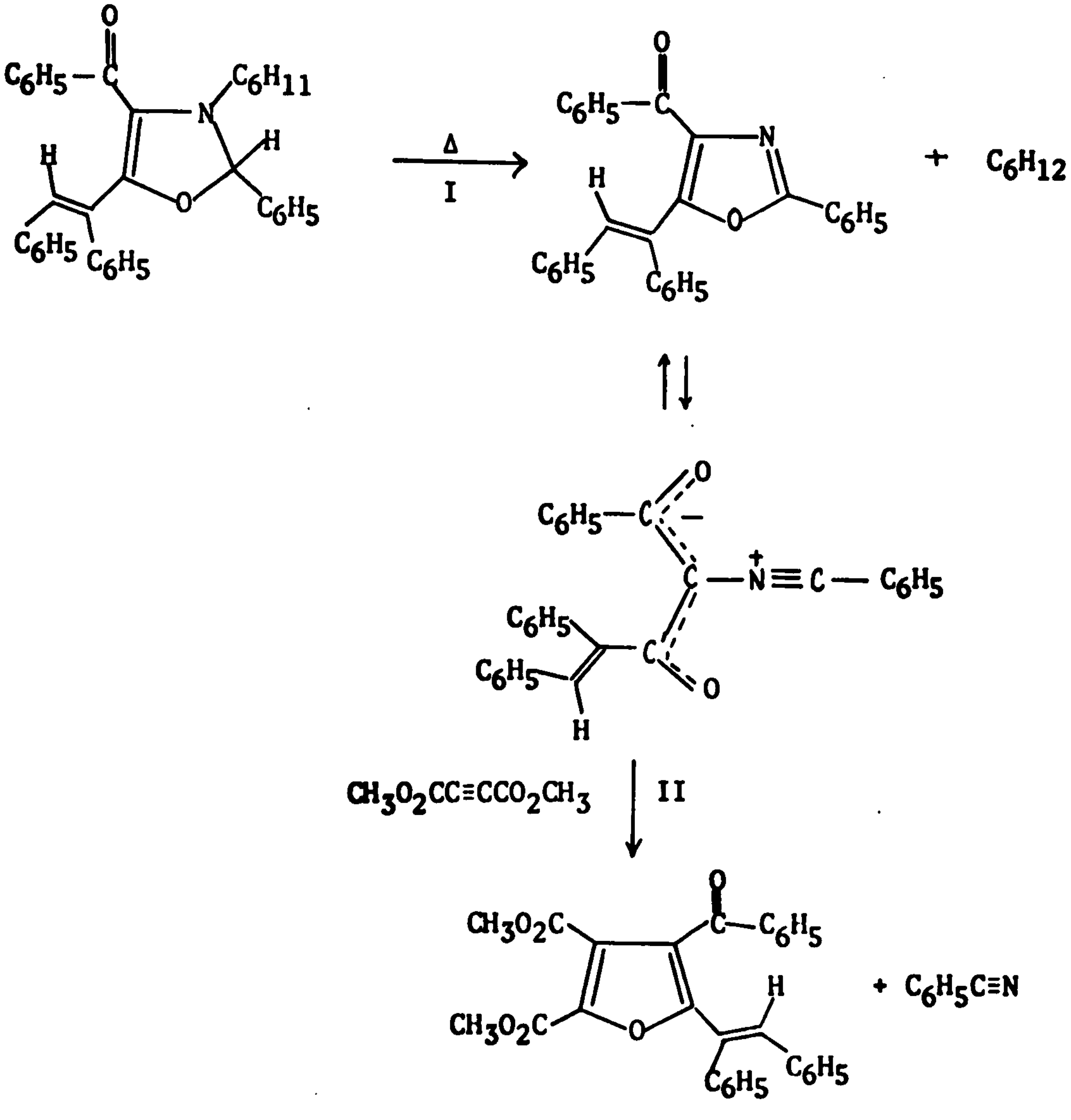
In 1967, Padwa and Hamilton postulated a 4-oxazoline intermediate in the diphenyliodonium iodide catalyzed rearrangement of 3-aroylaziridines leading to oxazoles.[187] This was discussed in Chapters I and III and is briefly outlined in equation [131].



[131]

It was therefore conceivable that in thermally induced reactions with, for example, dimethyl acetylenedicarboxylate, the 4-oxazolines could decompose to 4-aroyloxazoles prior to cycloaddition. In keeping with the Dewar explanation for the oxazole isomerization discovered by Cornforth,[12,225] these 4-aroyloxazoles could then cleave to produce analogous zwitterionic intermediates which could react with the acetylenic dipolarophile to produce furans as shown in Scheme XVII.

SCHEME XVII


O
C6H5—C
C6H11
N
H
H
O
C6H5
C6H5 C6H5
Δ
I
O
C6H5—C
N
H
O
C6H5
C6H5
C6H5
+ C6H12
O
C6H5—C
+
N≡C— C6H5
C6H5
C6H5
C
O
H
CH3O2CC≡CCO2CH3
II
O
CH3O2C
C—C6H5
H
CH3O2C
O
C6H5
C6H5
+ C6H5C≡N

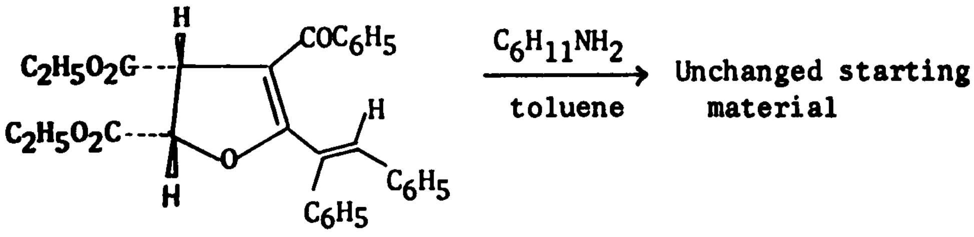
125A

This possible pathway was discarded on the basis that anils or more frequently their hydrolysis products, aromatic aldehydes, were detected in the products. Benzonitrile was never observed as would be required in the above scheme. Furthermore, Smalley[182] had shown that no cyclohexane was produced from a deliberate thermal decomposition of the 4-oxazoline 70A. A more detailed study of the thermal decomposition of this 4-oxazoline is described in Chapter III.

Assignment of the Orientation of the [2+3] Cycloaddition Reactions of 4-Aroyl-4-Oxazolines to Olefinic Dipolarophiles

Control reactions on both the *cis* and *trans*-4,5-dihydrofurans showed that they were stable to epimerization under the conditions of their formation, as shown in equation [132].

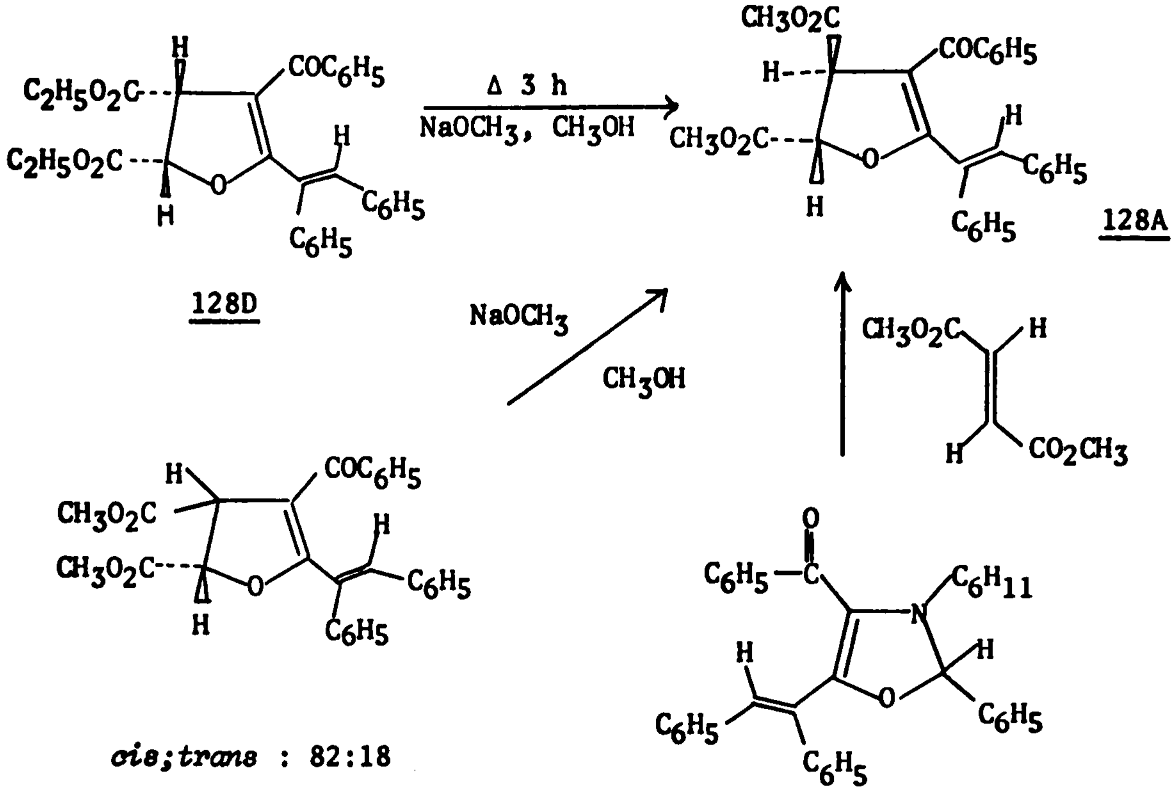
[132]



128D

However with a suitably powerful base, for example sodium methoxide, the *cis*-dihydrofurans were epimerized to their thermodynamically more stable *trans* counterparts. When a 3-fold excess of base was employed, not only epimerization but complete transesterification was observed to produce the identical *trans*-4,5-dihydrofuran 128A that was obtained from the reaction of the 4-oxazoline 70A with dimethyl fumarate as shown in Scheme XVIII.

SCHEME XVIII



Δ 3 h
NaOCH3, CH3OH
NaOCH3
CH3OH

128D

128A

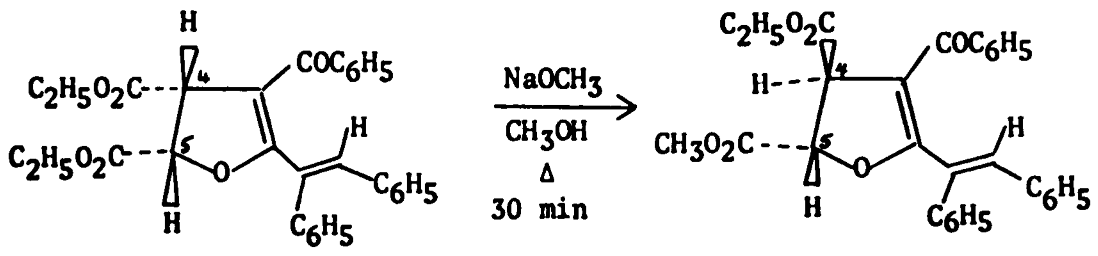
cis;trans : 82:18

128B

70A

However when this reaction was repeated with a catalytic quantity of sodium methoxide in dry methanol the product was the epimerized *trans* mixed methyl ethyl ester 128F, as shown in equation [133].

[133]

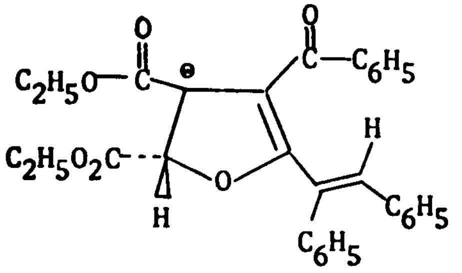


NaOCH3
CH3OH
Δ
30 min
4
5

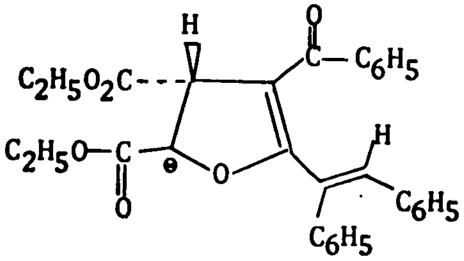
128D

128F

This assignment was based on the following rationalization. It was reasoned that the 4-position of the ring would be a more likely site for epimerization to proceed than the 5-position due to the greater stabilization of the carbanion generated by the removal of the proton by the base.



135 favoured



136 unfavoured

With the epimerization taking place at the 4-position, it seemed likely that the ester exchange would occur at group on the 5-position of the ring to produce the dihydrofuran 128F.

This rationalization was then applied to the p.m.r. spectra of these *trans*-4,5-dicarbomethoxydihydrofurans as shown in Table XXX.

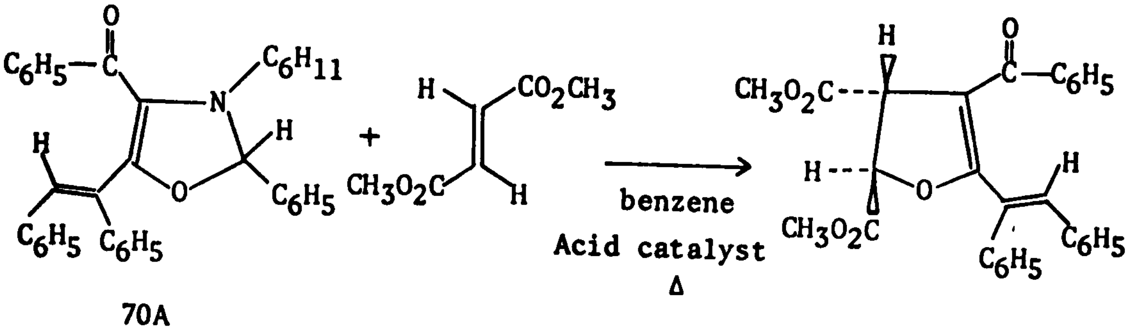
In direct contrast to the cases of the analogous furan 125A (see Table XXVIII), and the *cis*-dihydrofuran 128D (Table XXX), the carbomethoxy groups of the *trans*-4,5-dihydrofuran 128A are well separated in the p.m.r. spectrum due to their differing environments, and are located as singlets at 3.02 and 3.64 δ, respectively. The carbomethoxy group in the *trans* - mixed methyl ethyl ester 128F occurred as a singlet at 3.71, and by the explanation offered above was assigned to the 5-position of the dihydrofuran ring. Thus in the p.m.r. of compound 128A, the singlet at 3.64 was assigned to the carbomethoxy group at the 5-position and the other at 3.02 to the group at the 4-position. This rationalization is confined to cases where the 3-substituent is a benzoyl group, for replacement by an acetyl group renders the line positions too close for an assignment to be made with confidence.

These predictions were then tested in the reaction of the 4-oxazoline 70A and methyl acrylate, which being an unsymmetrical dipolarophile could add in two possible directions only one of which was observed. The product dihydrofuran 128K possessed a three-proton singlet in the p.m.r. spectra at 3.02 and thus the carbomethoxy group was assigned to the 4-position of the dihydrofuran ring.

Effect of Acid Catalysis on the Rates of Formation of Dihydrofurans

It has been previously mentioned that addition of a catalytic quantity of 4-toluenesulfonic acid to the reaction mixture of 4-oxazolines and olefinic and acetylenic species greatly reduced the time required for the preparation of the required cycloadduct. This was convincingly demonstrated by the reduction in time from 24 h to 6 h, for complete addition of diethyl maleate, and from 22 h to 75 min, for the same reaction with diethyl fumarate. Also the reaction of dimethyl fumarate with the 4-oxazoline 70A was reduced in time from 18 h to 45 min, by the catalytic influence of 4-toluenesulfonic acid. Furthermore in all these reactions the reaction temperature was reduced to 78° (benzene), and no loss in stereospecificity nor in yield was observed in the products. This remarkable effect was attributed in Chapter III to the acid assisting in the ring cleavage of the 4-oxazoline and in the separation of the anil moiety. It was not possible to accurately assign the position of protonation on the 4-oxazoline from p.m.r. studies, because addition of sufficient acid to affect the spectrum caused decomposition of the compound. In an attempt to gain further information about this process, the reaction of the 4-oxazoline 70A and dimethyl fumarate in benzene solution at reflux under the catalytic influence (1-6 mgs) of various acidic species was studied as shown in equation [134].

[134]



70A

128A

In each case the *trans*-4,5-dihydrofuran 128A was obtained and the reaction times and product yields are shown in Table XXXI. These values should be viewed in the light of the thermal reaction of these components which required 18 h for complete reaction and produced 128A in 73% yield.

TABLE XXXI

Effect of Acid Catalysis on the Rate of Formation of 4,5-Dihydrofurans

Acid catalyst	Reaction time	Product yield %
CH_3CO_2H	11 h	23.5
H_2SO_4	4 h	53
p-CH_3-$C_6H_4SO_2H$	45 min	69
BF_3	45 min	68
$ZnCl_2$	3½ h	59
$SnCl_4$	50 min	51
$AlCl_3$	2½ h	63
$(C_6H_5)_2\overset{+}{I}\overset{-}{I}$	40 min	62

Table XXXI shows that with the exception of the reaction catalyzed by acetic acid, the *trans*-dihydrofuran 128A was produced in fair to good yields and in markedly reduced reaction times when compared with the thermal reaction. In the cases of the Lewis acids BF_3, $SnCl_4$, and $AlCl_3$, an immediate bright red coloration was imparted to the solution at room temperature, while with $CH_3C_6H_4SO_3H$ and $ZnCl_2$ the change was more gradual. With sulfuric acid and diphenyliodonium iodide on the other hand the red colour did not appear till just prior to the onset of reflux.

These Lewis acids probably assist the 4-oxazoline ring cleavage by coordination with the oxygen atom of the ring and thus weaken the

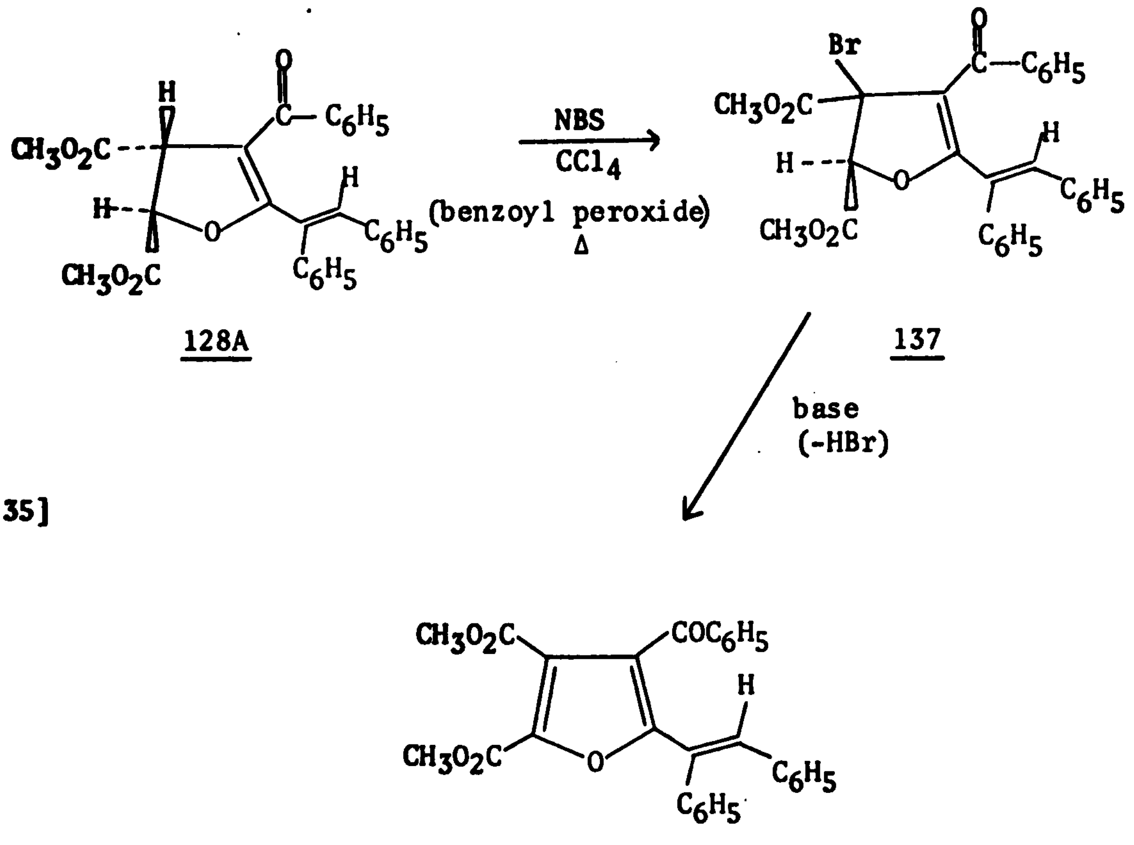
O-C_2 bond, and allow the ring to open under these milder conditions. The alternative mode, coordination at the nitrogen atom, is considered unlikely since this atom is already trisubstituted. Furthermore, as has been shown in Chapter III, the 4-oxazoline 70A was recovered in >80% yield from such acid treatment at room temperature thus eliminating any rearrangement product from contention.

In the synthesis of dihydrofurans under acid catalysis, benzene appeared to be the optimum solvent to employ, for in general no increase in the yield of the product nor decrease in the reaction time appeared to occur when toluene or xylene were substituted as the solvent.

Attempted Reduction of 4,5-Dihydrofurans

In attempts to further establish the dihydrofuran structure and to prepare new furan derivatives, various methods were tried to dehydrogenate the former compounds but without success. Attention was concentrated on the 4,5-dicarbomethoxy and 4,5-dicarboethoxydihydrofurans since the corresponding furans had already been prepared in the course of the work on 4-oxazolines and acetylenic dipolarophiles. These compounds were found to be particularly resistant to sulfur and to reactive high potential quinones, and in no case was any furan detected. This dehydrogenation failure has also been observed in the attempted reduction of imidazolines to imidazoles.[229]

The problem was then approached from a different angle as shown in reaction [135].



128A

137

[135]

125A

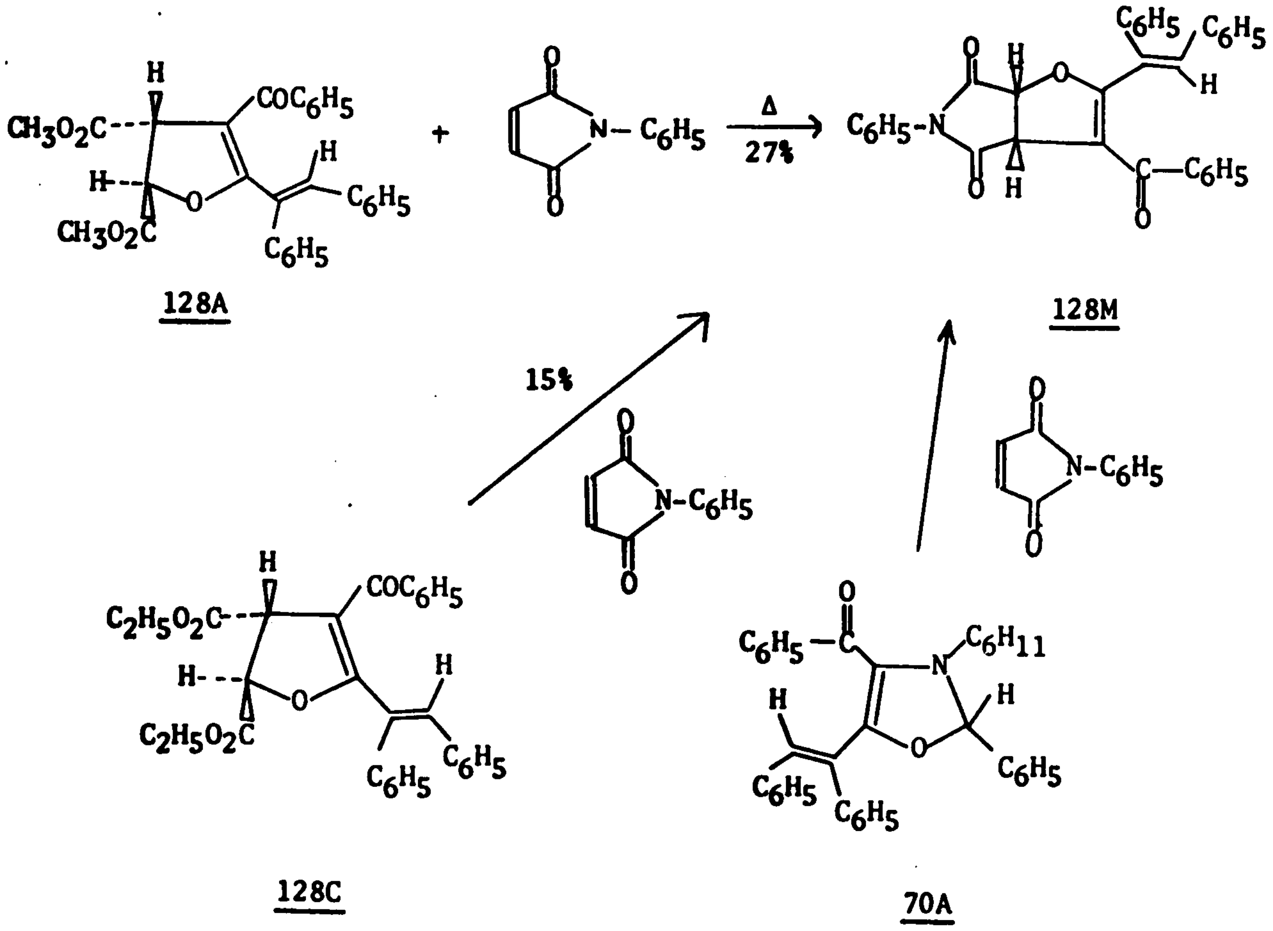
It was found however that no reaction occurred when compound 128A was treated with N-bromosuccinimide and this approach was therefore abandoned.

[2+3] Cycloaddition Reactions of 3-Aroyl-4,5-dihydrofurans

The most characteristic property of the dihydrofurans of Table XXIX is that they too give deep red melts at temperatures above 180°, and red solutions in hydrocarbon solvents at similar temperatures. This was seen to be indicative of a ring cleavage process to charged species in a manner analogous to that undergone by the 4-oxazolines. It also suggested the possibility of a novel extension of the [2+3] cycloaddition reaction to the dihydrofuran series of compounds.

Accordingly, reaction of the *trans*-4,5-dihydrofuran 128A with an equimolar quantity of N-phenylmaleimide in n-butylbenzene (b.p. 184°) under reflux produced a 27% yield of the previously prepared adduct *cis* 128M. This result and that of a parallel reaction are shown in Scheme XIX.

SCHEME XIX



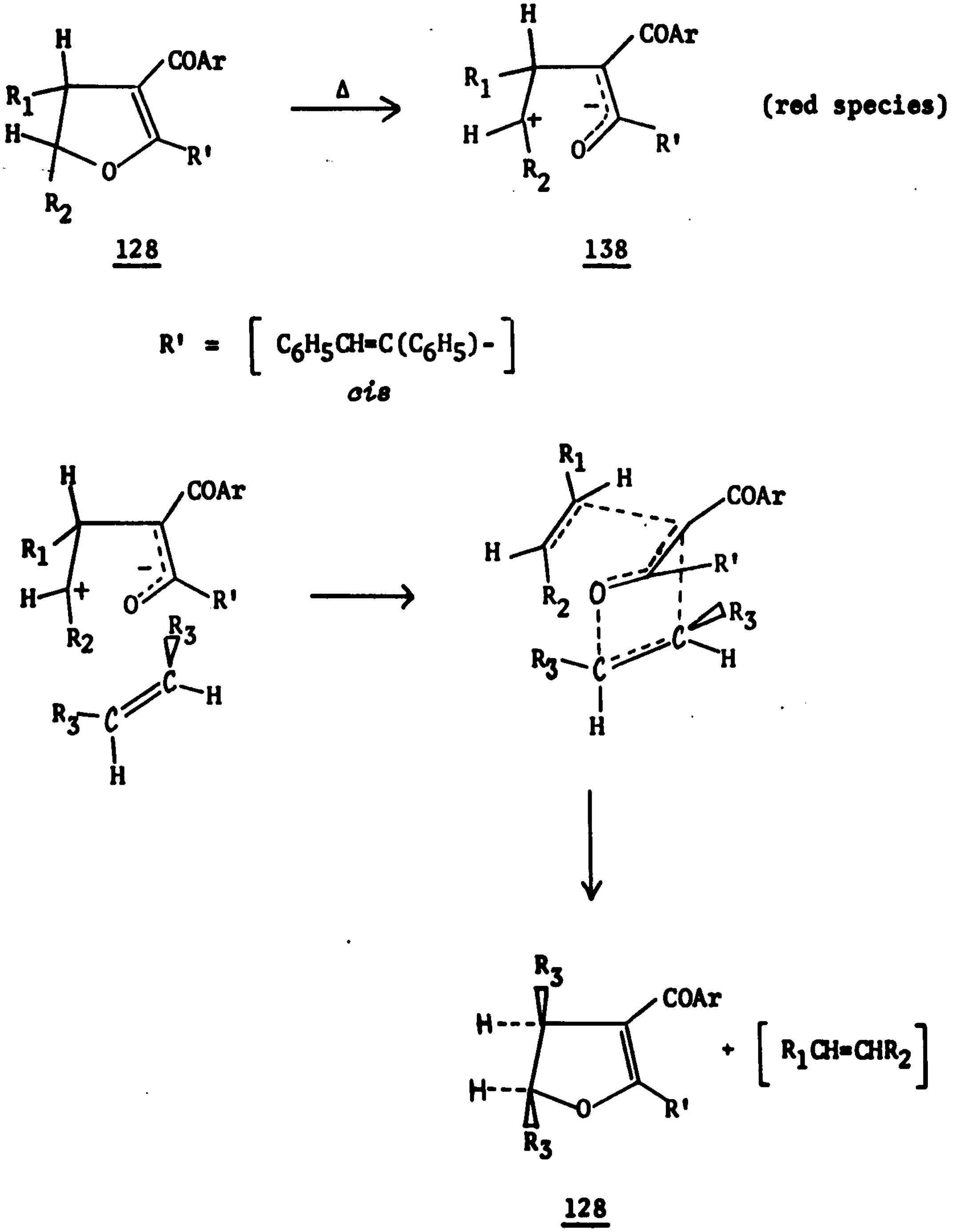
This reaction appears to be confined to the *trans*-4,5-dihydrofurans, for under comparable conditions the *cis*-4,5-dihydrofuran 128D failed to react with N-phenylmaleimide.

As might be expected, there are limitations on this reaction, the most important of which requires that the new 4,5-dihydrofuran produced must have greater stability under the conditions of its formation than the original dihydrofuran, otherwise it will merely ring open in the same manner. This severely limits the choice of suitable dipolarophiles for this reaction, and N-phenylmaleimide was the only one to be successfully employed. Several attempts to prepare a *trans*-4,5-dihydrofuran by this method were attempted without success, for no reaction was obtained from 128D and dimethyl fumarate nor from 128A and 1,2-dibenzoylethylene.

Because of this failure to prepare a *trans*-4,5-dihydrofuran from a *trans* olefin, the reaction in Scheme XIX can only be regarded as stereoselective at present. Further attempts were made to gain more information about this reaction by increasing the scale of the reaction, isolating the extruded olefin and determining its geometry. However despite a careful search no trace of the olefin was ever detected.

In a manner analogous to their mode of preparation, the [2+3] cycloaddition reactions of dihydrofurans can be considered to proceed via an externally stabilized ketocarbene as outlined in Scheme XX.

SCHEME XX


H
COAr
R1
H
O
R'
R2
128
Δ
H
COAr
R1
+
−
H
O
R'
R2
138
(red species)
R' = [C6H5CH=C(C6H5)-]
cis
H
COAr
R1
−
H
+
O
R'
R2
R3
C
H
R3
C
H
R1
H
COAr
H
R'
R2
O
R3
R3
C
C
H
H
R3
COAr
H
H
O
R'
R3
128
+ [R1CH=CHR2]

Survey of the Reactivity of Various Heteroatom Dipolarophiles in Cycloaddition Reactions with 4-Aroyl-4-oxazolines

With some noteable exceptions,[61,62] heteroatom dipolarophiles have been regarded as showing rather sluggish reactivity in [2+3] cycloaddition reactions.[62] However more recent work on new and more active 1,3-dipoles has shown the success of cycloadditions to heteroatom dipolarophiles to depend greatly on the stability of the 1,3-dipole.[119,144]

Our group has been interested in the cycloadditions of azomethine ylides derived from aziridines, and as part of a general program of developing synthetic routes to five-membered ring heterocycles, have reported the additions of 3-aroyl and 3-carboalkoxyaziridines to the following heteroatom dipolarophiles: a) the thiocarbonyl bond of arylisothiocyanates with the formation of 4-aroyl-5-arylamino-4-thiazolines,[193] b) the carbon-nitrogen double bond of imines and sulfonylimines with the formation of imidazolidines,[158] c) the carbon-nitrogen double bond of cyclopropenimines with the formation of imidazolidines and 4-imidazolines,[159] d) the carbonyl group of aldehydes and diphenylcyclopropenone with the formation of oxazolidines and 4-oxazolines as reported in this thesis.[182,230,231,232,233]

Having established the structures of the products obtained from the [2+3] cycloaddition reaction of 4-aroyl-4-oxazolines and acetylenic and olefinic dipolarophiles, attention was turned to the investigation of the possible reaction of the intermediate externally stabilized ketocarbenes with heteroatom dipolarophiles of the type studied with the more stable azomethine ylides.

Aromatic ketocarbenes have been successfully reacted in [2+3] cycloadditions with such dipolarophiles examples of which were shown in equation [32]. Though the yields from reactions of this type were fair to good, it was necessary to employ the dipolarophile as the solvent in order to trap the extremely reactive ketocarbene intermediate. This naturally seriously limited the choice of dipolarophilic species available for reaction.

Attention was accordingly turned to the reactions of the 4-oxazolines with dipolarophiles possessing the following reactive centers: a) C≡N, b) C=N, c) C=O, d) C=S.

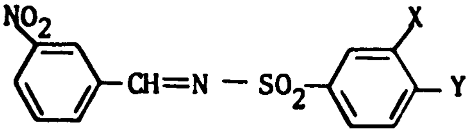
C≡N systems

The following compounds were screened: a) C_6H_5CN, b) p-O_2N-C_6H_4CN, c) $C_2H_5O_2CCN$, d) $CF_3(CF_2)_6CN$.

As suspected, reactions involving 1:1 ratios of 4-oxazolines and nitriles in toluene solution under reflux produced only decomposition of the 4-oxazoline. The same result was observed in cases where a) and c) were employed as the solvent.

C=N systems

Reactions were attempted with the active N-sulfonylanils which had been successfully reacted with substituted aziridines.[158] These anils were solids of the following structure.



X = NO_2 ; Y = Cl
X = H ; Y = NO_2

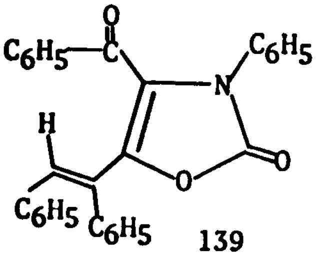
These anils were reacted in equimolar proportions with 4-oxazolines but produced only decomposition of both reactants. Attempts to prepare liquid N-sulfonyl anils were unsuccessful.

C=O systems

The following compounds were screened: a) Cl_3CCHO, b) p-O_2N-C_6H_4CHO, c) 2,4-(diO_2N)-C_6H_3CHO, d) $C_6H_5N{=}C{=}O$, e) p-O_2N-C_6H_4-$N{=}C{=}O$.

Once again when equimolar quantities of the reactants were employed in toluene solution under reflux, decomposition of the 4-oxazoline was observed producing among other unidentified products the α-pyrone 100 obtained from the original 4-oxazoline decomposition experiment.

However when the 4-oxazoline 70A was heated at 130° with phenylisocyanate in a pressure bottle for 5 h, the red colour of the solution faded to yellow, and produced after isolation, a 40% yield of a yellow product from whose infrared, p.m.r. and mass spectra, the 4-oxazoline-2-one structure 139 was tentatively assigned.



139

Although this compound gave a red melt at temperatures >210°, it did not appear to react in a further attempted [2+3] cycloaddition reaction with dimethylacetylenedicarboxylate in n-butylbenzene solution under reflux.

The lack of reaction between 4-oxazolines and aromatic aldehydes and chloral when compared with the ready cycloaddition reactions undergone by aziridines and these same aldehydes,serves to illustrate the great difference in stability between ketocarbenes and azomethine ylides as 1,3-dipoles.

C=S system

The dipolarophiles employed here were a) p-O_2N-C_6H_4-N=C=S, b) 1-naphthylisothiocyanate, and c) phenylisothiocyanate. The first two being solids were reacted in equimolar proportions with the 4-oxazoline 70A,but again the only products isolated were the α-pyrone 100 and trace quantities of the dipolarophiles. Due to contamination from side products, no clear assignment could be made of the structure of the product obtained from the reaction of phenylisothiocyanate under conditions comparable to the reaction involving phenylisocyanate as described above.

The almost complete lack of success in these reactions must be attributed to a combination of the instability of the intermediate ketocarbene and the sluggish nature of the heteroatom dipolarophiles with such 1,3-dipoles.

Summary

A series of 3-aroyl-2-arylaziridines were prepared by established methods, and their behaviour in [2+3] cycloaddition reactions with carbonyl groups as dipolarophiles has been studied in some detail.

In Chapter II the cycloaddition reactions of these aziridines with aromatic aldehydes and chloral to form oxazolidines has been established. The gross structure of the oxazolidines was demonstrated by detailed deuterium labelling experiments, and confirmed by acid hydrolysis results where the required aromatic aldehydes were isolated. These same labelling experiments also enabled the exact orientation of the cycloaddition to be determined.

Stereochemical control experiments showed the reaction not to be stereospecific, for independent reactions with isomerically pure *cis* and *trans*-3-aroyl-2-arylaziridines led to the identical *trans* oxazolidine. Furthermore, no epimerization at the 4- and 5-positions of the oxazolidine ring was detected although some decomposition was observed in these reactions.

These results were rationalized by thermal conrotatory cleavage of the aziridine ring at the 2,3 bond to yield an intermediate azomethine ylide, which then reacted in a [2+3] cycloaddition reaction with the aldehyde to form the oxazolidine. Since isomeric mixtures of aziridines were invariably employed, *cis* and *trans* azomethine ylides were generated *in situ*, but due to the known sluggish nature of the dipolarophile, the *cis* azomethine ylide had time to isomerize to the thermodynamically more stable *trans* isomer prior to cycloaddition with

the aldehyde.

The fact that with aromatic aldehydes *cis*,*trans* mixtures of oxazolidines were obtained,was accounted for by the fact that there exists two possible orientations of the aldehyde for reaction with the azomethine ylide (Scheme III).

Tentative assignments of the stereochemistry at positions 4 and 5 of the ring are offered. An attempt was made to check these assignments of stereochemistry by an unambiguous stereocontrolled synthesis of *cis* and *trans*-4,5-oxazolidines, but was unsuccessful. An alternative adaptation of this pathway has been proposed, but lack of time prevented a detailed study of this method, which though it may well solve the tentative p.m.r. assignment problems mentioned above, nevertheless lacks the overall stereochemical control offered by the [2+3] cycloaddition method.

This work was then extended to include diphenylcyclopropenone (DPP) as the dipolarophile, and reaction with the 3-aroyl-2-arylaziridines was observed to take place at the carbonyl group of DPP to form the little known 4-oxazoline group of compounds. A spiro-oxazolidine has been proposed as the initial product of [2+3] cycloaddition followed by rearrangement to the 4-oxazoline. Some of the details of this process have been elucidated by deuterium labelling studies (equation [104]).

The proposed structure for these compounds rests on a combination of spectral evidence, chemical properties and reactions of the compounds, and on work by Baldwin and coworkers, who had shown that

4-isoxazolines were thermally unstable and readily rearranged to 4-oxazolines. No such reverse process was detected by these workers.

It was found in the course of the work that for successful preparation of the 4-oxazoline ring system, the aziridine precursor must of necessity possess a carbonyl group at the 3-position. When this was not the case, other products were obtained.

The most characteristic property of these 4-oxazolines was their thermochromism and photochromism, which was attributed to contributions from charged species produced by cleavage of the ring at the $O-C_2$ bond. These observations led to successful [2+3] cycloaddition reactions with acetylenic and olefinic dipolarophiles to provide useful syntheses of furans and 4,5-dihydrofurans which occupy the bulk of Chapter IV.

While the acid hydrolysis of 4-oxazolines parallelled that of oxazolidines, the former series of compounds were remarkably resistant to bases and nucleophilic reagents. The carbonyl group could be reduced by lithium aluminum hydride, though it would give no normal carbonyl group derivatives. Once this group was reduced no further cycloaddition reactions took place with olefinic dipolarophiles.

Various attempts were made to provide an independent synthesis of the 4-oxazoline ring system but without success. Such a synthesis has since appeared in the literature.

Chapter IV concerns the chemistry of the furan and 4,5-dihydrofuran derivatives prepared from 4-oxazolines via an externally stabilized ketocarbene intermediate which then added to the acetylenic or olefinic dipolarophile (Scheme XVI). These reactions could proceed either thermally at about 113°, or under the influence of a catalytic quantity of a Lewis acid at 78° with considerable saving in reaction time.

The production of the dihydrofurans was a completely stereospecific process which strongly suggested the concerted nature of the cycloaddition process.

Significantly these 4,5-dihydrofurans also exhibited thermochromism and were found to undergo further [2+3] cycloaddition reactions with a suitable olefinic dipolarophile. A reaction scheme analogous to that invoked to explain their formation is employed to follow this dihydrofuran to dihydrofuran interconversion which as yet is stereoselective.

Finally attempts were made to react 4-aroyl-4-oxazolines with a variety of heteroatom dipolarophiles in [2+3] cycloaddition reactions, but little success was encountered due to a combination of low reactivity of the dipolarophile and the short lifetimes of the intermediate ketocarbene.

Table XXXII summarizes the results of the examination of the [2+3] cycloaddition reactions of 3-aroylaziridines with heteroatom dipolarophiles conducted thus far by the research group of Dr. Lown. Product classes A, B, and C are of the type described in Chapter II on the work on oxazolidines. The only cases in which a "ring expansion" reaction occurs to produce class C structures arise when a powerful nucleophile is employed.[193] Significantly only one case has been found where examples of both class A and class B products have occurred and this deals with the addition of nitroso derivatives. Recent evidence on their Diels-Alder additions to substituted dienes shows that the steric influence on the orientation of addition is very small.[234]

TABLE XXXII

Cycloaddition of 3-Aroylaziridines to Heteromultiple Bonds

Multiple Bond	Substrate	Product Type			Reference
		Class A	Class B	Class C	
C=O	Aromatic Aldehydes	Oxazolidines			Present work
C=O	Chloral	Oxazolidines			Present work
C=O	Diphenylcyclopropenone	4-Oxazolines			Present work
C=N-	Schiff Bases	Imidazolidines			158
C=N-	Sulphonylimines	Imidazolidines			158
C=N-	Iminocyclopropenes	{Imidazolidines 4-Imidazolines			159
C=S	Aryl Isothiocyanates	4-Aroyl-5-arylamino-4-thiazolines		2-Arylimino-4-aroyl-4-thiazolines	193
N=O	1-Nitroso-2-naphthol	2-Aroylnaphth[1,2-d]-oxazoles	2-Arylnaphth[1,2-d]-oxazoles		160
N=O	Aryl nitroso compounds		Schiff Bases		160
N=S=O	Aryl-N-sulphinyl compounds		Schiff Bases		235

Experimental

1. Attempted Decarbonylation of Diphenylcyclopropenone

A solution of diphenylcyclopropenone (0.50 g) in toluene (30 ml) containing cyclohexylamine (0.01 g) was heated under reflux for 24 h. The yellow translucent solution was cooled, and the toluene removed *in vacuo*, to give as a pale yellow solid the title compound (0.35 g, 70% recovery), m.p. 118.5-120° (lit. m.p. 119-120°).[183]

Comparison of the infrared spectrum of this compound with that of the authentic material confirmed this finding and no trace of the C≡C stretching frequency of diphenylacetylene was detected.

2. Synthesis of Substituted Furans by Reaction of 4-Aroyl-4-oxazolines with Acetylenic Dipolarophiles

Compounds 125E and 125F have already had their preparations described in Chapter III.

3-Benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)furan (125A)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.256 g, 0.0005 mole) and dimethyl acetylenedicarboxylate (0.072 g, 0.0005 mole) in toluene (30 ml) was heated under reflux for 15 h, by which time the initially deep red solution was pale yellow in colour. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting yellow oil on grade I alumina (BDH, 25 g) with benzene as eluant, gave as the main fraction a yellow oil which slowly crystallized on trituration with heptane and chilling to give the title furan as a yellow solid (0.10 g, 43%), m.p. 134-136° (ethanol).

Anal. Calcd. for $C_{29}H_{22}O_6$: C, 74.68; H, 4.72.

Found: C, 74.55; H, 4.59.

Mass spectrum: 466.1416 ($C_{29}H_{22}O_6$). Found: 466.1415.

Infrared spectrum ν_{max} ($CHCl_3$): 1744-1710 (C=O of esters), 1645 cm^{-1} (C=C).

P.m.r. spectrum ($CDCl_3$): 3.56 (singlet, 3H, ester $C\underline{H}_3$), 3.61 (singlet, 3H, ester $C\underline{H}_3$), 7.18-7.78 (multiplet, 15H, aryl protons), 7.86 (singlet, 1H, vinyl proton).

3-Benzoyl-4-carbomethoxy-2-(*cis*-1,2-diphenylvinyl)-5-phenylfuran (125B)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.256 g, 0.0005 mole) and methyl phenylpropiolate (0.10 g, 0.00062 mole) in toluene (25 ml) was heated under reflux for 48 h, by which time the initial red colour of the solution had changed to pale yellow. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting yellow oil on grade I alumina (BDH, 25 g) with benzene as eluant, gave a yellow oil which crystallized on trituration with heptane and chilling to give the title furan as a pale yellow solid (0.143 g, 59%), m.p. 178-180° (ethanol).

Anal. Calcd. for $C_{33}H_{24}O_4$: C, 81.79; H, 4.99.

Found: C, 81.84; H, 4.89.

Mass spectrum: 484.1675 ($C_{33}H_{24}O_4$). Found: 484.1678.

Infrared spectrum ν_{max} ($CHCl_3$): 1730 (C=O of ester), 1690 cm^{-1} (aryl C=O).

P.m.r. spectrum ($CDCl_3$): 3.47 (singlet, 3H, ester $C\underline{H}_3$), 7.00-7.90

(multiplet, 20H, aryl protons), 8.15 (singlet, 1H, vinyl proton).

3-Benzoyl-2-(*cis*-1,2-diphenylvinyl)-4-phenylfuran (125D)

This compound was prepared in 56% yield, m.p. 163-165° (ethanol), by heating under reflux for 80 min, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(3-nitrophenyl)-4-oxazoline (0.556 g, 0.001 mole) and phenylacetylene (0.11 g, 0.00108 mole) in xylene (60 ml). The yellow furan was isolated as previously described.

Anal. Calcd. for $C_{31}H_{22}O_2$: C, 87.32; H, 5.16.

Found: C, 87.06; H, 5.41.

Mass spectrum: 426.1620 ($C_{31}H_{22}O_2$). Found: 426.1624.

Infrared spectrum ν_{max} ($CHCl_3$): 1698 cm^{-1} (aroyl C=O).

P.m.r. spectrum ($CDCl_3$): 6.80 (singlet, 1H, ring proton), 6.93-7.82 (multiplet, 20H, aryl protons), 8.17 (singlet, 1H, vinyl proton).

3-Benzoyl-2-(*cis*-1,2-diphenylvinyl)benzofuran (125G)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.256 g, 0.0005 mole) and diphenyliodonium-2-carboxylate[223] (0.324 g, 0.001 mole) in 1,3,5-trimethylbenzene (50 ml, b.p. 165°) was heated under reflux for 20 min. The yellow solution was cooled,and the xylene removed *in vacuo*,giving a yellow oil, which was subjected to chromatography on grade I alumina (BDH, 35 g). Elution with n-pentane removed aromatic by-products from the intermediate benzyne, while the main fraction, a yellow band was obtained by elution with benzene. Removal of the solvent *in vacuo*,and trituration of the resulting yellow oil with 95% ethanol gave the title furan as a pale yellow solid (0.06 g, 30%), m.p. 83-85° (ethanol).

Anal. Calcd. for $C_{29}H_{20}O_2$: C, 87.00; H, 5.00.

Found: C, 86.51; H, 5.12.

Mass spectrum: 400.1463 ($C_{29}H_{20}O_2$). Found: 400.1470.

Infrared spectrum ν_{max} ($CHCl_3$): 1705 cm^{-1} (aroyl C=O).

P.m.r. spectrum ($CDCl_3$): 7.0-7.75 (multiplet, 19H, aryl protons), 7.84 (singlet, 1H, vinyl proton).

3-Benzoyl-4-carbomethoxy-2-(*cis*-1,2-diphenylvinyl)furan (125C)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and methyl propiolate (0.084 g, 0.001 mole) in benzene (50 ml) containing 4-toluenesulfonic acid (0.003 g) was heated under reflux for 4 h. Concentration of the cooled yellow solution *in vacuo*, and chromatography of the resulting yellow syrup on grade I alumina (BDH, 45 g) with benzene as eluant, gave as the main fraction a yellow oil which crystallized on trituration with a mixture of heptane and 95% ethanol and chilling to give the title furan as a yellow solid (0.317 g, 78%), m.p. 176-178° (ethanol).

Anal. Calcd. for $C_{27}H_{20}O_4$: C, 79.39; H, 4.90.

Found: C, 78.99; H, 4.82.

Mass spectrum: 408.1361 ($C_{27}H_{20}O_4$). Found: 408.1363.

Infrared spectrum ν_{max} ($CHCl_3$): 1728 (C=O of ester), 1706 cm^{-1} (aroyl C=O).

P.m.r. spectrum ($CDCl_3$): 3.54 (singlet, 3H, ester $\underline{CH_3}$), 7.12-7.66 (multiplet, 16H, aryl protons and ring proton), 7.93 (singlet, 1H, vinyl proton).

3-Benzoyl-2-(*cis*-1,2-diphenylvinyl)furo[2,3-b]naphthoquinone (125H)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.40 g, 0.00078 mole) and 1,4-naphthoquinone (0.126 g, 0.0008 mole) in benzene (40 ml) containing 4-toluenesulfonic acid (0.002 g) was heated under reflux for 52 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting brown oil on grade I alumina (BDH, 40 g) with benzene as eluant, gave as the main fraction a yellow-brown oil which crystallized on trituration with cold heptane to give the title furan as a yellow solid (0.225 g, 60%), m.p. 118-120° (ethanol).

Anal. Calcd. for $C_{33}H_{20}O_4$: C, 82.50; H, 4.17.

Found: C, 82.20; H, 4.37.

Mass spectrum: 480.1362 ($C_{33}H_{20}O_4$). Found: 480.1358.

Infrared spectrum ν_{max} ($CHCl_3$): 1707 (C=O), 1670 cm^{-1} (C=O).

P.m.r. spectrum ($CDCl_3$): 7.00-8.25 (multiplet, 19H, aryl protons), 8.00 (singlet, 1H, vinyl proton).

3-Benzoyl-4-carbomethoxy-2-(*cis*-1,2-diphenyldeuterovinyl)-5-phenylfuran (127)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenyldeuterovinyl)-2-(4-nitrophenyl)-4-oxazoline (0.557 g, 0.001 mole) and phenyl methylpropiolate (0.18 g, 0.0011 mole) in toluene (50 ml) was heated under reflux for 9 h. Concentration of the cooled pale yellow solution *in vacuo*, and chromatography of the resulting yellow oil on grade I alumina (BDH, 35 g) with benzene as eluant, gave as the main fraction a yellow oil which slowly crystallized on trituration with cold heptane to give the title furan as a yellow solid (0.31 g, 64%) m.p. 175-177° (m.p. of protium compound 178-180°).

Mass spectrum: 485.1753 ($C_{33}H_{23}DO_4$). Found 485.1758.

P.m.r. spectrum ($CDCl_3$): 3.40 (singlet, 3H, ester $C\underline{H}_3$), 7.00-7.80 (multiplet, 20H, aryl protons), 8.13 (singlet, 0.43H, vinyl proton).

This corresponded to 57% deuterium incorporation in the furan.

3. Synthesis of Substituted 4,5-Dihydrofurans by Reaction of 4-Aroyl-4-oxazolines with Olefinic Dipolarophiles

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline with Dimethyl Fumarate

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and dimethyl fumarate (0.144 g, 0.001 mole) in toluene (50 ml) was heated under reflux for 18 h. The resulting yellow translucent solution was cooled, and the solvent removed *in vacuo*, giving a yellow oil which was subjected to chromatography on grade I alumina (BDH, 40 g) with benzene as eluant. Removal of the solvent and trituration of the yellow syrup produced with heptane, gave 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128A) as a white solid (0.34 g, 73%), m.p. 188-190° (absolute ethanol).

Anal. Calcd. for $C_{29}H_{24}O_6$: C, 74.36; H, 5.13.

Found: C, 74.42; H, 5.16

Mass spectrum: 468.1572 ($C_{29}H_{24}O_6$). Found 468.1570.

Infrared spectrum ν_{max} ($CHCl_3$): 1736 (C=O of ester), 1701 cm^{-1} (aroyl C=O).

P.m.r. spectrum ($CDCl_3$): 3.02 (singlet, 3H, ester $C\underline{H}_3$ at 4-position), 3.64 (singlet, 3H, ester $C\underline{H}_3$ at 5-position), 4.07 and 4.25 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 3.7 Hz) 7.18-7.90 (multiplet, 16H, aryl protons and vinyl proton).

The same dihydrofuran was prepared in 75% yield by heating under reflux for 12 h, a solution of 4-benzoyl-2-(4-biphenylyl)-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-4-oxazoline[201] (0.587 g, 0.001 mole) and dimethyl fumarate (0.144 g, 0.001 mole) in toluene (40 ml). The product was isolated as described above and was identical to this dihydrofuran.

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline with Dimethyl Fumarate under Conditions of Acid Catalysis

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.08 g, 0.00016 mole) in benzene (20 ml) containing 4-toluenesulfonic acid (0.001 g) was prepared and shaken for a few moments till the characteristic wine-red colour was imparted to the solution. Dimethyl fumarate (0.023 g, 0.00016 mole) was added and the solution heated under reflux for 45 min. The yellow translucent solution obtained was concentrated *in vacuo*, and the resulting yellow oil was subjected to chromatography on grade I alumina (BDH, 15 g) with benzene as eluant. Removal of the solvent and trituration of the product yellow syrup with cold heptane gave 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128A) as a white solid (0.05 g, 69%), m.p. 188-190° (absolute ethanol).

Anal. Calcd. for $C_{29}H_{24}O_6$: C, 74.36; H, 5.13.

Found: C, 74.24; H, 5.43.

Mass spectrum: 468.1573 ($C_{29}H_{24}O_6$). Found: 468.1570.

Infrared spectrum ν_{max} ($CHCl_3$): 1736 (broad, C=O of ester), 1702 cm^{-1} (C=O of benzoyl group).

P.m.r. spectrum ($CDCl_3$): 3.11 (singlet, 3H, ester $C\underline{H}_3$), 3.72 (singlet, 3H, ester $C\underline{H}_3$), 4.06 and 4.24 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 3.8 Hz), 7.18-7.98 (multiplet, 16H, aryl protons and vinyl proton).

This same dihydrofuran (128A), was prepared in 69% yield by heating under reflux for 50 min, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline (0.556 g, 0.001 mole) and dimethyl fumarate (0.16 g, 0.0011 mole) in toluene (50 ml) containing 4-toluenesulfonic acid (0.002 g). The product was isolated as described above and was identical in all respects with that compound.

In a further experiment the above dihydrofuran (128A) was prepared in 65% yield, by heating under reflux for 100 min, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(3-nitrophenyl)-4-oxazoline (0.556 g, 0.001 mole) and dimethyl fumarate (0.16 g, 0.0011 mole) in toluene (50 ml) containing 4-toluenesulfonic acid (0.002 g). The product was isolated as described above and was identical with that compound.

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline with Dimethyl Maleate

A solution of the title 4-oxazoline (0.511 g, 0.001 mole) and dimethyl maleate (0.144 g, 0.001 mole) in toluene (50 ml) was heated under reflux for 22 h. The product was then isolated as previously described, to give a *cis,trans* mixture of 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-4,5-dihydrofuran as a white solid (0.31 g, 66%), m.p. 159-177° (absolute ethanol). This mixture was shown by p.m.r. to consist of a 78:22 *cis* to *trans* ratio but no separation could be performed.

Anal. Calcd. for $C_{29}H_{24}O_6$: C, 74.36; H, 5.13.

Found: C, 74.32; H, 5.13.

Mass spectrum: 468.1572 ($C_{29}H_{24}O_6$). Found: 468.1570.

Infrared spectrum ν_{max} ($CHCl_3$): 1742 (C=O of ester), 1699 cm^{-1} (C=O of benzoyl group).

P.m.r. spectrum ($CDCl_3$): 3.57 (singlet, 6H, ester $C\underline{H}_3$), 3.69 and 4.10 (AB quartet, 2H, 4,5 ring protons, *cis* coupled, J = 11.5 Hz), 7.17-7.83 (multiplet, 16H, aryl protons and vinyl proton).

This reaction was also performed under conditions of acid catalysis to give the above isomeric dihydrofuran 128B in 58% yield as an 82:18 *cis-trans* mixture as estimated by p.m.r. spectroscopy.

3-Benzoyl-4,5-dicarboethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128C)

This compound was prepared in 39% yield as a white solid, m.p. 114-115° (absolute ethanol), by heating under reflux for 75 min, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and diethyl fumarate (0.172 g, 0.001 mole) in benzene (50 ml) containing 4-toluenesulfonic acid (0.002 g). The product was isolated as previously described.

Anal. Calcd. for $C_{31}H_{28}O_6$: C, 75.00; H, 5.65.

Found: C, 74.86; H, 5.68.

Mass spectrum: 496.1886 ($C_{31}H_{28}O_6$). Found: 496.1882.

Infrared spectrum ν_{max} ($CHCl_3$): 1735 (C=O of ester), 1699 cm^{-1} (benzoyl C=O).

P.m.r. spectrum ($CDCl_3$): 0.64 (triplet, 3H, ester $\underline{CH}_3$), 1.09 (triplet, 3H, ester $\underline{CH}_3$) 3.48(quartet, 2H, ester $\underline{CH}_2$), 4.07 (quartet, 2H, ester $\underline{CH}_2$), 3.97 and 4.12 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 3.7 Hz), 7.18-7.94 (multiplet, 16H, aryl protons and vinyl proton).

3-Benzoyl-4,5-dicarboethoxy-2-(*cis*-1,2-diphenylvinyl)-*cis*-4,5-dihydrofuran (128D)

This compound was prepared in 51% yield as a white solid, m.p. 141-142° (absolute ethanol) by heating under reflux for 24 h, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and diethyl maleate (0.172 g, 0.001 mole) in toluene (50 ml) and employing the isolation procedure previously described.

Anal. Calcd. for $C_{31}H_{28}O_6$: C, 75.00; H, 5.65.

Found: C, 74.70; H, 5.70.

Mass spectrum: 496.1886 ($C_{31}H_{28}O_6$). Found: 496.1883.

Infrared spectrum ν_{max} ($CHCl_3$): 1735 (broad, C=O of ester), 1698 cm^{-1} (benzoyl C=O).

P.m.r. spectrum ($CDCl_3$): 1.06-1.30 (two groups of overlapping triplets, 6H, ester $\underline{CH_3}$), 3.90-4.24 (overlapping quartets, 4H, ester $\underline{CH_2}$), 3.74 and 4.14 (AB quartet, 2H, 4,5 ring protons, *cis* coupled, J = 11.5 Hz), 7.12-7.97 (multiplet, 16H, aryl protons and vinyl proton).

This same dihydrofuran (128D) was prepared in 60% yield by heating under reflux for 25 h, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline (1.11 g, 0.002 mole) and diethyl maleate (0.35 g, 0.00203 mole) in toluene (100 ml). The product was isolated as previously described.

A 39% yield of dihydrofuran (128D) was also obtained by the acid catalyzed procedure. A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.256 g, 0.0005 mole) and diethyl maleate (0.086 g, 0.0005 mole) in benzene (25 ml) containing 4-toluenesulfonic acid (0.002 g) was heated under reflux for 6 h. The product was isolated as described above.

3-Acetyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128E)

This compound was prepared in 25% yield as a white solid, m.p. 144-145° (absolute ethanol) by heating under reflux for 25 min, a solution of 4-acetyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.449 g, 0.001 mole) and dimethyl fumarate (0.144 g, 0.001 mole) in o-xylene (50 ml) containing 4-toluenesulfonic acid (0.002 g). The product was isolated as described above.

Anal. Calcd. for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46.

Found: C, 70.80; H, 5.38.

Mass spectrum: 406.1416 ($C_{24}H_{22}O_6$). Found: 406.1416.

Infrared spectrum ν_{max} ($CHCl_3$): 1730 (C=O of ester), 1695 cm^{-1} (acetyl C=O).

P.m.r. spectrum ($CDCl_3$): 1.60 (singlet, 3H, acetyl $\underline{CH_3}$), 3.64 (singlet, 3H, ester $\underline{CH_3}$), 3.72 (singlet, 3H, ester $\underline{CH_3}$), 3.72 and 4.21 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 3.8 Hz), 7.26-7.82 (multiplet, 11H, aryl protons and vinyl proton).

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-(4-nitrophenyl)-4-oxazoline with Acrylonitrile

A solution of the title 4-oxazoline (0.556 g, 0.001 mole) and acrylonitrile (0.06 g, 0.00114 mole) in toluene (50 ml) was heated under reflux for 15 h. The cooled yellow solution was concentrated to low bulk and subjected to chromatography on grade I alumina (BDH, 30 g). Eultion with benzene afforded two fractions which on solvent removal *in vacuo* gave i) a yellow oil, ii) a colorless oil.

Fraction (1): This yellow oil, (0.30 g), which could not be crystallized, was found by t.l.c. to consist of one major component contaminated by two minor ones from which it could not be separated. The main component was found to be C-(4-nitrophenyl)-N-cyclohexylmethylimine by compatibility of its spectral data with that of authentic material synthesized for comparison purposes. One of the minor components was 4-nitrobenzaldehyde as deduced from the i.r., p.m.r. and mass spectra. Details of the major component are:

Mass spectrum: 232.1211 ($C_{13}H_{16}N_2O_2$). Found: 232.1209.

Infrared spectrum: 1640 (C=N), 1523 (NO_2), 850 cm^{-1} (1,4-disubstituted benzene ring).

P.m.r. spectrum ($CDCl_3$): 1.05-2.20 (multiplet, 10H, cyclohexyl $C\underline{H_2}$), 2.88-3.96 (multiplet, 1H, cyclohexyl $C\underline{H}$), 7.44-8.30 (multiplet, 5H, aryl protons and imine $C\underline{H}$).

Fraction (ii): This colorless oil was induced to crystallize by trituration with heptane containing a little 95% ethanol to give 3-benzoyl-4-cyano-2-(*cis*-1,2-diphenylvinyl)-4,5-dihydrofuran as a white solid (0.105 g, 28%), m.p. 184-186° (absolute ethanol).

Anal. Calcd. for $C_{26}H_{19}NO_2$: C, 82.76; H, 5.04; N, 3.71.

Found: C, 82.61; H, 5.05; N, 4.00.

Mass spectrum: 377.1416 ($C_{26}H_{19}NO_2$). Found: 377.1417.

Infrared spectrum ν_{max} ($CHCl_3$): 2225 (C≡N), 1704 cm^{-1} (C=O).

P.m.r. spectrum ($CDCl_3$): ABX spectrum centered at 3.68 (H_A), 3.10 (H_B), and 2.89 (H_C), respectively (J_{AB} = 9.0 Hz, J_{AC} = 4.5 Hz, J_{BC} = 12.5 Hz; 4 and 5 ring protons, from first order treatment), 7.23-7.80 (multiplet, 16H, aryl protons and vinyl proton).

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline with *trans*-1,2-Dibenzoylethylene

A solution of the title 4-oxazoline (1.022 g, 0.002 mole) and *trans*-1,2-dibenzoylethylene (0.480 g, 0.00204 mole) in toluene (100 ml) containing 4-toluenesulfonic acid (0.009 g, 0.00005 mole) was heated under reflux for 7 h. Concentration of the cooled pale orange solution *in vacuo*, and chromatography of the resulting orange oil on grade I alumina (BDH, 75 g) with a 2:3 mixture of hexane and benzene as solvent, gave as the main fraction a pale yellow oil which crystallized on trituration with cold hexane containing a few drops of 95% ethanol to give a *cis*,*trans* mixture (2:1 by p.m.r.) of 2-(*cis*-1,2-diphenylvinyl)-3,4,5-tribenzoyl-4,5-dihydrofuran as a white solid (0.527 g, 47%), m.p. 188-189° (absolute ethanol). The isomers were separated (upper and lower bands) by preparative t.l.c. on silica plates with benzene as eluant.

Upper band: A colorless oil was obtained which crystallized on trituration with hexane to give 2-(*cis*-1,2-diphenylvinyl)-3,4,5-tribenzoyl-*cis*-4,5-dihydrofuran (128J) as a white solid, m.p. 189.5-191.5° (absolute ethanol).

Anal. Calcd. for $C_{39}H_{28}O_4$: C, 83.57; H, 5.00.

Found: C, 83.78; H, 5.16.

Mass spectrum: 324.1150 ($C_{23}H_{16}O_2$; M-$C_{16}H_{12}O_2$) and 236.0837 ($C_{16}H_{12}O_2$; M-$C_{23}H_{16}O_2$). Found: 324.1151 and 236.0839.

Infrared spectrum ν_{max} ($CHCl_3$): 1706 (C=O of unconjugated benzoyl groups), 1685 cm^{-1} (conjugated benzoyl C=O).

P.m.r. spectrum ($CDCl_3$): 4.85 and 5.23 (AB quartet, 2H, 4,5 ring protons, *cis* coupled, J = 7.1 Hz), 6.90-7.88 (multiplet, 26H, aryl protons and vinyl proton).

Lower band: From this a pale yellow oil was obtained which was induced to crystallize as described above to give 2-(*cis*-1,2-diphenylvinyl)-3,4,5-tribenzoyl-*trans*-4,5-dihydrofuran (128H) as a white solid, m.p. 125-128° (absolute ethanol).

Anal. Found for $C_{39}H_{28}O_4$: C, 83.46; H, 5.50.

Mass spectrum: 324.1154 ($C_{23}H_{16}O_2$) and 236.0839 ($C_{16}H_{12}O_2$).

Infrared spectrum ν_{max} ($CHCl_3$): 1705 (C=O of unconjugated benzoyl groups), 1676 cm^{-1} (conjugated benzoyl C=O).

P.m.r. spectrum ($CDCl_3$): 4.89 and 5.42 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 4.75 Hz), 6.92-7.84 (multiplet, 26H, aryl protons and vinyl proton).

3-Benzoyl-4-carbomethoxy-2-(*cis*-1,2-diphenylvinyl)-4,5-dihydrofuran (128K)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and methyl acrylate (0.09 g, 0.00105 mole) in toluene (50 ml) was heated under reflux for 19 h. Work-up of the product as described above gave the title dihydrofuran as a white solid (0.242 g, 59%), m.p. 150-152° (absolute ethanol).

Anal. Calcd. for $C_{27}H_{22}O_4$: C, 78.98: H, 5.37.

Found: C, 78.63; H, 5.39.

Mass spectrum: 410.1518 ($C_{27}H_{22}O_4$). Found: 410.1528.

Infrared spectrum ν_{max} ($CHCl_3$): 1732 (ester C=O), 1698 cm^{-1} (benzoyl C=O).
P.m.r. spectrum ($CDCl_3$): ABX spectrum centered at 3.60 (H_A), 2.96 (H_B), and 2.73 (H_C) respectively (J_{AB} = 9.4 Hz, J_{AC} = 4.1 Hz, J_{BC} = 14.9 Hz; 4 and 5 ring protons from first order treatment), 3.02 (singlet, 3H, ester $C\underline{H_3}$ at 4 position), 7.20-7.88 (multiplet, 16H, aryl protons and vinyl proton).

3-Benzoyl-2-(*cis*-1,2-diphenylvinyl)-4-nitro-5-phenyl-*trans*-4,5-dihydrofuran (128L)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.256 g, 0.0005 mole) and ω-nitrostyrene (0.075 g, 0.0005 mole) in toluene (25 ml) was heated under reflux for 24 h. Work-up of the product as previously described gave the title dihydrofuran as a white solid (0.024 g, 10%), m.p. 197-199° (ethanol).

Anal. Calcd. for $C_{31}H_{23}NO_4$: C, 78.65; H, 4.86; N, 2.96.

Found: C, 78.42; H, 4.69; N, 3.07.

Mass spectrum: 473.1698 ($C_{31}H_{23}NO_4$). Found: 473.1698.

Infrared spectrum ν_{max} ($CHCl_3$): 1701 (C=O), 1555 cm^{-1} (NO_2).

P.m.r. spectrum ($CDCl_3$): 4.53 and 5.48 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 5.2 Hz), 6.86-7.95 (multiplet, 21H, aryl protons and vinyl proton).

3-Benzoyl-2-(*cis*-1,2-diphenylvinyl)-5-phenylfuro[2,3-c]pyrrolidinedione (128M)

This compound was prepared in 66% by the method described by Smalley,[236] m.p. 222-224° (lit. 222-224°).

2-(*cis*-1,2-Diphenylvinyl)-5-phenyl-3-(4-toluoyl)furo[2,3-c]pyrrolidinedione (128N)

This compound was prepared in 64.5% yield as a white solid, m.p. 155-158° (heptane), by heating under reflux for 48 h, a solution of 5-(*cis*-1,2-diphenylvinyl)-3-isopropyl-2-phenyl-4-(4-toluoyl)-4-oxazoline (0.256 g, 0.0005 mole) and N-phenylmaleimide (0.10 g, 0.00058 mole) in toluene (30 ml). The product was isolated as previously described.

Anal. Calcd. for $C_{34}H_{25}NO_4$: C, 79.84; H, 4.89; N, 2.74.

Found: C, 79.63; H, 4.93; N, 2.60.

Mass spectrum: 511.1784 ($C_{34}H_{25}NO_4$). Found: 511.1783.

Infrared spectrum ν_{max} ($CHCl_3$): 1780 and 1725 (C=O of cyclic imide),[238] 1705 cm^{-1} (toluoyl C=O).

P.m.r. spectrum ($CDCl_3$): 2.38 (singlet, 3H, toluoyl C$\underline{H}_3$), 4.05 and 4.09 (AB quartet, 2H, ring junction protons, *cis* coupled, J = 9.25 Hz), 6.80-8.00 (multiplet, 20H, aryl protons and vinyl proton).

3-Benzoyl-*cis*-8,9-dihydro-2-(*cis*-1,2-diphenylvinyl)furo[2,3-b]benzoquinone (128P)

A solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and 1,4-benzoquinone (0.324 g, 0.003 mole) in benzene (50 ml) containing 4-toluenesulfonic acid (0.002 g) was heated under reflux for 2 h. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting yellow gum on grade I alumina (BDH, 40 g) with benzene as eluant gave two main fractions. From the first was isolated unreacted 1,4-benzoquinone (0.040 g) as determined by spectral comparison with authentic material.

The second fraction when worked-up as described before gave the title dihydrofuran (0.043 g, 10%), m.p. 190-193°.

Anal. Calcd. for $C_{29}H_{20}O_4$: C, 80.56; H, 4.63.

Found: C, 80.72; H, 4.72.

Mass spectrum: 432.1367 ($C_{29}H_{20}O_4$). Found: 432.1367.

Infrared spectrum ν_{max} ($CHCl_3$): 1705 (benzoyl C=O), 1665 and 1643 cm^{-1} (C=O of ring).

P.m.r. spectrum ($CDCl_3$): 3.75-4.08 (multiplet, 2H, ring junction protons), 6.40-7.90 (multiplet, 18H, aryl protons and vinyl proton).

3-Benzoyl-10,11-dihydro-2-(*cis*-1,2-diphenylvinyl)furo[1,2-b]acenaphthalene (128Q)

This compound was prepared in 75.6% yield as a pale yellow solid, m.p. 210-212° (ethanol), by heating under reflux for 18 h, a solution of 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (0.511 g, 0.001 mole) and acenaphthalene (0.152, 0.001 mole) in benzene (50 ml) containing 4-toluenesulfonic acid (0.002 g). The product was isolated as previously described.

Anal. Calcd. for $C_{35}H_{24}O_2$: C, 88.24; H, 5.04.

Found: C, 88.20; H, 5.17.

Mass spectrum: 476.1775 ($C_{35}H_{24}O_2$). Found: 476.1776.

Infrared spectrum ν_{max} ($CHCl_3$): 1695 cm^{-1} (C=O).

P.m.r. spectrum ($CDCl_3$): 4.58 and 4.68 (AB quartet, 2H, ring junction protons, *cis* coupled, J = 6.4 Hz), 6.91-7.89 (multiplet, 21H, aryl protons and vinyl proton).

Control Reactions on Olefinic Substrates Required for Stereochemical Studies

Dimethyl maleate

a) A solution of dimethyl maleate (1.44 g, 0.01 mole) in toluene (100 ml) was heated under reflux for 24 h. Removal of the solvent *in vacuo* gave a colorless oil, which was shown by g.l.c. and p.m.r. to consist of a 84:16 mixture of dimethyl maleate and dimethyl fumarate.

b) A solution of dimethyl maleate (0.72 g, 0.005 mole) and cyclohexylamine (0.49 g, 0.005 mole) in toluene (50 ml) was heated under reflux for 24 h. Removal of the solvent and cyclohexylamine *in vacuo* gave a white solid (0.65 g), m.p. 96-98°. This was shown by p.m.r. and undepressed mixed melting point with authentic material to be dimethyl fumarate. This corresponded to 90% isomerization.

c) A solution of dimethyl maleate (1.44 g, 0.01 mole) and C-phenyl-N-cyclohexylmethylimine (1.87 g, 0.01 mole) in toluene (50 ml) was heated under reflux for 24 h. Removal of the solvent gave a pale yellow oil the p.m.r. spectrum of which showed a 88:12 mixture of *cis* and *trans* isomers.

trans-1,2-Dibenzoylethylene

A solution of *trans*-1,2-dibenzoylethylene (0.236 g, 0.001 mole) and cyclohexylamine (0.099 g, 0.001 mole) in toluene (20 ml) was heated under reflux for 24 h. The solvent and cyclohexylamine were removed *in vacuo* giving a yellow-brown oil, which was placed *under vacuo* (0.05 mm) for 24 h. Examination of this product by p.m.r. showed that cyclohexylamine had added to the olefinic substrate. Since this oily product contained three components, no isolation of the adduct was possible.

Isomerization Studies on 4,5-Dihydrofurans

a) 3-Benzoyl-4,5-dicarboethoxy-2-(*cis*-1,2-diphenylvinyl)-*cis*-4,5-dihydrofuran (128D)

i) A solution of the title compound (0.05 g, 0.0001 mole) in toluene (20 ml) containing cyclohexylamine (0.02 g, 0.0002 mole) was heated under reflux for 24 h. Removal of the solvent *in vacuo* gave the starting material as a white solid (0.015 g, 30% recovery), m.p. 138-140°.

ii) A solution of the title dihydrofuran (0.08 g, 0.00016 mole) in dry methanol (15 ml) containing sodium methoxide (0.026 g, 0.00048 mole) was heated under reflux for 3 h. Concentration of the cooled yellow solution *in vacuo* gave an orange gum, the organic portion of which was taken up in benzene, and washed with water, and then dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a pale yellow oil, which crystallized on trituration with 95% ethanol to give 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128A) as a white solid (0.03 g, 40%), m.p. 186-188° (ethanol).

This compound was identical in all respects with the dihydrofuran obtained from the [2+3]cycloaddition reaction of the 4-oxazoline (70A) and dimethyl fumarate.

iii) A solution of the title dihydrofuran (0.10 g, 0.0002 mole) in dry methanol (10 ml) containing sodium methoxide (*ca.* 0.005 g) was heated under reflux for 30 min. The cooled yellow solution was concentrated *in vacuo*, and the yellow oil obtained was dissolved in benzene, washed with water, and then dried ($MgSO_4$). Removal of the solvent *in vacuo*, and trituration of the yellow oil obtained with cold heptane gave 3-benzoyl-4-carboethoxy-5-carbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128F), as a white solid (0.045 g, 46%), m.p. 163-164° (absolute ethanol).

Anal. Calcd. for $C_{30}H_{26}O_6$: C, 74.69; H, 5.39.

Found: C, 74.47; H, 5.41.

Mass spectrum: 482.1729 ($C_{30}H_{26}O_6$). Found: 482.1724.

Infrared spectrum ν_{max} ($CHCl_3$): 1732 (ester C=O), 1701 cm^{-1} (benzoyl C=O).

P.M.R. spectrum ($CDCl_3$): 0.75 (triplet, 3H, ethyl ester CH_3), 3.52 (quartet, 2H, ethyl ester CH_2), 3.71 (singlet, 3H, methyl ester CH_3), 4.03 and 4.22 (AB quartet, 2H, 4,5 ring protons, *trans* coupled, J = 3.5 Hz), 7.20-7.93 (multiplet, 16H, aryl protons and vinyl proton).

b) 3-Benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-4,5-dihydrofuran (128B, *cis*:*trans* as 82:18).

A solution of the title isomeric dihydrofuran (0.07 g, 0.00015 mole) in dry methanol (20 ml) containing sodium methoxide (0.010 g, 0.00018 mole) was heated under reflux for 45 min. Work-up of the solution as described above gave 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran (128A) as a white solid (0.03 g, 43%), m.p. 185-187°. This product was identical in all respects to the authentic (128A).

Parallel experiments on the *trans*-dihydrofurans (128A and 128C) showed them to be configurationally stable,as were the olefins diethyl and dimethyl fumarate,to isomerization under the reaction conditions.

Effect of Acid Catalysis on the Rate of Formation of 4,5-Dihydrofurans

In this series of reactions 4-benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (70A) was reacted in benzene solution with dimethyl fumarate under the influence of various acid catalysts to yield exclusively 3-benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans* 4,5-dihydrofuran (128A). The reaction with 4-toluenesulfonic acid has already been described in detail.

a) Acetic acid

A solution of the 4-oxazoline (0.256 g, 0.0005 mole) in benzene (30 ml) containing glacial acetic acid (*ca.* 0.006 g) was prepared. No red colour was imparted to the solution. Dimethyl fumarate (0.072 g, 0.0005 mole) was added,and the solution heated under reflux for 11 h. Concentration of the cooled yellow solution *in vacuo,* and chromatography of the oil produced in grade I alumina (BDH, 30 g) with benzene as eluant gave two main fractions. From the first solution was obtained unreacted 4-oxazoline (0.115 g, 45% recovery), m.p. 158-160°. From the latter solution the expected *trans*-4,5-dihydrofuran (128A) was obtained as a white solid (0.055 g, 23.5%), m.p. 187-189°.

b) Sulfuric acid

The reaction was repeated with 0.1N sulfuric acid (0.006 g) as catalyst. This time a pale red colour was imparted to the solution on reflux and faded after 4 h. The product dihydrofuran (128A) was isolated as previously described (0.125 g, 53%).

c) Zinc chloride

With this catalyst (0.003 g) a pink colouration was imparted to the reaction mixture on shaking for *ca.* 5 min. at room temperature. The colour deepened on heating and the reaction was complete in 3½ h. The product yield was 59%.

d) Stannic chloride (0.006 g).

An immediate red colour was imparted to the solution at room temperature on addition of the catalyst. The reaction was complete in 50 min under reflux to give the dihydrofuran in 51% yield.

e) Aluminum chloride (0.003 g).

An immediate red colour was imparted to the solution at room temperature on addition of the catalyst. After 2½ h under reflux the reaction was complete and the product was isolated in 63% yield.

f) Boron trifluoride-Ether Complex (0.006 g).

An immediate bright red colour was imparted to the solution at room temperature on addition of the catalyst. The reaction was complete after 45 min under reflux and the product obtained in 68% yield.

g) Diphenyliodonium Iodide (0.003 g).

No immediate red colouration was adopted by the solution on the addition of diphenyliodonium iodide prepared by the method of Beringer and coworkers.[237] At the boiling point of benzene the red colour appeared, and the reaction was complete in 40 min, giving a 62% yield of the dihydrofuran.

[2+3] Cycloaddition reactions of 3-Aroyl-4,5-dihydrofurans

Reaction of 3-Benzoyl-4,5-dicarbomethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran with N-Phenylmaleimide

A solution of the title dihydrofuran (0.161 g, 0.00034 mole) and N-phenylmaleimide (0.060 g, 0.00034 mole) in *n*-butylbenzene (25 ml) was heated under reflux for 2½ h, by which time the red solution had faded to a straw colour. Concentration of the cooled solution *in vacuo*, and chromatography of the resulting yellow syrup on a grade I alumina (BDH, 50 g) with benzene as eluant, gave a yellow oil which crystallized on trituration with cold 95% ethanol to give 3-benzoyl-2-(*cis*-1,2-diphenylvinyl)-5-phenylfuro[2,3-c]pyrrolidinedione (128M) as a white solid (0.046 g, 27%), m.p. 218-220° (absolute ethanol).

Anal. Calcd. for $C_{33}H_{23}NO_4$: C, 79.64; H, 4.85; N, 2.87.

Found: C, 79.25; H, 4.60; N, 3.00.

Mass spectrum: 497.1627 ($C_{33}H_{23}NO_4$). Found: 497.1631.

Infrared spectrum ν_{max} ($CHCl_3$): 1780w, 1725 (cyclic imide)[238], 1698 sh cm^{-1} (benzoyl C=O).

P.m.r. spectrum ($CDCl_3$): 3.99 and 4.33 (AB quartet, 2H, ring junction protons, *cis* coupled, J = 9.05 Hz), 6.95-8.08 (multiplet, 21H, aryl protons and vinyl proton).

Reaction of 3-Benzoyl-4,5-dicarboethoxy-2-(*cis*-1,2-diphenylvinyl)-*trans*-4,5-dihydrofuran with N-phenylmaleimide

A solution of the title dihydrofuran (0.10 g, 0.0002 mole) and N-phenylmaleimide (0.038 g, 0.00022 mole) in tetrahydronaphthalene

(25 ml) was heated under reflux for 1.3/4 h, by which time the red solution had faded to a straw colour. The product was isolated in the manner described above as a pale yellow oil, which crystallized on trituration with heptane containing a few drops of 95% ethanol to give 3-benzoyl-2-(*cis*-1,2-diphenylvinyl)-5-phenylfuro[2,3-c] pyrrolidinedione (128M) as a white solid (0.015 g, 15%). This compound was shown to be identical with authentic material synthesized from a 4-oxazoline and N-phenylmaleimide, and with the product obtained from the previous reaction.

Reaction of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline with Phenylisocyanate

A solution of the title 4-oxazoline (0.511 g, 0.001 mole) in phenylisocyanate (15 ml) was heated at 130° in a pressure bottle for 5 h. The yellow solution was cooled, the bottle opened, and the excess phenylisocyanate removed by distillation (bath temp. 130°/0.02 mm). The orange residue was taken up in a little benzene, and subjected to chromatography on grade I alumina (BDH, 50 g) with benzene as eluant. Removal of the solvent from the main yellow fraction gave an oil which crystallized on trituration with cold 95% ethanol to give 4-benzoyl-5-(*cis*-1,2-diphenylvinyl)-3-phenyl-4-oxazoline-2-one as a yellow solid (0.17 g, 40%), m.p. 178-181° (orange melt which turned red at >225°). Mass spectrum: 398.1540 ($C_{29}H_{20}NO$; $M-CO_2$). Found: 398.1544. Infrared spectrum ν_{max} ($CHCl_3$): 1777s, 1760s (C=O), 1657 cm^{-1} (C=C). P.m.r. spectrum ($CDCl_3$): 6.60-8.08 (aryl protons and vinyl proton).

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