

$\Delta^4$ -Isoxazolines (2,3-Dihydroisoxazoles)

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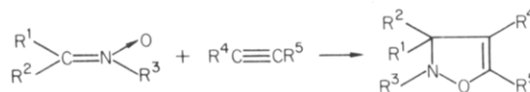


Jeremiah P. Freeman was born in Detroit, MI, and did his undergraduate work at the University of Notre Dame, where he completed a senior thesis under Professor Ernest L. Eliel in 1950. His graduate work was done at the University of Illinois, where he received an M.S. degree in 1951 and the Ph.D. degree in 1953 under the guidance of the late Professor R. C. Fuson. He joined the Redstone Arsenal Research Division of the Rohm and Haas Co. in 1953, where he worked with Dr. William D. Emmons until 1957. He was group leader of organic research from 1957 to 1964, when he joined the University of Notre Dame as Associate Professor and Assistant Chairman of the Department of Chemistry. He became Professor in 1968 and was Chairman from 1970 to 1979. Dr. Freeman was an A. P. Sloan Fellow, 1966-1968. He has been Secretary-Treasurer (1969-1973) and Chairman (1974-1975) of the Organic Division of the American Chemical Society. Since 1979 he has been Secretary of Organic Syntheses, Inc. He is married and the father of four boys and two girls.

## II. Preparation

## A. Cycloaddition of Nitrones and Alkynes

There are only two significant routes to  $\Delta^4$ -isoxazolines. The most general and widely used one is due to Huisgen and his co-workers, the cycloaddition of nitrones and alkynes:<sup>1</sup>



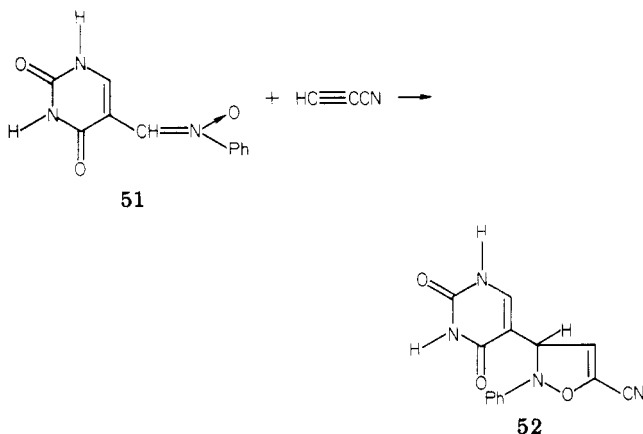
However, more often than not, the isoxazolines have not been isolated and characterized because they are unstable under the conditions at which they are formed. The ultimate products will be discussed in the section on thermal rearrangements. However, investigators are urged to be wary of early reports of isoxazolines formed by cycloadditions that are unsupported by spectral characterization. The compounds listed in Tables I and II are those we believe have been so characterized (Table III).

## I. Introduction

Why should a relatively small (and elusive) group of heterocycles merit a review? In effect this question paraphrases a similar one raised by Huisgen in his Tilden lecture in 1975. The lability of this ring system, which is associated with the presence of the weak nitrogen-oxygen bond connected to a  $\pi$  system, has produced a dazzling array of rearrangement reactions and it is the intent of this review to collect these together and examine them for common features that can rationalize the observations already made and that can act as a guide for future investigators.

### 1. Regiochemistry

In general, unsymmetrical terminal acetylenes would be expected to yield 5-substituted isoxazolines. This regiochemistry is determined by the dominant HOMO of the acetylene and the LUMO of the nitron.<sup>2</sup> But as the electron deficiency of the substituent increases (and the HOMO energy decreases) the 4-substituted product appears in significant amounts. Tables I and II show examples in which the 4-substituted product predominates (compounds 1, 6, 8, 9, 11, 16, 44, 49). The regioselectivity with acetylenes appears to be less than that with alkenes. With other unsymmetrical acetylenes, it appears that the more electron-deficient group usually appears as a 4-substituent (Table I, compounds 3, 4; Table II, compounds 41, 42). (The report<sup>3</sup> that



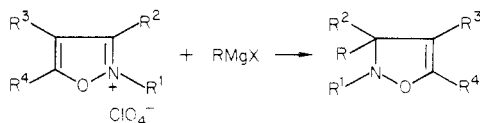
nitron **51** and cyanoacetylene produce isoxazoline **52** probably needs authentication in the light of Houk's findings.<sup>2</sup> Indeed the structure of all the acetylene cycloaddition products reported in this paper need to be authenticated. There is no spectral proof that 4-isoxazolines were obtained and the reaction conditions suggest that rearranged structures are more likely.)

Noland and Modler<sup>4</sup> and Bond and Hooper<sup>5</sup> observed the expected regiochemistry in the reaction of 2-phenylisatogen with phenylacetylene. (This was inferred from the structure of the subsequent rearrangement product (section IIIB1b) since the isoxazoline itself was not isolable.) However, when cuprous phenylacetylide in pyridine was the dipolarophile, the regiochemistry was apparently reversed (section IVB).<sup>5</sup> The difference was attributed to steric effects due to pyridine solvation of the metal, but, of course, it may simply reflect a change in the energy of the HOMO due to the presence of the metal.

### B. Isoxazolium Salts

#### 1. Grignard Reagents

One of the limitations of the cycloaddition method is that the most reactive dipolarophiles are those with electron-withdrawing functions, particularly ester groups. Another route that allows the introduction of a wider range of alkyl and aryl groups involves the addition of Grignard reagents to isoxazolium salts.<sup>6</sup>



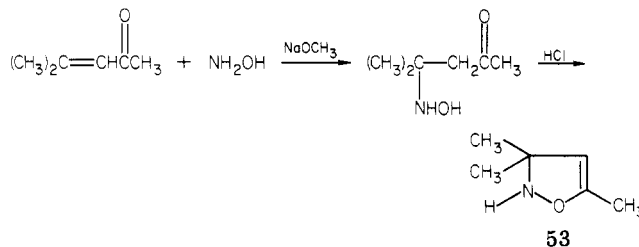
#### 2. Sodium Borohydride

Isoxazolium salts can be reduced with sodium borohydride to 4-isoxazolines.<sup>7,73</sup> The principal limitation of these methods is the availability of a particular isoxazolium salt.

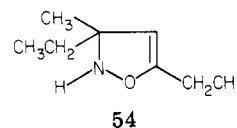
### C. Miscellaneous Methods

#### 1. From Unsaturated Ketones and Hydroxylamine

In 1889 Harries and Jablonski reported that under strongly alkaline conditions hydroxylamine reacted with mesityl oxide to give the conjugate addition product rather than the normal oxime. Furthermore, they claimed that treatment of this compound with dry HCl in ether gave a product, isomeric with the oxime, to which they assigned the structure of 3,3,5-trimethyl-4-isoxazoline (**53**).<sup>8</sup> Little has been done with this re-



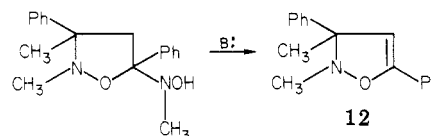
action in the meantime although there is an obscure report that indeed **53** is obtained along with the 2-oxazoline when this reaction is carried out under neutral conditions.<sup>9</sup> The 4-isoxazoline **54** appeared to be the



principal product from a homologous ketone. 4-Isoxazolines were also obtained from other unsaturated ketones.<sup>10</sup> Unfortunately no spectral information or structure proof is available.

#### 2. Elimination from Isoxazolidines

Some nitrones dimerize by aldol addition to yield 5-(hydroxyamino)isoxazolidines. In one instance base-catalyzed elimination of the hydroxyamino group produced isoxazoline **12**.<sup>11</sup> However, this reaction was

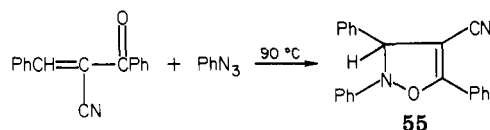


observed only as a side reaction during an attempted Reformatsky reaction of the parent nitron, *C*-phenyl-*C,N*-dimethylnitron. Apparently the Reformatsky reagent catalyzed both the aldolization and the elimination.<sup>12</sup> Since it is possible to prepare isoxazolidines with leaving groups in the 5-position by cycloadditions of nitrones and alkenes, it would seem that this route is worthy of further examination.

#### 3. Unsaturated Ketones and Phenyl Azide

It has been reported that a 4-isoxazoline **55** is obtained by the decomposition of phenyl azide in  $\alpha$ -cyano-

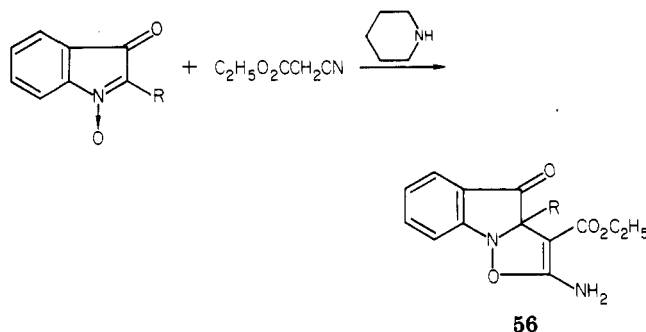
nochalcone.<sup>14</sup> However, there was little proof presented



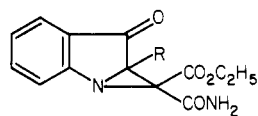
for the structure of **55** except the absence of a carbonyl band and the presence of a band at  $1593\text{ cm}^{-1}$  in its infrared spectrum. Although *N*-aryl-4-isoxazolines are very labile, it has also been noted that a cyano group at the 4-position stabilizes the ring.<sup>15</sup>

#### 4. Cyclization of Unsaturated Hydroxylamines

From the reaction of ethyl cyanoacetate with 2-substituted isatogens in the presence of piperidine, 5-aminoisoxazolines **56** were claimed as reaction prod-

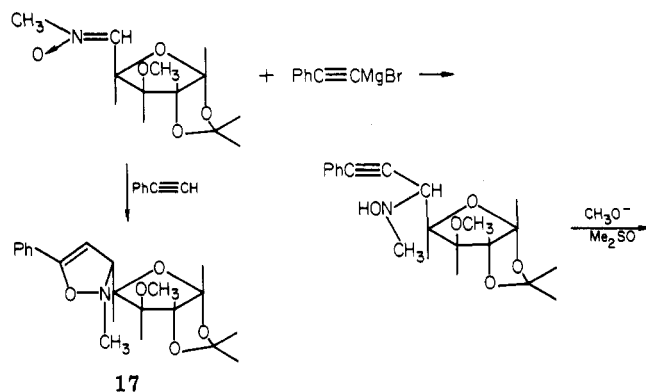


ucts.<sup>16</sup> (Unfortunately, the spectral data<sup>16</sup> and reduction product<sup>17</sup> do not rule out the alternative aziridine structure:



More extensive structure proofs have apparently been carried out<sup>17</sup> but remain unpublished.)

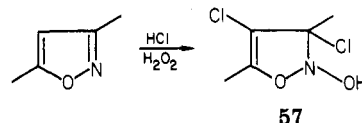
There is a single example of a 4-isoxazoline prepared by the base-catalyzed cyclization of an acetylenic hydroxylamine.<sup>18</sup> The product **17** was identical with that



obtained by direct cycloaddition of the nitron with phenylacetylene.

#### 5. Additions to Isoxazoles

There have been suggestions that isoxazolines are intermediates in the reduction of isoxazoles (section VIA), but none have been isolated. Sokolov and Kochetkov have claimed that *N*-hydroxy-4-isoxazolines **57** are obtained by the action of hydrochloric acid and hydrogen peroxide on isoxazoles.<sup>19</sup> Since compounds



of this structure might have been expected to lose HCl very readily to produce isoxazole *N*-oxides, one should view these claims with some skepticism until they are verified independently.

#### D. Spectral Properties

4-Isoxazolines lack highly characteristic spectral properties but a few generalizations may be made. (Table III summarizes the data that have been reported.) Most of the compounds contain strong absorption in the carbon-carbon double bond stretching region ranging from  $1615$  to  $1680\text{ cm}^{-1}$ , due to the vinyl ether group. The presence of this group and the absence of a carbonyl band serve to distinguish this heterocycle from the isomeric acylaziridine, which is so often a product of attempts to prepare isoxazolines (section III).

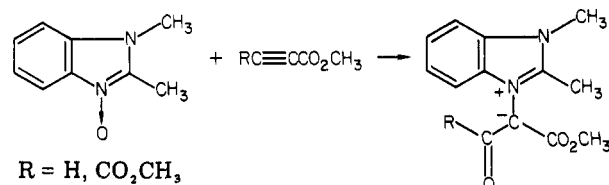
Their nuclear magnetic resonance spectra are less useful for characterization except in determining regioisomers from nitron-terminal acetylene reactions. The vinyl hydrogen at C5 is strongly deshielded, appearing in the region of  $\delta$  7.0, while that at C4 is shifted upfield near  $\delta$  5.5.

### III. Thermal Isomerizations

#### A. Introduction

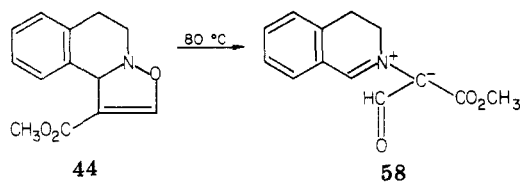
The first investigators of  $\Delta^4$ -isoxazolines were unprepared for the lability of this heterocycle both thermally and in the presence of acids and bases. Thus, some of the earliest reports in the 1960s suggested structures that subsequently had to be substantially modified. In other cases it is not clear whether the investigators simply assigned structures on the assumption of a straightforward reaction or whether they in fact had satisfied themselves, with data not reported, of the correctness of the structures published.

Kano and co-workers, examining the cycloaddition reactions of heteroaromatic *N*-oxides, were the first to recognize the deep-seated transformations that have come to be commonplace in the chemistry of  $\Delta^4$ -isoxazolines.<sup>20</sup> They showed that the products from the treatment of 1,2-dimethylbenzimidazole 3-oxide with dimethyl acetylenedicarboxylate or with methyl propiolate at room temperature were betaines. No  $\Delta^4$ -



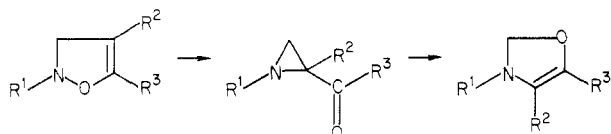
isoxazoline was detected but it was presumed to be a first-formed intermediate. (No isoxazoline has been isolated from any heteroaromatic *N*-oxide cycloaddition.) A similar result was observed in the reaction of phenanthridine 5-oxides with acetylenic esters.<sup>21,22</sup>

These results led Huisgen to reexamine the thermal behavior of isoxazoline **44**, which had been isolated and characterized earlier. Indeed a betaine **58** was also

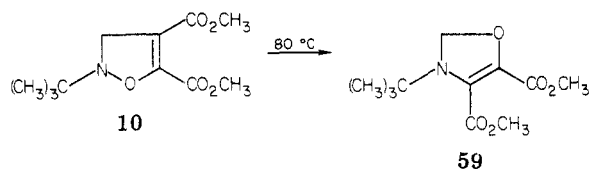


obtained when 44 was heated briefly in refluxing ethyl acetate.<sup>23</sup>

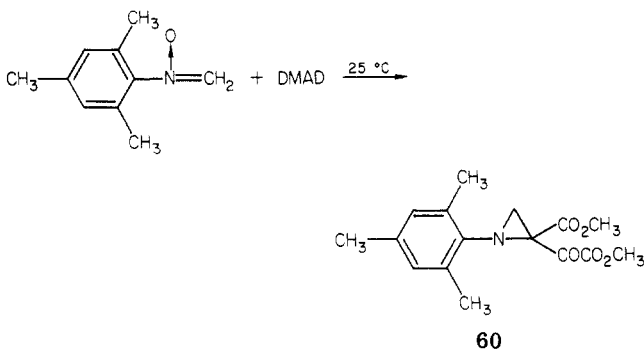
At about this point an important communication appeared that clarified much of the confusion in this area and also served to alert future workers to the problems that might be encountered. Baldwin and his co-workers described the interconversion of 4-isoxazolines to 2-acylaziridines and thence in some cases to 4-oxazolines.<sup>24</sup> The 4-isoxazoline 10, formed rapidly



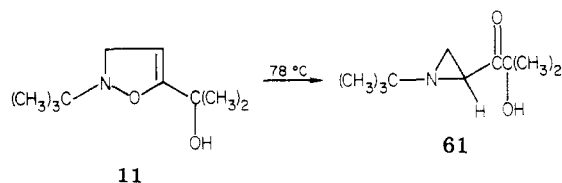
at 0 °C by addition of *N*-*tert*-butylnitron to dimethyl acetylenedicarboxylate, (DMAD), isomerized at 80 °C to the 4-oxazoline 59. In contrast when *N*-mesitylni-



trone was treated with DMAD at room temperature it furnished directly the acylaziridine 60. Finally, isox-



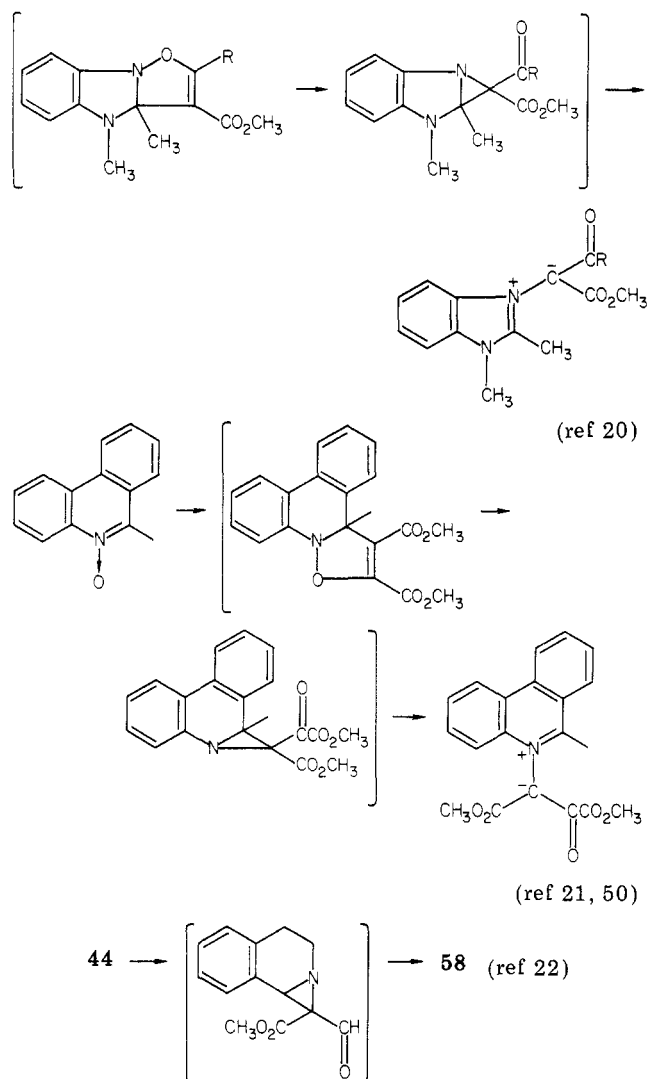
azoline 11 was formed at 74 °C from 3-methylbutyn-3-ol and isomerized at 78 °C to the acylaziridine 61.



The key intermediate in these reactions is the acylaziridine since most of the prior and subsequent observations of rearrangements of 4-isoxazolines can be interpreted in terms of it. For example, the previously cited results of Kano,<sup>20</sup> Acheson,<sup>21</sup> and Huisgen<sup>22,23</sup> are readily rationalized in Scheme I.

Further rearrangement to the 4-oxazolines is much less common but recently some additional examples have been reported. For clarity we will divide the rest of this section into those reactions that yield acylaziridines and those that produce their transformation products.

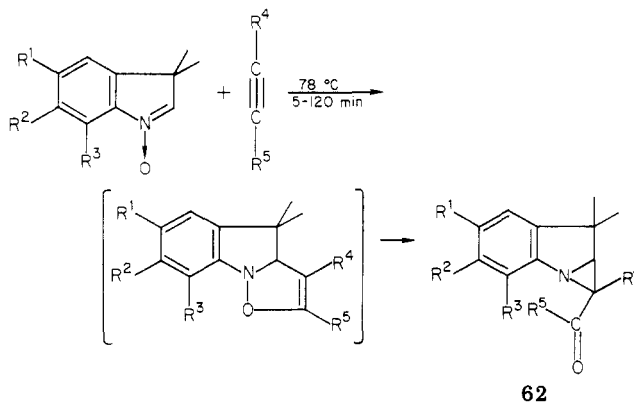
Scheme I



## B. 4-Isoxazolines → 2-Acylaziridines

In addition to the examples cited above several others are scattered through the literature. However, their relationships are obscured by subsequent reactions of the acylaziridines that lead to very different kinds of final products.

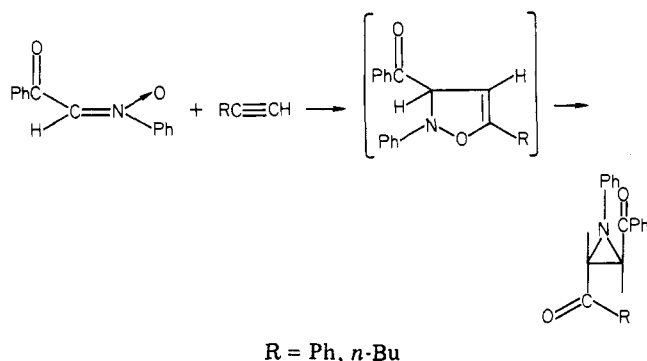
Some straightforward examples of this interconversion are the formation of aziridinodihydroindoles 62



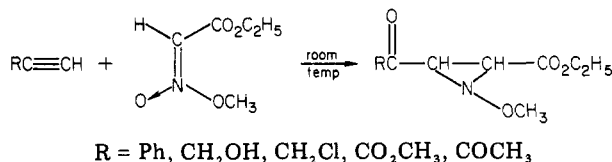
from the reaction of indolenine *N*-oxides with acetylenes<sup>25</sup> (Table IV).

Niklas reported that the reaction of *C*-benzoyl-*N*-phenylnitron with phenylacetylene and 1-hexyne

yielded acylaziridines.<sup>26</sup> Only the trans isomers were detected.

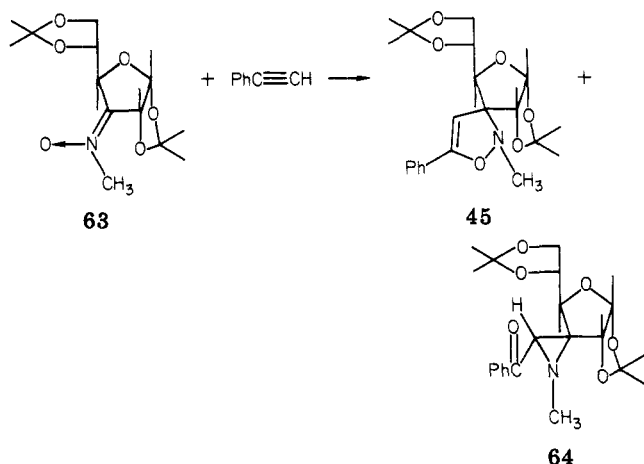


Russian workers first reported that nitronic esters condensed with acetylenes to produce acylaziridines<sup>27</sup>

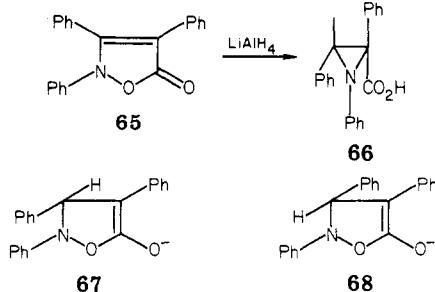


and recognized that this was due to isomerization of the first-formed 4-isoxazoline. This reaction was explored in more detail by Greé and Carrie<sup>28</sup> with respect to the stereochemistry of this ring contraction. This work will be examined in more detail when the mechanism of this isomerization is discussed.

In the sugar series the condensation of nitrone **63** and phenylacetylene produced a small amount of the acylaziridine **64** along with the 4-isoxazoline, **45**.<sup>18</sup>



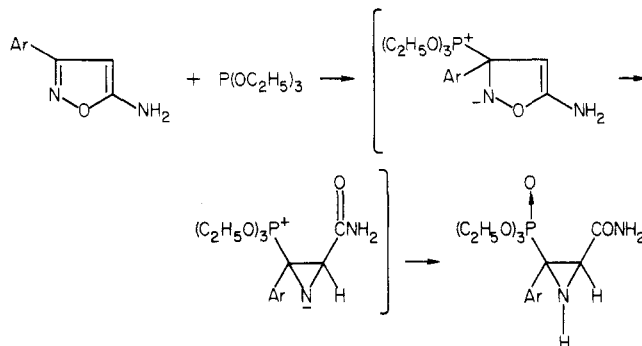
An indirect approach to the 4-isoxazoline nucleus also produced an acylaziridine. Reduction of 2,3,4-triphenyl-3-isoxazolin-5-one **65** with lithium aluminum hydride yielded *trans*-2-carboxy-1,2,3-triphenylaziridine (**66**).<sup>29</sup> Enolates **67** and **68**, resulting from 1,4-hydride



attack, are proposed to be the key intermediates. It is of some interest to the mechanism of the ring con-

traction that only one aziridine isomer **66**, probably the more stable one, was obtained from what must reasonably be assumed to be two stereoisomeric intermediates, **67** and **68**.

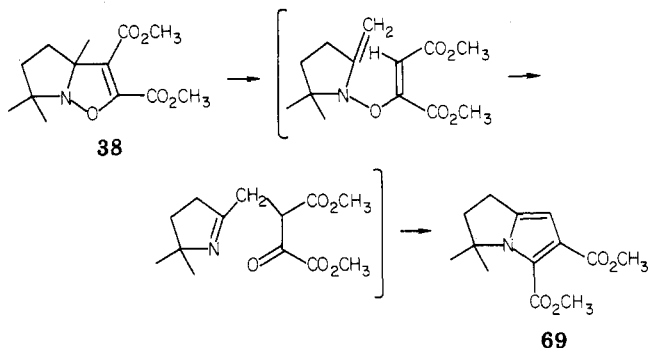
The formation of aziridinylphosphonates from the reaction of 5-aminoisoxazoles with triethyl phosphite may involve a 4-isoxazoline intermediate although the authors suggest a thermal isoxazole-azirine isomerization as a first step.<sup>30</sup>



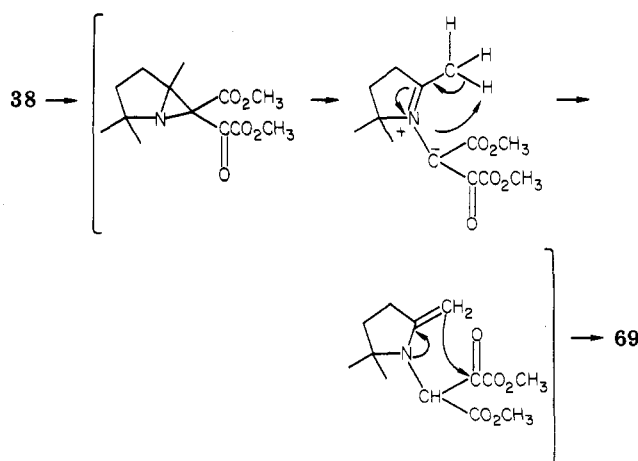
### 1. Further Transformations of Acylaziridines

**a. Pyrrole Formation.** It has been illustrated above that the acylaziridines that arise by isomerization of the first-formed 4-isoxazoline may in some cases exist as open-chain betaines. In addition the betaines may undergo further reactions leading to pyrroles.

Grigg reported the thermal conversion of isoxazoline **38** to pyrrole **69**<sup>31</sup> and suggested a reaction path in-

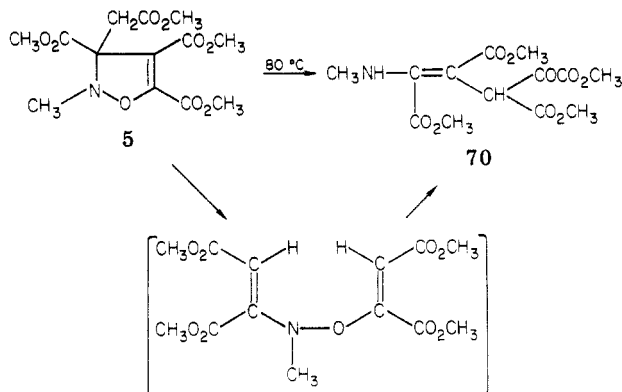


volving enamine formation, a hetero-Cope rearrangement, and finally cyclization. The ring-opening step, proposed also by Winterfeldt<sup>32</sup> (vide infra), lacks mechanistic precedent, however. Alternatively, isomerization to the acylaziridine followed by ring opening to a betaine, a proton shift, and ring closure would produce the same product:

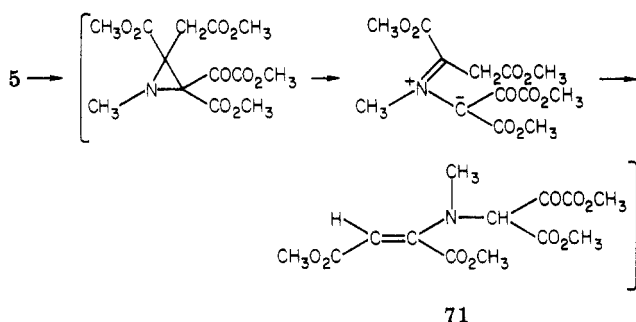


A similar pathway can rationalize pyrrole formation in the phenanthridine system.<sup>21</sup>

Later Winterfeldt and co-workers<sup>13</sup> showed that at least in two cases the product pyrrole cannot arise by the acylaziridine route. Heating isoxazoline **5** at 80 °C converted it to the enamino ketone **70**. The acyl-

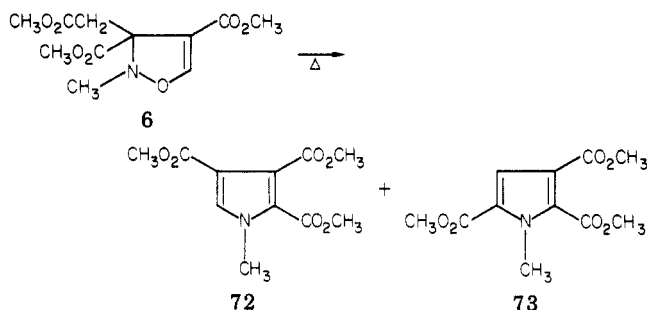


aziridine route would produce amino ketone **71** which was explicitly excluded. However, both **70** and **71**



would produce the same pyrrole.

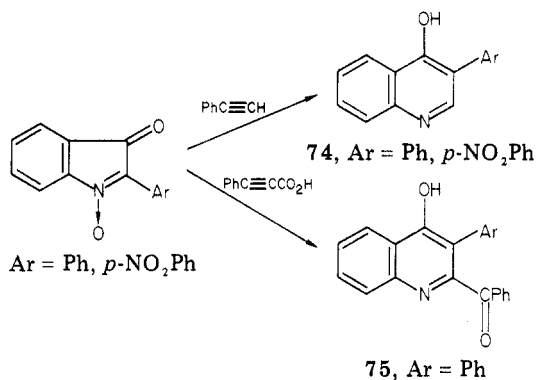
However, the related isoxazoline **6**, when heated at 110 °C, was converted to a mixture of two pyrrole derivatives, **72** and **73**, the former arising by the hetero-



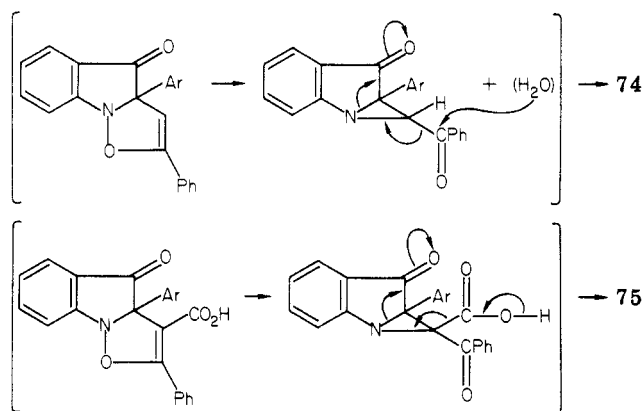
Cope process and the latter from the acylaziridine.<sup>32</sup>

Pyrroles were also obtained from 4-isoxazolines by Kano and co-workers<sup>6</sup> but the structures of their products could all be rationalized from acylaziridine intermediates. Apparently, this isoxazoline-pyrrole transformation also can occur in the mass spectrometer.<sup>11</sup>

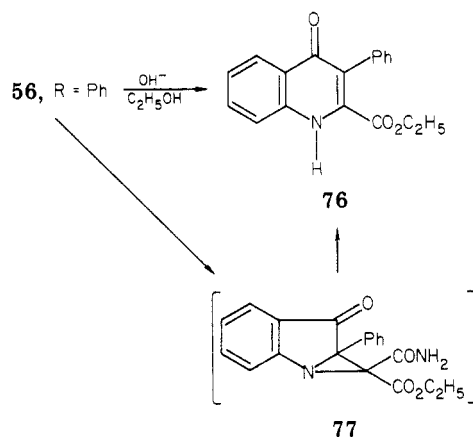
**b. Ring Expansion.** Another group of reactions that probably involves 2-acylaziridine intermediates are those of isatogens with acetylenes. Noland and Modler<sup>4</sup> reported that 2-phenyl- and 2-(*p*-nitrophenyl)isatogen reacted with phenylacetylene to yield 3-phenyl- and 3-(*p*-nitrophenyl)-4-quinolinol (**74**), respectively, while 2-phenylisatogen reacted with phenylpropionic acid to produce 2-benzoyl-3-phenyl-4-quinolinol (**75**). The reactions appeared to be catalyzed by propionic acid.



These results may be satisfactorily rationalized by the following scheme:<sup>33</sup>



Bond and Hooper<sup>5</sup> observed a similar reaction leading to **74**, Ar = Ph, when 2-phenylisatogen was treated with (*o*-nitrophenyl)acetylene. *o*-Nitrobenzoic acid was obtained as a byproduct. Hooper also reports in a review article<sup>17</sup> that isoxazoline **56** (section IIC4) is converted to quinolone **76** by the action of base in ethanol.

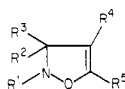


Possibly **77** is an intermediate but one might have thought the ester group rather than the amido group would have been lost from **77**.

Modler<sup>34</sup> also reported that ethyl phenylpropionate yielded ethyl 4-hydroxy-3-phenylquinolone albeit in low yield. Similarly,<sup>34</sup> treatment of the hydrate (section V) of the 2-phenylisatogen-dimethyl acetylenedicarboxylate adduct with acid yielded the methyl ester corresponding to **76**.

The susceptibility of these acylaziridines to decylation-ring expansion is undoubtedly due to the presence of the second  $\alpha$ -carbonyl group. The acylaziridines derived from dihydroindoles<sup>25</sup> are not re-

TABLE I. Monocyclic 4-Isoxazolines

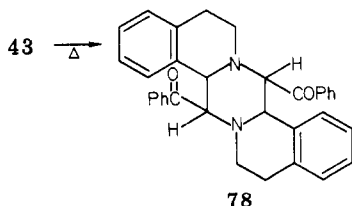


compd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	mp (bp), °C	method <sup>c</sup>	ref
1	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	CO <sub>2</sub> CH <sub>3</sub>	H	oil	A	23
2	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	CO <sub>2</sub> CH <sub>3</sub>	oil	A	23
3	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	CO <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>	oil	A	26
4	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	CO <sub>2</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	104	A	26
5	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	89	A	13
6	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	H	70	A	13
7	CH <sub>3</sub>	H	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	oil	A	13
8	CH <sub>3</sub>	H	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	H	A	A	13
9	CH <sub>3</sub>	H	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	H	(70/0.3)	A	32
10	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	A	A	24
11	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	(CH <sub>3</sub> ) <sub>2</sub> COH	H	A	A	24
12	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	C2	11
13	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	H	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	A	15
14	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	H	oil	A	15
15	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	CN	H	A	A	15
16a	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	H	CN	A	A	15
16b	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	CN	H	A	A	15
17 <sup>a</sup>	CH <sub>3</sub>	H		H	C <sub>6</sub> H <sub>5</sub>	115-117	A	18
18 <sup>b</sup>	CH <sub>3</sub>	H		H	C <sub>6</sub> H <sub>5</sub>	oil	A	71
19	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
20	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
21	CH <sub>3</sub>	H	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil, (148-150/710 mm)	B1	6, 73
22	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
23	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	67-68, 81	B1	6, 73
24	CH <sub>3</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
25	CH <sub>3</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> - <i>p</i>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
26	CH <sub>3</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>	H	C <sub>6</sub> H <sub>5</sub>	76-77	B1	6
27	CH <sub>3</sub>	H	CH <sub>2</sub> CH=CH <sub>2</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
28	CH <sub>3</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
29	C <sub>2</sub> H <sub>5</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	116-117	B1	6
30	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
31	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	oil	B1	6
32	CH <sub>3</sub>	H	H	H	C <sub>6</sub> H <sub>5</sub>	oil	B2	7
33	C <sub>2</sub> H <sub>5</sub>	H	H	H	C <sub>6</sub> H <sub>5</sub>	oil	B2	7
34	(CH <sub>3</sub> ) <sub>3</sub> C	H	H	H	C <sub>6</sub> H <sub>5</sub>	oil	B2	7
35	C <sub>6</sub> H <sub>5</sub>	H	H	H	CH <sub>3</sub>	72-75	B2	7
36	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	H	oil	B2	7

<sup>a</sup> One of two diastereoisomers at C3. <sup>b</sup> Mixture of diastereoisomers at C3. <sup>c</sup> Letters refer to appropriate sections in text, section II.

ported to undergo this kind of transformation.

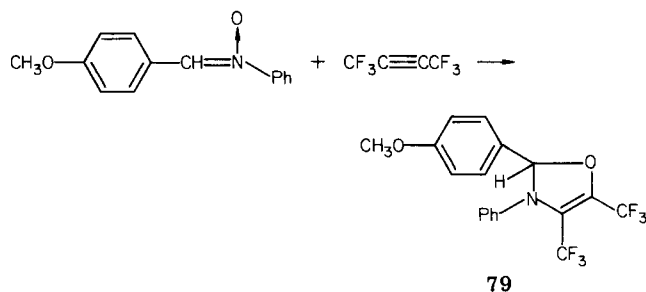
**c. Dimer Formation.** Niklas<sup>26</sup> observed some cases in which the betaines dimerized to piperazine derivatives. When isoxazoline 43 was heated at 120 °C in dimethylformamide, piperazine 78 was obtained in 56% yield. (Various stereoisomers were in the mixture.)



Similar dimers were obtained from isoxazolines 41 and 42.

**d. 4-Oxazoline Formation.** Although Baldwin<sup>24</sup> pointed out that 4-oxazolines are more stable than 4-isoxazolines, few examples of this isomerization have actually been reported. Recently Niklas<sup>26</sup> observed a few more examples (Table V).

The cycloaddition of hexafluoro-2-butyne with *N*-phenyl-*C*-(*p*-anisyl)nitron was reported to lead directly even at room temperature to the 4-oxazoline 79.<sup>35</sup> This



product could be converted to 2,3-bis(trifluoromethyl)indole by treatment with silica gel.

In a related reaction it has been shown that *N*-aryl-isoxazolin-3-ones 80 rearrange quantitatively at 150 °C to *N*-aryloxazolin-2-ones 81.<sup>36</sup> A mechanism involving a 2-acyl- $\alpha$ -lactam was suggested. Benzo derivatives of 80 rearrange similarly in a light-catalyzed reaction.<sup>37</sup> Similar photocatalyzed isomerizations have also been

TABLE II. Polycyclic 4-Isoxazolines

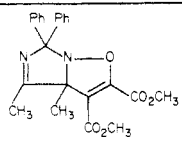
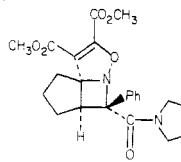
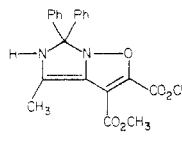
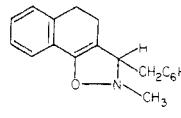
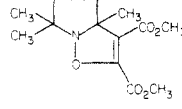
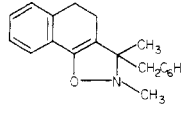
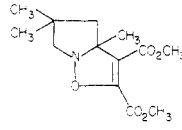
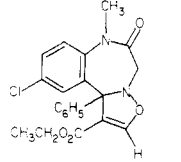
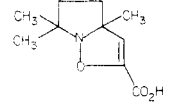
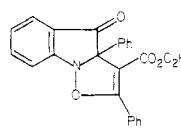
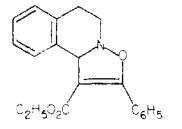
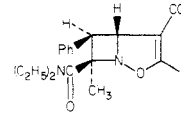
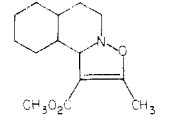
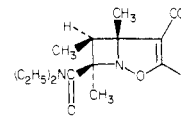
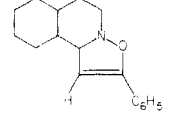
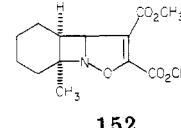
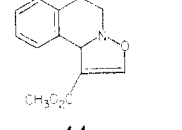
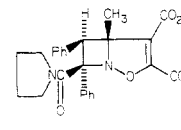
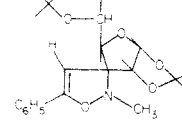
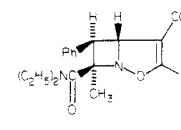
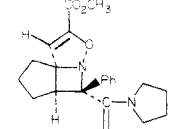
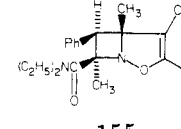
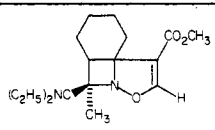
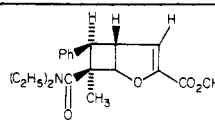
compd	mp (bp), °C	method <sup>c</sup>	ref	compd	mp (bp), °C	method <sup>c</sup>	ref
	oil	A	60		140-142	A	45
<b>37a</b>				<b>46b</b>			
	174-175	A	60		oil	B1	6
<b>37b</b>				<b>47</b>			
		A	31		oil	B1	6
<b>38</b>				<b>48</b>			
		A	31		141-142 <sup>b</sup>	A	54
<b>39</b>				<b>49</b>			
		A	31		146-147	A	23, 24
<b>40</b>				<b>50</b>			
	127-128 <sup>a</sup>	A	23		78-80	A	72
<b>41</b>				<b>150</b>			
	43-45	A	26, 67		114-116	A	72
<b>42</b>				<b>151</b>			
	99.5-101	A	26		76-78	A	72
<b>43</b>				<b>152</b>			
	53-55	A	23		142-144	A	72
<b>44</b>				<b>153</b>			
	147-149	A	18		> 135 dec	A	72
<b>45</b>				<b>154</b>			
	124-126	A	45		103-105	A	72
<b>46a</b>				<b>155</b>			



TABLE II (Continued)

compd	mp (bp), °C	method <sup>c</sup>	ref	compd	mp (bp), °C	method <sup>c</sup>	ref
	83.5-85.5	A	72		oil	A	72
156				157			

<sup>a</sup> Originally<sup>22</sup> reported as a 3-isoxazoline as a result of a prototropic shift but later established as an authentic 4-isoxazoline.<sup>15</sup> <sup>b</sup> Mixture of two diastereoisomers caused by low rate of ring inversion. <sup>c</sup> Letters refer to appropriate sections in text, section II.

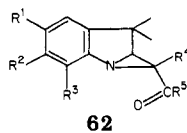
TABLE III. Spectral Properties of 4-Isoxazolines

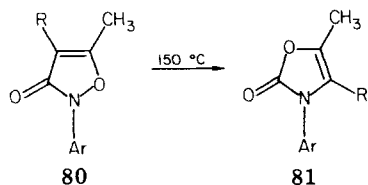
compd	IR, C=C, cm <sup>-1</sup>	NMR substituent, $\delta$ (multiplicity, <i>J</i> , Hz)	ref	compd	IR, C=C, cm <sup>-1</sup>	NMR substituent, $\delta$ (multiplicity, <i>J</i> , Hz)	ref
Monocyclic <sup>a</sup>							
1		R <sup>5</sup> , 4.82 (s)	23	20	1649	R <sup>2</sup> , 1.30 (s); R <sup>4</sup> , 5.17 (s)	6
2		R <sup>4</sup> , 5.78 (d, <i>J</i> = 3)	23	21	1649	R <sup>2</sup> , 3.83 (qd, <i>J</i> = 6.2, 2.4); R <sup>4</sup> , 5.19 (d, <i>J</i> = 2.4)	6
3	1660	R <sup>3</sup> , 4.78 (d, <i>J</i> = 3) R <sup>2</sup> , 2.29 (d, <i>J</i> = ~1) R <sup>3</sup> , 4.89 (br s)	26	22	1682	R <sup>2</sup> , 3.66 (td, <i>J</i> = 6.5, 2.7); R <sup>4</sup> , 5.23 (d, <i>J</i> = 2.7)	6
4	1635	R <sup>3</sup> , 5.10 (s)	26	23	1649	R <sup>2</sup> , 4.82 (d, <i>J</i> = 2.4); R <sup>4</sup> , 5.32 (d, <i>J</i> = 2.4)	6
5	1660	R <sup>3</sup> , CH <sub>2</sub> , (q [AB], <i>J</i> = 15)	13	24	1649	R <sup>2</sup> , 3.93 (td, <i>J</i> = 7.0, 2.4); R <sup>4</sup> , 5.13 (d, <i>J</i> = 2.4)	6
6	1640	R <sup>3</sup> , 7.6; R <sup>3</sup> , CH <sub>2</sub> , 3.04	13	25	1646	R <sup>2</sup> , 3.93 (td, <i>J</i> = 7.0, 2.4); R <sup>4</sup> , 5.15 (d, <i>J</i> = 2.4)	6
7	1665	R <sup>2</sup> , 4.52	13	26	1646	R <sup>2</sup> , 3.92 (td, <i>J</i> = 6.6, 2.8); R <sup>4</sup> , 5.14 (d, <i>J</i> = 2.8)	6
8	1640	R <sup>3</sup> , 7.32; R <sup>2</sup> , 4.33	13	27	1649	R <sup>2</sup> , 3.78 (td, <i>J</i> = 6.6, 2.5)	7
9		R <sup>5</sup> , 7.22; R <sup>2</sup> , 4.30	32	28	1670	R <sup>2</sup> , 3.76 (m); R <sup>4</sup> , 1.82 (d, <i>J</i> = 1.1)	6
10	1660	R <sup>2</sup> , R <sup>3</sup> , 4.18 (s)	24	29	1671	R <sup>2</sup> , R <sup>3</sup> , 2.18-3.12 (m); R <sup>4</sup> , 1.37 (s)	6
11		R <sup>2</sup> , R <sup>3</sup> , 3.97 (d, <i>J</i> = 2.0); R <sup>5</sup> , 4.68 (t, <i>J</i> = 2.0)	24	30	1649	R <sup>2</sup> , 1.20 (s); R <sup>4</sup> , 5.10 (s)	6
12	1648		11	31	1677	R <sup>2</sup> , 1.17 (s); R <sup>4</sup> , 1.68 (s)	6
13	1640	R <sup>2</sup> , R <sup>3</sup> , 4.00 (d, <i>J</i> = 2.5); R <sup>4</sup> , 5.60 (t, <i>J</i> = 2.5)	15	32	1651	R <sup>2</sup> , R <sup>3</sup> , 4.05 (m); R <sup>4</sup> , 5.18 (t, <i>J</i> = 2.5)	7
14	1650	R <sup>2</sup> , R <sup>3</sup> , 4.00 (d, <i>J</i> = 2); R <sup>5</sup> , 7.00 (t, <i>J</i> = 2)	15	33			
15		R <sup>2</sup> , 4.78 (d, <i>J</i> = 2); R <sup>5</sup> , 7.10 (d, <i>J</i> = 2)	15	34	1657	R <sup>2</sup> , R <sup>3</sup> , 4.12 (d, <i>J</i> = 2.5); R <sup>4</sup> , 5.15 (t, <i>J</i> = 2.5)	7
16a		R <sup>2</sup> , R <sup>3</sup> , 4.05 (d, <i>J</i> = 2); R <sup>4</sup> , 5.62 (t, <i>J</i> = 3)	15	35	1651		7
16b		R <sup>2</sup> , R <sup>3</sup> , 4.05 (d, <i>J</i> = 2); R <sup>5</sup> , 7.0 (t, <i>J</i> = 2)	15	36	1618	R <sup>2</sup> , 4.93 (t, <i>J</i> = 2.5); R <sup>4</sup> , 4.64 (t, <i>J</i> = 2.5); R <sup>5</sup> , 4.97 (d, <i>J</i> = 2.0)	7
17	1640	R <sup>3</sup> , 4.08 (dd); R <sup>4</sup> , 5.08 (d, <i>J</i> = 2.2)	18	37a		CH <sub>3</sub> (C3), 1.48 (s)	
18		R <sup>4</sup> , 5.33 (d, <i>J</i> = 1.2) <sup>a</sup> R <sup>4</sup> , 5.10 (d, <i>J</i> = 1.2) <sup>a</sup>	71				
19	1681	R <sup>2</sup> (H), 3.66 (qq, <i>J</i> = 6.2, 1.1); R <sup>4</sup> , 1.86 (d, <i>J</i> = 1.1)	6				
Polycyclic <sup>b</sup>							
41	1625	H (C3), 5.97 (s)	23	150		H (C3), 4.84 (d, <i>J</i> = 3.9)	72
42	1631	H (C3), 5.80 (s); CH <sub>3</sub> (C5), 2.61 (s)	26	151		CH <sub>3</sub> (C3), 1.15 (s)	72
43	1642	H (C3, C4), 5.72 (d, <i>J</i> = 2.2); 5.30 (d, <i>J</i> = 2.2)	26	152			72
44	1628	H (C3), 5.54 (br s) <sup>c</sup>	23	153		CH <sub>3</sub> (C3), 1.25 (s)	72
45	1655	H (C4), 5.10 (s)	18	154		H (C3), 4.72 (d, <i>J</i> = 3.9) H (C5), 7.57 (d, <i>J</i> = 1.8)	72
46a	1635	H (C4), 6.00 (s)	45	155		CH <sub>3</sub> (C3), 1.04 (s)	72
46b	1640		45	156		H (C5), 7.52 (s)	72
47	1682	H (C3), 3.88 (t, <i>J</i> = 6.4)	6	157		H (C5), 7.46 (s)	72
49	1615 (?)	H (C5), 6.91, 6.98 (br s)	54			H (C3), 4.77 (m)	72
50	1617		23			H (C4), 6.15 (d, <i>J</i> = 2.4)	

<sup>a</sup> The compound numbers and substituent designations correspond to those in Table I. <sup>b</sup> The compound numbers correspond to those in Table II. <sup>c</sup> The C5 hydrogen is hidden in the aromatic absorption.

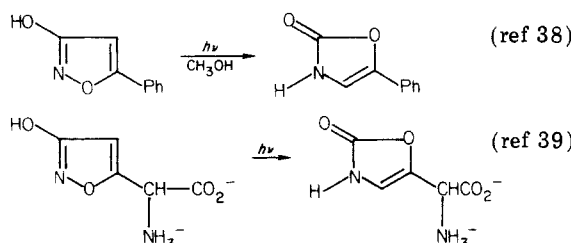
TABLE IV. Acylaziridines from Indolenine Oxides<sup>25</sup>

compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	mp, °C	yield, %
62a	H	(CH <sub>3</sub> ) <sub>3</sub> C	H	Ph	H	116	57
62b	(CH <sub>3</sub> ) <sub>3</sub> C	H	(CH <sub>3</sub> ) <sub>3</sub> C	Ph	H	160	59
62c	H	(CH <sub>3</sub> ) <sub>3</sub> C	H	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	CH <sub>3</sub>	102	97
62d	(CH <sub>3</sub> ) <sub>3</sub> C	H	(CH <sub>3</sub> ) <sub>3</sub> C	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	CH <sub>3</sub>	154	97
62e	H	(CH <sub>3</sub> ) <sub>3</sub> C	H	Ph	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	90	88





reported in the 3-hydroxyisoxazoline series.<sup>38,39</sup> Pos-



sibly these reactions occur by way of the NH tautomer.

### C. Mechanism of 4-Isoxazoline-2-Acylaziridine Transformation

In his seminal communication Baldwin<sup>24</sup> did not comment on the mechanism of these rearrangements except to indicate that he expected an *N*-aryl substituent to enhance the rate of the isoxazoline-acylaziridine reaction. Clearly Baldwin identified that reactivity (lability) of the 4-isoxazoline system with the relatively low thermochemical stability of the N-O bond which he expected to be further weakened with aryl substitution.

Sims and Houk noted that the 4-substituted isoxazolines **14**, **15**, and **16b** rearranged readily at 88 °C while their 5-substituted counterparts were stable under the same conditions.<sup>15</sup> They considered that these results provided further confirmation of the structures of the products implying that a substituent at C4 has a stabilizing effect on the transition state or intermediates in the transformation. (However, Niklas concluded that potential radical-stabilizing groups seemed to have little effect.<sup>26</sup>)

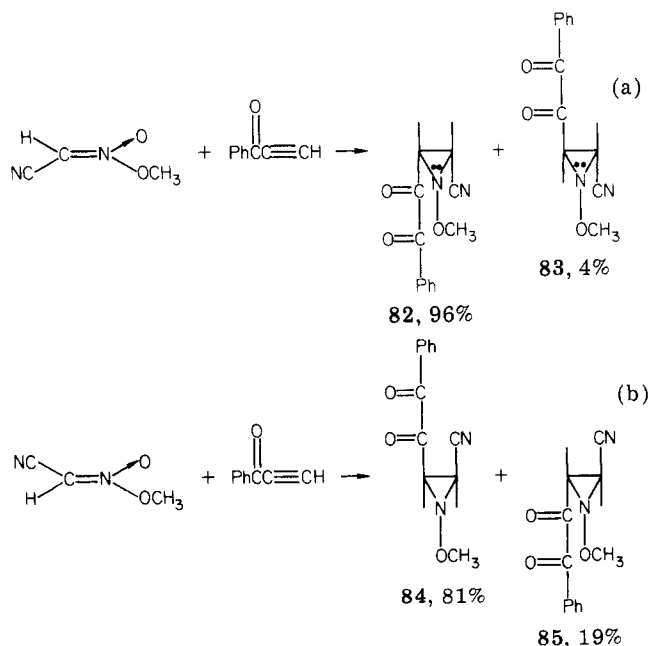
Three kinds<sup>40</sup> of mechanisms may be envisioned: (1) rate-determining heterolytic N-O bond cleavage; (2) rate-determining homolytic N-O bond cleavage; or (3) a concerted reaction, allowed or forbidden. The first alternative, which is akin to the transition state of the Stieglitz rearrangement, cannot be involved in the conversion of isoxazoline **44** to betaine **61** (section IVA) since Niklas<sup>26</sup> has shown that this reaction is insensitive to solvent polarity. (This is the only isoxazoline reaction for which any kinetic data are available so it must be used as a model for all these reactions.)

The other two possibilities have been most often invoked but both have some problems associated with them. Just as the trimethylene problem has proved a most tantalizing and elusive one for researchers of cyclopropane isomerization, 1-pyrazoline decompositions, and the vinylcyclopropane-cyclopentene rearrangement, so the biradical that would be obtained by homolytic cleavage of the relatively weak (~55 kcal/mol) N-O bond has intrigued investigators in this area. Since Huisgen was able to show considerable analogy in energetics between the vinylcyclopropane-cyclopentene rearrangement and that of *N*-cyclopropylimines to 1-pyrrolines,<sup>42,43</sup> and that trimethylene biradicals were implicated in the latter,<sup>42</sup> it is tempting to extrapolate these results to the isoxazoline-acyl-

aziridine rearrangements. However, there are some pitfalls along this path.

Firstly, we are dealing with an irreversible ring contraction rather than a ring enlargement. Secondly, since some of these isomerizations occur under very mild conditions (room temperature or below), the activation energies must be very low and highly sensitive to the nature of substituents. Just what the nature of the substituent effect, however, is difficult to establish. Clearly *N*-aryl groups sensitize the system to rearrangement. Only three *N*-aryl-4-isoxazolines, **30**, **35**, and **50**, have been well characterized and they rearrange readily. (Others have been claimed but their structures have not been proven.<sup>3,14</sup>) Similarly, *N*-alkoxy groups are highly activating.<sup>27,28</sup> On the other hand, Niklas<sup>26</sup> found that placing radical-stabilizing groups at the 4-position of the isoxazolines had very little effect. (However, compare the results of Sims and Houk.<sup>15</sup>) Finally, a significant difference between the analogues referred to above and the isoxazoline-acylaziridine system is that there are competing processes in the former which involve isomerization within the cyclopropane ring itself. No such reactions have been detailed for the present system and it is by no means certain in the former systems that common intermediates for the various processes are required. That is, the cyclopropane isomerizations could be occurring by way of biradical species while the ring expansions could be concerted.

Greé and Carrié<sup>28</sup> have argued the case against biradical or even "extended diradical"<sup>44</sup> intermediates based largely on the high stereospecificity of reactions a and b. The complete retention of the stereochemical



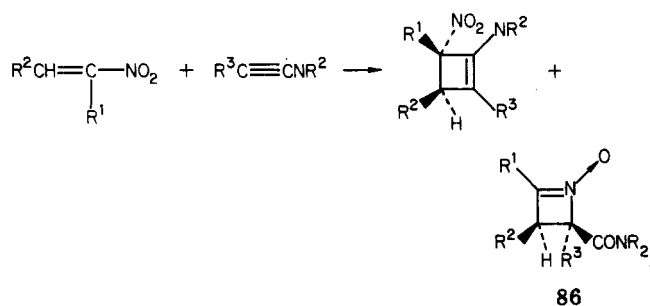
relationship of the cyano and methoxy functions in the two reactions with no crossover places great restrictions on any intermediate in the isoxazoline ring contraction step. Also the high preference for the formation of the aziridine in both series with the acyl and cyano groups cis to each other led Greé and Carrié to argue that the reactions must be concerted. However, while the formation of **82** and **85** may be due to an "allowed"  $\sigma_2^s + \pi_2^a$  process, that of **83** and **84** demands a "forbidden"  $\sigma_2^s + \pi_2^s$  mode. While such forbidden concerted reac-

tions have been shown to be competitive in other systems, it is not very clear in the present case, if these reactions are indeed concerted, why one reaction (b) favors the "forbidden" route, while the other (a) follows the "allowed" path. These results may simply emphasize that, in addition to a lack of knowledge of substituent effects on sigmatropic processes, we still have problems when hetero atoms are involved in such reactions.

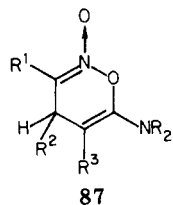
Cum, Uccella, and co-workers have also argued for the concerted mechanism in the reductive route to acylaziridines from isoxazolinones.<sup>29</sup> However, their system is much less compelling because their *N*-aryl substituent favors rather than hinders nitrogen inversion and it has to be argued that the aziridine invertomers are obtained stereospecifically but invert rapidly after formation.

The least satisfactory feature of the concerted process is the severe restricted orbital environment in which it must occur. In order for the sigma orbitals of the N—O bond, which start nearly orthogonal to the  $\pi$  orbitals, to begin to interact with those orbitals considerable twisting of the N—O bond must occur so that it is not clear how much stabilization from this interaction is available early in the transition state. A least motion pathway in which oxygen lone-pair interactions with the  $\pi$  bond are important very early in the process needs to be examined. One of the difficulties in sorting out concerted processes in hetero atom systems is determining whether lone pair orbitals in the starting materials become bonding orbitals in the products.

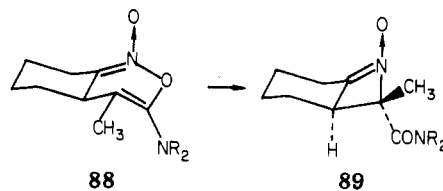
A mechanistically related reaction has been reported recently. Ynamines react with nitroalkenes to give mixtures of unstable 4-nitrocyclobutenes and 2,3-dihydroazete 1-oxides 86.<sup>45</sup> The latter were proposed to



arise by rearrangement of the first formed Diels–Alder-type cycloadduct 87. This 1,3-N→C shift in a sys-

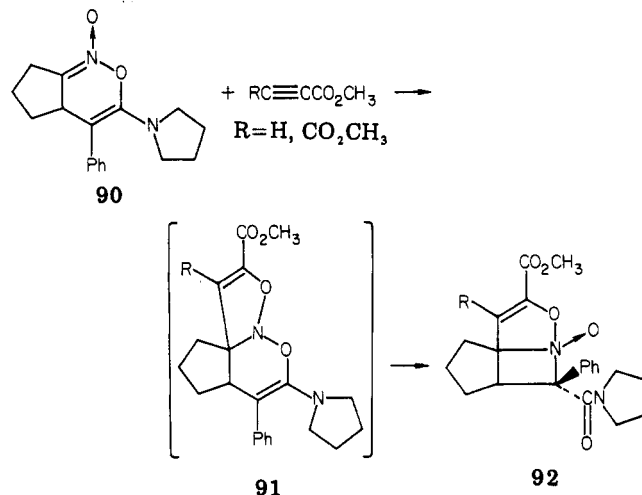


tem, N—O—C=C, parallels the 4-isoxazoline–acylaziridine transformation and the authors, noting the stereospecificity of the ring contraction that places the carboxamido group and the larger group at C-3 cis to each other, propose that this is brought about by a forbidden concerted  $\sigma_2 + \pi_2$  process from a conformation of the ring in which  $R_2$  occupies an axial position in order to minimize the  $R^1$ ,  $R^2$ , and  $R^3$  interactions. In the case of the formation of 89, in which the bulky groups at C2 and C3 are trans, it is assumed that the



same process is followed but that the preferred chair conformation of the cycloadduct 88 forces  $R^2$  of 87 to be equatorial which leads to the trans geometry in the azete oxide.

An interesting contrast between the isoxazoline and oxazine ring contractions was observed in the reactions of the stable oxazine oxide 90 with DMAD and methyl propiolate that produced isoxazolines 92.<sup>45</sup> Since the



oxazine does not ring contract under the conditions of the cycloaddition, it must be assumed that the cycloadduct 91 is formed and then isomerizes. Thus, at least in this system the azete formation has the lower activation energy. However, in this fused system, the barrier to ring contraction of the isoxazoline might well be prohibitively high.

Ironically, the process that in principle is more analogous to the vinylcyclopropane–cyclopentene rearrangement, the acylaziridine–4-oxazoline rearrangement, has not been investigated in any detail. Partly that is because there are only a few examples available. But what is known suggests that this isomerization is very different from its carbon counterpart in that it probably proceeds through a zwitterionic intermediate, the azomethine ylide derived from ring opening of the acylaziridine. This significant difference is related to the presence of the hetero atoms and signals caution in attempting simple extrapolations from carbon to hetero atom systems.

#### D. More Extensive Rearrangements

In 1971 the condensation of dimethyl acetylenedicarboxylate with the novel "nitron" 93 produced a remarkable result in that the bicyclic ketone 94 was produced in high yield.<sup>46</sup> This result was rationalized

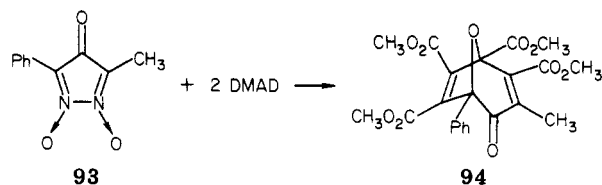
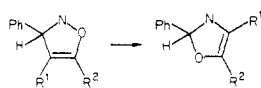


TABLE V.



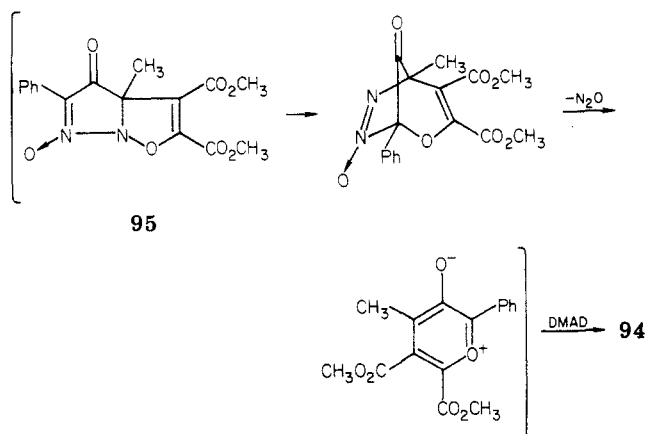
R	R <sup>1</sup>	R <sup>2</sup>	conditions
CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	Ph	a
Ph	CO <sub>2</sub> CH <sub>3</sub>	Ph	b
Ph	H	CO <sub>2</sub> CH <sub>3</sub>	c

<sup>a</sup> Isoxazoline heated in boiling mesitylene (160 °C).

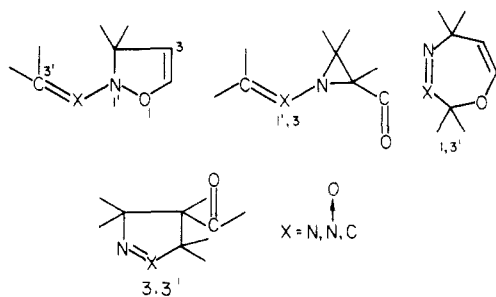
<sup>b</sup> Obtained directly from cycloaddition reactions in boiling ethyl acetate; no 4-isoxazoline isolated.

<sup>c</sup> Obtained directly from cycloaddition reactions in boiling benzene; no 4-isoxazoline isolated.

by assuming that the first-formed (but not detected or isolated) 4-isoxazoline **95** had rearranged not by the customary 1,3-shift but by an alternative 1,3'-shift that was followed by loss of nitrous oxide and a second cycloaddition. Although not recognized at that time, it

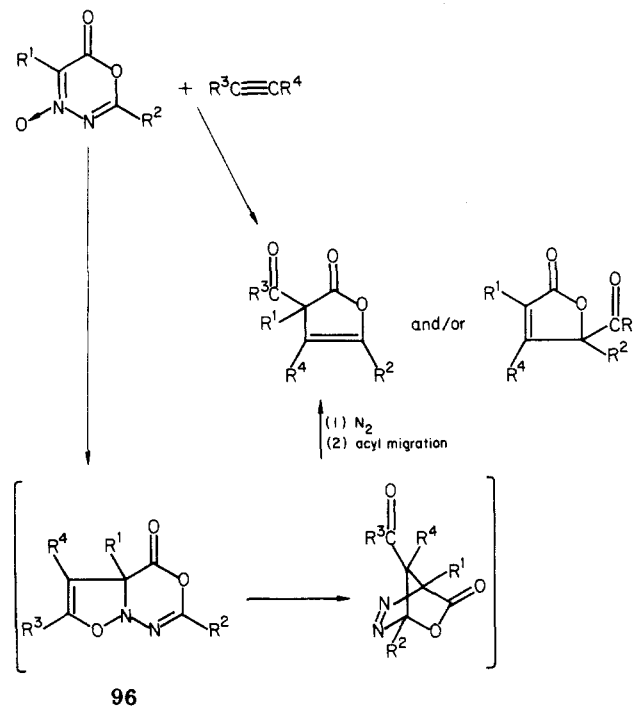


became apparent subsequently that attachment of a  $\pi$  system to the nitrogen of a 4-isoxazoline allowed alternative rearrangement pathways of interesting diversity. These may be generalized as follows:



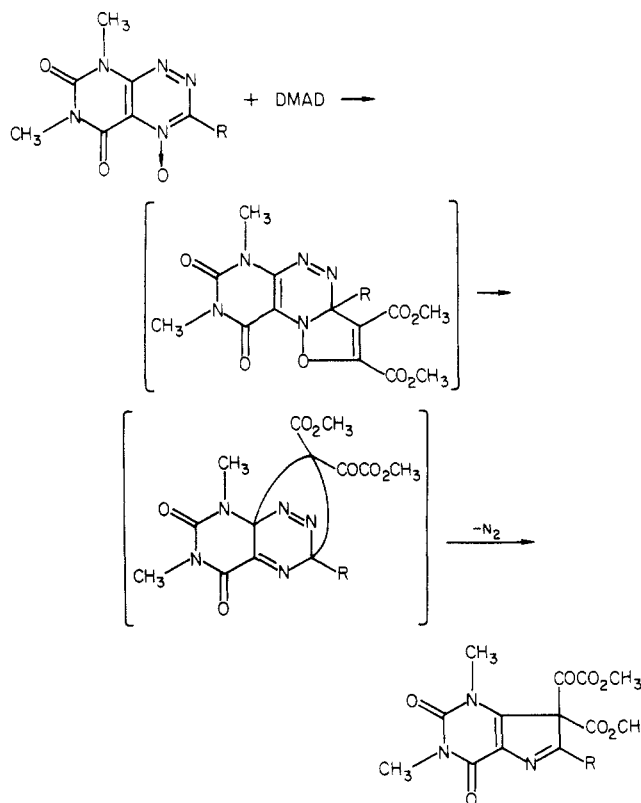
There are too few examples at this time to make any sensible generalizations about the course a particular reaction may take but some trends are apparent and will be examined in individual cases. For example, while isoxazoline **95** might have followed any of these paths, the 3,3' route (the hetero-Cope rearrangement) would have required the formation of a cyclobutanone and is presumably avoided for that reason. However, because of the polarized bonds present in most of the known examples, we must not assume that concerted sigmatropic (or biradical) processes are involved in these reactions. Indeed there is some reason to believe these reactions may be of a much more ionic type than the simple 1,3 reactions discussed above. This point will be examined later.

A six-membered ring isomer of **93** reacted with a wide variety of acetylenes to produce acylbutenolides.<sup>47</sup> This remarkable result has been rationalized as due first to the 3,3' rearrangement followed by loss of nitrogen from intermediate **96** and further rearrangement. Presum-

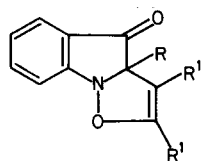


ably the larger ring size of the starting "nitron" allows the more favorable 3,3' process (formation of a carbonyl group) to proceed.

A somewhat related reaction has been reported in the cycloaddition of fervenulin 4-oxides.<sup>48</sup> In this case loss of nitrogen from the bicycloheptene intermediate produces a pyrazole without further rearrangement.

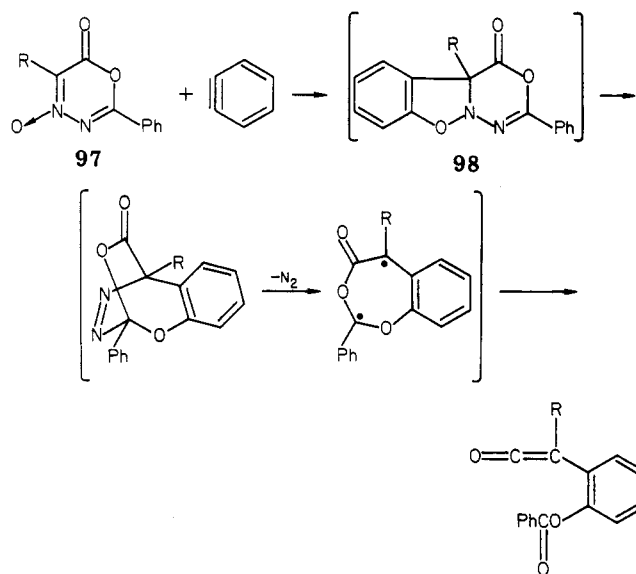


The isotogen cycloadditions investigated by Noland and Modler<sup>4,34</sup> also produced a system allowing either a 3,3' or a 1,3' rearrangement,



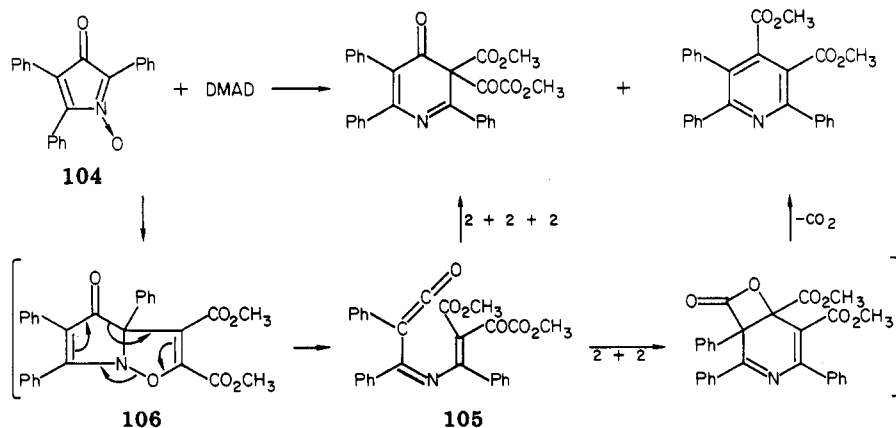
but neither is observed. Presumably the former is inhibited by the forced cyclobutanone formation while both it and the latter would require disruption of the aromaticity of the benzo ring.

The preservation of aromaticity in the rearrangement step similarly seemed to direct the rearrangement of the presumed isoxazoline intermediate **98** in the cycloaddition of **97** and benzyne.<sup>49</sup> In this case a 1,3' process

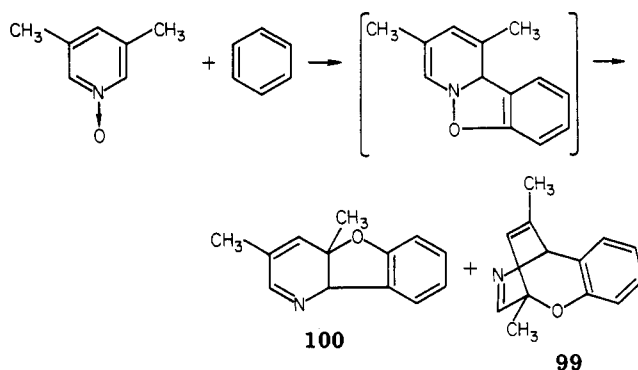


rather than a 3,3' process is followed also. The ultimate products, benzofurans and coumarones, have been shown to be obtained from the ketene prepared by an independent route. In addition the ketene also could be trapped by the benzyne precursor.<sup>49</sup>

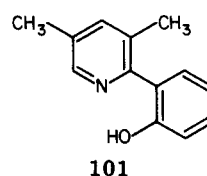
Heteroaromatic amine oxides that were first examined in cycloaddition reactions with alkynes produced betaines directly.<sup>20-22</sup> Later Abramovitch and co-workers examined a wider range of amine oxides and observed some novel rearrangements.<sup>41</sup>



An intermediate **99** related to **98**, was isolated when 3,5-lutidine 1-oxide was treated with benzyne under mild conditions.<sup>50</sup> A product of a 1,5 shift, **100**, was

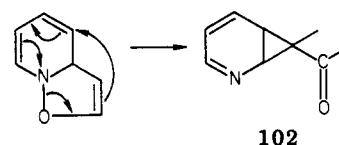


also obtained. Upon heating both **99** and **100** gave **101**,

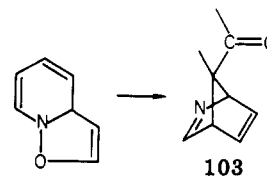


presumably by  $\beta$ - or vinylogous  $\beta$ -elimination. Such eliminations are discussed in more detail in section IV.

In the case of unsubstituted pyridine N-oxides and simple alkynes, intermediates were not isolated but  $\beta$ -alkylation products as well as  $\alpha$ -alkylation products (as exemplified by **101**) were obtained. Abramovitch has proposed<sup>41</sup> that the former arise from the presumed isoxazoline intermediate by another type of sigmatropic process,  $\sigma_2 + \pi_2 + \pi_4$ , producing **102**. Alternatively,



a 3,3' process leading to **103** might be involved. This



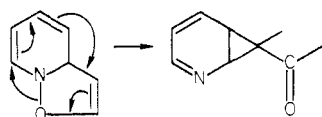
common intermediate could be the precursor of both

the 2- and 3-alkylation products. Efforts were made to detect such an intermediate without success.<sup>74</sup> In addition, 3-alkylation was also observed with quinoline *N*-oxide<sup>51</sup> and an intermediate of type 103 could not account for that result. The eight-electron process is analogous to one proposed for the opening of another isoxazoline which will be discussed below.

It is of some interest that 3-arylation is also the main process observed in the reaction of pyridine 1-oxide and benzyne.<sup>50</sup> Whether that product arises from an intermediate analogous to 102 or 103, in either case the rearrangement involves disruption of the aromatic system of the migrating aryl group, a process not observed in the examples cited above.

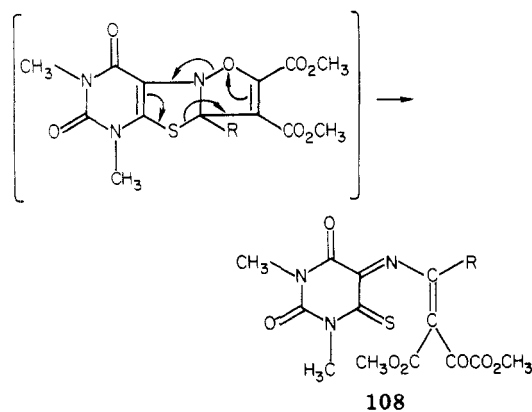
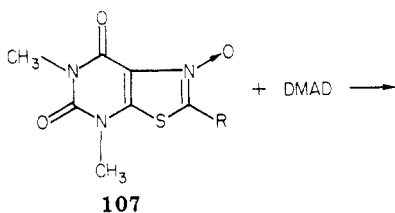
A different type of rearrangement process was observed in the reaction of nitron 104 with dimethyl acetylenedicarboxylate.<sup>52</sup> Two principal products were obtained but it is believed that they arise from a common intermediate 105 derived by ring opening of the 4-isoxazoline 106. Similar cleavages of oxabicyclocadionones are known but require higher temperatures; presumably the weak N–O bond in the present system accounts for its greater lability.

Note the similarity in the ring opening of the isoxazoline in this case and the rearrangement of the isoxazolines derived from heteroaromatic *N*-oxides:



In those cases three  $\pi$  bonds and a single bond in the starting material are transformed to three  $\pi$  bonds and a single bond in the product. In the present case two  $\pi$  bonds and two  $\sigma$  bonds in the starting isoxazoline are transformed to four  $\pi$  bonds in the product.

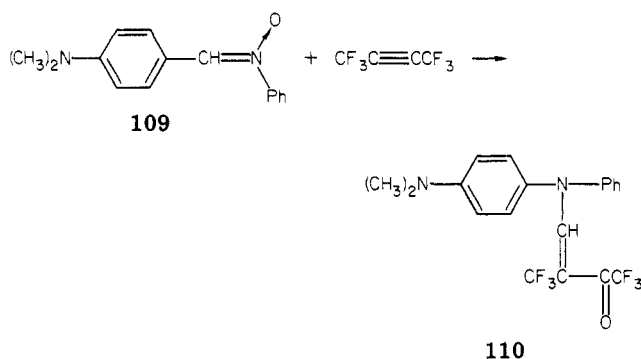
Another example of this kind has recently been reported. Thiazole oxide 107 and DMAD produce 108, which may undergo further cyclization.<sup>53</sup> (The reaction



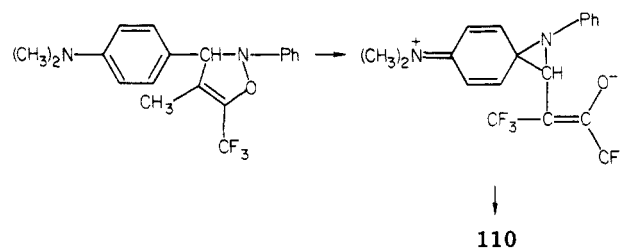
path illustrated here represents a slight modification of that proposed by the original investigators.)

Finally, there have recently been reported two examples of 1,2 rearrangements of 4-isoxazolines. Nitron

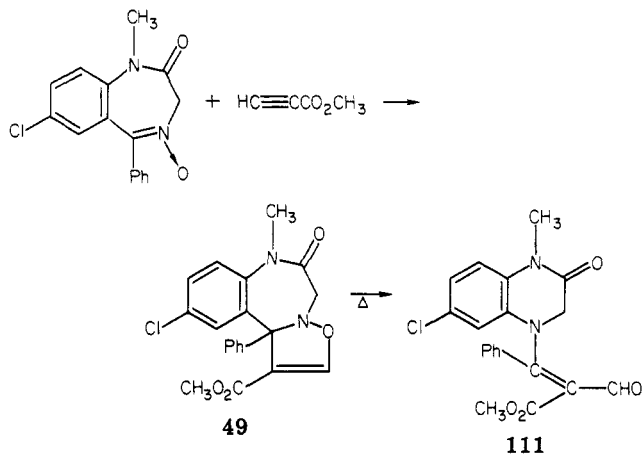
109 and hexafluoro-2-butyne produced enamine 110.<sup>35</sup>



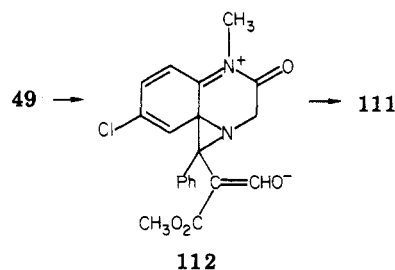
No yields were given. The following reaction path was suggested:



The isoxazoline 49 was stable enough to be isolated from the reaction of valium *N*-oxide with methyl propiolate but it rearranged smoothly at 80 °C to produce the quinoxaline derivative 111.<sup>54</sup> Again a spiro inter-



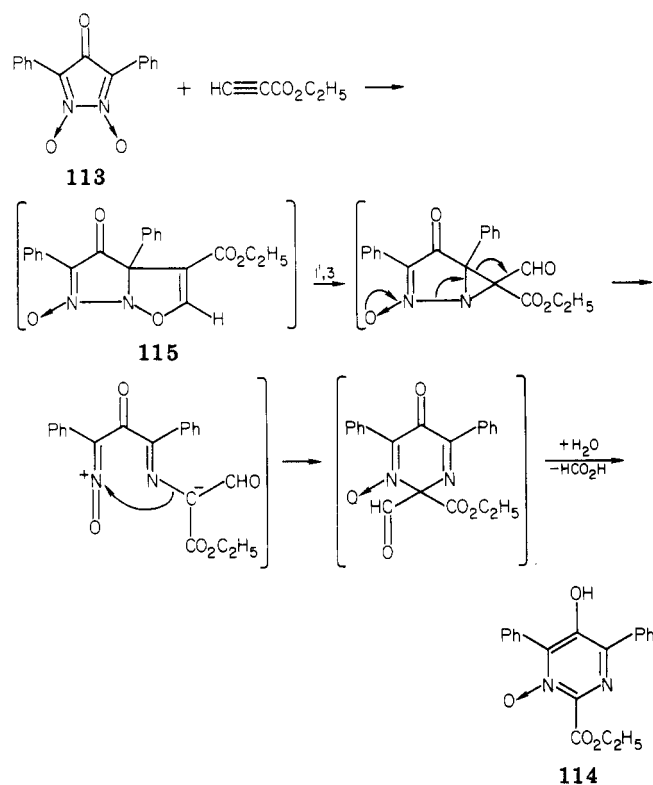
mediate 112 may be involved. The Japanese workers<sup>35</sup>



attributed this reaction path to the presence of the electron-donating *p*-dimethylamino group. In the valium *N*-oxide example, the geometry of isoxazoline 49 placed the migrating phenyl group nearly anti-periplanar to the leaving enolate group and this was thought to provide a driving force but in this case also an electron donor is in an activating position.

Finally, one unique rearrangement has been observed. In the reaction of 113 with ethyl propiolate, in addition

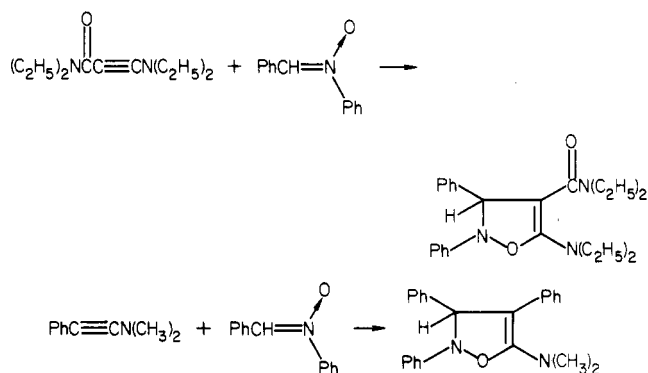
to the oxabicyclooctadienone analogous to that obtained with dimethyl acetylenedicarboxylate (cf., 94), a novel nitrogen-containing product, 114, was also obtained consistently.<sup>55</sup> While probably many speculative mechanisms may be envisioned, one that has the appeal of involving the partitioning of a common intermediate (115) is



What causes the isoxazolines to fragment by so many different paths? Are we in a position to make any generalizations? At this point it does not appear possible to respond meaningfully to these questions. The highly polar nature of many of the isoxazolines, e.g., 95, 96, and 106, probably biases them to much more polar, even ionic transition states, that may not be available to less polar systems. The systems that lose nitrogen or similar gaseous fragments readily from some intermediate may follow reaction paths that develop from intermediates formed in very small concentrations but irreversibly, while in other systems the same intermediates do not proceed to products because they are formed reversibly. More examples must become available before a completely unifying picture emerges.

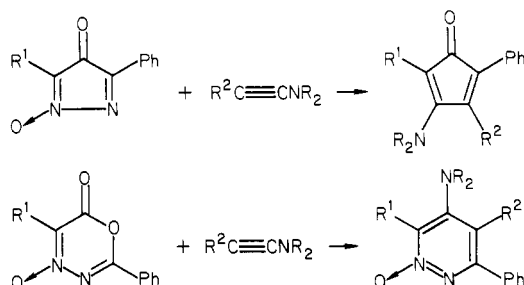
### E. Nitrono-Ynamine Adducts

The reaction of nitrones with ynamines needs special comment. Viehe and co-workers have reported two cycloadditions of *C*-phenyl-*N*-phenylnitrono with ynamines and in both instances claimed isoxazolines as the products.<sup>56,57</sup> In neither case were the products characterized and no spectral data were reported. Since these reports appeared before the lability of isoxazolines had been generally recognized, it is possible that the products actually isolated have rearranged structures. Two structural features support this suggestion. Firstly, as indicated earlier, *N*-arylisoxazolines are particularly prone to rearrangement. Secondly, if the development of the carbonyl double bond is felt in the decomposition transition state, it would seem that these isoxazolines, which would lead to an amide carbonyl group, would



be particularly labile. Further investigation seems warranted.

In the special case of the reactions of ynamines with diazacyclopentadienone monoxides and oxazinone *N*-oxides, isoxazolines are not formed. Rather the products seem to be best explained by stepwise reactions initiated by nucleophilic addition of the ynamine to the electrophilic imine carbon of both systems. The diazacyclopentadienone *N*-oxides yield aminocyclopentadienones<sup>58</sup> and the oxazinone *N*-oxides lead to aminopyridazine *N*-oxides.<sup>59</sup> These reactions super-



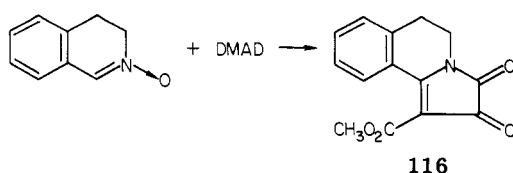
ficially appear to be of the Diels-Alder type but the regiochemistry is better explained by stepwise processes involving ionic intermediates.

## IV. Prototropic Ring Opening of Isoxazolines

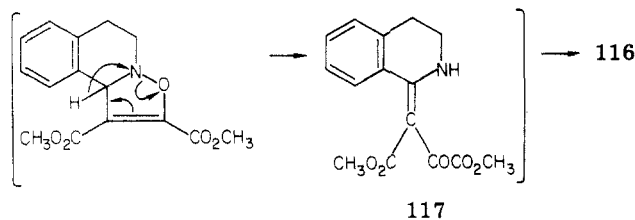
### A. Acid- and Base-Catalyzed Reactions

Early investigations of 4-isoxazolines were complicated by the fact that the thermal isomerizations were sometimes superseded by other decomposition pathways that now seem to be prototropic processes that can be accelerated by acids or bases. However, since the products are isomeric with those obtained from the thermal acylaziridine-forming process, there was some early confusion as to the true course of these reactions. Such prototropic processes occur when hydrogen is a substituent at carbon 3 of the isoxazoline.

Treatment of dihydroisoquinoline *N*-oxide with DMAD produced a pyrrolinedione derivative 116.<sup>23</sup> It

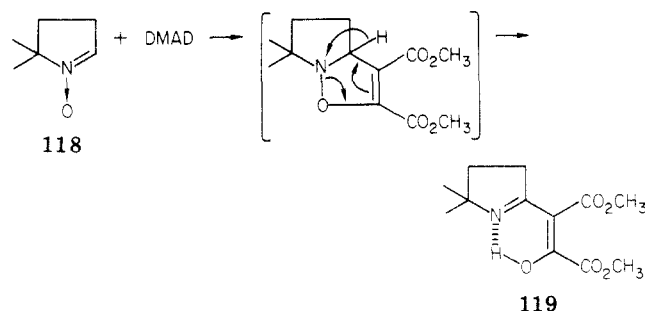


was proposed that the first-formed isoxazoline ring opened to the enamine 117 which subsequently cyclized. (Recall that the structurally similar adduct 44 from

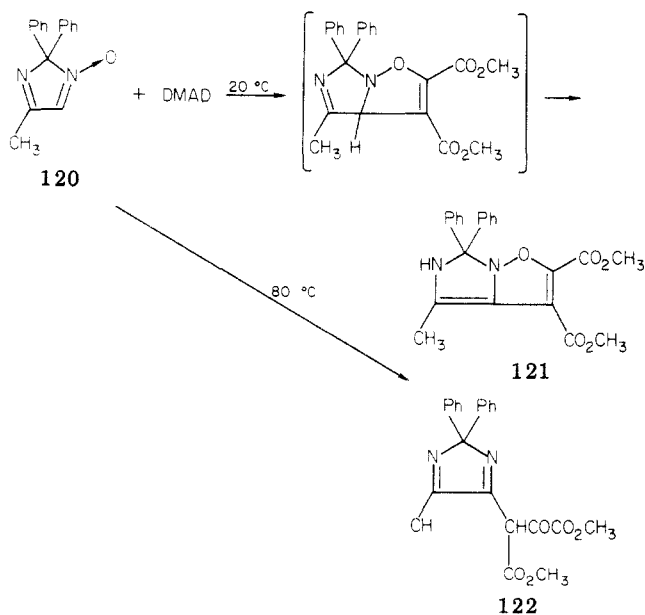


methyl propiolate did not react this way but rearranged via the acylaziridine to the betaine.<sup>23</sup> However, when **44** was treated with methanol and sulfuric acid, an enamine similar to **117** was obtained. Similarly the ethyl phenylpropiolate adduct **41** was converted to an enamine.<sup>26)</sup>

Similarly Grigg observed that pyrroline oxide **118** and DMAD produced an alkylated pyrroline derivative **119**.<sup>31</sup>

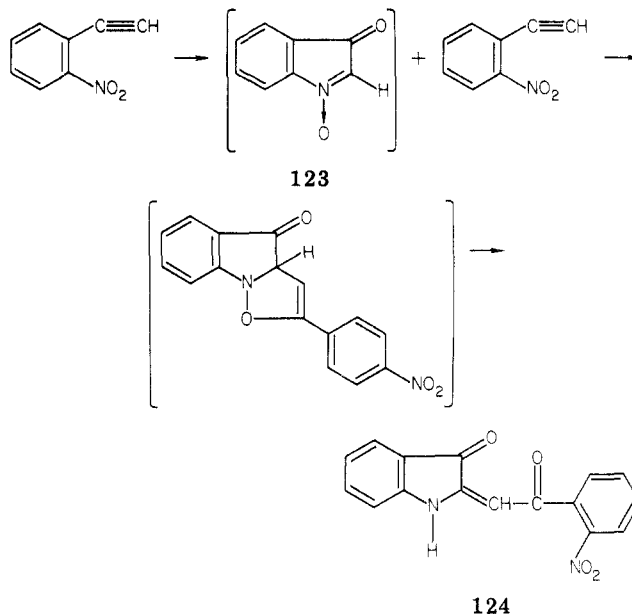


While the imidazole oxide **120** condensed slowly with DMAD at 20 °C to give isoxazoline **121**, it formed the ring-opened product **122** when the reaction was conducted in boiling benzene.<sup>60</sup> It was not reported

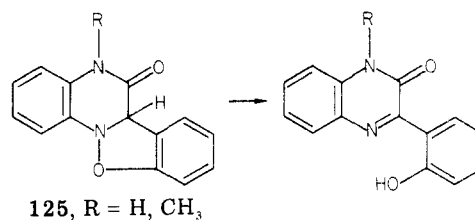


whether **121** opens to **122** under these conditions. In any event this ring opening is probably a base-catalyzed rather than a thermal process. Kano and co-workers also observed ring-opened enamino ketone side products in their preparation of isoxazolines from isoxazolium salts and Grignard reagents.<sup>6</sup>

Bond and Hooper observed that the cyclization of (*o*-nitrophenyl)acetylene, a reaction that should lead to the parent of the isotogen family **123**, produced instead the enamino ketone **124**.<sup>5</sup> They proposed the following process:

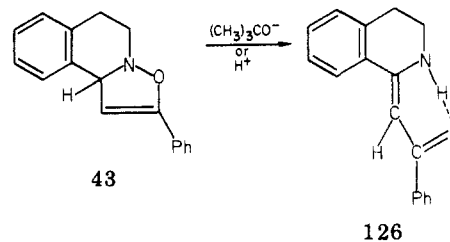


A similar ring opening of quinoxalin-3(4*H*)-one 1-oxide-benzynes adducts **125** (not isolated) yielded 2-

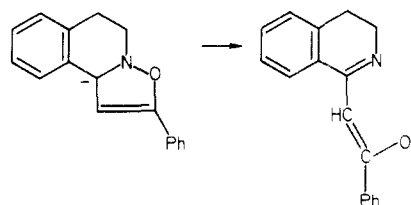


arylquinoxalin-3(4*H*)-ones.<sup>61</sup>

Niklas used the isolable dihydroisoquinoline *N*-oxide-phenylacetylene adduct **43** to study this process.<sup>26</sup>



Treatment of this adduct with an equimolar amount of potassium *tert*-butoxide in *tert*-butyl alcohol for 15 h at room temperature yielded the open chain enamine **126** in 82% yield. This product also could be obtained from **43** by heating in acetic acid containing a drop of sulfuric acid. The base-catalyzed process is envisioned by Huisgen as an example of the heteropentadienyl anion retroelectrocyclization.<sup>62</sup>



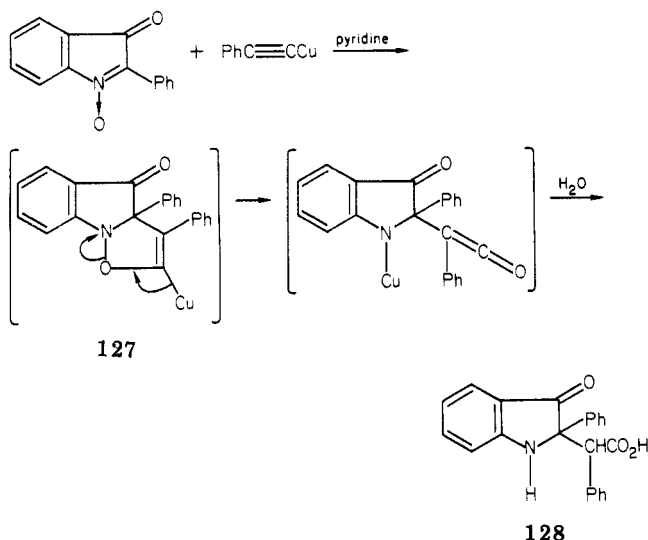
## B. Formation of $\beta$ -Lactams

The fate of cuprous acetylide-nitrone adducts appears related to these prototropic processes in that high



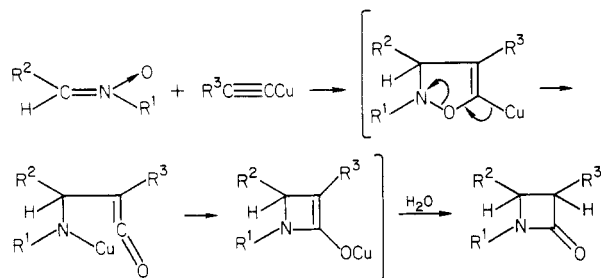
electron density is developed in the ring. In these adducts it is generated through the polarity of the carbon-copper bond at C5 rather than by removal of a proton at C3.

There are two reports of the reaction of cuprous acetylides with nitrones. Bond and Hooper reported that 2-phenylisatogen reacted with cuprous phenylacetylide in pyridine to yield the indolone **128**, which is presumed to arise from isoxazoline **127**.<sup>5</sup> (A discrete



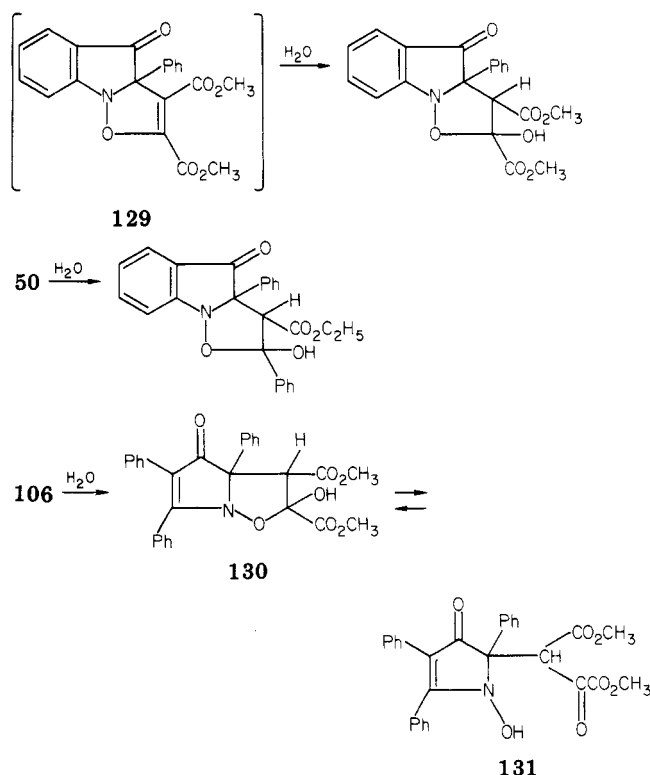
ketene intermediate was not proposed by these authors<sup>5</sup> who pictured hydrolysis of isoxazoline **127** as leading directly to the final product. We have included it to related this reaction to the more general one described below.)

More recently it has been reported that more conventional nitrones react with cuprous acetylides to yield  $\beta$ -lactams.<sup>63</sup> While the authors invoke an isoxazoline as an intermediate, their proposed conversion of it to the final product has no parallel in isoxazoline chemistry. However, if the route described for the isatogen reaction is followed,  $\beta$ -lactam formation can be readily accounted for (note the regiochemistry of these additions is the same as that observed with 2-phenylisatogen.)



## V. Addition Reactions of Isoxazolines

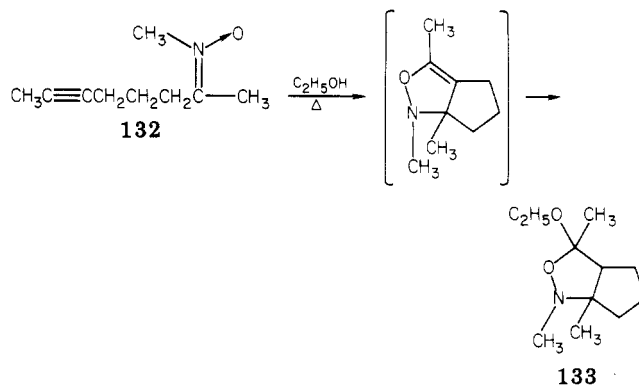
Jones apparently was the first to observe the addition of hydroxylic compounds to the 4-isoxazoline double bond,<sup>64</sup> but Modler made the first systematic investigation of the reaction.<sup>34</sup> Hydrates of isoxazolines **129**,<sup>34</sup> **50**,<sup>22</sup> and **106**<sup>52</sup> have been reported, but only parent isoxazoline **50** has been isolated in the free state. Hydrates may also have been obtained from isoxazolines in the indolenine oxide series; 1:1:1 indolenine



oxide-acetylene-water products were isolated in two cases<sup>25</sup> but were not characterized. Adducts of **50** with methanol and ethanol have also been isolated.<sup>34</sup> (A reported product<sup>23</sup> of **50** and methanol may be the methanol adduct but its reported melting point of 128.5–130 °C is not the same as that of Modler,<sup>34</sup> 145–148 °C.)

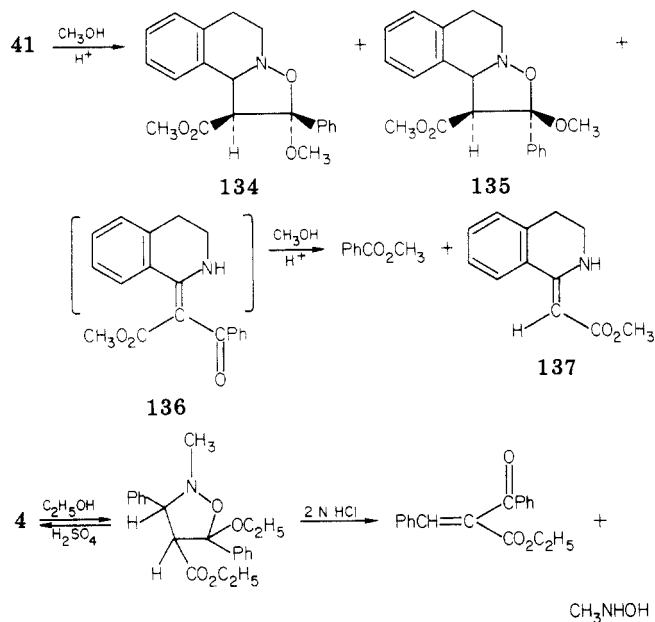
In the case of adduct **130** it was apparent from its spectral properties that not only was it a mixture of diastereomers but it was also in equilibrium with the open chain keto hydroxylamine **131**.<sup>52</sup>

LeBel and Banucci obtained ethanol adduct **133** from the intramolecular cycloaddition of *C*-methyl-*C*-4-hexynyl-*N*-methyl-nitrone (**132**) in ethanol.<sup>65</sup> Niklas<sup>26</sup>



isolated diastereomeric methanol adducts (**134** and **135**) from isoxazoline **41** when it was refluxed in methanol containing 7% sulfuric acid. Small amounts of methyl benzoate and enamine **137** were also obtained; their formation is attributed to methanolysis of the enamine **136** expected of the ring opening described above [cf., **43** → **126** (section IVA)]. The yield of these products increased as the acid concentration increased.

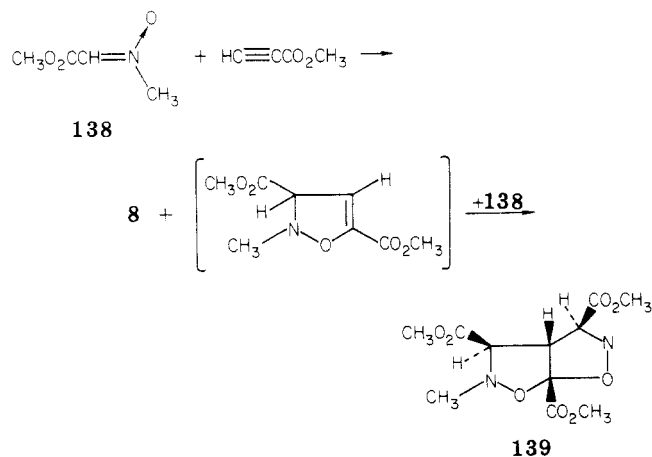
The ethanol adduct of isoxazoline **4** was obtained in a similar manner and was converted back to its parent in concentrated sulfuric acid.<sup>26</sup> However, it was cleaved



in hot 2 N hydrochloric acid to ethyl 2-benzoylcinnamate and methylhydroxylamine (acetal-like cleavage).<sup>26</sup>

The role of the hydrates in the further reactions of some of the isoxazolines is obscure. They may play a crucial role in the ring expansions in the isotogen series where a deacylation must occur to accomplish aromatization of the final product. We have proposed that this occurs *after* the isoxazoline-acylaziridine ring contraction but Modler<sup>34</sup> has argued that the ring contraction-ring expansion occurs from the hydrate. In other cases where solvolysis is not a part of the total process it seems more likely that the reaction of isoxazoline with hydrolytic solvents is simply a side reaction.

In one instance the cycloaddition of first-formed isoxazoline to unreacted nitron was observed. The reaction of methyl propiolate with *C*-carbomethoxy-*N*-methylnitron (138) produced heterocycle 139 along with the normal adduct 8.<sup>13</sup> The other primary cy-



cloadduct 8 also underwent further reaction but the structure of that product was not established.

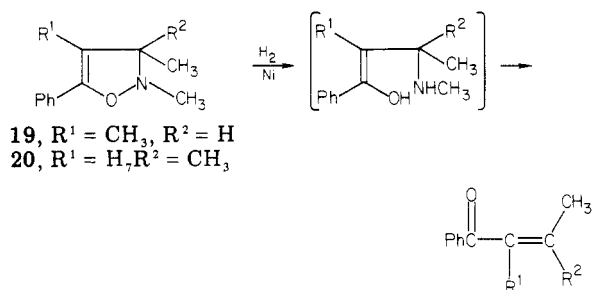
## VI. Reduction of 4-Isoxazolines

### A. Catalytic Hydrogenation

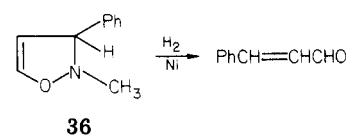
The first reduction of 4-isoxazolines was claimed in 1950 when it was proposed that the first step in the

reduction of isoxazoles was the formation of 4-isoxazolines, which could not be isolated but suffered further reduction by N-O bond cleavage.<sup>66</sup>

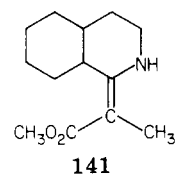
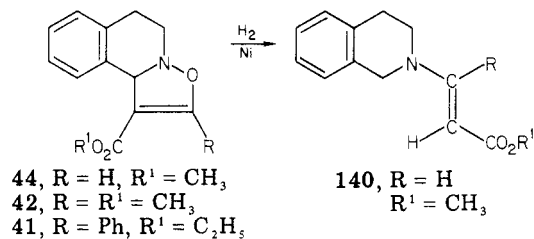
Kano and co-workers first reported the hydrogenation of authentic 4-isoxazolines using it as a tool to establish the structure of their products.<sup>6</sup> They observed ring cleavage and elimination of amines which was rationalized as follows:



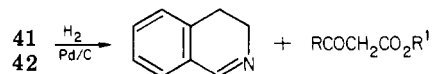
Similarly isoxazoline 36 was reduced to cinnamaldehyde.<sup>7</sup>



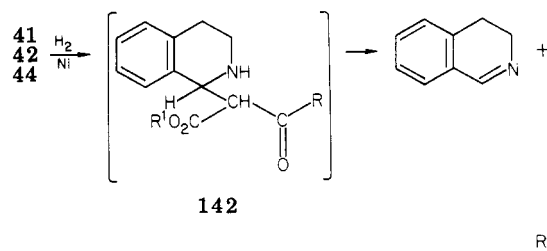
The hydrogenation of isoxazoline 44 was originally proposed to yield enamine 141,<sup>23</sup> but it was later shown that the product was actually 140.<sup>67</sup> Niklas,<sup>26</sup> using a



more active catalyst and a shorter reaction time with homologues, 41 and 42, was able to isolate dihydroisoxazoline and the respective β-keto ester. In these

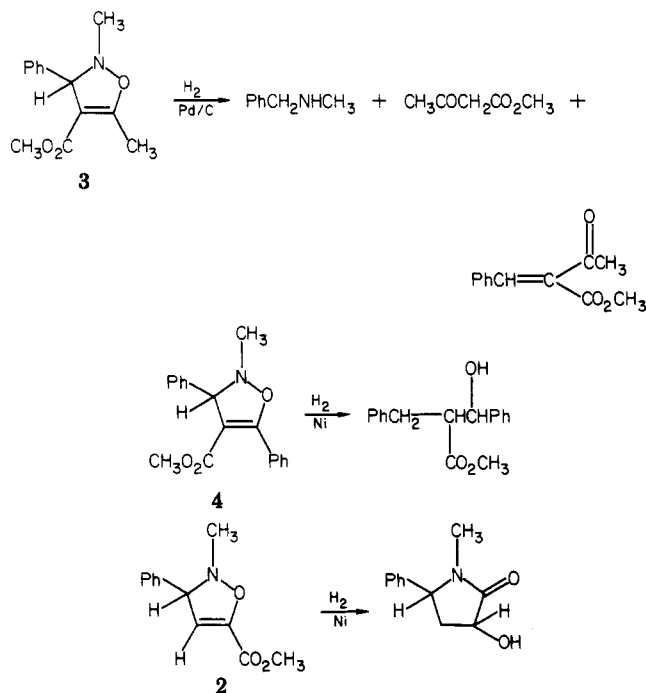


cases a retro-aldol rather than a retro-Michael reaction of the primary reduction product 142 takes place due to the stabilizing effect of the additional carbonyl function. Further reduction of the imine to tetra-



hydroisoquinoline followed by its condensation with the  $\beta$ -keto ester yields 140.

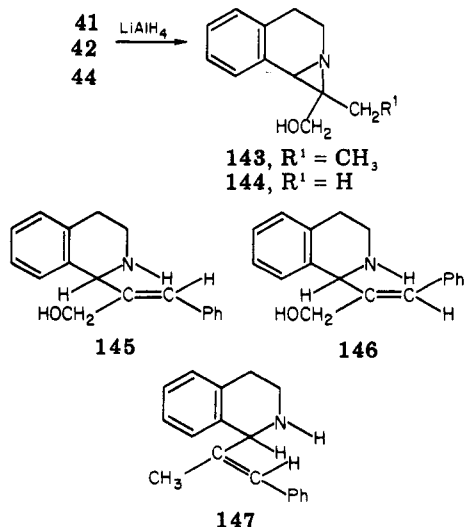
Niklas also examined the hydrogenation of some additional monocyclic isoxazolines.<sup>26</sup> In some cases products corresponding to those of Kano and co-workers<sup>6</sup> were obtained but retro-aldol reactions were observed when an ester function was at C-4. It had previously been observed that a secondary reaction also leading to a pyrrolidone occurred when an ester function was present at C-5.<sup>23</sup> Apparently these reductions are sensitive to both substituents and catalyst.



## B. Lithium Aluminum Hydride

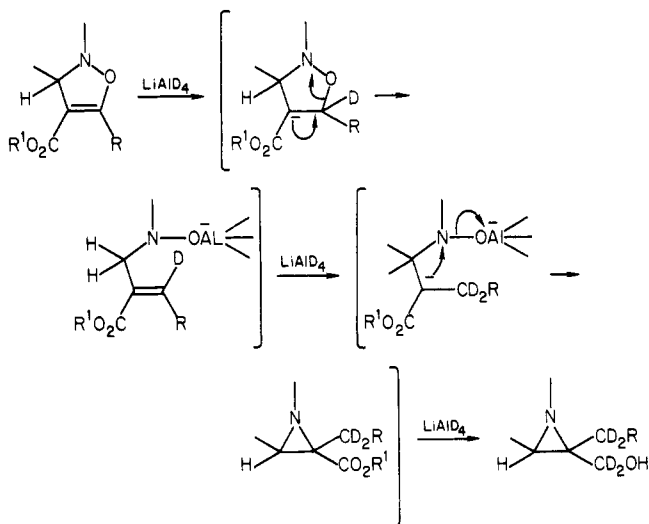
Kano reported that 4-isoxazolines were not reduced by sodium borohydride.<sup>7</sup> Niklas<sup>26</sup> observed that the relatively simple isoxazoline 43 was also inert to lithium aluminum hydride. However, when the double bond was activated by the presence of ester functions, he observed rearrangement as well as reduction.<sup>26,67</sup> However, the nature of the products was dependent upon other substituents also.

For example, isoxazolines 42 and 44 yielded aziridines 143 and 144. However, isoxazoline 41 and its isopropyl



analogue yielded open-chain products 145, 146, and 149 also while only these open-chain products were obtained from the methyl ester corresponding to 41.

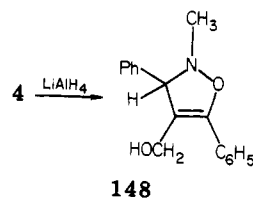
Although superficially the aziridines might appear to be the reduction products of the rearranged acyl-aziridines, the reaction cannot follow that course since the isoxazolines are stable to rearrangement at the temperatures of the reduction. The following mechanism was proposed:<sup>26</sup>



This mechanism is analogous to that proposed by Kotera and co-workers for the reduction of oximes and 2-oxazolines.<sup>68</sup>

In the cases where R = C<sub>6</sub>H<sub>5</sub>, it appears that addition to the highly conjugated ester is less facile and reduction of the ester itself competes to give the open-chain amino alcohols 145 and 146. This latter course was diminished when a more hindered ester, the isopropyl ester, was used. Amine 147 was proposed to arise by competitive abstraction of the C-3 proton by hydride with subsequent ring opening and reduction.

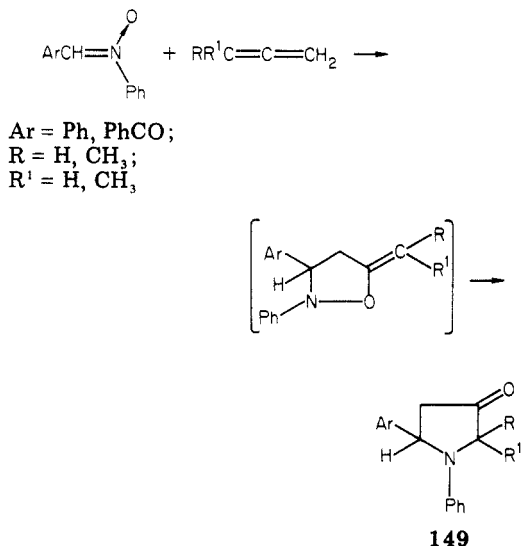
Interestingly monocyclic isoxazolines were more resistant to reduction.<sup>26</sup> For example, 4 was reduced in good yield to carbinol 148. When the ethyl ester cor-



responding to 4 was used, some ring-opened carbinol was obtained also. No aziridines were obtained from these isoxazolines suggesting that the ring-forming displacement has some conformational requirements that are met when the C-N bond is part of a rigid ring system.

## VII. Related Reactions

Nitrones add to allenes to produce 3-pyrrolidinones,<sup>69</sup> 149. The reaction is proposed to proceed through a 5-methylene derivative. If diketene is used in place of the allene, similar products are obtained since the *exo*-methylene group is generated by decarboxylation of the  $\beta$ -lactone formed in the cycloaddition step.<sup>70</sup> In this case, however, the pyrrolidinones are further acetoacetylated by diketene.



Formally, the formation of 149 from the cycloaddition intermediate is similar to that of acylaziridines from 4-isoxazolines in that an N-O bond is broken and a 1,3 shift to form a C-N bond occurs. The authors portray this reaction as proceeding through ionic cleavage of the N-O bond but there is no evidence available to do more than speculate about mechanism.

LeBel and Banucci reported intramolecular versions of these reactions in which the adducts could be isolated.<sup>65</sup>

### VIII. Conclusion

4-Isoxazolines display a dazzling array of rearrangements that are especially impressive in view of the simplicity of the heterocyclic structure. While much of this review has been speculative because of the elusiveness of intermediates in many of the reactions, the reaction paths suggested have been consistent with the expected chemistry of proposed intermediates. More compelling is the fact that they have been useful in suggesting reactivity in new systems and in sorting out the myriad products whose structures often bear little direct relationship to their distant precursors. We hope that this review may serve to stimulate more quantitative mechanistic investigations in this area.

### IX. References and Notes

- Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205-221.
- Houk, K. N. In "Pericyclic Reactions", Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, pp 181-271.
- Sasaki, T.; Ando, M. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2960-2963.
- Noland, W. E.; Modler, R. F. *J. Am. Chem. Soc.* **1964**, *86*, 2086-2087.
- Bond, C. C.; Hooper, M. J. *Chem. Soc. C* **1969**, 2453-2460.
- Adachi, T.; Harada, K.; Miyazaki, R.; Kano, H. *Chem. Pharm. Bull.* **1974**, *22*, 61-69.
- Adachi, I.; Miyazaki, R.; Kano, H. *Chem. Pharm. Bull.* **1974**, *22*, 70-77.
- Harries, C.; Jablonski, L. *Chem. Ber.* **1898**, *31*, 1371-1384.
- Esafov, V. I.; Azarova, V. I. *Izv. Vyssh. Uchebn. Zaved. Khim. Tekhnol.* **1975**, *18*, 148-150; *Chem. Abstr.* **1975**, *83*, 9871f.
- Esafov, V. I.; Azarova, V. I.; Tugannova, I. N. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1974**, *17*, 65-67; *Chem. Abstr.* **1974**, *80*, 82766t.
- Stamm, H.; Steudle, H. *Arch. Pharm. (Weinheim, Ger.)* **1976**, *309*, 1014-1016.
- It is possible that another example of this process was observed by Winterfeldt and co-workers.<sup>13</sup> They showed that phenylhydroxylamine and DMAD lead to nitrone ii, which is transformed in boiling benzene to enamines ii and other unidentified products. These reactions may involve a 4-isoxazoline intermediate but that compound was not invoked by the authors.
- Winterfeldt, E.; Krohn, W.; Stracke, H.-U. *Chem. Ber.* **1969**, *102*, 2346-2361.
- Texier, F.; Carrié, R. *Tetrahedron Lett.* **1969**, 823-826.
- Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798-5800.
- Bunney, J. E.; Hooper, M. *Tetrahedron Lett.* **1966**, 3857-3860.
- Hiremath, S. P.; Hooper, M. *Adv. Heterocycl. Chem.* **1978**, *22*, 123-181.
- Tronchet, J. M. J.; Mihaly, E. *Helv. Chim. Acta* **1971**, *55*, 1266-1271.
- Sokolov, S. D.; Kochetkov, N. K. *Dokl. Chem. (Engl. Transl.)* **1964**, *156*, 649-652.
- Takahashi, S.; Kano, H. *J. Org. Chem.* **1965**, *30*, 1118-1122.
- Acheson, R. M.; Bailey, A. S.; Selby, I. A. *J. Chem. Soc. C* **1967**, 2066-2071.
- Huisgen, R.; Seidl, H.; Wulff, J. *Chem. Ber.* **1969**, *102*, 915-925.
- Seidl, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, *102*, 904-914.
- Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. J. *Am. Chem. Soc.* **1968**, *90*, 5325-5326.
- Döpp, D.; Nour-el-din, A. M. *Tetrahedron Lett.* **1978**, 1463-1466.
- Niklas, K. Dissertation, University of München, 1975.
- Tartakovskii, V. A.; Luk'yanov, Qu.; Novikov, S. S. *Dokl. Chem. (Engl. Transl.)* **1968**, 21-24.
- Greé, R.; Carrié, R. *J. Am. Chem. Soc.* **1977**, *99*, 6667-6672.
- Chidichimo, G.; Cum, G.; Lelj, F.; Sindoma, G.; Uccella, N. J. *Am. Chem. Soc.* **1980**, *102*, 1372-1377.
- Nishiwaki, T.; Saito, T. *J. Chem. Soc. C* **1971**, 3021-3027.
- Grigg, R. J. *Chem. Soc., Chem. Commun.* **1966**, 607-608.
- Schmidt, G.; Stracke, H. U.; Winterfeldt, E. *Chem. Ber.* **1970**, *103*, 3196-3204.
- It should be noted that Noland and Modler<sup>4</sup> reported that propionic acid was required for this transformation. However, Bond and Hooper<sup>5</sup> observed similar reactions in the absence of added acid. Modler<sup>34</sup> believed that the hydrate of the oxazoline was a key intermediate. Our picture of the reaction may be oversimplified.
- Modler, R. Dissertation, University of Minnesota, 1965.
- Kobayashi, Y.; Kumadaki, I.; Yoshida, T. *Heterocycles* **1977**, *8*, 387-390.
- Gagneux, A. R.; Göschke, R. *Tetrahedron Lett.* **1966**, 5451-5454.
- Darlage, L. J.; Kinstle, T. H.; McIntosh, C. L. *J. Org. Chem.* **1971**, *36*, 1088-1093.
- Nakagawa, M.; Nakamura, T.; Tomita, K. *Agric. Biol. Chem.* **1974**, *38*, 2205-2208; *Chem. Abstr.* **1975**, *82*, 111986p.
- Göth, H.; Gagneux, A. R.; Eugster, C. H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 137-142.
- There have been suggestions that 4-isoxazolines might fragment to imines and keto carbenes<sup>41</sup> or their equivalent<sup>21</sup> and subsequently recombine by addition of the carbene to the imine, but there seems little support for this path. In the one case where such a carbene-imine reaction was examined,<sup>41</sup> the product ratios obtained were far from those obtained from the cycloaddition reaction.
- Abramovitch, R. A.; Shinkai, I. *Acc. Chem. Res.* **1976**, *9*, 192-200. Abramovitch, R. A.; Grins, G.; Rogers, R. B.; Shinkai, I. *J. Am. Chem. Soc.* **1975**, *97*, 5671-5677.
- Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2997-2999.
- Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2999-3000.
- Doering, W. von E.; Sachdev, K. *J. Am. Chem. Soc.* **1974**, *96*, 1168-1187.
- Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816-1823.
- Freeman, J. P.; Hoare, M. J. *J. Org. Chem.* **1971**, *36*, 19-23.

- (47) Freeman, J. P.; Kassner, J. A.; Grabiak, R. C. *J. Org. Chem.* 1975, 40, 3402-3407.
- (48) Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.* 1979, 44, 3830-3834.
- (49) Freeman, J. P.; Grabiak, R. C. *J. Org. Chem.* 1976, 41, 2531-2535.
- (50) Abramovitch, R. A.; Shinkai, I. *J. Am. Chem. Soc.* 1974, 96, 5265-5267.
- (51) Abramovitch, R. A.; Grins, G.; Rogers, R. B.; Atwood, J. L.; Williams, M. D.; Crider, S. *J. Org. Chem.* 1972, 37, 3383-3384.
- (52) Freeman, J. P.; Haddadin, M. J. *J. Org. Chem.* 1980, 45, 4898-4902.
- (53) Senga, K.; Ichiba, M.; Kanazawa, H.; Nishigaki, S. *J. Chem. Soc., Chem. Commun.* 1981, 278-280.
- (54) Freeman, J. P.; Duchamp, D. J.; Chidester, C. G.; Slomp, G.; Szmuszkovicz, J.; Raban, M. *J. Am. Chem. Soc.* 1982, 104, 1380-1386. It was mistakenly claimed in this paper that the first 1,2 rearrangement had been observed. Clearly this distinction belongs to the Japanese workers.<sup>35</sup>
- (55) Freeman, J. P.; Duthie, E. G.; O'Hare, M. J.; Hansen, J. F. *J. Org. Chem.* 1972, 37, 2756-2757.
- (56) Fuks, R.; Buijle, R.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* 1966, 5, 585.
- (57) Buijle, R.; Viehe, H. G. *Tetrahedron* 1969, 25, 3447-3451.
- (58) Freeman, J. P.; Grabiak, R. C. *J. Org. Chem.* 1976, 41, 1887-1888.
- (59) Freeman, J. P.; Grabiak, R. C. *J. Org. Chem.* 1976, 41, 3970-3974.
- (60) Clark, B. A. J.; Evans, T. J.; Simmonds, R. F. *J. Chem. Soc., Perkin Trans. 1*, 1975, 1803-1806.
- (61) Mason, J. C.; Tennant, G. *J. Chem. Soc., Chem. Commun.* 1972, 218-219.
- (62) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* 1980, 19, 947-973.
- (63) Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* 1976, 2382-2386.
- (64) Jones, D. A. Dissertation, University of Minnesota, 1961.
- (65) LeBel, N. A.; Banucci, E. *J. Am. Chem. Soc.* 1970, 92, 5278-5280.
- (66) Stagno d'Alcontres, G. *Gazz. Chim. Ital.* 1950, 80, 441-445.
- (67) Christl, M. Dissertation, University of München, 1969.
- (68) Kotera, K.; Takano, Y.; Matsumura, A.; Kitahonoki, Y. *Tetrahedron* 1970, 26, 539-556.
- (69) Aversa, M. C.; Cum, G.; Uccella, N. *J. Chem. Soc., Chem. Commun.* 1971, 156-157.
- (70) Aversa, M. C.; Cum, G.; Stagno d'Alcontres, G.; Uccella, N. *J. Chem. Soc., Perkin Trans. 1*, 1972, 222-225.
- (71) Paulsen, H.; Budzis, M. *Chem. Ber.* 1974, 107, 2009-2015.
- (72) Pennings, M. L. M.; Okay, G.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* 1982, 47, 4413-4418.
- (73) Alberola, A.; Gonzalez, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* 1982, 1067-1068.
- (74) Abramovitch, R. A. *Lect. Heterocycl. Chem.* 1980, 5, S15-S26.