PREPARATION AND THERMAL CYCLOADDITIONS OF 4-OXAZOLIN-2-ONES

BY

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To My Parents
Dorothy Alberta
and
Henry Fry Gingrich
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PREPARATION AND THERMAL CYCLOADDITIONS OF 4-OXAZOLIN-2-ONES

By

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Major Department: Chemistry

The structure of the products obtained from the reactions of 2-aminoamides with thionyl chloride was reinvestigated by means of $^{13}$C nmr spectroscopy. As a result of these investigations and comparisons with appropriate model compounds, the 2-aminoamide-thionyl chloride products were reassigned the 1-oxo-1,2,5-thiadiazolidin-3-one structure rather than the initially assigned 2-oxo-5-imino-1,2,3-oxathiazolidine structure. The reactions of 2-hydroxyalkylamides with thionyl chloride were also examined. In contrast to the related 2-hydroxyarylamides, the predominant products obtained from these reactions were the corresponding 2-chloroalkylamides, rather than the expected 2-oxo-1,2,3-oxathiazolidin-4-ones. However, upon substituting 1,1'-thionyldiimidazole for thionyl chloride, the 2-hydroxyalkylamides afforded the desired 2-oxo-1,2,3-oxathiazolidin-4-ones as the major products. Finally, the reactions of 1,1'-carbonyldiimidazole with 2-hydroxyamides and 2-amino-
amides gave 2,4-oxazolidinediones and hydantoin, respectively. In the case of the 2-aminoamides, hydantoin formation required the presence of an alkoxide catalyst.

The feasibility of preparing cyclic cis β-aminoalcohols via thermal cycloaddition reactions of 4-oxazolin-2-ones and hydrolysis of the subsequent cycloadducts was investigated. The preparation of the required 4-oxazolin-2-one and its 3-acetyl and 3-methyl derivatives, as well as the more sterically hindered 5-phenyl-4-oxazolin-2-one and its 3-acetyl derivative are described. 4-Oxazolin-2-one was found to be an electron-rich dienophile, which added to the highly reactive 1,3-diphenylisobenzofuran and to electron-deficient dienes, such as hexachlorocyclopentadiene and o-chloranil. However, 4-oxazolin-2-one was not stable at the higher temperatures required for successful additions to more electron-rich dienes. 3-Acetyl-4-oxazolin-2-one, however, added to electron-rich dienes, such as cyclopentadiene and anthracene, as well as 1,3-diphenylisobenzofuran. The successful addition of 3-acetyl-4-oxazolin-2-one to electron-rich dienes appeared to be a result of its greater thermal stability compared to 4-oxazolin-2-one. 3-Acetyl-4-oxazolin-2-one also appeared to be a less electron-rich dienophile than 4-oxazolin-2-one. The acetyl cycloadducts were smoothly deacetylated under mild conditions. The adduct of 3-acetyl-4-oxazolin-2-one and anthracene or its deacetylated derivative yielded cis-11-hydroxy-12-amino-9,10-dihydro-9,10-ethanoanthracene upon alkaline
hydrolysis. This result demonstrated the utility of this approach to cyclic cis β-aminoalcohols.

The reaction of these 4-oxazolin-2-ones with s-tetrazines was also examined. The initially-formed 4,5-dihydropyridazines were thermally labile toward decarboxylation or loss of isocyanates to give 4-amino- or 4-hydroxy- pyridazines, respectively. The 4,5-dihydropyridazines also formed regioisomeric addition products with alcohols. The structures of these isomeric addition products were established largely on the basis of nmr spectroscopy.
CHAPTER I

1-OXO-1,2,5-THIAZOLIDIN-3-ONES: A STRUCTURAL REASSIGNMENT

Introduction

Deyrup and co-workers have reported the reaction of 2-aminoamides (1) with thionyl chloride and base to produce 2-oxo-5-imino-1,2,3-oxathiazolidines (3) rather than the expected 2-aminoketenes (2) as illustrated in Scheme I. Structure 3 was based on mass spectral and elemental analyses.

Scheme I

\[
\text{R}^1\text{-NH-C} = \begin{array}{c}
\text{SOCl}_2 \\
\text{base}
\end{array} \rightarrow \begin{array}{c}
\text{R}^1\text{-N} = \text{Cl} \\
\text{base}
\end{array} \rightarrow \begin{array}{c}
\text{R}^1\text{-N} = \text{C} = \text{CHNH-R}^2 \\
\text{R}^1\text{-N} = \text{C} = \text{CHNH-R}^2
\end{array}
\]

\[
\text{R}^1\text{-N} = \text{O-SO} \\
\text{or} \\
\text{R}^1\text{-N} = \text{O-SO}
\]

a, \( \text{R}^1 = \text{o-C}_6\text{H}_4\text{CH}_3; \text{R}^2 = \text{t-Bu} \)

b, \( \text{R}^1 = \text{o-C}_6\text{H}_4\text{CH}_3; \text{R}^2 = \text{C}_6\text{H}_5 \)

c, \( \text{R}^1 = \text{t-Bu}; \text{R}^2 = \text{C}_6\text{H}_5 \)

d, \( \text{R}^1 = \text{CH}_2\text{C}_6\text{H}_5; \text{R}^2 = \text{t-Bu} \)
ir and nmr spectral data, and the mild acid hydrolysis of 3a to its precursor 2-aminoamide (1a).

Mechanistically, the formation of 3 could be rationalized by considering the two pathways shown in Scheme II. If the initial reaction occurs at the amide oxygen to give 5, then neighboring-group participation by nitrogen must be faster than ionization and chloride collapse to give the imidoyl chloride. Alternately, the initial reaction could occur at the amino nitrogen to give 6, followed by neighboring-group participation by the amide oxygen (path b₂).
More recently, Chupp reported a similar reaction between 2-hydroxyarylamides (7) and thionyl chloride.\(^2\) Consideration of the ir, uv, and nmr spectral data led Chupp to prefer the 2-oxo-1,2,3-oxathiazolidin-4-one structure (8) over the isomeric 2-oxo-4-imino-1,3,2-dioxathiolane structure (9). For example, Chupp suggested that the strong ir absorption at 1725 cm\(^{-1}\) would be much more consistent with a lactam structure such as 8 than an iminolactone structure such as 9. Chupp also argued that the uv spectra of the 2-hydroxyarylamide-thionyl chloride products also favored structure 8 because of the absence of a K band (\(\epsilon_{\text{max}} > 10,000\)). Such a band would be expected for structure 9 because of the formal conjugation of the imino group with the aromatic

\[
\begin{align*}
\text{Ar-NH-C} & \xrightarrow{\text{SOCl}_2} \text{Ar-} & & \text{N-SO} \\
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2 \\
\end{array} & \text{or Ar-N} & & \text{O-SO} \\
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2 \\
\end{array}
\end{align*}
\]

10a 11a
ring. However, Schmir and Cunningham have reported IR (CHCl₃) absorptions at 1684 and 1701 cm⁻¹ for lactam 10a and iminolactone 11a, respectively.³ The UV spectrum of iminolactone 11a does not exhibit a K band, presumably because the imino plane and the phenyl plane are nearly perpendicular, thus allowing nitrogen lone pair conjugation with the phenyl π system.⁴ Thus, Chupp's spectral data did not, in fact, clearly favor structure 8 over structure 9.

Nevertheless, Chupp and Dahm later employed ¹⁸O labeling and x-ray crystallography to confirm structure 8a (Ar = 3,4-Cl₂C₆H₃; R¹ = CH₃; R² = H; 5-methyl group trans to the sulfinyl oxygen).⁵ At the same time Chupp and Dahm also pointed out that the evidence reported by Deyrup and co-workers for structure 3 was equally compatible with the isomeric 1-oxo-1,2,5-thiadiazolidin-3-one structure (4), which would result upon neighboring-group participation by the amide nitrogen of 6 as shown in path b₂ of Scheme II. These observations led to a reexamination of the structure of the 2-aminoamide-thionyl chloride products. Since the product structure could depend upon the precise nature of the amide nitrogen substituent, a more general technique than either ¹⁸O labeling or x-ray crystallography was sought for differentiating between structures 3 and 4.

**Results**

A potentially important difference in the reaction of 2-aminoamides (1) and 2-hydroxyarylamides (7) with thionyl
chloride is that the latter reaction does not require an acid scavenger. In fact, Chupp has been able to ascertain from the nmr spectra of certain 2-hydroxyarylamides (7) in thionyl chloride solution that the hydroxy group is the site of initial attack (analogous to path b in Scheme I). While this was not practical for the 2-aminoamides (1) because of the increased basicity of the α-amino group, it appeared feasible to react 2-aminoamides (1) with methyl chlorosulfinate in hopes of determining which site of the 2-aminoamides (1) was more reactive. Thus, 1a was reacted with methyl chlorosulfinate in the presence of triethylamine (TEA). The product of this reaction was clearly shown to be 12 rather than 13 since the amide moiety was still intact as shown by ir and nmr spectroscopy, while the amine NH proton was absent and the t-butyl singlet was deshielded ca. 0.3 ppm relative to its position in 1a. Unfortunately, it is not known if 12 is a kinetic or thermodynamic product. Although it seems likely that the amino group of 1a is the initial site of attack, the possibility of initially forming 13, which then rearranges to 12, cannot be ruled out.
It was hoped that examination of the mass spectral fragmentation patterns of the 2-aminoamide-thionyl chloride products might provide useful structural information. Unfortunately, most of the fragmentation patterns were complicated by t-butyl fragmentations or were consonant with either structure. However, the 2-aminoamide-thionyl chloride product 3b or 4b showed a peak at m/e 222 (8% of base peak), which corresponded to the facile loss of SO₂ from the parent ion. This appeared to support the original structural assignment, since 4b would not be expected to lose SO₂. The possibility of mass spectral rearrangement could not be excluded, however; so additional evidence was sought.

Since the 1-oxo-1,2,5-thiadiazolidin-3-one structure (4) is formally analogous to the hydantoin structure (14), it appeared feasible to prepare 4 by an independent route modeled after a common synthetic approach to hydantoins (14). Specifically, hydantoins (14) have been prepared by the reaction of α-aminoesters (15) with isocyanates. Thus, a rational approach to 4 would involve the reaction of
α-aminoesters (15) with N-sulfinylamines (16) according to equation (4). Unfortunately, α-aminoesters 15a and 15b failed to show any sign of reacting with N-sulfinyl-o-toluidine (16a) even upon heating at reflux in toluene for 24 hours. However, upon conversion of methyl N-t-butylglycine (15a) to its sodium amide with sodium hydride, a reaction occurred with 16a in refluxing dioxane after 1 hour. The product of this reaction was not the expected 4a, but rather a material which spectrally resembled the 2-aminoamide 1a. The nmr spectrum of this material exhibited an amide NH signal and an aromatic pattern with one ortho-deshielded proton as in the case of 1a. However, the t-butyl singlet was deshielded ca. 0.2 ppm relative to its position in 1a, while both the amine NH and methylene signals were absent. A one proton singlet appeared at ca. δ 7.6, which was suggestive of an aldimine proton. Finally, the ir spectrum was also similar to the spectrum of 1a, except for the absence of the amine N-H stretch and the presence of a new band at 1645 cm⁻¹, consonant with a C=N stretch.

The spectral data for this reaction product are consistent
with the 2-iminoamide structure 17, which may have resulted from the methoxide catalyzed decomposition of the initially formed 4a as depicted in Scheme III. Possible supportive evidence for this mode of formation of 17 comes from the observation that 3a or 4a also afforded 17 when heated at reflux in dioxane for 1 hour in the presence of potassium t-butoxide (or sodium methoxide). Finally, as a structural proof, 17 was reduced with sodium borohydride in ethanol to afford 1a in 85% yield.

Ducker and Gunter recently reported the natural abundance $^{13}$C chemical shifts for the C-2 carbons of lactam 18 (170.4 ppm)
and iminolactone 19 (155.7 ppm). The reasons for this chemical shift difference are not obvious, particularly considering that the C-2 carbons of 18 and 19 bear essentially the same three substituents. A possible explanation, based on the greater electronegativity of oxygen (compared to nitrogen) is that canonical structure 18a is a more important contributing structure than 19a. This would result in the deshielding of carbon C-2 of 18 relative to the same carbon of 19. Thus, it appeared that $^{13}$C nmr spectroscopy might provide a simple, unambiguous method for differentiating between the amide and imidate moieties, and ultimately between structures 3 and 4.

To test the validity of this approach, the $^{13}$C nmr spectra were obtained for the following model compounds: N-methylacetanilide (20), O-methyl N-phenylacetimidate
(21), 13-15 the 1-substituted 2-pyrrolidinones (10a-c), 16,17 and the N-substituted 2-iminotetrahydrofurans (11a-c). 3,18 The assignments of the $^{13}$C chemical shifts of these model compounds are shown in Tables I-IV.

The $^{13}$C spectra for the acyclic amide 20 and the lactams 10a-c were all easily assigned with the lactam carbonyl carbons appearing at ca. 174 ppm, while the amido carbon of 20 appeared at ca. 170 ppm.

The spectra of imidate 21 and iminolactones 11a-c proved to be more complex because of syn-anti isomerism. Moriarty et al. reported that 21 exists as the configurationally stable Z isomer (21-Z) on the basis of 100-MHz $^1$H nmr studies. 15

![21-Z](image)

The $^{13}$C spectrum of 21 confirmed the presence of only one isomer. In contrast, Saito and Nukada reported that 11a exists as a mixture of syn-anti isomers 11a-Z and 11a-E. 4
<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C=O&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-α</th>
<th>C-β</th>
<th>C-β'</th>
<th>CH&lt;sub&gt;3&lt;/sub&gt; or CH&lt;sub&gt;2&lt;/sub&gt;Ph</th>
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<tr>
<td><img src="image" alt="Structure" /></td>
<td>20</td>
<td>170.0</td>
<td>22.3</td>
<td></td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>10a</td>
<td>174.0</td>
<td>32.7</td>
<td>17.8</td>
<td>48.5</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>10b</td>
<td>173.8</td>
<td>32.6</td>
<td>17.8</td>
<td>48.6</td>
<td>20.7</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>10c</td>
<td>174.4</td>
<td>30.7</td>
<td>17.6</td>
<td>46.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Chemical shifts are in parts per million downfield from Me<sub>4</sub>Si. <sup>b</sup> Assignments may be interchanged.
Table II. Amide and Lactam $^{13}$C (Aromatic) Chemical Shifts

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>20</td>
<td>144.7</td>
<td>127.1</td>
<td>129.7</td>
<td>127.6</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>10a</td>
<td>139.6</td>
<td>119.6</td>
<td>128.6</td>
<td>124.1</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>10b</td>
<td>137.2</td>
<td>119.7</td>
<td>129.2</td>
<td>133.6</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>10c</td>
<td>136.8</td>
<td>127.9$^b$</td>
<td>128.6$^b$</td>
<td>127.4</td>
</tr>
</tbody>
</table>

$^a$Chemical shifts are in parts per million downfield from Me$_4$Si. $^b$Assignments may be interchanged.
Table III. Imidate and Iminolactone $^{13}$C (Aliphatic) Chemical Shifts

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C=O</th>
<th>C-α</th>
<th>C-β</th>
<th>C-β’</th>
<th>CH₃ or CH₂Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>21-Z</td>
<td>161.5</td>
<td>15.7</td>
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<td></td>
<td>53.0</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>11a-Z</td>
<td>163.5</td>
<td>29.8</td>
<td>22.9</td>
<td></td>
<td>71.2</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>11a-E</td>
<td>168.9</td>
<td>25.0ᵇ</td>
<td>23.4ᵇ</td>
<td></td>
<td>69.1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>11b-Z</td>
<td>163.1</td>
<td>29.8</td>
<td>22.9</td>
<td></td>
<td>71.1 20.8</td>
</tr>
</tbody>
</table>
Table III. (Continued)

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C-N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-α</th>
<th>C-β</th>
<th>C-β'</th>
<th>CH&lt;sub&gt;3&lt;/sub&gt; or CH&lt;sub&gt;2&lt;/sub&gt;Ph</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Structure" /></td>
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<td></td>
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<tr>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1lb-E                                           | 168.8 | 24.8<sup>b</sup> | 23.4<sup>b</sup> | 68.9 | 20.7 |
| 1lc-Z                                           | 163.6 | 28.8            | 23.4            | 70.1 | 51.2 |
| 1lc-E                                           | 169.2 | 23.6<sup>b</sup> | 23.3<sup>b</sup> | 67.9 | 54.5 |

<sup>a</sup>Chemical shifts are in parts per million downfield from Me<sub>4</sub>Si.  
<sup>b</sup>Assignments may be interchanged.
<table>
<thead>
<tr>
<th>Structure</th>
<th>C-1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-Z</td>
<td>149.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11a-Z</td>
<td>147.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11a-E</td>
<td>149.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11b-Z</td>
<td>144.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Imidate and Iminolactone 13C (Aromatic) Chemical Shifts

- C-1<sup>a</sup> values in ppm for chemical shifts of aromatic carbon atoms.
- C-2, C-3, and C-4 values correspond to the indicated positions in the structures.
Table IV. (Continued)

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C-1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>11b-E</td>
<td>147.0</td>
<td>121.0</td>
<td>129.5</td>
<td>132.1</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>11c-Z</td>
<td>141.3</td>
<td>127.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>128.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>126.2</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>11c-E</td>
<td>140.8</td>
<td>127.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>128.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>126.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Chemical shifts are in parts per million downfield from Me₄Si.  
<sup>b</sup>Assignments may be interchanged.
On the basis of ir, uv, and 100-MHz $^1$H nmr studies, Saito and Nukada suggested that the imino plane and the phenyl plane of 11a are nearly perpendicular, the hybridization of the nitrogen atom is sp$^2$, and the nitrogen lone pair electrons conjugate with the $\pi$ electrons of the phenyl ring. As a result of phenyl anisotropy, the $\alpha$-methylene protons of 11a appear as two triplets. The less intense high field triplet was assigned to the $\alpha$-methylene protons syn to the phenyl group of 11a-E, while the low field triplet was assigned to the $\alpha$-methylene protons anti to the phenyl group of 11a-Z. Thus, Saito and Nukada assigned the major isomer the Z configuration. This result was rationalized by comparing the Van der Waals radii of the oxygen atom (1.4 Å) and the methylene group (2.0 Å).

The $^{13}$C and $^1$H nmr spectra of iminolactones 11a-c confirmed the existence of syn-anti isomerism. The possibility that the peaks attributed to the minor isomers were instead due to N-substituted-4-hydroxybutanamides (22),

$$\text{Ar-NH-C-CH}_2\text{CH}_2\text{CH}_2\text{-OH}$$

22

hydrolysis products of the iminolactones (11),$^3$ was ruled out, at least in the case of 11a, by examination of the proton nmr spectrum of a mixture of 11a and N-phenyl-4-hydroxybutanamide (22a) (Ar = C$_6$H$_5$).$^{19,20}$ The major isomer in each case was assigned the Z configuration based on the
work of Saito and Nukada. Possible support for this assignment based on the $^{13}$C spectra comes from the observation that the $\alpha$-methylene carbon of the minor isomer is ca. 5 ppm upfield from the $\alpha$-methylene carbon of the major isomer in each case. This upfield shift is probably a steric compression shift similar to those observed for $\alpha$-syn carbons of oximes. Sauers and Relles have reported the $^{13}$C chemical shifts of two N-aryl-2,2-dimethylsuccinisoimides (23a) and (23b), which exhibit syn-anti isomerism. As in the case of the iminolactones 11a-c, the methylene carbon $\alpha$ to the imino group in the E isomer of 23a and 23b exhibited a steric compression shift of 3.0-3.6 ppm. In addition, the 100-MHz $^1$H nmr spectrum of iminolactone 11b also supports the assignment of the Z isomer as the major isomer. The aromatic region of the proton spectrum of 11b exhibits a singlet at $\delta$ 6.98 for the major isomer and the expected two doublets centered at $\delta$ 6.68 (protons ortho to the nitrogen) and at $\delta$ 7.02 (protons ortho to the methyl group) for the minor isomer. Thus, in the major isomer of 11b the protons ortho to the nitrogen are being deshielded relative to the corresponding protons in the minor isomer, resulting in a
fortuitous equivalence of chemical shift for all four aromatic protons. This deshielding effect can best be attributed to the iminolactone oxygen atom, which can exert its deshielding influence on only the ortho aromatic protons of the Z isomer.

A surprising feature of the $^{13}$C spectra of the iminolactones $\text{lla-c}$ was the marked chemical shift difference between the imino carbons of the E and Z isomers. Although it is not clear why the chemical shift for the imino carbon of the E isomers is deshielded relative to the same carbon in the Z isomers, it is possible that repulsive interactions between the $\alpha$-methylene protons and the phenyl ring cause the angle between the C=N and the N-phenyl bond to become slightly larger than 120°. The concomitant rehybridization of the nitrogen atom from sp$^2$ toward sp would increase s character in the nitrogen orbital participating in the C-N $\sigma$ bond and thereby cause a deshielding of the imino carbon. Sauers and Relles have also reported a similar unexplained deshielding of 8-10 ppm for the imino carbons of the E isomers of 23a and 23b.$^{23}$
The $^{13}$C nmr peak heights were used to approximate the positions of equilibria for the iminolactones 11a-c. The results of these approximations are shown in Table V along with the values determined from the 100-MHz $^1$H nmr spectra. As can be seen the values determined from the $^{13}$C peak heights generally agree favorably with the values determined by proton nmr.$^{24-26}$ This implies that the $T_1$'s, spin-lattice relaxation times, do not differ markedly from positions in one isomer to the corresponding positions in the other isomer. (Alternately, the $T_1$'s of the carbons are small relative to the pulse delay employed in obtaining the spectra.)$^{23}$

The $^{13}$C spectra were obtained for the 2-aminoamide-thionyl chloride products 3a-d or 4a-d and for compound 8a. These spectral results are shown in Tables VI and VII. An examination of these spectra reveals that the low-field resonance corresponding to the imino carbon in structure 3 or amido carbon in structure 4 appears in the range of 169-172 ppm. This chemical shift range is in good agreement with the chemical shift of ca. 174 ppm observed for lactams 10a-c. The slight shielding effect could be due to the adjacent sulfinyl group in structure 4. The observed $^{13}$C chemical shift of 170.5 ppm for the amido carbon of 8a supports this assignment. Of equal or greater significance is the failure to observe any sign of syn-anti isomerism in the $^{13}$C spectra of the 2-aminoamide-thionyl chloride
Table V. Iminolactone Isomer Distribution Obtained from $^{13}$C Peak Heights

<table>
<thead>
<tr>
<th>No.</th>
<th>C=O&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-α</th>
<th>C-β</th>
<th>C-β'</th>
<th>CH&lt;sub&gt;3&lt;/sub&gt; or CH&lt;sub&gt;2&lt;/sub&gt;Ph</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>$^1$H nmr</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>64</td>
<td>65</td>
<td>64</td>
<td>64</td>
<td>66</td>
<td>63</td>
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<td>65</td>
<td>65</td>
<td>70&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>11b</td>
<td>69</td>
<td>67</td>
<td>65</td>
<td>67</td>
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<td>11c</td>
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<td>92</td>
<td>88</td>
<td>87</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>The percentage of the Z isomer as determined at the various carbons is given.  
<sup>b</sup>This value was reported by Saito and Nukada<sup>4</sup> for neat 11a and by Sauers and Relles<sup>2,3</sup> for a CC<sub>4</sub> solution of 11a.
Table VI. $^{13}$C (Aliphatic) Chemical Shifts of 2-Aminoamide-Thionyl Chloride Products and 8a

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C=O&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C-α</th>
<th>C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</th>
<th>C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</th>
<th>$\frac{CH_{3}}{CH_{2}Ph}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4a</td>
<td>170.9</td>
<td>46.1</td>
<td>55.8</td>
<td>27.9</td>
<td>18.0</td>
</tr>
<tr>
<td>o-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-N-t-Bu</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>o-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-N-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>4b</td>
<td>169.2</td>
<td>48.4</td>
<td></td>
<td></td>
<td>18.0</td>
</tr>
<tr>
<td>t-Bu-N-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>4c</td>
<td>171.0</td>
<td>49.8</td>
<td>58.4</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-CH-2-N-t-Bu</td>
<td>4d</td>
<td>171.9</td>
<td>46.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55.4</td>
<td>27.9</td>
<td>43.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3,4-Cl&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;-N-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8a</td>
<td>170.5</td>
<td>76.4</td>
<td></td>
<td></td>
<td>17.0</td>
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</tbody>
</table>

<sup>a</sup>Chemical shifts are in parts per million downfield from Me<sub>4</sub>Si. <sup>b</sup>Assignments may be interchanged.
Table VII. $^{13}$C (Aromatic) Chemical Shifts of 2-Aminoamide-Thionyl Chloride Products and 8a

<table>
<thead>
<tr>
<th>Structure</th>
<th>No.</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
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<tr>
<td><img src="image" alt="Structure 4a" /></td>
<td>4a</td>
<td>131.3$^b$</td>
<td>137.6$^b$</td>
<td>131.1$^c$</td>
<td>129.5$^c$</td>
<td>127.0$^c$</td>
<td>129.6$^c$</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 4b" /></td>
<td>4b</td>
<td>130.6$^b$</td>
<td>137.9$^b$</td>
<td>131.4$^c$</td>
<td>129.7$^c$</td>
<td>127.2$^c$</td>
<td>130.1$^c$</td>
<td>139.6</td>
<td>117.2</td>
<td>129.9</td>
<td>123.9</td>
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<tr>
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<tr>
<td><img src="image" alt="Structure 4d" /></td>
<td>4d</td>
<td>135.5</td>
<td>128.2$^b$</td>
<td>128.7$^b$</td>
<td>127.9</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 8a" /></td>
<td>8a</td>
<td>133.4$^b$</td>
<td>128.1$^c$</td>
<td>133.8$^b$</td>
<td>131.0$^b$</td>
<td>131.4$^c$</td>
<td>125.4$^c$</td>
<td></td>
<td></td>
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</tr>
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</table>

*Chemical shifts are in parts per million downfield from Me$_4$Si. $^b,c$Assignments may be interchanged.
products. The 169-172 ppm chemical shift range could be consistent with structure 3, if the products existed solely as the configurationally stable E isomer 3-E. It appears unlikely, however, that the configurational preference of these compounds should be completely opposite that of the iminolactones 11a-c. Alternately, it might be argued that the failure to observe any sign of syn-anti isomerization in the $^{13}$C nmr spectra of the 2-aminoamide-thionyl chloride products could be consistent with structure 3 if syn-anti isomerization is fast at room temperature and/or the concentration of the minor isomer is too low to be detected by $^{13}$C nmr, which is less sensitive than $^1$H nmr. However, the proton spectrum of the 2-aminoamide-thionyl chloride product 3d or 4d failed to show any additional signals even upon cooling to -50°.

Finally, inspection of the $^{13}$C chemical shifts of the aromatic ring carbons of imidate 21 and the iminolactones 11a and 11b (Table IV) reveals a pattern qualitatively consistent with nitrogen lone pair conjugation with the phenyl π system. In these spectra the ortho and para carbons are shielded by at least 5 ppm relative to the meta
carbons. Lactams 10a and 10b (Table II) also show a similar shielding pattern due to amide-phenyl conjugation, while the ortho and para ring carbons of amide 20 are not shielded presumably due to steric inhibition of amide-phenyl conjugation. Inspection of the o-tolyl ring carbons of the

2-aminoamide-thionyl chloride products 3a or 4a and 3b or 4b (Table VII) reveals the absence of any appreciably shielded carbons. Molecular models of these compounds suggest that the o-tolyl methyl group should sterically inhibit the amide-phenyl conjugation in 4a and 4b, while not interfering with the nitrogen lone pair-phenyl conjugation in 3a and 3b. Thus, the absence of a shielded ortho or para carbon in the o-tolyl ring of these two compounds also favors
On the basis of these $^{13}$C spectra, the 2-aminoamide-thionyl chloride products should be reassigned the 1-oxo-1,2,5-thiadiazolidin-3-one structure (4) rather than the initially assigned 2-oxo-5-imino-1,2,3-oxathiazolidine structure (3). The results of this $^{13}$C spectral study have recently been published. $^{28}$
CHAPTER II
HETEROCYCLIC SYNTHESSES WITH DIIMIDAZOLE REAGENTS

Introduction

As a result of the discovery that 2-aminoamides (1) react with thionyl chloride to form 1-oxo-1,2,5-thiadiazolidin-3-ones (4)\textsuperscript{1,28}, it appeared likely that a variety of other heterocyclic systems should be available upon modification of the reactants. For example, Chupp has reported the reaction of 2-hydroxyarylamides (7) with thionyl chloride to afford 2-oxo-1,2,3-oxathiazolidin-4-ones (8) as shown in equation (1).\textsuperscript{2} Similarly, the reaction of 2-aminoamides and 2-hydroxyamides with phosgene or a phosgene substitute should also produce related heterocycles.

1,1'-Thionyldiimidazole (TDI) (24)\textsuperscript{29} and 1,1'-carbonyl-diimidazole (CDI) (25)\textsuperscript{30} were initially prepared by Staab and Wendel by the reaction of thionyl chloride and phosgene, respectively, with 4 equivalents of imidazole in anhydrous tetrahydrofuran. Removal of the imidazole hydrochloride by-product afforded tetrahydrofuran solutions of 24 and 25. Since 24 is difficult to purify and readily reacts with water at room temperature, tetrahydrofuran solutions of 24 can be employed directly for most purposes. Compound 25 is somewhat more stable and, as such, is commercially available as a crystalline solid.\textsuperscript{31}
1,1'-Carbonyldiimidazole (25) has proven to be a versatile substitute for phosgene since it is non-toxic and more convenient to handle than toxic, gaseous phosgene. Also, the reactions of 25 avoid the formation of hydrochloric acid and are accompanied by the formation of imidazole, which is relatively inert and readily separated from most reaction products.

Staab has reviewed the use of 25 as a reagent for the preparation of amides, carbamates, esters, ureas, etc. Wright has reported the utility of 25 for the synthesis of 2-imidazolidinones (26) and 2-oxazolidinones (27) from diamines and aminoalcohols, respectively, as indicated in equation (6).
1,1'-Thionyldiimidazole (24) has received less attention as a thionyl chloride substitute, particularly for heterocyclic syntheses. Wright, however, has reported the use of 24 for the preparation of 1-oxo-1,2,5-thiadiazolidines (28) from diamines as shown in equation (7). Also, 24 was found to be somewhat more reactive than thionyl chloride (and triethylamine) for the preparation of 1-oxo-1,2,5-thiadiazolidin-3-ones (4) from 2-aminoamides (1) (see, for example, the preparation of 4a in the Experimental Section). Thus, the reactions of some 2-hydroxyamides with thionyl chloride and 1,1'-thionyldiimidazole (24) and the reactions of some 2-hydroxyamides and 2-aminoamides with 1,1'-carbonyldiimidazole (25) were examined.

Results

2-Oxo-1,2,3-oxathiazolidin-4-ones

Since Chupp has reported only the reaction of 2-hydroxyaryl amides (7) with thionyl chloride, the reactions of two 2-hydroxyalkylamides, N-t-butylmandelamide (29a) and N-t-butylglycolamide (29b), were examined. The preparation of the 2-hydroxyalkylamides 29 presented a minor synthetic
problem. The classical routes to amides by ammonolysis of acyl halides and esters were of little value in the preparation of 29. The required α-hydroxyacyl halides were inaccessible, while the steric bulk of the t-butyl group was prohibitive in the case of ester ammonolysis. 2-Hydroxyamides 29a and 29b were ultimately prepared in 50% and 34% yields from t-butyl alcohol and mandelonitrile or glycononitrile, respectively, via a modified Ritter reaction. 2-Hydroxyamide 29b was also prepared in 63% yield from t-butyl isonitrile and aqueous formaldehyde by a modified Passerini reaction.

Treatment of N-t-butylmandelamide (29a) with excess thionyl chloride at ambient temperature for 1 hour; i.e., Chupp's conditions, afforded predominantly N-t-butyl-2-chlorophenylacetamide (30a) rather than the expected 2-oxo-1,2,3-oxathiazolidin-4-one 31a. Chloroamide 30a was isolated in a 96% yield by recrystallization and was identified by comparison with an authentic sample prepared from 2-chlorophenylacetyl chloride and t-butylamine. Examination of the mother liquor, which remained after isolation of 30a, revealed the presence of a trace of 31a. Similar treatment of N-t-butylglycolamide (29b) gave N-t-butyl-2-chloroacetamide.
(30b) as the predominant product. Chloroamide 30b, which was isolated in 61% yield by recrystallization, was also identified by comparison with an authentic sample prepared from 2-chloroacetyl chloride and t-butylamine. Examination by nmr spectroscopy of the residue which remained after isolation of 30b indicated a mixture of unreacted hydroxyamide 29b, residual chloroamide 30b, and the expected 2-oxo-1,2,3-oxathiazolidin-4-one 31b.

Scheme IV
These results, which are summarized in Scheme IV, suggest that thionyl chloride reacts initially with the \( \alpha \)-hydroxy group of \( \text{29} \) to afford chlorosulfite \( \text{32} \). Apparently neighboring-group participation by the amide nitrogen of \( \text{32} \) to give heterocycle \( \text{31} \) (path b) does not compete effectively with chloroamide formation (path a). The reasons for the preferential formation of chloroamides \( \text{30} \), as well as their mode of formation, are not obvious. Speculation in this regard appears fruitless, particularly considering the limited number of 2-hydroxyalkylamides (\( \text{29} \)) examined. However, it appeared that this problem could be circumvented by employing 1,1'-thionylldiimidazole (\( \text{24} \)) rather than thionyl chloride.

Thus, the reaction of the 2-hydroxyalkylamides \( \text{29} \) with 1,1'-thionylldiimidazole (\( \text{24} \)) was examined in hopes of improving the yields of the desired 2-oxo-1,2,3-oxathiazolidin-4-ones (\( \text{31} \)). Accordingly, N-t-butylmandelamide (\( \text{29a} \)) was added to a tetrahydrofuran solution of \( \text{24} \). After stirring at room temperature for 2 hours, the reaction mixture was worked up to yield an oil, which was shown by nmr spectroscopy to consist largely of the desired 2-oxo-1,2,3-oxathiazolidin-4-one \( \text{31a} \). As expected \( \text{31a} \) was formed as a diastereomeric mixture (ca. 50:50) due to the presence of a carbon center of asymmetry as well as the dissymmetric sulfinyl moiety.\(^1,2,44\) The two diastereomers were characterized by benzylic singlets at \( \delta 5.6 \) and 5.9. The isomers were assigned on the basis of the known anisotropic effects of the sulfinyl bond reported for 2-oxo-1,2,3-oxathiazolidines (\( \text{33} \))\(^44\) and
recently confirmed for 2-oxo-1,2,3-oxathiazolidin-4-ones (8)

by Chupp and Dahm.\textsuperscript{5} This anisotropy results in the deshielding of ring substituents which are cis to the sulfinyl oxygen. Thus, the isomer with the benzylic singlet at \(\delta 5.9\) was assigned the trans configuration (i.e., the C-5 proton is cis to the sulfinyl oxygen). Column chromatography of the crude reaction mixture afforded a 77% yield of an almost pure 50:50 diastereomeric mixture of 31a. Fractional crystallization yielded the pure cis isomer, while the trans isomer could not be isolated free of the cis isomer. Similarly, N-t-butylglycolamide (29b) was reacted with 24 to afford, after work-up, an oil, which was shown by nmr spectroscopy to be largely a mixture of the desired 2-oxo-1,2,3-oxathiazolidin-4-one 31b and the linear sulfite
34b in a ratio of ca. 77:23, respectively. Heterocycle 31b was characterized by a t-butyl singlet at δ 1.60 and an AB quartet centered at δ 4.82 for the geminal methylene protons. The nonequivalence of these methylene protons is again a result of the pyrimidal nature of the sulfinyl linkage, which causes the two ring faces to be nonequivalent. Heterocycle 31b was isolated in 33% yield after column chromatography and recrystallization. When this reaction was repeated employing inverse addition of the reactants (i.e., addition of 24 to 29b), a mixture of 31b and linear sulfite 34b was again obtained in a ratio of 16:84. Linear sulfite 34b, which was characterized by a t-butyl singlet at δ 1.38, a methylene singlet at δ 4.38, and a broad NH signal centered at δ 6.32, was isolated from this mixture by recrystallization in 78% yield.

These results, which are summarized in Scheme V, can be explained by assuming that 1,1'-thionyldiimidazole (24) reacts initially with the α-hydroxy group of 29 to give intermediate 35. Neighboring-group participation by the amide nitrogen of 35 then affords heterocycle 31 upon displacement of the remaining imidazole (path a). However, in the case of 35b, a competitive process also occurs, which involves intermolecular displacement of the remaining imidazole by a second molecule of 29b to give linear sulfite 34b (path b).

It is worth noting that linear sulfite formation is a competitive process with 2-oxo-1,2,3-oxathiazolidin-4-one formation in the case of 2-hydroxyalkylamide 29b. In fact,
linear sulfite 34b becomes the major product under conditions of inverse addition. On the other hand, the order of addition appears to be fairly unimportant in the case of 29a. It appears reasonable that intermolecular addition of a second molecule of 2-hydroxyamide (29) to intermediate 35 should be a more facile process for 29b, which has less steric bulk than 29a. However, it also appears likely that the intramolecular cyclization of intermediate 35a (to afford heterocycle 31a) is faster than cyclization of 35b also for steric
reasons. Chupp has reported that 2-hydroxyarylamides (7) with an i-propyl substituent adjacent to the hydroxy group underwent cyclization with thionyl chloride at room temperature, whereas with less bulky α-substituents had to be heated to affect cyclization. Although Chupp did not explain this steric acceleration, it is presumably an extension of the well-known "gem-dialkyl effect," whereby the rates (and equilibria) of many ring-closure reactions are enhanced by increasing the bulk of substituents on the ring "backbone." This steric acceleration has been attributed to "stereo-population control" or "conformational locking;" i.e., a restriction of rotational freedom which favors the population of the rotamer(s) leading to cyclization. Recently the relative importance of this factor compared to conventional relief of ground state strain upon cyclization has been questioned.

The obvious importance of these results is that the desired 2-oxo-1,2,3-oxathiazolidin-4-ones (31) were obtained as the major products of the 2-hydroxyalkylamides when 1,1'-thionyldiimidazole (24) was substituted for thionyl chloride. Thus, 1,1'-thionyldiimidazole (24) appears to be an important complementary reagent to thionyl chloride for heterocyclic syntheses of this type. For instance, Chupp and co-workers recently reported the reaction of N-hydroxyureas with thionyl chloride to afford 2-oxo-1,2,3,5-oxadiadiazolidin-4-ones (36). However, this reaction was accompanied by side reactions, and heterocycle 36 was obtained in poor yields.
Successful preparation of 36 required deactivating (e.g., halogen or CF₃) aryl substituents and the hydroxy group had to be attached to the N-alkyl nitrogen of the urea; otherwise aromatic chlorination occurred. Substitution of 1,1'-thionyldiimidazole (24) for thionyl chloride in this preparation may well alleviate these structural limitations and, in general, improve the yields.

2,4-Oxazolidinediones

The reaction of two 2-hydroxyamides with 1,1'-carbonyldiimidazole (25) was examined next. The 2-hydroxyamides employed in this study were 3',4'-dichlorolactanilide (7a)²

\[ \text{R}^1\text{NH}-\text{C} \quad \text{OH} \quad \text{CDI} \quad \text{R}^1\text{NH}-\text{C} \quad \text{OH} \]

7a, \( R^1 = 3,4-\text{Cl}_2\text{C}_6\text{H}_3; R^2 = \text{CH}_3 \)  
29a, \( R^1 = \text{t-Bu}; R^2 = \text{C}_6\text{H}_5 \)  
37a, \( R^1 = 3,4-\text{Cl}_2\text{C}_6\text{H}_3; R^2 = \text{C}_6\text{H}_5 \)  
37b, \( R^1 = \text{t-Bu}; R^2 = \text{C}_6\text{H}_5 \)
and N-t-butylmandelamide (29a). Reaction of 2-hydroxyamides 7a and 29a with 1,1'-carbonyldiimidazole (24) in refluxing benzene afforded 2,4-oxazolidinediones 37a and 37b in 88% and 94% yields, respectively.

2,4-Oxazolidinedione 37a has been reported previously (in a patent). Heterocycle 37a was presumably prepared from ethyl lactate and 3,4-dichlorophenyl isocyanate upon heating in toluene in the presence of metallic sodium. The melting point of the material obtained in this study agreed favorably with the reported melting point of 37a.51

2,4-Oxazolidinedione 37b has also been reported previously by Rekker et al.; however, the melting point of the material obtained in this study was at least 30° lower than the reported melting point of 37b. So, 37b was prepared by a slight modification of the literature procedure (Scheme VI). Ethyl mandelate was condensed with excess t-butyl isocyanate in refluxing toluene to give carbamate 38 in 95% yield. (The reported yield was only 61%; however, an excess of t-butyl isocyanate was not employed.) Carbamate 38 was cyclized

\[
\text{EtO-C} \quad + \quad \begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{N=C=O} \\
\text{CH}_3
\end{array} \quad \xrightarrow{\text{Na}} \quad \begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{N=O} \\
\text{CH}_3
\end{array}
\]

\(37a\)
in refluxing toluene in the presence of metallic sodium to afford the desired 2,4-oxazolidinedione 37b in 48% yield. Rekker et al. reported a 7.5% yield of 37b upon reaction of ethyl mandelate and t-butyl isocyanate in the presence of sodium and a 3% yield of 37b upon the thermally induced cyclization of carbamate 38. Curiously, the sodium-promoted cyclization of carbamate 38, employed here, was not reported. At any rate, this material was identical in all respects, including the melting point, to the material prepared according to equation (9). Thus, it appears that the reported melting point of 37b is in error. 52

A cursory survey of the literature reveals that 2,4-oxazolidinediones have been prepared from 2-hydroxyamides and chloroformates (with potassium carbonate) or dialkyl carbonates (with sodium methoxide). 53 Apparently phosgene has not been employed for this purpose. The use of 1,1'-carbonyldiimidazole (25) for the preparation of 2,4-oxazolidinediones from
2-hydroxyamides avoids the necessity of an alkaline condensing agent. Both N-aryl and sterically hindered N-alkyl 2-hydroxyamides were cyclized in high yield. Thus, the reaction of 25 and 2-hydroxyamides represents a potentially useful route to a variety of 2,4-oxazolidinediones.

**Hydantoins**

Finally, the reaction of two 2-aminoamides, 2-t-butylamino-o-acetotoluidide (1a)\textsuperscript{1} and 2-anilino-o-acetotoluidide (1b),\textsuperscript{1} with 1,1'-carbonyldiimidazole (25) was investigated. Treatment of 2-aminoamides 1a or 1b with 1,1'-carbonyldiimidazole (25) in refluxing benzene or anhydrous tetrahydrofuran for several hours afforded little, if any, of the expected hydantoins (14).

\[
\begin{align*}
\text{R}^1\text{NH-C} & \xrightarrow{\text{CDI}} \text{N-C} \O & \\
\text{NH-R}^2 & & \text{N-N} & \\
\end{align*}
\]

\[\text{R}^1 = \text{o-C}_6\text{H}_4\text{CH}_3; \text{R}^2 = \text{t-Bu} \]

\[\text{R}^1 = \text{o-C}_6\text{H}_4\text{CH}_3; \text{R}^2 = \text{C}_6\text{H}_5 \]

Staab has reported that unlike primary amines, which react with 1,1'-carbonyldiimidazole (25) at room temperature to yield ureas (39), secondary amines react with 25 at room temperature to afford only imidazole-N-carboxamides (40) as
shown in Scheme VII. Compounds $40^\text{32}$ yield carbamates ($41^\text{32}$), for example, only upon heating with equimolar quantities of alkoxide.

**Scheme VII**

```
CDI \rightarrow 2 \text{RNH}_2 \rightarrow \text{R-NH} \text{NH-R} \quad \text{39}
```

```
\text{R}_1^2 \text{NH \rightarrow 20°} \rightarrow \quad \text{R-NH} \text{NH-R} \quad \text{39}
```

```
\text{R}^1_2 \text{N}^\text{C} \text{N}^\text{N} \text{R}^1_2 \text{NH} \rightarrow \text{R}^1_2 \text{N}^\text{C} \text{N}^\text{N} \text{R}^1_2 \text{NH}^\text{R}^3 \quad \text{41}
```

Similarly, $1,1'$-carbonyldiimidazole ($25^\text{32}$) reacts with alcohols to give carbonates ($42^\text{32}$) only upon heating. (Presumably, the addition of the second molecule of alcohol necessitates the heating.) However, in the presence of catalytic amounts of sodium ethoxide or imidazolylsodium, this reaction proceeds at room temperature. $t$-Butyl alcohol, on
the other hand, reacts with 25 at room temperature under catalytic conditions to afford only the imidazole-N-carboxylic ester (43, \( R^1 = t-Bu \)). While ethanol reacts with 43 (\( R^1 = t-Bu \)) at room temperature using the catalytic method to yield ethyl t-butyl carbonate (42, \( R^1 = t-Bu, R^2 = Et \)), di-t-butyl carbonate (42, \( R^1 = R^2 = t-Bu \)) is formed from 43 (\( R^1 = t-Bu \)) and t-butyl alcohol only upon heating even under catalytic conditions.

Since the 2-aminoamides 1a and 1b are secondary amines, it would appear reasonable to assume that they react with 25 to form intermediates 44, which failed to cyclize under the reaction conditions. However, the possibility that 1a and 1b failed to react at all with 25 under the reaction conditions, previously described, cannot be ruled out. In fact, at least for 1a, examination of the crude reaction mixture, after solvent removal, by nmr spectroscopy suggested that this was the case.

In any event, alkoxide catalysis appeared promising. Therefore, 2-aminoamides 1a and 1b were allowed to react with 1,1'-carbonyldiimidazole (25) for several hours in refluxing anhydrous tetrahydrofuran in the presence of a
catalytic amount of potassium t-butoxide. The desired hydantoins 14a and 14b were obtained in 75% and 62% yields, respectively.

Hydantoin 14b has been prepared previously by Deck and Dains by the route shown in Scheme VIII. The melting point of the material obtained in this study was a few degrees higher than the reported melting point of 14b.

A cursory review of the literature reveals that hydantoins have been prepared from 2-aminoamides and phosgene. However, this method of hydantoin preparation has apparently received little attention. The results of this brief investigation suggest that the reaction of 2-aminoamides with 1,1'-carbonyldiimidazole (25) in the presence of alkoxide catalyst is a potentially versatile route to unsymmetrically 1,3-disubstituted hydantoins.
CHAPTER III
PREPARATION AND THERMAL CYCLOADDITIONS OF 4-OXAZOLIN-2-ONES

Introduction

In the course of considering the design and synthesis of conformationally rigid catecholamines (45) as probes for β-adrenoreceptor sites, a cycloaddition-hydrolysis sequence, shown in equation (13), was proposed as a possible approach to 45. This sequence appeared to be a potentially attractive and general route to cyclic cis β-aminoalcohols (46). This approach to 46 was modeled after a similar approach to cyclic cis diols (49). Vinylene carbonate (50) has
been successfully employed as a dienophile in thermal

\[
\begin{align*}
\text{\ding{115}} & \quad \text{\ding{116}} \\
\Delta & \quad \text{OH}^{-}
\end{align*}
\]

\[50 \quad 51 \quad 49\]

\([2+4]\) cycloadditions, i.e., Diels-Alder reactions, with a variety of dienes, such as 1,3-butadienes,\(^{57}\) cyclopentadienes,\(^{57b, 58, 59}\) dimethylfulvene,\(^{60}\) anthracenes,\(^{57b, 61}\) furan,\(^{57b}\) and isobenzofurans.\(^{62, 63}\) The resulting cycloadducts (51) readily afford cyclic cis diols (49) upon alkaline hydrolysis.

The feasibility of this approach to cyclic cis \(\beta\)-aminoalcohols (46) shown in equation (13) depends on the ease of hydrolysis of the cycloadducts 48, as well as the ability of the 4-oxazolin-2-ones (47) to function as dienophiles in the required cycloaddition reactions. There is ample precedent for the hydrolysis of 2-oxazolidinones, the heterocyclic system of 48, under both acidic and alkaline conditions to afford \(\beta\)-aminoalcohols.\(^{64}\) The potential dienophilicity of the 4-oxazolin-2-ones (47), however, remained to be examined.

Although numerous mono-, di-, and trisubstituted 4-oxazolin-2-ones have been reported,\(^{65, 66}\) the parent compound 47a was unknown at the start of this study. Thus, the first part of this research involved the preparation
of 47a and its 3-acetyl (47b) and 3-methyl (47c) derivatives, as well as the more sterically hindered 47d, which had previously been reported, and its 3-acetyl (47e) derivative. The second part of this study concerns the reactivity of these 4-oxazolin-2-ones with a variety of dienes, ranging from electron-deficient to electron-rich, and the chemistry of the resulting adducts. Although the actual preparation of the conformationally rigid catecholamines (45) by a cycloaddition-hydrolysis sequence remains for another study, the feasibility of such an approach has been investigated.

Results

4-Oxazolin-2-one Syntheses

Since vinylene carbonate (50) and its diaza analogue, 4-imidazolin-2-one (52), had both been reported, it was some-
what surprising that 4-oxazolin-2-one (47a) had not. In an attempt to devise a synthetic approach to 37a, it appeared logical to consider the reported preparations of 50 and 52. 4-Imidazolin-2-one (52) was first prepared by Marckwald in 1892 by heating ureidocetaldehyde diethyl acetal (54) in dilute aqueous sulfuric acid. Heterocycle 52 was subsequently prepared from dihydroxymaleic acid (55) and urea by Fenton and Wilks in 1909 and from tartaric acid (56) and urea by Hilbert in 1932 as shown in Scheme IX. Although the

\[
\begin{align*}
\text{NH}_2\text{CH}_2\text{CH}\text{(OEt)}_2 + \text{KOCN} & \xrightarrow{\text{HCl}} \text{NH}_2\text{CNHCH}_2\text{(OEt)}_2 \\
\text{H}_2\text{O} & \xrightarrow{\Delta} \text{N}_2 \text{H}_2 \text{CO}_2 \text{H} \\
\text{H}_2\text{O} & \xrightarrow{220^\circ} \text{H}_2\text{O} \text{C}_2 \text{H}_2 \text{OH} \\
\text{H}_2\text{O} & \xrightarrow{\text{fuming H}_2\text{SO}_4} \text{N}_2 \text{H}_2 \text{CO}_2 \text{H}
\end{align*}
\]
physical properties of the compounds obtained by these alternate routes compared favorably, they were not in agreement with the properties of the material described by Marckwald. It remained for Duschinsky and Dolan to resolve this discrepancy in 1946. These authors found that Marckwald's reaction actually afforded a mixture of 52 and a higher melting dimer or polymer. Vacuum sublimation of the mixture yielded 52. The properties of 52 were in agreement with those reported by Fenton and Wilks and by Hilbert. Finally, in 1966 Zigeuner and Rauter assigned the structure of the higher melting by-product as dimer 57, which they also prepared from 52 in 75% yield as indicated in equation (16).

Vinylene carbonate (50) was first prepared in 1953 by Newman and Addor from ethylene carbonate (58) by the photoclorination-dehydrohalogenation sequence shown in equation (17).

![Chemical structures and equations](image-url)
Although it appeared feasible to prepare 4-oxazolin-2-one (47a) by routes modeled after either Marckwald's preparation of 52 or Newman and Addor's preparation of 50, the former approach seemed more promising. Gagneux and Göschke have successfully employed an analogous route for the synthesis of 5-methyl-3-phenyl-4-oxazolin-2-one (47f, R = C₆H₅; R¹ = CH₃) as indicated in Scheme X. Thus, a similar route modeled after Marckwald's preparation of 4-imidazolin-2-one (52) was chosen for the synthesis of 4-oxazolin-2-one (47a) as shown in Scheme XI.

The required hydroxyacetal 61 was prepared from bromoacetaldehyde diethyl acetal (59) according to the procedure of Parham and Reiff. This involved preparation of benzyl-oxyacetaldehyde diethyl acetal (60) from 59 and sodium benzoate. Hydroxyacetal 61 was obtained upon the sodium/liquid ammonia hydrogenolysis of 60. The preparation of carbamate-acetal 62a presented a minor synthetic problem. An attempt
Scheme XI

\[
\begin{align*}
\text{BrCH}_2\text{CH(OEt)}_2 + \text{C}_6\text{H}_5\text{CH}_2\text{ONa} & \xrightarrow{59} \text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH(OEt)}_2 \\
\text{Na} + \text{NH}_3 \xrightarrow{} \text{HOCH}_2\text{CH(OEt)}_2 & \xrightarrow{1) \text{CDI}} \text{R-NH-C} \xrightarrow{2) \text{RNH}_2} \text{OCH}_2\text{CH(OEt)}_2 \\
\text{HOAc} \xrightarrow{\Delta} & \text{R} \\
\end{align*}
\]

(a, \( R = \text{H} \))

(c, \( R = \text{CH}_3 \))

To prepare 62a from 61 according to the procedure employed to convert aminoacetal 53 to ureidoacetal 54 (i.e., treatment of 61 with aqueous potassium cyanate and 5N hydrochloric acid at low temperature, followed by heating for 90 minutes) resulted only in the recovery of unreacted 61. Attempts to prepare 62a from 61 by the sodium cyanate/trifluoroacetic acid method of Loev and Kormendy resulted in a complex mixture of products. Carbamate 62a was ultimately prepared in excellent yield by employing 1,1'-carbonyldiimidazole (CDI) (25). Accordingly, one equivalent of hydroxyacetal 61 was added to a slight excess of 25 in anhydrous tetrahydrofuran at room temperature, followed by the addition
of an excess of concentrated ammonium hydroxide. Work-up, followed by chromatography over neutral alumina eluting with chloroform, afforded 62a in 90-95% yield as an oil, which was used without further purification.

A solution of 62a in glacial acetic acid was heated at reflux for 6 hours. Concentration of the reaction mixture and recrystallization of the residue from ethyl acetate:hexanes afforded the desired 4-oxazolin-2-one (47a) in 41% yield. The structure of 47a was confirmed by elemental and mass spectral analysis, by ir and nmr spectral analysis, and by catalytic reduction of 47a to 2-oxazolidinone (63). The nmr (Me₂SO-d₆) spectrum of 47a was characterized by two doublets at δ 6.81 and 6.95 (J=2 Hz). The upfield doublet was assigned to the C-4 proton (i.e., the proton on the carbon adjacent to nitrogen) on the basis of the electronegativities of nitrogen and oxygen and on the basis of the nmr chemical shifts of the vinyl protons for vinylene carbonate (50) (δ 7.24 in CDCl₃) and 4-imidazolin-2-one (52) (δ 6.23 in Me₂SO). Concentration of the ethyl acetate:hexanes mother liquor of 47a afforded an oil, which was shown by nmr spectroscopy to be primarily a mixture of residual 47a and two additional
components. A small amount of one of the components was isolated as a colorless solid, which deposited from a dichloromethane solution of the oil upon sitting at room temperature overnight. This material was subsequently identified as a dimer of 4-oxazolin-2-one (47a) (vide infra). The second component of the mixture was shown by nmr spectroscopy to still contain an ethoxy group with nonequivalent methylene protons and an ABX spin system. Based on this spectral evidence, this material was tentatively identified as 4-ethoxy-2-oxazolidinone (64a). It appeared likely that 64a was an intermediate in the cyclization of 62a to 47a. In fact, when a solution of 62a in glacial acetic acid was heated at reflux for only 1 hour, 64a was the primary component of the concentrated reaction mixture. Although 64a was not isolated from the reaction mixture, an authentic sample was prepared for spectral comparison according to the procedure of Strumza and Ben-Ishai as shown in Scheme XII. An interesting nmr spectral feature of 64a, which proved to be of general utility later in this study, was the slight broadening of the \( H_X \) doublet of doublets at \( \delta 5.08 \) by the adjacent nitrogen proton. Upon washing out the NH signal with \( D_2O \), the \( H_X \) doublet of
doublets sharpened perceptibly, while the $H_A$ and $H_B$ signals remained unaffected.

**Scheme XII**

$$\text{ClCH}_2\text{CH(OEt)}_2 + 2 \text{C}_6\text{H}_5\text{CH}_2\text{OCNH}_2 \xrightarrow{\text{H}^+} \Delta \text{C}_6\text{H}_5\text{CH}_2\text{O}_2\text{CHN-N}=\text{O}$$

An acetic acid solution of authentic 64a afforded 4-oxazolin-2-one (47a) when heated in glacial acetic acid for 3 hours; thus confirming the intermediacy of 64a in the conversion of 62a to 47a. Additionally, when a mixture of 4-amino-2-oxazolidinone hydrochloride (66) and glacial acetic acid was heated at reflux for 5 hours, 47a was also obtained. A possible explanation for these reactions of 66 involves
carbonium ion 67, which undergoes either elimination or substitution depending on the solvent as indicated in Scheme XIII.

Scheme XIII

As mentioned previously, a dimer of 4-oxazolin-2-one (47a) was isolated from the oil which remained upon concentration of the ethyl acetate:hexanes mother liquor of 47a. The nmr (Me$_2$SO-d$_6$) spectrum of this dimer was characterized by three one-proton doublet of doublets centered at $\delta$ 4.31, 4.58, and 5.68 (i.e., an ABX spin system), two one-proton doublets centered at $\delta$ 7.07 and 7.14 (J=2 Hz), and a one-proton NH signal at $\delta$ 8.51. This spectral evidence immediately suggested structures such as 68 and 69 with carbon-nitrogen ring linkages, as opposed to structures 70-73 with carbon-carbon ring linkages. Structures 70-73, which are analogous
to the 4-imidazolin-2-one dimer structure (57), can obviously be ruled out since they contain two amide protons and only one vinyl proton. Structure 68 was chosen over 69 for this dimer on the basis of mechanistic considerations. That is, it appears likely that the dimer is formed by trapping of carbonium ion 67 by 47a. Further support for structure 68
over 69 comes from the nmr spectrum of the dimer upon D₂O exchange. This caused the NH signal to wash out and the Hₓ doublet of doublets at δ 5.68 to sharpen slightly as in the case of 64a, which suggested C-4 substitution of the 2-oxazolidinone ring. An attempt to prepare dimer 68 from 47a under the conditions employed by Zigeuner and Rauter for the preparation of dimer 57 from 4-imidazolin-2-one (52) was not successful. 75

The structural assignment of 4-imidazolin-2-one dimer 57 was based largely on chemical evidence (e.g., the formation of a tetraacetyl derivative upon heating with acetic anhydride and pyridine). 75 Since no spectral data was reported, it appeared worthwhile to briefly reinvestigate the structure of dimer 57. Accordingly, 57 was prepared from 4-imidazolin-2-one (52) according to the procedure of Zigeuner and Rauter. 75 4-Imidazolin-2-one (52) was, in turn, prepared from aminoacetal 53, via ureidoacetal 54, according to the procedure of Duschinsky and Dolan. 74 Dimer 57 was a rather insoluble material; however, an nmr spectrum of 57 was obtained in trifluoroacetic acid. The spectrum was characterized by a three-proton ABX spin system and a one-proton vinyl signal; 82 thus confirming Zigeuner and Rauter's structural assignment. It was also interesting to note that the mass spectrum of dimer 57 exhibited a parent ion (52% of base peak), as well as a fragmentation pattern derived therefrom. Dimer 68, on the other hand, did not exhibit a parent ion and, in fact, gave the same mass spectrum as 4-oxazolin-2-one (47a). This
difference in mass spectral behavior can be rationalized on the basis of the expected lability of parent ion $68'$ towards cycloreversion via a six-membered cyclic transition state, which is not available in the case of the parent ion of 57.

![structure](image)

It is not obvious why 4-imidazolin-2-one (52) forms a carbon-carbon linked dimer, while 4-oxazolin-2-one (47a) forms a carbon-nitrogen linked dimer.

3-Acetyl-4-oxazolin-2-one (47b) was prepared by acetylation of the crude product mixture obtained upon refluxing carbamateacetal $62a$ in glacial acetic acid for 6 hours. After concentration of the reaction mixture, the residue was redissolved in acetic anhydride and heated at reflux for 1 hour. Fractionation of this mixture afforded 47b as a colorless oil, which solidified upon refrigeration. The yield of 47b for this two step sequence was 76%. The ir (CHCl$_3$) spectrum of
this material exhibited two carbonyl stretches at 1780 (oxazolinone) and 1725 cm\(^{-1}\) (acetyl), which ruled out the possibility of O-acetylation to give oxazole 74a. Gompper\(^65\)

![74a](image)

and deStevens\(^83\) have also reported that acetylation of 4-oxazolin-2-ones with acetic anhydride occurs on nitrogen rather than oxygen. The 100-MHz \(^1\)H nmr (CDCl\(_3\)) spectrum of 47b exhibited vinyl doublets at \(\delta\) 6.89 and 7.30 (J=2.3 Hz). The upfield doublet was again assigned to the C-4 proton. This assignment is only tentative due to uncertainties concerning the anisotropy of the acetyl carbonyl bond.

3-Methyl-4-oxazolin-2-one (47c) was prepared from hydroxy-

![47c](image)

acetal 61 by a sequence similar to that employed for the preparation of 47a. One equivalent of 61 was added to a slight excess of 1,1\(^{\prime}\)-carbonyldiimidazole (25) at room temperature, followed by the addition of an excess of 40% aqueous
methylamine. Work-up, followed by chromatography over neutral alumina eluting with chloroform, afforded carbamateacetal 62c in 98% yield as an oil, which was used without further purification. A solution of 62c in glacial acetic acid was heated at reflux for 6 hours. Work-up afforded a solid which was shown by nmr spectroscopy to be primarily the desired 3-methyl-4-oxazolin-2-one (47c) contaminated with lesser amounts of two impurities, tentatively identified as 3-methyl-4-ethoxy-2-oxazolidinone (64c) and 3-methyl-4-hydroxy-2-oxazolidinone (75).

\[
\text{CH}_3 \text{N} \equiv \text{O} \quad \text{CH}_3 \text{N} \equiv \text{O}
\]

64c 75

Although the desired 47c could be obtained free of 64c by recrystallization, the last traces of 75 were difficult to remove. Compound 47c was finally purified by vacuum sublimation. Although 47c was ultimately obtained in 52% yield, it appears likely that the yield could be substantially increased and the purification simplified by extending the reaction time. Both 64c and 75 should ultimately be converted to 47c upon further heating in glacial acetic acid.\(^{84,85}\)

The 100-MHz \(^1\text{H}\) nmr (CDCl\(_3\)) spectrum of 47c exhibited vinyl doublets at \(\delta\) 6.71 and 6.90 (J=2 Hz). Again the upfield doublet was assigned to the C-4 proton. The \(^{13}\text{C}\) nmr (CDCl\(_3\)) spectra of 47b and 47c are summarized below, along with the
reported $^{13}$C-H coupling constants for vinylene carbonate (50). The assignment of the C-4 carbon of 47c was substantiated by the observed three-bond $^{13}$C-H coupling ($^{3}J$) of this carbon to the methyl protons. For both 47b and 47c the one-bond $^{13}$C-H coupling constant $^{1}J$ is larger for the C-5 carbon than for the C-4 carbon, presumably due to the greater electronegativity of the oxygen substituent on the C-5 carbon. Interestingly, the two-bond $^{13}$C-H coupling constant $^{2}J$ is larger for the C-4 carbon than the C-5 carbon for both 47b and 47c.
While this work was in progress, Scholz, Heine, and Hartmann reported the preparation of 4-oxazolin-2-one (47a), as well as 47b and 47c. Their approach, although it necessitated an N-acetyl protecting group, was analogous to the method employed by Newman and Addor for the preparation of vinylene carbonate (50) (Scheme XIV). The spectroscopic data (IR and $^1$H NMR) reported by these authors for 47a-c were in general agreement with the data obtained in this study, although there were slight differences presumably due to solvent effects. However, the melting points of 3a and 3c reported by Scholz, Heine, and Hartmann were 6° and 10°, respectively, higher than those obtained in this study.

The $^{13}$C NMR (Me$_2$CO-$d_6$) spectrum reported by these authors for

![Scheme XIV](image-url)
47a, which is summarized below, substantiates the trends observed for 47b and 47c in this study with regard to the

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{O} \\
114.24 & \quad 157.10 \\
129.49 & \quad \\
\end{align*}
\]

relative magnitudes of \( J^1 \) and \( J^2 \) for the C-4 and C-5 carbons.

The route employed by Scholz, Heine, and Hartmann for the preparation of 47a-c appears to be superior in overall yields to the approach employed in this study. Also, the starting material for their route, 3-acetyl-2-oxazolidinone (76),\(^7^9\) is more readily accessible than hydroxyacetaldehyde diethyl acetal (61),\(^7^7\) the starting material for this route. In short, Scholz, Heine, and Hartmann's preparation of 47a-c is economically more feasible than the route employed here, particularly from an industrial point of view. It should be mentioned, however, that although the yield of 4-oxazolin-2-one (47a) from carbamateacetal 62a is not impressive (i.e., only 41%), the yield of 3-acetyl-4-oxazolin-2-one (47c) is more respectable (i.e., 76%). Thus, it appears that the overall yield of 47a by this route could be improved by preparing it from 47c by employing the deacetylation procedure of Scholz, Heine, and Hartmann.

The last two 4-oxazolin-2-ones required for this study were 5-phenyl-4-oxazolin-2-one (47d) and 3-acetyl-5-phenyl-
4-oxazolin-2-one (47e). 5-Phenyl-4-oxazolin-2-one (47d)

![Chemical structure](image)

\[ R = H \quad 47d, \quad R = \text{CH}_3\text{CO} \quad 47e, \]

was prepared according to the procedure of Strumza and Ben-Ishai as shown in Scheme XV. An interesting sidelight of this

Scheme XV

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CHCH(OCH}_3)^2_2 + 2 \text{EtOCNH}_2 & \xrightarrow{\text{H}^+} 25^\circ \\
\text{C}_6\text{H}_5\text{CHCH(NHCOEt)}_2 \xrightarrow{o\text{-xylene}} \Delta & \rightarrow \text{Et}_2\text{OCHN} \\
\Delta & \rightarrow \text{toluene} \\
\end{align*}
\]
preparation involved 2-oxazolidinone 77. Since 77 has two centers of asymmetry, the possibility of forming two isomers (cis or trans) bears consideration. Strumza and Ben-Ishai, however, reported a single product without assigning its stereochemistry. (Since the elimination of 77 to afford the desired presumably proceeds via an E1 mechanism, the sterechemistry of 77 should be inconsequential.) Upon repeating this preparation and recrystallizing the crude product, the initial crop of crystals was found to be the material reported by Strumza and Ben-Ishai. The subsequent, smaller crops of crystals, however, had progressively lower and broader melting points due to contamination by a second isomer.

The stereochemistry of these isomers was assigned on the basis of their nmr (Me2SO-d6) spectra, utilizing both the vicinal coupling constants (JAB) and the chemical shifts of the C-4 and C-5 protons. It has generally been observed that Jcis is larger than Jtrans for five-membered rings which cannot deviate appreciably from planarity. Additionally, it has been found that cis vicinal protons appear downfield from trans vicinal protons in five-membered rings. This chemical shift difference is presumably due to the shielding effect of the substituents attached to the adjacent carbon atoms in the trans isomer. The nmr spectrum of the major isomer of 77 was characterized by a doublet of doublets centered at δ 5.17 with JAB=4 Hz and JBX=8 Hz, which collapsed to a doublet with JAB=4 Hz upon D2O exchange, and a doublet centered at δ 5.33 with JAB=4 Hz. The minor isomer
was characterized by a doublet of doublets centered at δ 5.61 with $J_{AB} = 7$ Hz and $J_{BX} = 8.5$ Hz, which collapsed to a doublet with $J_{AB} = 7$ Hz upon D$_2$O exchange, and a doublet centered at δ 5.83 with $J_{AB} = 7$ Hz. Thus, the major isomer of 77 was

trans 77  cis

$J_{AB} = 4$ Hz  
$J_{AB} = 7$ Hz

$J_{BX} = 8$ Hz  
$J_{BX} = 8.5$ Hz

assigned the trans configuration on the basis of the smaller vicinal coupling constant and the shielded C-4 and C-5 protons. These trends were substantiated by the nmr spectra of the 4-substituted 2-oxazolidinones prepared in the course of this
study, representative examples of which are indicated above.91

Finally, 3-acetyl-5-phenyl-4-oxazolin-2-one (47e) was prepared in 91% yield by refluxing a mixture of 47d and acetic anhydride for 1 hour. The ir (KBr) spectrum of 47e exhibited two carbonyl stretches at 1775 (oxazolinone) and 1720 cm⁻¹ (acetyl), which again ruled out the possibility of O-acetylation to give oxazole 74b.

Thermal Cycloadditions of 4-Oxazolin-2-ones92

Cycloadditions of 4-oxazolin-2-one (47a) - product structure assignments

4-Oxazolin-2-one (47a) added to the highly reactive 1,3-diphenylisobenzofuran (78)62 and to electron-deficient dienes, such as hexachlorocyclopentadiene (79) and o-chloranil.
(80) (Table VIII). However, 47a was not stable at the higher temperatures required for successful additions to more electron-rich dienes, such as anthracene and cyclopentadiene. The limited solubility of 47a in common organic solvents (e.g., chloroform and benzene) also proved troublesome.

The nmr (Me$_2$SO-d$_6$) spectrum of adduct 81a (obtained from 47a and 78) was characterized by a broad doublet centered at δ 4.54 and a sharp doublet centered at δ 5.29 (J=9 Hz). Examination of the residue which remained upon concentration of the toluene filtrate of 81a revealed the presence of a second minor isomer. The nmr (CDCl$_3$) spectrum of this minor isomer exhibited a broad doublet centered at δ 4.19 and a sharper doublet centered at δ 4.96 (J=6 Hz). The major isomer of 81a was assigned endo stereochemistry on the basis of the more shielded vicinal protons of the minor isomer (vide infra). It appears likely that the larger vicinal

![Diagram](image)

endo-81a (major isomer)  
exo-81a (minor isomer)

coupling constant observed for the major isomer of 81a also supports this endo stereochemical assignment. It is interesting to note that related systems (e.g., norbornenes
Table VIII. Cycloadducts of 4-Oxazolin-2-one (47a) and 3-Acetyl-4-Oxazolin-2-one (47b)

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>Adduct</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>47a</td>
<td>81a</td>
<td>toluene 2 hr., 111°</td>
<td>60%</td>
</tr>
<tr>
<td>47b</td>
<td>81b</td>
<td>toluene 5 hr., 111°</td>
<td>65%</td>
</tr>
<tr>
<td>47a</td>
<td>82</td>
<td>ethyl acetate 79 hr., 77°</td>
<td>54%</td>
</tr>
<tr>
<td>47a</td>
<td>83</td>
<td>benzene 24 hr., 80°</td>
<td>86%</td>
</tr>
<tr>
<td>47b</td>
<td>84b</td>
<td>o-xylene 5 hr., 144°</td>
<td>63%</td>
</tr>
<tr>
<td>47b</td>
<td>85b</td>
<td>o-xylene 72 hr., 144°</td>
<td>87%</td>
</tr>
</tbody>
</table>
and benzonorbornenes) exhibit almost identical $J_{\text{exo,exo}}$ and $J_{\text{endo,endo}}$ coupling constants.\textsuperscript{93} Finally, it should be mentioned that the nmr spectral assignments of the C-4 and C-5 protons of endo- and exo-81a were facilitated by the broadening of the C-4 proton doublet by the adjacent NH proton. Broadening of this type was also observed, for example, in the case of 4-ethoxy-2-oxazolidinone (64a). This broadening effect was employed to assign the chemical shifts of the C-4 protons of all the N-unsubstituted adducts prepared in this study. As in the case of 64a, the broadening disappeared upon washing out the NH signal with D$_2$O.

Newman has reported the analogous reaction of vinylene carbonate (50) with 1,3-diphenylisobenzofuran (78) in refluxing xylene (for 20 minutes) or in refluxing toluene (for 1 hour).\textsuperscript{62} This author reported only a single adduct (86) and did not assign its stereochemistry. Lown and Matsumoto, however, later reported that the reaction of 50 and 78 presumably in refluxing benzene afforded a mixture of adducts in a ratio of ca. 85:15.\textsuperscript{63} The nmr spectrum of the major

![Diagram](endo-86_major_isomer.png) 5.26 endo-86 (major isomer)  

![Diagram](exo-86_minor_isomer.png) 5.13 exo-86 (minor isomer)
isomer was characterized by a singlet at δ 5.26 for the vicinal protons, while the minor isomer exhibited a singlet at δ 5.13. Lown and Matsumoto assigned endo stereochemistry to the major isomer on the basis of the expected shielding of the endo vicinal protons of the exo isomer by the benzene ring.

Further structural support for 81a was obtained from its acid catalyzed dehydration. This reaction was patterned after the work of Jones and Wife. These authors reported that adduct 86 in a mixture of glacial acetic acid and concentrated hydrochloric acid was converted to 1,4-diphenyl-naphthalene-2,3-diol (87). Accordingly, a suspension of

![Diagram](image)

adduct 81a in glacial acetic acid and hydrochloric acid was heated at reflux for 4 hours. Upon cooling, a colorless solid was collected by suction filtration. The acid insolubility of this material indicated that it was not amino-alcohol 89. The IR (KBr) spectrum of this material exhibited an intense carbonyl stretch at 1750 cm⁻¹, which was suggestive of the naphthoxazolin-2-one structure 88. This assignment was confirmed by the high resolution mass spectrum which showed a parent ion at m/e 337.1103 (calcd for C₂₃H₁₅NO₂: 337.1102).
Adduct 82, obtained from 47a and hexachlorocyclopenta-diene (79), was assumed to have endo stereochemistry, as indicated in Table VIII. Ample precedent exists for endo addition of cyclic dienophiles to 79. In this case, the vicinal coupling constant of 8 Hz observed for adduct 82 appears to be of little value with regard to confirming this stereochemical assignment. For example, the \( J_{\text{exo,exo}} \) and \( J_{\text{endo,endo}} \) vicinal coupling constants of the hexachloronorbornene 90 have recently been reported and differ only slightly.

Since o-chloranil (80) contains a carbodiene system and a heterodiene system, two types of thermal cycloadducts, 91 and 92, could be formed, depending upon the nature of the dienophile. It is normally quite easy to differentiate between diketone adducts 91 and 1,4-dioxene adducts 92.
on the basis of ir spectroscopy. However, in the case of the adduct obtained from 47a and 80, the presence of the 2-oxazolidinone carbonyl absorption precluded an unambiguous structural assignment based solely on ir spectroscopy. The ir (KBr) spectrum of this adduct also exhibited a fairly intense absorption at 1435 cm$^{-1}$, which was absent in the spectrum of adduct 82. Since 1,4-dioxene adducts 92 have been reported to exhibit a characteristic C-O stretch in this region, the presence of this band is at least suggestive of structure 83. The nmr (Me$_2$SO-d$_6$) chemical shifts of the vicinal protons of this adduct also appear to be more consistent with structure 83 than 93. The vicinal protons of this adduct appeared as doublets centered at $\delta$ 6.30 and
6.68 (J=6 Hz). These protons are deshielded by over 1 ppm relative to the vicinal protons of adduct 82, which appears to be a reasonable model for endo-93. This deshielding appears consistent with the substitution of an additional oxygen atom on the C-4 and C-5 carbons of the 2-oxazolidinone ring as in structure 83. With the aid of molecular models, the long-range deshielding effects of the carbonyl groups of endo- and exo-93 were examined employing the calculated anisotropy of the carbonyl group. This semiquantitative approach predicted that the vicinal protons of endo- and exo-93 should experience a carbonyl deshielding effect of no more than ca. 0.1 ppm. Structure 83 is also supported by the reported formation of 1,4-dioxene (92) adducts from 80 and electron-rich dienophiles, such as enamines.

Cycloadditions of 3-acetyl-4-oxazolin-2-one (47b) - product structure assignments

3-Acetyl-4-oxazolin-2-one (47b) added to 1,3-diphenylisobenzofuran (78), cyclopentadiene, and anthracene as indicated in Table VIII. The successful addition of 47b to the electron-rich dienes cyclopentadiene and anthracene
may simply be a result of its greater thermal stability and solubility compared to 47a. However, 47b also appears to be a less electron-rich dienophile than 47a (vide infra).

The addition of 47b to 1,3-diphenylisobenzofuran afforded a single adduct (81b). Adduct 81b was deacetylated to endo-81a, thus confirming the endo stereochemistry of 81b.

\[
\begin{array}{c}
\text{81b} \\
\text{C}_6\text{H}_5\text{O} \\
\text{C}_6\text{H}_5\text{N} \\
\text{CH}_3 \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{O} \\
\text{C}_6\text{H}_5 \\
\text{N} \\
\text{O} \\
\end{array}
\quad
\begin{array}{c}
\text{NH}_3 \\
\text{H}_2\text{O}/\text{EtOH} \\
25^\circ \\
\end{array}
\quad
\begin{array}{c}
\text{81a} \\
\text{C}_6\text{H}_5\text{O} \\
\text{C}_6\text{H}_5\text{N} \\
\text{CH}_3 \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{O} \\
\text{C}_6\text{H}_5 \\
\text{N} \\
\text{O} \\
\end{array}
\rightleftharpoons
\begin{array}{c}
\text{end}-81a \\
\text{C}_6\text{H}_5\text{O} \\
\text{C}_6\text{H}_5\text{N} \\
\text{CH}_3 \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{O} \\
\text{C}_6\text{H}_5 \\
\text{N} \\
\text{O} \\
\end{array}
\]

This deacetylation was accomplished by allowing a suspension of 81b to stir overnight at room temperature in ethanolic aqueous ammonia. Gompper has described a similar procedure for the deacetylation of 3-acetyl-4-oxazolin-2-ones. This general procedure was successfully employed to deacetylate the other N-acetyl adducts prepared in this study.

The addition of 47b to cyclopentadiene was performed according to the method described by Scharf and Küsters for the reaction of dichlorovinylene carbonate (94) and

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Cl} \\
\text{O} \\
\end{array}
\]

\text{94}
cyclopentadiene. This involved reacting equimolar amounts of 47b and cyclopentadiene monomer in refluxing o-xylene for 1 hour. Upon cooling, a second equivalent of cyclopentadiene was added, and the mixture was refluxed an additional hour. This process was repeated until a total of five equivalents of cyclopentadiene had been employed. Examination of the concentrated reaction mixture by nmr spectroscopy indicated that ca. 80% of the 3-acetyl-4-oxazolin-2-one (47b) starting material had been consumed. Chromatography over silica gel afforded adduct 84b as a pale yellow oil, which was used without further purification. The yield of 84b was 63% based on the amount of 47b initially employed. The endo stereochemistry of adduct 84b was established by nmr spectroscopy and by conversion to a substance of known endo stereochemistry. The vicinal protons H2 and H3 of 84b each appeared as a doublet of doublets with \( J_{2,3} = 8.4 \) Hz, \( J_{1,2} = 4.0 \) Hz, and \( J_{3,4} = 3.6 \) Hz. Since \( J_{1,2,exo} \) coupling constants for norbornenes have been reported to be in the range of 2.9-4.3 Hz, while \( J_{1,2,endo} \) coupling constants are negligible, the magnitudes of the \( J_{1,2} \) and \( J_{3,4} \) coupling constants of 84b are indicative of endo stereochemistry. Addi-
tionally, adduct \(84b\) was smoothly deacetylated in 98\% yield to give \(84a\). Compound \(84a\) gave the known endo-95 upon catalytic hydrogenation as indicated in equation (25). The melting point and nmr spectrum of the material obtained here agreed favorably with those reported for endo-95. \(^{102}\)

Scheme XVI
Adduct 85b, obtained from 47b and anthracene, was deacetylated in 92% yield to afford 85a. Both 85a and 85b
gave aminoalcohol 96 in 89% and 74% yields, respectively,
upon hydrolysis in refluxing ethanolic aqueous sodium hydroxide
as shown in Scheme XVI above. These results indicate the
utility of this approach to cyclic cis-β-aminoalcohols.

**Cycloadditions of 4-oxazolin-2-ones to s-tetrazines**

In an attempt to ascertain if 3-acetyl-4-oxazolin-2-one (47b) was in fact a less electron-rich dienophile than
4-oxazolin-2-one (47a), the reactions of 47a and 47b with
1,2,4,5- or s-tetrazines (97) were examined. Cycloadditions
of these s-tetrazines (97) proved to be more complex (and
interesting) than those of the previously discussed dienes
and therefore are treated separately.

Normal Diels-Alder reactions readily occur between
electron-rich dienes and electron-deficient dienophiles.
However, additions also occur readily between electron-
deficient dienes and electron-rich dienophiles. Additions
of this type are appropriately referred to as Diels-Alder
reactions with "inverse" electron demand. Sustmann has
rationalized these two extremes of the Diels-Alder reaction
using the frontier molecular orbital approach. For
normal Diels-Alder reactions, the dominant interaction is
between the LUMO of the dienophile and the HOMO of the diene.
In contrast, for inverse Diels-Alder reactions, the dominant
interaction is between the HOMO of the dienophile and the
LUMO of the diene. Electron-withdrawing substituents in the dienophile lower the energy of both the HOMO and LUMO, while electron-donating substituents increase the energy of both the HOMO and LUMO. Thus, for normal Diels-Alder reactions, electron-withdrawing substituents in the dienophile increase the LUMO-dienophile - HOMO-diene interaction. For inverse Diels-Alder reactions, electron-donating substituents in the dienophile increase the HOMO-dienophile - LUMO-diene interaction.

s-Tetrazines (97), as well as hexachlorocyclopentadiene (79) and o-chloranil (80), are dienes which display "inverse" electron demand in [4+2] cycloadditions. The reactions of 97 with olefins was discovered by Carboni and Lindsey. It has been shown that addition of the dienophile to the 3,6-positions of 97 is the rate-determining step. The initially-formed 1:1 adducts 98, which cannot be isolated, rapidly lose nitrogen to afford 1,4-dihydropyridazines (100) via the tautomerization of the 4,5-dihydropyridazines (99) as shown in Scheme XVII. The structures of the 1,4-dihydropyridazines (100) have been established by ir and nmr spectroscopy. Sauer and co-workers have taken advantage of the reactivity of s-tetrazines (97) with electron-rich dienophiles, such as enol ethers and ketene N,O-acetals, for example, to devise a one-step pyridazine (101) synthesis as illustrated in Scheme XVIII.
Scheme XVII

\[
\begin{align*}
\text{Scheme XVIII}
\end{align*}
\]
The first s-tetrazine examined was 3,6-diphenyl-1,2,4,5-tetrazine (97a, \( R^1 = C_6H_5 \)). An equimolar mixture of 4-oxazolin-2-one (47a) and the blue-red tetrazine 97a was refluxed in ethyl acetate for 80 hours. The reaction was terminated at this point even though it had not gone to completion. Work-up afforded a small amount of a high melting solid. The ir (KBr) spectrum of this material was characterized by several bands in the 3500-3000 cm\(^{-1}\) region and by two fairly intense bands at 1635 and 1585 cm\(^{-1}\). The nmr (\( \text{Me}_2\text{SO-d}_6 \)) spectrum exhibited a broad two-proton signal centered at \( \delta 6.04 \), a one-proton singlet at \( \delta 7.19 \), and ten aromatic protons, two of which were deshielded. Additionally, the mass spectrum showed a parent ion at m/e 247 with a base peak at m/e 246. These spectral data appeared to be consistent with the 4-aminopyridazine structure 102, although the melting point of this material was ca. 10\(^0\) lower than that reported for 102. The presence of only two deshielded ortho phenyl protons, rather than four, suggested that the phenyl group adjacent to the amino group was forced out of the pyridazine plane. The formation of 102 can be rationalized by assuming that the initial product, dihydropyridazine
103, decarboxylated under the reaction conditions as indicated in Scheme XIX. This sequence seems reasonable in light of the pyridazine synthesis shown in Scheme XVIII. Additionally, a one-step synthesis of substituted phenols (106) from vinylene carbonate (50) and cyclopentadienones (104) has been reported, which involved a similar decarboxylation.\textsuperscript{113} As indicated in Scheme XX, 50 and 104 react to form adducts 105, which may be isolated or thermolyzed directly to afford phenols 106 upon decarbonylation and decarboxylation.

Since the reaction of 47a and 97a appeared to be somewhat sluggish, the reaction of 47a with a more electron-deficient s-tetrazine was investigated. A mixture of 47a and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (97b, R\textsuperscript{1} = 2-C\textsubscript{5}H\textsubscript{4}N)\textsuperscript{114} was allowed to stir in ethyl acetate at room temperature.
Decolorization was complete within 24 hours to afford a 95% yield of a rather insoluble yellow solid with a broad melting range. The ir (KBr) spectrum of this solid exhibited an N-H stretch at 3300 cm\(^{-1}\) and an intense carbonyl stretch at 1760 cm\(^{-1}\). The elemental analysis for this material corresponded to a 1:1 adduct of 47a and 97b minus N\(_2\). Thus, this material appeared to be a dihydropyridazine. Three
tautomeric structures, 107a-109a, were possible. Although this dihydropyridazine was too insoluble to be characterized directly by nmr spectroscopy, structure 107a was assigned on the basis of an indirect nmr spectroscopic technique to be described later (see page 101).

A suspension of 107a was heated in refluxing toluene for 6 hours. Upon cooling, a greenish-brown solid was collected by suction filtration. Recrystallization from dimethyl sulfoxide afforded pale yellow needles. This material was shown to be the expected 4-aminopyridazine 110a

![Chemical structure of 110a](image)

on the basis of its ir, nmr, and mass spectra, as well as by elemental analysis. Concentration of the toluene filtrate of 110a gave an orangish solid, which afforded fine yellow needles upon recrystallization from benzene. The ir (KBr) spectrum of this material exhibited a weak, broad band centered at 3440 cm\(^{-1}\) and failed to show any bands in the 1800-1600 cm\(^{-1}\) region of the spectrum. The nmr (CDCl\(_3\)) spectrum was characterized by a broad one-proton signal at \(\delta \, 14.8\), which washed out with D\(_2\)O, a one-proton singlet at \(\delta \, 8.10\), and aromatic resonances indicative of two non-equivalent pyridyl rings. These spectral data were strongly
suggestive of the 4-hydroxypyridazine 111. The extremely
low field chemical shift of the OH signal is presumably a
result of intramolecular hydrogen-bonding with the adjacent
pyridyl nitrogen. This intramolecular hydrogen-bonding also
explains why 111 exists as the 4-hydroxypyridazine, whereas
the parent 4-hydroxypyridazine has been shown by ir spectros-
copy to exist predominantly as the tautomeric 4-pyridazone
112.115 This structural assignment was also supported by
the high resolution mass spectrum, which showed a parent ion
at m/e 250.0851 (calcd for C_{14}H_{10}N_{4}O: 250.0854). These
results, which are summarized in Scheme XXI, suggest that
upon thermolysis of dihydropyridazine 107a, decarboxylation
and loss of isocyanic acid to give 110a and 111, respectively,
are competitive processes.

The reaction of vinylene carbonate (50)80 and 3,6-di-
(2'-pyridyl)-1,2,4,5-tetrazine (97b) was examined next. The
purposes of this experiment were to prepare an authentic
sample of 4-hydroxypyridazine 111 and to compare the reac-
tivities of 4-oxazolin-2-one (47a) and 50 with 97b. In
contrast to 47a, 50 did not react at room temperature with
97b. Reaction did occur in refluxing benzene with a required
Scheme XXI

97b

Py = —N

- $\text{RNCO}$

- $\text{CO}_2$

110

a, $R = H$
b, $R = \text{CH}_3\text{CO}$
c, $R = \text{CH}_3$

Scheme XXII

97b

- $\text{N}_2$

- $\text{CO}_2$

111
reaction time in excess of 24 hours. The initially-formed dihydropyridazine 113 was unstable under these conditions and decarboxylated to give 111 in 90% yield as shown in Scheme XXII. The 4-hydroxypyridazine 111 obtained in this reaction was identical in all respects to the material obtained upon thermolysis of dihydropyridazine 107a. Since vinylene carbonate (50) and 4-oxazolin-2-one (47a) have similar steric requirements, this result strongly suggests that 47a is a more electron-rich dienophile than 50.

Reaction of 3-acetyl-4-oxazolin-2-one (47b) and s-tetrazine 97b occurred only upon refluxing in toluene for 46 hours. Again the dihydropyridazine 107b decarboxylated under the reaction conditions to give the 4-acetamidopyridazine 110b (see Scheme XXI). The failure to observe an N-H stretch above 3000 cm\(^{-1}\) in the ir (KBr) spectrum of 110b, as well as a chemical shift of \(\delta\) 13.4 for the amide proton, suggests that the amide NH proton is also intramolecularly hydrogen-bonded to the adjacent pyridyl nitrogen. Authentic 110b was prepared in 64% yield by acetylation of 4-amino- pyridazine 110a with acetic anhydride. It is worth noting
that examination of the toluene filtrate of 110b failed to show any sign of the 4-hydroxypyridazine 111. Unlike dihydropyridazine 107a, loss of acetyl isocyanate from 107b to form 111 does not appear to compete effectively with decarboxylation to form 110b. The reasons for this difference are not clear.

Although 4-oxazolin-2-one (47a) was appreciably more reactive than 3-acetyl-4-oxazolin-2-one (47b) with s-tetrazine 97b, it was not obvious whether this reactivity difference was due to electronic effects or to the steric bulk of the acetyl group. In an attempt to evaluate the importance of steric factors in these reactions, the reaction of 3-methyl-4-oxazolin-2-one (47c) and s-tetrazine 97b was investigated. Thus, a chloroform solution of 47c and 97b was allowed to stir at room temperature. The progress of this reaction was monitored by periodically removing and concentrating aliquots from the reaction mixture. The residues were then examined by nmr spectroscopy. Interestingly, it appeared that the ethanol present in reagent chloroform was somehow being incorporated into the products. Although this reaction appeared to have gone 50% toward completion in ca. 2.5 days, the reaction mixture failed to decolorize even after stirring at room temperature for 18 days. Nevertheless, the reaction mixture was concentrated to give a reddish oil, which was shown by nmr spectroscopy to be largely a mixture of unreacted 47c and two ethanol-containing products in a ratio of ca. 80:20. Repeated
chromatography over silica gel eluting with chloroform, followed by recrystallization, afforded the major ethanol-containing product in 30% yield as a colorless solid.

Since the minor ethanol-containing product was not isolated, the preparation of the analogous methanol-containing products was attempted in hopes of isolating both products. Accordingly, a mixture of 47c and 97b was refluxed in absolute methanol until the color of the reaction mixture had faded to a pale pink (ca. 32 hours). Concentration of the reaction mixture gave a pinkish oil, which was shown by nmr spectroscopy to contain the two corresponding methanol-containing products in a ratio of ca. 67:33. Chromatography of this oil over silica gel eluting with ether containing 2% (v/v) methanol afforded the major product in 33% and the minor product in 19% yield, after recrystallization. Both compounds gave elemental analyses consistent with a 1:1 adduct of 47c and 97b minus N₂ plus methanol. Thus, it appeared that these compounds were isomeric dihydropyridazine-methanol addition products. A similar addition of alcohols across the carbon-nitrogen double bond of diazanorcaradienes (114) as shown in equation (27) has been reported. The

\[
\begin{align*}
\text{114} & \quad \text{ROH} \quad \text{115} \\
\end{align*}
\]
structures of these addition products (115) were established by ir and nmr spectroscopy.

Since the carbon-nitrogen double bonds of dihydropyridazine 107c are nonequivalent, two possible regioisomeric methanol addition products, 116c and 117c, are possible. Additionally, since the methanol can add to the top or bottom

Scheme XXIII

**Py**

97b + 47c → 107c

trans-116c

cis-116c

cis-117c

trans-117c

CH₃OH
face of 107c, each regioisomer can have either a cis or trans configuration. (Cis and trans refer to the relative configurations of the methoxy group and the 2-oxazolidinone ring.) These possibilities are indicated in Scheme XXIII. The fact that only two isomers, rather than four, were actually formed appears consistent with addition of methanol to the least hindered face of dihydropyridazine 107c to afford trans-116c and trans-117c. Additionally, it appears reasonable that addition of methanol to the least hindered carbon-nitrogen double bond of 107c to afford trans-116c should be favored over addition to the more hindered carbon-nitrogen double bond to give trans-117c. Thus, on the basis of these chemical considerations, the major dihydropyridazine-methanol

\[
\begin{align*}
\text{trans-116c (major isomer)} & \quad \delta_A = 5.64 \\
& \quad \delta_B = 5.26 \\
& \quad \delta_{NMe} = 2.71 \\
& \quad \delta_{OMe} = 2.91 \\
& \quad J_{AB} = 9.4 \text{ Hz} \\
& \quad J_{BX} = 2.5 \text{ Hz} \\
\text{trans-117c (minor isomer)} & \quad \delta_A = 6.17 \\
& \quad \delta_B = 4.54 \\
& \quad \delta_{NMe} = 2.10 \\
& \quad \delta_{OMe} = 2.85 \\
& \quad J_{AB} = 9.3 \text{ Hz} \\
& \quad J_{BX} = 2.3 \text{ Hz}
\end{align*}
\]
addition product was assigned structure trans-116c, while the minor isomer was assigned as trans-117c. These structural assignments along with pertinent nmr (CDCl₃) spectral data are summarized above.

The ir (KBr) and nmr (CDCl₃) spectra of the dihydro-pyridazine-methanol addition products substantiated these assignments. Both isomers exhibited N-H and carbonyl stretches in their ir spectra. The presence of the N-H stretch, while consistent with structures 116c and 117c, ruled out the possibility of azo structures such as 118 and 119. The

![Diagram of structures 118 and 119]

nmr spectra revealed for each isomer that one of the vicinal protons appeared as a doublet, while the other vicinal proton appeared as a doublet of doublets. The larger coupling of 9.3-9.4 Hz appears consistent with the expected cis vicinal coupling in both 116c and 117c, while the smaller coupling of 2.3-2.5 Hz is apparently due to the four-bond coupling of H_B with the NH proton. This four-bond coupling is presumably a consequence of the "W" pattern arrangement of these protons. 117 The relative magnitudes of the chemical shift differences observed for the vicinal protons of the major and minor isomers are also consonant with structures 116c
and 117c, respectively. For structure 116c, \( H_B \) would be expected to occur at a lower field than \( H_A \) because of the greater electronegativity of oxygen compared to nitrogen. However, the deshielding effect of the \( \alpha\text{-C}=\text{N} \) causes \( H_A \) to actually occur at a slightly lower field than \( H_B \). In the case of structure 117c, the initial chemical shift difference of the vicinal protons (based on electronegativity considerations) is enhanced by the deshielding of \( H_A \) by the \( \alpha\text{-C}=\text{N} \). Finally, the observed shielding of ca. 0.6 ppm for the N-methyl singlet of the minor isomer relative to the N-methyl singlet of the major isomer appears compatible only with structure trans-117c. Only in trans-117c can the N-methyl group be shielded by the pyridyl \( \pi \) system.

The structural assignments of the corresponding dihydropyridazine-ethanol addition products along with pertinent

\[
\begin{align*}
\text{trans-}120c \text{ (major isomer)} & \quad \delta_A = 5.67 \\
& \quad \delta_B = 5.29 \\
& \quad \delta_{\text{NMe}} = 2.73 \\
& \quad J_{\text{AB}} = 9.5 \text{ Hz} \\
& \quad J_{\text{BX}} = 2.5 \text{ Hz} \\
\text{trans-}121c \text{ (minor isomer)} & \quad \delta_A = 6.18 \\
& \quad \delta_B = 4.56 \\
& \quad \delta_{\text{NMe}} = 2.10 \\
& \quad J_{\text{AB}} = \text{ca. 9Hz} \\
& \quad J_{\text{BX}} = \text{ca. 2.5 Hz}
\end{align*}
\]
nmr (CDCl₃) spectral data are summarized above. As mentioned previously, minor isomer trans-12lc was not isolated. However, major isomer trans-120c gave an elemental analysis consistent with a 1:1 adduct of 47c and 97b minus nitrogen plus ethanol and exhibited N-H and carbonyl stretches in its ir (KBr) spectrum. In addition to the signals indicated above, the nmr spectrum of trans-120c also showed nonequivalent ethoxy methylene protons and a nine-proton pyridyl resonance, including the buried NH signal.

Sauer and co-workers have reported the nmr spectrum of 1,4-dihydropyridazine 122. The Hₓ proton of 122 appeared as a doublet of doublets with Jₓ,y=6 Hz and Jₓ,x=2 Hz. Addition of trifluoroacetic acid catalyzed rapid exchange of Hₓ, which caused Hₓ to collapse to a doublet with Jₓ,y=6 Hz. Upon attempting a similar nmr experiment with trans-120c, it was found that the Hₓ,ᵧ doublet of doublets did not collapse to a doublet upon addition of trifluoroacetic acid vapor. However, the spectrum underwent two immediate changes, i.e., the appearance of trans-121c and of free ethanol. The ratio of trans-120c to trans-121c was ca. 80:20, the same product ratio observed upon the reaction of 3-methyl-4-
oxazolin-2-one (47c) and s-tetrazine 97b in ethanol-containing chloroform. This result suggests that this 80:20 ratio represents a thermodynamic product distribution. This appears reasonable, since trans-120c would be expected to be thermodynamically favored over trans-121c on the basis of steric considerations. Upon sitting at room temperature, the signals due to trans-120c and trans-121c gradually diminished, while the ethanol signals increased. Additionally, signals attributed to 4-hydroxypyridazine 111 and 4-methylaminopyridazine 110c gradually appeared. These results are consistent with an acid-catalyzed equilibration of trans-120c and trans-121c via dihydropyridazine 107c. Dihydropyridazine 107c, which was not observed spectrally, apparently readily decarboxylated or lost methyl isocyanate under these conditions to form 110c or 111, respectively.

In a related nmr experiment, the NH proton of trans-120c failed to wash out with D2O until a trace of trifluoroacetic acid vapor was added to the sample. While this caused the H3 doublet of doublets of trans-120c to collapse to a doublet with JAB=9.5 Hz, it also resulted in the liberation of ethanol and the apparent formation of trans-121c. However, the major change in the spectrum was the appearance of a major new product, presumed to be a deuterium oxide addition product of dihydropyridazine 107c. This new product was characterized by a methyl singlet at δ 2.77 and two doublets centered at δ 4.80 and 5.70 with JAB=ca. 9 Hz. Since the chemical shifts of the methyl singlet and the low-
field doublet were almost identical to those of trans-116c and trans-120c, this new product was assigned structure trans-123c with the same regio- and stereochemistry as trans-116c and trans-120c. The fact that the vicinal protons of

\[
d_{A} = 5.70 \\
d_{B} = 4.80 \\
d_{NMe} = 2.77 \\
J_{AB} = \text{ca. } 9\text{ Hz}
\]

123c appear as an AB quartet with \(J_{AB} = \text{ca. } 9\text{ Hz}\) can be taken as indirect evidence that dihydropyridazine 107c has a 4,5-dihydro structure. Addition of \(D_2O\) to 1,4-dihydro structures

108c and 109c would have resulted in the formation of 123c with a deuterium on either the C-4 or C-5 carbons of the 2-oxazolidinone ring.

When a solution of 3-methyl-4-oxazolin-2-one (47c) and s-tetrazine 97b was heated at reflux in chloroform, decolorization was complete within 14 hours. However, heating was continued for an additional 17 hours until the last traces of dihydropyridazine-ethanol addition products 120c and 121c
were destroyed. Concentration of the reaction mixture and chromatography of the residue afforded 4-methylanilinopyridazine 110c and 4-hydroxypyridazine 111. The structure of 110c was established by ir, nmr, and mass spectroscopy, as well as by elemental analysis. These results are consistent with a thermal equilibration of 120c and 121c with dihydropyridazine 107c,116a which can then decarboxylate or lose methyl isocyanate to give 110c or 111, respectively (see Scheme XXI).

Finally, it appeared desirable to examine the reaction of 47c and s-tetrazine 97b under conditions where the initially-formed dihydropyridazine 107c could not be trapped by alcohol. Thus, 47c and 97b were allowed to react in refluxing benzene for 8 hours. Upon cooling, a colorless solid was collected by suction filtration. This solid, which was rather insoluble in common organic solvents, was characterized by an intense carbonyl stretch at 1760 cm\(^{-1}\). Although this material was not investigated extensively, its nmr\(^{118}\) (CF\(_3\)COOH) and mass spectra suggested that it was a mixture of 2:1 adducts, 124 and 125, formed upon the addition of a second molecule of 47c to dihydropyridazine 107c as shown in Scheme XXIV.
Despite the fact that no attempt was made to separate these isomers, their regio- and stereochemistries were tentatively assigned on the basis of steric considerations and their simple nmr spectra. Because the steric bulk of the 2-oxazolidinone ring in 107c opposes the approach of the second molecule of 47c from the top, attack must occur from the bottom. Thus,

Scheme XXIV

exo,exo-124 (major isomer)  exo,exo-125 (minor isomer)
the 2-oxazolidinone ring of 107c necessarily becomes cis to the developing azo linkage. Symmetry-controlled secondary orbital interactions, which are expected to be operative in the transition state for cycloaddition of 107c and 47c, predict exo,exo configurations for 124 and 125. The assignment of the head-to-tail structure 124 as the major isomer is consistent with minimum steric interactions between the N-methyl groups in this transition state. The exo,exo configurations of 124 and 125 were supported by their nmr spectra. That is, a single methyl singlet and a single AB quartet were observed for each isomer. The endo,exo isomers of 124 and 125 would be expected to display more complex nmr spectra. Cyclopropenes, norbornene, and cyclobutadiene have been reported to form 2:1 adducts with s-tetrazines (97), and in each case the products were assigned exo,exo stereochemistry.

The benzene filtrate of 124 and 125 was concentrated to give an orangish oil. The predominant product present in this oil was shown by nmr (CDCl₃) spectroscopy to be characterized by a methyl singlet at δ 2.68 and two doublets centered at δ 5.77 and 6.19 with J=10.3 Hz. It appeared
reasonable that this product was the previously unobserved 4,5-dihydropyridazinone 107c. Although no attempt was made to isolate 107c from this oil, its structure was confirmed by the addition of one drop of methanol to the nmr sample containing 107c. This resulted in the immediate disappearance of the signals attributed to 107c and the appearance of new signals due to the dihydropyridazinone-methanol addition product trans-116c and presumably trans-117c. It should be mentioned that the chemical shifts of $H_A$ and $H_B$ of 107c substantiate the assignments of the $H_A$ resonances in the nmr spectra of trans-116c, trans-117c, trans-120c, and trans-121c.

$$\delta_A = 6.19$$

$$\delta_B = 5.77$$

$$\delta_{NMe} = 2.68$$

$$J_{AB} = 10.3 \text{ Hz}$$
It appeared worthwhile to briefly investigate the reaction of 4-oxazolin-2-one (47a) and s-tetrazine 97b in the presence of alcohols. Accordingly, a mixture of 47a and 97b in absolute methanol was allowed to stir at room temperature. Decolorization was complete within 48 hours. Concentration of the reaction mixture afforded a yellow oil, which was shown by nmr spectroscopy to contain the expected dihydropyridazine-methanol addition products trans-116a and trans-117a in a ratio of ca. 4:1, respectively. No attempt was made to separate or isolate these isomers. Similarly, a mixture of 47a and 97b in absolute ethanol was allowed to stir at room temperature. Again decolorization was complete within
48 hours. However, the major product of this reaction was
dihydropyridazine 107a, which was obtained in 68% yield upon
collection by suction filtration. This result, while surpris-
ing, was presumably due to the decreased solubility of
107a in ethanol compared to methanol. Concentration of the
ethanol filtrate of 107a gave a yellow oil, which was shown
by nmr spectroscopy to contain a small amount of the ex-
pected dihydropyridazine-ethanol addition products trans-
120a and trans-121a.

As a result of the experience gained working with di-
hydropyridazine 107c and its alcohol addition products, it
was now possible to indirectly show that dihydropyridazine
107a also has a 4,5-dihydrostructure rather than 1,4-dihydro
structures 108a or 109a. Thus, a few drops of D₂O and a

![formula_images]

107a 108a 109a

trace of trifluoroacetic acid vapor were added to a suspension
of 107a in CDCl₃. Solution occurred with shaking over a
period of ca. 30 minutes. The predominant product present
in this nmr solution was characterized by two doublets cen-
tered at δ 4.76 and 5.04 with J=ca. 8 Hz. By analogy to
trans-123c, this product was assigned structure trans-123a.
As pointed out for trans-123c, the fact that the vicinal
protons of trans-123a appear as an AB quartet is consistent only with 4,5-dihydropyridazine structure 107a. Addition of D$_2$O to 108a or 109a would have resulted in the incorporation of a deuterium on the C-4 or C-5 carbons of the 2-oxazolidinone ring. Similarly, a few drops of methanol and a trace of trifluoroacetic acid vapor were added to a suspension of 107a in CDCl$_3$. The nmr spectrum of the resulting solution exhibited peaks attributable to dihydropyridazine-methanol addition product trans-116a. Thus, dihydropyridazines 107a and 107c have been shown to have 4,5-dihydro structures, rather than the normally preferred 1,4-dihydro structures (see Scheme XVII and the related discussion). However, several other compounds with 4,5-dihydropyridazine structures have been reported in the literature, e.g., 114a,$^{122}$ 126,$^{119}$ and 127.$^{109}$ A feature that these compounds and 107a and
all have in common is a second ring fused to the C-4 and C-5 carbons of the dihydropyridazine ring.

From these results, it is apparent that 3-methyl-4-oxazolin-2-one (47c) does not add to s-tetrazine 97b as readily as does 4-oxazolin-2-one (47a). This reactivity difference is presumably a result of the steric bulk of the 3-methyl substituent in 47c. Nevertheless, 47c does add to 97b at a slow but observable rate at room temperature. This suggests that the decreased reactivity of 3-acetyl-4-oxazolin-2-one (47b) towards s-tetrazine 97b is at least partially electronic in origin. That is, the electron-withdrawing ability of the 3-acetyl group makes 47b a less electron-rich dienophile than 47a. However, since the effective size of an acetyl group is presumably greater than that of a methyl group, the actual magnitude of this electronic effect cannot be evaluated at present.

Attempted cycloadditions of 5-phenyl-4-oxazolin-2-one (47d) and 3-acetyl-4-oxazolin-2-one (47e)

As the final phase of this study, several Diels-Alder reactions were attempted with the sterically hindered 5-phenyl-4-oxazolin-2-one (47d). Heterocycle 47d was found

\[
\text{C}_6\text{H}_5
\]

47d, \( R = \text{H} \)

\[
\text{CH}_3\text{CO}
\]

47e, \( R = \text{CH}_3\text{CO} \)
to be a poor dienophile as it failed to react with cyclopentadiene at 200° in a sealed tube or with 1,3-diphenylisobenzofuran (78) in refluxing o-xylene. However, its 3-acetyl derivative 47e did react with anthracene in refluxing p-cymene to afford adduct 85e in 67% yield. Adduct 85e was deacetylated in 86% yield to give 85d as shown in Scheme XXV. Although time did not permit further exploration of the
dienophilicity of 47e, this preliminary result appears encouraging. It appears likely that the dienophilicity of 4-oxazolin-2-ones towards electron-rich dienes can be further enhanced by N-substitution with groups of even greater electron-withdrawing ability than the acetyl group, such as the trifluoroacetetyl (CF₃CO) and trifluoromethanesulfonyl (CF₃SO₂) groups. However, this expected electronic
enhancement will be diminished, in part, by the steric bulk of the N-substituent, particularly for sterically hindered 4-oxazolin-2-ones, such as 47d.
CHAPTER IV
EXPERIMENTAL

Melting points and boiling points are uncorrected. Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus. Boiling points were determined by conventional distillation techniques. Infra-red spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer or a Beckman Model IR-10 spectrophotometer. Frequencies reported in the 3500-3000 cm\(^{-1}\) region which were determined on the Beckman spectrophotometer are indicated by an asterisk (*) superscript. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A60-A spectrometer for 60-MHz proton spectra, and a Varian XL-100-15 spectrometer for 100-MHz proton spectra. Carbon-13 nmr spectra were recorded on a Varian XL-100-15 nmr spectrometer, equipped with a Transform Technology FT attachment, operating at 25.16 MHz under conditions of full proton decoupling (unless otherwise indicated) at a probe temperature of \(\text{ca. } 38^\circ\). Samples were observed in 12-mm o.d. tubes as saturated solutions (for solid compounds) or approximately 50% solutions (for liquid compounds) in CDCl\(_3\). All chemical shifts (\(\delta\)) are reported in parts per million (ppm) downfield from internal tetramethylsilane (Me\(_4\)Si). Low resolution mass
spectra, exact mass, and molecular weight data were measured on an AEI-MS-30 double beam spectrometer at an ionizing potential of 70 eV. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Separations by column chromatography employed Fisher Neutral Alumina (Brockman Activity 1, 80-200 mesh) or MCB Silica Gel (Grade 62, 60-200 mesh). Thin-layer chromatography (tlc) was accomplished with Eastman Silica Gel Chromagram Paper with fluorescent indicator. Results were visualized by exposure to ultraviolet light or iodine vapor. Solvent evaporations were performed with a Büchi Rotavapor-T rotary evaporator equipped with a water aspirator.

1-Oxo-2-o-tolyl-5-t-butyl-1,2,5-thiadizolidin-3-one (4a)

Procedure A: A solution of thionyl chloride (2.62 g, 1.58 mL, 22.0 mmol) in benzene (25 mL) was added dropwise to a stirred solution of 2-t-butylamino-o-acetotoluidide\(^1\) (4.41 g, 20.0 mmol) and triethylamine (4.45 g, 6.14 mL, 44.0 mmol) in benzene (150 mL) at room temperature. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 24 hours.\(^{1,23}\) The reaction mixture was then washed with water (100 mL) to remove the triethylamine hydrochloride precipitate. The dried (MgSO\(_4\)) benzene layer was evaporated at reduced pressure to give a solid, which was recrystallized from absolute ethanol to afford 4a as colorless prisms (4.79 g, 90%): mp 123.5-125.5\(^0\) (lit.\(^1\) mp 123-125\(^0\)); see Appendix NMR No. 1.
Procedure B: A solution of thionyl chloride (3.57 g, 2.16 mL, 30.0 mmol) in anhydrous tetrahydrofuran (25 mL) was added dropwise to a stirred solution of imidazole (8.17 g, 120 mmol) in anhydrous tetrahydrofuran (50 mL) chilled with an ice water bath. Upon completion of this addition and after stirring at room temperature for 10 minutes, the imidazole hydrochloride precipitate was removed by rapid suction filtration. A solution of 2-t-butylamino-o-aceto-toluidide$^1$ (4.41 g, 20.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise at room temperature to the stirred tetrahydrofuran solution of 1,1'-thionylidimidazole prepared above. Following this addition, the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated at reduced pressure. The residue was taken up in dichloromethane (100 mL) and washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO$_4$) dichloromethane layer was evaporated at reduced pressure to give a solid, which was recrystallized from absolute ethanol to afford 4a as colorless prisms (4.94 g, 93%): mp 123.5-125.5° (lit.$^1$ mp 123-125°); see Appendix NMR No. 1.

1-Oxo-2-o-tolyl-5-phenyl-1,2,5-thiadiazolidin-3-one (4b)

A solution of thionyl chloride (4.16 g, 2.52 mL, 35.0 mmol) in anhydrous tetrahydrofuran (35 mL) was added dropwise to a stirred solution of imidazole (9.53 g, 140 mmol) in anhydrous tetrahydrofuran (60 mL) chilled with an ice
water bath. Upon completion of this addition and after stirring for 10 minutes, the imidazole hydrochloride precipitate was removed by rapid suction filtration. A suspension of 2-anilino-o-acetotoluidide\(^1\) (2.40 g, 10.0 mmol) in anhydrous tetrahydrofuran (100 mL) was added dropwise at room temperature to the stirred tetrahydrofuran solution of 1,1'-thionyl-diimidazole prepared above. Following this addition, the reaction mixture was allowed to stir at room temperature for 19 hours. The reaction mixture was then concentrated at reduced pressure. The residue was taken up in dichloromethane (150 mL) and washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO\(_4\)) dichloromethane layer was evaporated at reduced pressure to give a yellow solid, which was recrystallized from absolute ethanol to afford 4b as colorless, glistening micro-plates (2.32 g, 81\%): mp 130-131.5\(^\circ\) (lit.\(^1\) mp 129-131\(^\circ\)); ms m/e (rel intensity) 286 (M\(^+\), 0.5), 222 (M\(^+\)-SO\(_2\), 8), 153 (6), 106 (10), 105 (100), 104 (18), 77 (13).

\[3',4'-\text{-Dichlorolactanilide (7a)}\]

3',4'-Dichlorolactanilide was prepared in 49\% yield according to the procedure of Chupp,\(^2\) although it was necessary to wash the reaction mixture repeatedly with dilute hydrochloric acid to remove the unreacted 3,4-dichloroaniline before the lactanilide would crystallize: mp 97-98.5\(^\circ\) (lit.\(^2\) mp 93-95\(^\circ\)); ir (KBr) 3410\(^*\) (O-H stretch), 3315\(^*\) (N-H stretch), 1670 (C=O stretch), 1585 (aromatic C=C stretch),
1525 cm\(^{-1}\) (N-H bend); nmr (CDCl\(_3\)) \(\delta\) 1.48 (d, \(J=7\) Hz, 3H, CH\(_3\)CH), 3.40 (br, 1H, OH), 4.33 (q, \(J=7\) Hz, 1H, CH\(_3\)CH), 7.30 (d, 2H, ArH), 7.73 (t, 1H, ArH), 8.53 (br, 1H, NH).

2-Oxo-3-(3',4'-dichlorophenyl)-5-methyl-1,2,3-oxathiazolidin-4-one (8a)

Procedure A (Chupp's\(^{2,5}\) Procedure): A solution of 3',4'-dichlorolactanilide (4.68 g, 20.0 mmol) and thionyl chloride (35 mL) was heated at reflux with stirring for 1 hour. Upon cooling, the reaction mixture was concentrated at reduced pressure. The residue was diluted with anhydrous ether and again concentrated at reduced pressure. This process was repeated several times (until the excess thionyl chloride had been removed) to afford a yellow-brown oil (5.72 g): nmr (CDCl\(_3\)) \(\delta\) 1.65 (d, \(J=\text{ca.}\ 7\) Hz, CH\(_3\)CH of trans diastereomer), 1.80 (d, \(J=\text{ca.}\ 7\) Hz, CH\(_3\)CH of cis diastereomer), 4.98 (q, \(J=\text{ca.}\ 7\) Hz, CH\(_3\)CH of cis diastereomer), 5.29 (q, \(J=\text{ca.}\ 7\) Hz, CH\(_3\)CH of trans diastereomer), 7.08-7.67 (m, ArH of cis and trans diastereomers). The trans:cis ratio was ca. 53:47.

Upon attempting to isolate the trans diastereomer by fractional crystallization from the recommended solvent, absolute ethanol, it was discovered that the process was not particularly efficient and, more importantly, ethanol was not an inert solvent.

Procedure B: A solution of thionyl chloride (2.62 g, 1.58 mL, 22.0 mmol) in benzene (25 mL) was added dropwise to a stirred solution of 3',4'-dichlorolactanilide (4.68 g, 22.0 mmol) and triethylamine (4.45 g, 6.14 mL, 44.0 mmol)
in benzene (150 mL) at room temperature. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was then washed with water (100 mL) to remove the triethylamine hydrochloride precipitate. The dried (MgSO₄) benzene layer was concentrated at reduced pressure to give a yellow-brown oil (5.98 g). The nmr spectrum of this oil was identical to the spectrum of the oil obtained using Chupp's procedure, except for the presence of residual benzene and a slight shift in the trans:cis ratio to ca. 49:51. Three crystallizations from ethyl acetate:hexanes afforded the trans diastereomer of 8a as fine, colorless needles (1.19 g, 21%): mp 92.5-94⁰ (lit.² mp 95-96⁰); ir (KBr) 1725 cm⁻¹ (C=O stretch); nmr (CDCl₃) δ 1.66 (d, J=6.8 Hz, 3H, CH₃CH), 5.29 (q, J=6.8 Hz, 1H, CH₃CH), 7.07-7.67 (m, 3H, ArH); ¹³C nmr (CDCl₃) δ 17.0 (CH₃), 76.4 (C-α), 125.4, 128.1, 131.4 (C-2, C-5, C-6), 131.0, 133.4, 133.8 (C-1, C-3, C-4), 170.5 (C=O), see Appendix NMR No. 2; ms m/e (rel intensity) 281 (M⁺+2,8), 279 (M⁺,11), 215 (M⁺-SO₂,7), 191 (11), 189 (64), 187 (M⁺-SO₂-CO,100), 186 (12), 174 (48), 173 (11), 172 (M⁺-SO₂-CO-CH₃,80), 161 (13), 159 (11), 147 (14), 145 (C₆H₃Cl₂,23), 126 (13), 124 (37), 109 (13), 97 (11), 75 (12), 74 (11), 73 (12), 64 (26), 55 (12), 48 (11), 43 (26).

**Sulfurous Acid Ester Amide (12) of Methanol and 2-t-Butylamino-o-acetotoluidide (1a)**

A solution of methyl chlorosulfinate⁶ (1.26 g, 11.0 mmol) in benzene (25 mL) was added dropwise to a stirred solution of
2-t-butylamino-o-acetotoluidide \(^1\) (2.20 g, 10.0 mmol) and triethylamine (1.11 g, 1.53 mL, 11.0 mmol) in benzene (100 mL) at room temperature. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was then washed with water (50 mL) to remove the triethylamine hydrochloride precipitate. The dried (MgSO\(_4\)) benzene layer was evaporated at reduced pressure to give a light yellow solid, which was recrystallized from petroleum ether (bp 65-110°) to afford \(\underline{12}\) as fine, colorless needles (1.54 g, 52%): mp 75-76°; ir (KBr) 3300* (N-H stretch), 1660 (C=O stretch), 1510 (N-H bend), 1150 or 1115 cm\(^{-1}\) (S=O stretch); nmr (CDCl\(_3\)) \(\delta\) 1.37 (s, 9H, t-Bu), 2.27 (s, 3H, ArCH\(_3\)), 3.59 (s, 3H, OCH\(_3\)), 3.97 (AB q, \(J_{AB}\) =17.2 Hz, \(\delta_{AB}\) =23.1 Hz, 2H, CH\(_2\)), 6.83-7.37 (m, 3H, ArH), 7.83-8.08 (m, 1H, ArH\(_6\)), 8.46 (br, 1H, NH).

**Anal.** Calcd for C\(_{14}\)H\(_{22}\)N\(_2\)O\(_3\)S: C, 56.35; H, 7.43; N, 9.39. Found: C, 56.34; H, 7.45; N, 9.44.

**Methyl N-t-Butylglycine (15a)**

A solution of methyl bromoacetate (45.9 g, 0.300 mole) in anhydrous ether (100 mL) was added dropwise to a stirred solution of t-butylamine (65.8 g, 94.6 mL, 0.900 mole) in anhydrous ether (150 mL) chilled with an ice water bath. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 36 hours. The t-butylamine hydrobromide precipitate was then removed by suction filtration and washed with anhydrous ether. The
combined ethereal filtrates were then concentrated at reduced pressure at room temperature to give a yellow liquid, which was vacuum distilled at 83-84°/20 mm Hg to afford 15a as a colorless liquid (39.4 g, 90%): mp (HCl salt) 170-171° (lit.8 mp 171-172°); ir (liquid film) 3330* (N-H stretch), 1740 cm⁻¹ (C=O stretch); nmr (CDCl₃) δ 1.08 (s, 9H, t-Bu), 1.43 (br, 1H, NH, washes out with D₂O), 3.38 (s, 2H, CH₂), 3.71 (s, 3H, OCH₃).

**Ethyl N-Phenylglycine (15b)**

A solution of ethyl bromoacetate (35.5 g x 94%, 0.200 mole) and aniline (37.3 g, 0.400 mole) in benzene (200 mL) was heated at reflux with stirring for 19 hours. Upon cooling, the aniline hydrobromide precipitate was removed by suction filtration and washed with benzene. The combined benzene filtrates were then concentrated at reduced pressure to give an orange oil, which was crystallized from 70% aqueous ethanol to afford 15b as colorless plates (23.8 g, 66%): mp 53.5-55° (lit.9 mp 57-58°); ir (KBr) 3250 (N-H stretch), 1725 (C=O stretch), 1600 (aromatic C=C stretch), 1220 cm⁻¹ (C-O stretch); nmr (CDCl₃) δ 1.19 (t, J=7 Hz, 3H, CH₃CH₂O⁻), 3.78 (s, 2H, CH₂), 4.16 (q, J=7 Hz, 3H, CH₃CH₂O and NH), 6.38-7.38 (m, 5H, ArH).

**N-Sulfinyl-o-toluidine (16a)**

A solution of thionyl chloride (41.6 g, 25.2 mL, 0.350 mole) in benzene (50 mL) was added dropwise to a stirred
solution of o-toluidine (32.1 g, 32.2 mL, 0.300 mole) in benzene (150 mL) chilled with an ice water bath. Upon completion of this addition, the reaction mixture was heated at reflux with stirring for 2 hours. After cooling, the reaction mixture was concentrated at reduced pressure to give a brown liquid, which was vacuum distilled at 131-132.5\(^\circ\)/22 mm Hg (lit.\(^\text{10}\) bp 184\(^\circ\)/100 mm Hg) to afford 16a as a yellow-orange liquid (43.5 g, 94%): ir (liquid film) 1165 cm\(^{-1}\) (N=S=O stretch); nmr (CDCl\(_3\)) \(\delta\) 2.32 (s, 3H, ArCH\(_3\)), 6.95-7.33 (m, 3H, ArH), 8.17-8.50 (m, 1H, ArH\(_6\)).

Attempted Reaction of Methyl N-t-Butylglycine (15a) and N-Sulfinyl-o-toluidine (16a)

A solution of methyl N-t-butylglycine (1.45 g, 10.0 mmol) and N-sulfinyl-o-toluidine (1.53 g, 10.0 mmol) in toluene (25 mL) was heated at reflux with stirring for 24 hours. Concentration of the reaction mixture at reduced pressure afforded a brown liquid, which was shown by nmr spectroscopy to be a mixture of unreacted starting materials, residual toluene, and o-toluidine (presumably formed upon hydrolysis of some of the N-sulfinyl-o-toluidine).

Attempted Reaction of Ethyl N-Phenylglycine (15b) and N-Sulfinyl-o-toluidine (16a)

A solution of ethyl N-phenylglycine (1.79 g, 10.0 mmol) and N-sulfinyl-o-toluidine (1.53 g, 10.0 mmol) in toluene (25 mL) was heated at reflux with stirring for 24 hours. Concentration of the reaction mixture at reduced pressure
afforded an orange liquid, which was shown by nmr spectroscopy to be a mixture of unreacted starting materials, residual toluene, and o-toluidine (presumably formed upon hydrolysis of some of the N-sulfinyl-o-toluidine).

**Reaction of the Sodium Amide of Methyl N-t-Butylglycine (15a) with N-Sulfinyl-o-toluidine (16a)**

A 57% sodium hydride mineral oil dispersion (526 mg x 57%, 12.5 mmol) was washed with anhydrous ether (3 x 10 mL) under a nitrogen atmosphere and was then suspended in anhydrous dioxane (25 mL). A solution of methyl N-t-butylglycine (1.45 g, 10.0 mmol) in anhydrous dioxane (10 mL) was added dropwise to the stirred sodium hydride suspension at room temperature. Upon completion of this addition, the reaction mixture was heated at reflux with stirring for 10 minutes. After cooling, a solution of N-sulfinyl-o-toluidine (1.53 g, 10.0 mmol) in anhydrous dioxane (10 mL) was added dropwise to the stirred reaction mixture at room temperature. Upon completion of this second addition, the reaction mixture was allowed to stir at room temperature for 13 hours. An aliquot (5 mL) was then removed from the reaction mixture, diluted with ether (10 mL), and washed with water (2 x 5 mL). The dried (MgSO$_4$) ethereal layer was then evaporated at reduced pressure to afford an orange liquid, which was shown by nmr spectroscopy to be a mixture of unreacted methyl N-t-butylglycine and o-toluidine, formed upon hydrolysis of the N-sulfinyl-o-toluidine during the work-up.

The remainder of the reaction mixture was heated at
reflux with stirring for 1 hour. Work-up, as described above, afforded a brown liquid (1.68 g), which was shown by nmr spectroscopy to be 2-t-butylimino-o-acetotoluidide (17) contaminated with o-toluidine: ir (liquid film) 3215 (N-H stretch), 1695 (C=O stretch), 1645 (C=N stretch), 1590 (aromatic C=C stretch), 1535 (N-H bend), 1460 cm\(^{-1}\) (aromatic C=C stretch); nmr (CDCl\(_3\)) \(\delta\) 1.22 (s, 9H, t-Bu), 2.20 (s, 3H, ArCH\(_3\)), 6.80-7.40 (m, 3H, ArH), 7.58 (s, 1H, CH=N), 8.03-8.32 (m, 1H, ArH\(_6\)), 9.08 (br, 1H, NH).

Treatment of 1-Oxo-2-o-tolyl-5-t-butyl-1,2,5-thiadiazolidin-3-one (4a) with Potassium t-Butoxide

A mixture of 1-oxo-2-o-tolyl-5-t-butyl-1,2,5-thiadiazolidin-3-one (2.66 g, 10.0 mmol) and potassium t-butoxide (1.18 g, 10.5 mmol) in anhydrous dioxane (50 mL) was heated at reflux with stirring for 1 hour. Upon cooling, the reaction mixture was diluted with ether (100 mL) and washed with water (4 x 50 mL). The dried (MgSO\(_4\)) ethereal layer was then concentrated at reduced pressure to give a yellow-brown liquid (2.01 g), which was eluted with petroleum ether (bp 20-40\(^{\circ}\)) through a short column of Florex to remove tar and polymeric material. The petroleum ether eluent was evaporated at reduced pressure to give a yellow liquid, which after several crystallizations from petroleum ether (bp 20-40\(^{\circ}\)), chilled with dry ice/acetone bath, afforded 2-t-butylimino-o-acetotoluidide (17) as fine colorless needles (1.02 g, 47\%): mp 52-53\(^{\circ}\); ir (KBr) 3340* (N-H stretch), 1700 (C=O stretch), 1640 (C=N stretch), 1585 (aromatic C=C stretch),
1525 (N-H bend), 1450 cm\(^{-1}\) (aromatic C=C stretch); nmr (CDCl\(_3\))
\[\delta 1.28 (s, 9H, t-Bu), 2.28 (s, 3H, ArCH\(_3\)), 6.83-7.42 (m, 3H, ArH), 7.61 (s, 1H, CH=\text=N), 7.97-8.28 (m, 1H, ArH\(_6\)), 9.09 (br, 1H, NH); ms m/e (rel intensity) 218 (M\(^+\), 5), 203 (M\(^+\)-CH\(_3\), 11), 135 (C\(_8\)H\(_9\)NO, 10), 107 (C\(_7\)H\(_7\)NH\(_2\), 14), 106 (C\(_7\)H\(_7\)NH, 14), 57 (C\(_4\)H\(_9\), 100); m/e (calcd for C\(_{13}\)H\(_{18}\)N\(_2\)O) 218.1418, (found) 218.1426.

Reduction of 2-t-Butylimino-o-acetotoluidide (17) with Sodium Borohydride

Sodium borohydride (114 mg, 3.00 mmol) was added in several small portions to a stirred solution of 2-t-butylimino-o-acetotoluidide (655 mg, 3.00 mmol) in absolute ethanol (25 mL) chilled in an ice water bath. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was then diluted with water (50 mL) and extracted with dichloromethane (4 x 25 mL). The combined, dried (MgSO\(_4\)) dichloromethane extracts were evaporated at reduced pressure to give a light yellow oil, which was crystallized from petroleum ether (bp 65-110\(^{\circ}\)) to afford colorless cubic crystals (560 mg, 85\%), which were identified as 2-t-butylamino-o-acetotoluidide (1a) by comparison of the melting point and ir and nmr spectra with those of an authentic sample.\(^1\)

N-Methylacetanilide (20)

N-Methylacetanilide was prepared in 89\% yield by the acetylation of N-methylaniline with acetyl chloride:
mp 97-99° (lit.\textsuperscript{12} mp 104°); ir (KBr) 1660 (C=O stretch),
1595 cm\textsuperscript{-1} (aromatic C=C stretch); nmr (CDCl\textsubscript{3}) \delta 1.86 (s, 3H, CH\textsubscript{3}CO), 3.25 (s, 3H, NCH\textsubscript{3}), 7.08-7.72 (m, 5H, ArH);
\textsuperscript{13}C nmr (CDCl\textsubscript{3}) \delta 22.3 (C-\alpha), 37.0 (C-\beta'), 127.1 (C-2), 127.6 (C-4), 129.7 (C-3), 144.7 (C-1), 170.0 (C=O).

O-Methyl N-Phenylacetimidate (21)

O-Methyl N-phenylacetimidate was prepared in 34\% yield from acetanilide by methylation using methyl fluorosulfonate:
bp 98-100°/24 mm Hg (lit.\textsuperscript{13} bp 81-82°/12 mm Hg; lit.\textsuperscript{14} bp 91-92°/17 mm Hg); ir (liquid film) 1675 (O-C=N stretch), 1600 cm\textsuperscript{-1} (aromatic C=C stretch); nmr (CDCl\textsubscript{3}) \delta 1.76 (s, 3H, CCH\textsubscript{3}), 3.75 (s, 3H, OCH\textsubscript{3}), 6.58-7.45 (m, 5H, ArH);
\textsuperscript{13}C nmr (CDCl\textsubscript{3}) \delta 15.7 (C-\alpha), 53.0 (C-\beta'), 121.2 (C-2), 122.9 (C-4), 129.0 (C-3), 149.4 (C-1), 161.5 (C=N).

N-Phenyl-4-chlorobutanamide

N-Phenyl-4-chlorobutanamide was prepared in 96\% yield from aniline and 4-chlorobutyryl chloride:\textsuperscript{124} mp 67.5-69.5° (lit.\textsuperscript{16} mp 69-70°); ir (KBr) 3200 (N-H stretch), 1670 (C=O stretch), 1535 cm\textsuperscript{-1} (N-H bend); nmr (CDCl\textsubscript{3}) \delta 1.80-2.68 (m, 4H, CH\textsubscript{2}CH\textsubscript{2}CO), 3.53 (t, J=ca. 6 Hz, 2H, CH\textsubscript{2}Cl), 6.89-7.67 (m, 5H, ArH), 8.51 (br, 1H, NH).

N-p-Tolyl-4-chlorobutanamide

N-p-Tolyl-4-chlorobutanamide was prepared in 84\% yield from p-toluidine and 4-chlorobutyryl chloride:\textsuperscript{124} mp 90-91°
(lit. $^{16}$ mp 91-92.5$^\circ$); ir (KBr) 3200 (N-H stretch), 1655 (C=O stretch), 1595 (aromatic C=C stretch), 1525 cm$^{-1}$ (N-H bend); nmr (CDCl$_3$) $\delta$ 1.79-2.65 (m, 4H, CH$_2$CH$_2$CO), 2.23 (s, 3H, ArCH$_3$), 3.48 (t, $J=\text{ca.}$ 6 Hz, 2H, CH$_2$Cl), 7.11 (AA'BB'm, 4H, ArH), 8.22 (br, 1H, NH).

**N-Benzyl-4-chlorobutanamide**

N-Benzyl-4-chlorobutanamide was prepared in 83% yield from benzy1amine and 4-chlorobutyryl chloride: $^{124}$ mp 64.5-66$^\circ$ (lit. $^{17}$ mp 68$^\circ$); ir (KBr) 3200 (N-H stretch), 1640 (C=O stretch), 1535 cm$^{-1}$ (N-H bend); nmr (CDCl$_3$) $\delta$ 1.67-2.45 (m, 4H, CH$_2$CH$_2$CO), 3.39 (t, $J=\text{ca.}$ 6 Hz, 2H, CH$_2$Cl), 4.26 (d, $J=5.7$ Hz, 2H, ArCH$_2$), 7.10 (s, 6H, ArH and NH).

**l-Phenyl-2-pyrrolidinone (10a)**

A solution of N-phenyl-4-chlorobutanamide (9.88 g, 50.0 mmol) and potassium hydroxide (2.86 g, 51.0 mmol) in absolute methanol (100 mL) was heated at reflux with stirring for 30 minutes. Upon cooling, the reaction mixture was concentrated at reduced pressure, and the residue was partitioned between water (50 mL) and dichloromethane (100 mL). The phases were separated, and the aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined, dried (MgSO$_4$) dichloromethane extracts were evaporated at reduced pressure to give a colorless crystalline solid, which was recrystallized from benzene:hexanes to afford 10a as fine, colorless needles (5.18 g, 64%): mp 65.5-
67° (lit. \(16^\circ\) mp 68-69°); ir (KBr) 1675 (C=O stretch), 1595 cm\(^{-1}\) (aromatic C=C stretch); nmr (CDCl\(_3\)) \(\delta\) 1.63-2.70 (m, 4H, \(\alpha\)-CH\(_2\) and \(\beta\)-CH\(_2\)), 3.63 (t, \(J=\text{ca.} \ 7\ \text{Hz}, 2H, \beta'\)-CH\(_2\)), 6.89-7.78 (m, 5H, ArH); \(^{13}\)C nmr (CDCl\(_3\)) \(\delta\) 17.8 (C-\(\beta\)), 32.7 (C-\(\alpha\)), 48.5 (C-\(\beta'\)), 119.6 (C-2), 124.1 (C-4), 128.6 (C-3), 139.6 (C-1), 174.0 (C=O).

1-p-Tolyl-2-pyrrolidinone (10b)

A mixture of N-p-tolyl-4-chlorobutanamide (6.35 g, 30.0 mmol) and powdered potassium hydroxide (19.0 g) was heated with a low flame until the mixture started to fuse. Upon cooling, the solidified reaction mixture was partitioned between water (100 mL) and ether (100 mL). The phases were separated, and the aqueous layer was extracted with additional ether (100 mL). The combined, dried (MgSO\(_4\)) ethereal extracts were evaporated at reduced pressure to give an off-white solid, which was recrystallized from benzene:petroleum ether (bp 65-110°) to afford 10b as colorless prisms (4.06 g, 77%): mp 85-86° (lit. \(16^\circ\) mp 88-89°); ir (KBr) 1680 cm\(^{-1}\) (C=O stretch); nmr (CDCl\(_3\)) \(\delta\) 1.74-2.70 (m, 4H, \(\alpha\)-CH\(_2\) and \(\beta\)-CH\(_2\)), 2.26 (s, 3H, ArCH\(_3\)), 3.71 (t, \(J=\text{ca.} \ 7\ \text{Hz}, 2H, \beta'\)-CH\(_2\)), 7.38 (AA'BB' m, 4H, ArH); \(^{13}\)C nmr (CDCl\(_3\)) \(\delta\) 17.8 (t, C-\(\beta\)), 20.7 (q, CH\(_3\)), 32.6 (t, C-\(\alpha\)), 48.6 (t, C-\(\beta'\)), 119.7 (d, C-2), 129.2 (d, C-3), 133.6 (s, C-4), 137.2 (s, C-1), 173.8 (s, C=O), see Appendix NMR Nos. 3 and 4.
1-Benzyl-2-pyrrolidinone (10c)

1-Benzyl-2-pyrrolidinone was prepared in 68% yield by potassium hydroxide fusion of N-benzyl-4-chlorobutanamide as described above for 10b: bp 96-97°/ca. 0.5 mm Hg (lit.\textsuperscript{17} bp 122.5-123°/2 mm Hg); ir (CHCl\textsubscript{3}) 1675 cm\textsuperscript{-1} (C=O stretch); nmr (CDCl\textsubscript{3}) \(\delta\) 1.54-2.52 (m, 4H, \(\alpha\)-CH\textsubscript{2} and \(\beta\)-CH\textsubscript{2}), 3.14 (t, \(J=\text{ca.} 7\) Hz, 2H, \(\beta'\)-CH\textsubscript{2}), 4.34 (s, 2H, ArCH\textsubscript{2}), 7.13 (s, 5H, ArH); \(^{13}\text{C}\) nmr (CDCl\textsubscript{3}) \(\delta\) 17.6 (C-\(\gamma\)), 30.7 (C-\(\alpha\)), 46.3 and 46.4 (ArCH\textsubscript{2} and C-\(\beta'\)), 127.4 (C-4), 127.9 and 128.6 (C-2 and C-3), 136.8 (C-1), 174.4 (C=O).

2-Phenyliminotetrahydrofuran (11a)

2-Phenyliminotetrahydrofuran was prepared in 95% yield from N-phenyl-4-chlorobutanamide upon treatment with silver tetrafluoroborate, according to the general procedure of Peter et al.,\textsuperscript{125} as applied by Schmir and Cunningham\textsuperscript{3} for this preparation, and as described below for 11b: bp \textsuperscript{ca.} 105°/ca. 0.2 mm Hg (lit.\textsuperscript{18} bp 128°/2 mm Hg); ir (CHCl\textsubscript{3}) 1700 (O-C=\(\text{N}\) stretch), 1600 (aromatic C=C stretch), 1190, 1040 cm\textsuperscript{-1}; nmr 60-MHz (CDCl\textsubscript{3}) \(\delta\) 1.64-2.84 (m, 4H, \(\alpha\)-CH\textsubscript{2} and \(\beta\)-CH\textsubscript{2}, E and Z), 4.14 (t, \(J=\text{ca.} 6-7\) Hz, 2H, \(\beta'\)-CH\textsubscript{2}, E and Z), 6.47-7.48 (m, 5H, ArH, E and Z); nmr\textsuperscript{24} 100-MHz (CDCl\textsubscript{3}) \(\delta\) 1.60-2.12 (m, 2H, \(\beta\)-CH\textsubscript{2}, E and Z), 2.28 (t, \(J=\text{ca.} 8\) Hz, 0.9H, \(\alpha\)-CH\textsubscript{2}, E), 2.60 (t, \(J=\text{ca.} 8\) Hz, 1.1H, \(\alpha\)-CH\textsubscript{2}, Z), 4.12 (t, \(J=\text{ca.} 6-7\) Hz, 2H, \(\beta'\)-CH\textsubscript{2}, E and Z), 6.40-7.40 (m, 5H, ArH, E and Z); \(^{13}\text{C}\) nmr (CDCl\textsubscript{3}) \(\delta\) 22.9 (C-\(\beta\), Z), 23.4, 25.0 (C-\(\beta\), C-\(\alpha\), E), 29.8 (C-\(\alpha\), Z), 69.1 (C-\(\beta'\), E), 71.2 (C-\(\beta'\), Z), 121.2 (C-2, E), 122.8 (C-2, Z), 123.1
(C-4, E), 123.3 (C-4, Z), 128.5 (C-3, Z), 129.0 (C-3, E), 147.5 (C-1, Z), 149.5 (C-1, E), 163.5 (C=N, Z), 168.9 (C=N, E).

2-p-Tolyliminotetrahydrofuran (1lb)

A solution of silver tetrafluoroborate (3.50 g, 18.0 mmol) in benzene (60 mL) and dichloromethane (40 mL) was added dropwise to a stirred solution of N-p-tolyl-4-chlorobutanamide (3.39 g, 16.0 mmol) in dichloromethane (250 mL) cooled to -20° with a dry ice/carbon tetrachloride bath. Upon completion of this addition, the reaction mixture was allowed to stir at -20° for 1 hour, at 0° (ice water bath) for 1 hour, and at room temperature for 1.5 hours. Triethylamine hydrochloride (1.00 g) was then added to the reaction mixture to destroy the excess silver tetrafluoroborate. The silver chloride precipitate was removed by suction filtration through a bed of Celite 545. The filtrate was then washed successively with 2N sodium carbonate (2 x 200 mL) and saturated aqueous sodium chloride (3 x 100 mL). The dried (MgSO₄) organic layer was concentrated at reduced pressure to give a mixture of a yellow-orange liquid and a solid (triethylamine hydrochloride). This mixture was diluted with anhydrous ether (25 mL) and the triethylamine hydrochloride was removed by suction filtration. The ether-eal filtrate was evaporated at reduced pressure to give a yellow-orange liquid, which was vacuum distilled (Kugelrohr) at ca. 115°/ca. 0.2 mm Hg (lit.¹⁸ bp 141°/2 mm Hg) to afford 1lb as a colorless liquid (2.36 g, 84%): ir (CHCl₃) 1695 (O-C=N stretch), 1185, 1035 cm⁻¹; nmr 60-MHz (CDCl₃)
δ 1.58-2.73 (m, 4H, α-CH₂ and β-CH₂, E and Z), 2.20 (s, 3H, ArCH₃, E and Z), 4.06 (t, J=ca. 6.5-7 Hz, 2H, β'-CH₂, E and Z), 6.60 (BB' d, J=ca. 8 Hz, 0.7H, ArH₂, E), 6.89 (AA'BB' s, 2.6H, ArH₂ and ArH₃, Z), 6.94 (AA; d, J=ca. 8 Hz, 0.7H, ArH₃, E); nmr 100-MHz (CDCl₃) δ 1.60-2.06 (m, 2H, β-CH₂, E and Z), 2.22 (s, 3H, ArCH₃, E and Z), 2.24 (t, J=ca. 8 Hz, 0.7H, α-CH₂, E), 2.55 (t, J=8 Hz, 1.3H, α-CH₂, Z), 4.06 (t, J=ca. 6.5-7 Hz, 2H, β'-CH₂, E and Z), 6.68 (BB' d, J=ca. 8 Hz, 0.7H, ArH₂, E), 6.98 (AA'BB' s, 2.6H, ArH₂ and ArH₃, Z), 7.02 (AA' d, J=ca. 8 Hz, 0.7H, ArH₃, E), see Appendix NMR No. 5; ¹³C nmr (CDCl₃) δ 20.7 (CH₃, E), 20.8 (CH₃, Z), 22.9 (C-β, Z), 23.4, 24.8 (C-β, C-α, E), 29.8 (C-α, Z), 68.9 (C-β', E), 71.1 (C-β', Z), 121.0 (C-2, E), 122.8 (C-2, Z), 129.0 (C-3, Z), 129.5 (C-3, E), 132.1 (C-4, E), 132.4 (C-4, Z), 144.8 (C-1, Z), 147.0 (C-1, E), 163.1 (C=N, Z), 168.8 (C=N, E), see Appendix NMR No. 6.

2-Benzyliminotetrahydrofuran (11c)

2-Benzyliminotetrahydrofuran was prepared in 78% yield from N-benzyl-4-chlorobutanamide upon treatment with silver tetrafluoroborate, according to the general procedure of Peter et al.,¹²⁵ as described above for 11b: bp ca. 115⁰/0.5 mm Hg (lit.¹⁸ bp 126-127⁰/2 mm Hg); ir (CHCl₃) 1700 (O-C=N stretch), 1180, 1045 cm⁻¹; nmr 60-MHz (CDCl₃) δ 1.60-2.65 (m, 4H, α-CH₂ and β-CH₂, E and Z), 3.97 (t, J=ca. 6.5-7 Hz, 0.2H, β'-CH₂, E), 4.05 (t, J=ca. 6.5-7 Hz, 1.8H, β'-CH₂, Z), 4.26 (s, 0.2H, ArCH₂, E), 4.38 (s, 1.8H, ArCH₂, Z), 6.97-7.42 (m, 5H, ArH, E and Z); nmr 100-MHz (CDCl₃) δ 1.81
(quintet, J=ca. 7 Hz, 2H, β-CH₂, E and Z), 2.22 (t, J=ca. 7 Hz, 0.2H, α-CH₂, E), 2.40 (t, J=7 Hz, 1.8H, α-CH₂, Z), 3.92 (t, J=ca. 6-7 Hz, 0.2H, β'-CH₂, E), 4.00 (t, J=ca. 6-7 Hz, 1.8H, β'-CH₂, Z), 4.27 (s, 0.2H, ArCH₂, E), 4.43 (s, 1.8H, ArCH₂, Z), 7.00-7.46 (m, 5H, ArH, E and Z);

¹³C nmr (CDCl₃) δ 23.3, 23.6 (C-β, C-α, E), 23.4 (C-β, Z), 28.8 (C-α, Z), 51.2 (PhCH₂, Z), 54.5 (PhCH₂, E), 67.9 (C-β', E), 70.1 (C-β', Z), 126.2 (C-4, Z), 126.4 (C-4, E), 127.4, 128.1 (C-2, C-3, E), 127.7, 128.1 (C-2, C-3, Z), 140.8 (C-1, E), 141.3 (C-1, Z), 163.6 (C=N, Z), 169.2 (C=N, E).

**Succinanilic Acid**

Succinanilic acid was prepared in essentially quantitative yield from succinic anhydride and aniline according to the procedure described by Vogel:¹²⁶ mp 146-147° (lit.¹²⁷ mp 148.5°); ir (KBr) 3200 (N-H stretch), 3000-26000 (O-H stretch), 1700 (C=O stretch, acid), 1670 (C=O stretch, amide), 1605 (aromatic C=C stretch), 1545 cm⁻¹ (N-H bend).

**N-Phenylsuccinimide**

N-Phenylsuccinimide was prepared in 83% yield from succinanilic acid by analogy to the procedure of Cava et al.¹²⁸ for the preparation of N-phenylmaleimide: mp 153.5-155.5° (lit.¹²⁷ mp 151-152°); ir (KBr) 1710 cm⁻¹ (C=O stretch).

**N-Phenyl-4-hydroxybutanamide (22a)**

N-Phenyl-4-hydroxybutanamide was prepared in 52% yield by the sodium borohydride reduction of N-phenylsuccinimide
according to the procedure of Horii et al.:\textsuperscript{19} mp 68.5-70.5\degree C (lit.\textsuperscript{19} mp 83-84\degree C; lit.\textsuperscript{20} mp 74-75\degree C); ir (KBr) 3320* (N-H stretch), 3265* (O-H stretch), 1655 (C=O stretch), 1605 (aromatic C=C stretch), 1535 cm\textsuperscript{-1} (N-H bend); nmr (CDCl\textsubscript{3}) \delta 1.83 (br quintet, J=ca. 6 Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}CO), 2.38 (br t, J=ca. 6 Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}CO), 3.55 (br q, J=ca. 5.5-6 Hz, 2H, CH\textsubscript{2}OH), 4.32 (br t, J=ca. 5 Hz, 1H, CH\textsubscript{2}OH), 6.75-7.58 (m, 5H, ArH), 8.87 (br, 1H, NH).

N-t-Butylmandelamide (29a)

N-t-Butylmandelamide was prepared by a modified Ritter reaction.\textsuperscript{39} Concentrated sulfuric acid (35 mL) was added dropwise to a stirred solution of crude mandelonitrile\textsuperscript{37} (39.9 g, 0.300 mole) in t-butyl alcohol (300 mL) without allowing the temperature of the reaction mixture to rise above 50\degree C (with the aid of an ice water bath). Upon completion of this addition, the reaction mixture was allowed to stir at room temperature overnight and at 75\degree C for 1 hour. After cooling, the reaction mixture was poured into water (450 mL), chilled with an ice water bath, and neutralized with sodium hydroxide pellets. The resulting precipitate was collected by suction filtration and washed with copious quantities of water. After air drying briefly, the precipitate was dissolved in chloroform (300 mL), and the residual water was removed in a separatory funnel. Meanwhile, the aqueous filtrate was extracted with chloroform (2 x 200 mL).
The combined, dried (MgSO₄) chloroform solutions were concentrated at reduced pressure to give a light yellow semisolid, which was recrystallized from benzene to afford 29a as colorless plates (31.4 g, 50%): mp 119.5-121° (lit. 114-116°); ir (KBr) 3350* (N-H stretch), 3250* (O-H stretch), 1645 (C=O stretch), 1535 cm⁻¹ (N-H bend); nmr (CDCl₃) δ 1.27 (s, 9H, t-Bu), 4.48 (d, J=4 Hz, 1H, OH, washes out with D₂O), 4.75 (d, J=4 Hz, 1H, ArCH, collapses to a singlet with D₂O), 6.36 (br, 1H, NH), 7.27 (s, 5H, ArH).

The benzene mother liquor was concentrated initially at water aspirator pressure (ca. 20-25 mm Hg) and finally by heating at ca. 90° at ca. 1 mm Hg to give a light orange liquid, which was shown by nmr spectroscopy to be largely a single component believed to be α-t-butoxy-N-t-butyphenylacetamide. Crystallization from absolute ethanol afforded a small amount of light yellow amorphous solid (1.00 g), which represented only a fraction of the material actually present: mp 99-103° (lit. 8 mp 107-108°); ir (KBr) 3200 (N-H stretch), 1650 (C=O stretch), 1545 cm⁻¹ (N-H bend); nmr (CDCl₃) δ 1.22 (s, 9H, t-Bu), 1.32 (s, 9H, t-Bu), 4.77 (s, 1H, ArCH), 6.63 (br, 1H, NH), 7.05-7.55 (m, 5H, ArH).

N-t-Butylglycolamide (29b)

Procedure A (Modified Ritter Reaction): Concentrated sulfuric acid (35 mL) was added dropwise to a stirred solution of glycolonitrile (13.8 g, 0.242 mole) in t-butyl alcohol (300 mL) without allowing the temperature to rise above 50° (with the aid of an ice water bath). Upon completion
of this addition, the reaction mixture was allowed to stir at room temperature for 48 hours and at 75° for 1 hour. After cooling, the reaction mixture was poured into water (450 mL), chilled with an ice water bath, and neutralized with sodium hydroxide pellets. Since no precipitate was evident, the slightly alkaline aqueous layer was extracted with chloroform (3 x 200 mL). The combined, dried (MgSO₄) chloroform extracts were concentrated at reduced pressure to give a yellow oil, which was crystallized from benzene:petroleum ether (bp 65-110°) to afford 29b as colorless prisms (10.7 g, 34%): mp 76-77° (lit. 36 mp 77-78.5°); ir (KBr) 3360* (N-H stretch), 3235* (O-H stretch), 1635 (C=O stretch), 1535 cm⁻¹ (N-H bend); nmr (CDCl₃) δ 1.38 (s, 9H, t-Bu), 3.92 (br d, J=5 Hz, 2H, CH₂, collapses to a singlet with D₂O), 5.19 (br t, J=5 Hz, 1H, OH, washes out with D₂O), 6.79 (br, 1H, NH).

The benzene:petroleum ether mother liquor was concentrated at reduced pressure to give a yellow liquid, which was vacuum distilled at 61°/0.6 mm Hg to afford a colorless liquid (11.5 g, 25%) believed to be α-t-butoxy-N-t-butylacetamide: ir (liquid film) 3200 (N-H stretch), 1665 (C=O stretch), 1510 cm⁻¹ (N-H bend); nmr (CDCl₃) δ 1.23 (s, 9H, t-Bu), 1.37 (s, 9H, t-Bu), 3.73 (s, 2H, CH₂), 6.42 (br, 1H, NH).

Procedure B (Modified Passerini Reaction): Concentrated sulfuric acid (15 mL) in water (120 mL) was added dropwise to a stirred mixture of t-butyl isonitrile (16.6 g, 0.200 mole) and a 36% aqueous solution of formaldehyde (83.4 g x 36%, 1.00 mole) chilled with an ice water bath.
Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 3 hours. The reaction mixture was then neutralized with sodium carbonate and extracted with chloroform (3 x 100 mL). The combined, dried (MgSO₄) chloroform extracts were concentrated at reduced pressure to give a light yellow oil, which was crystallized from benzene: petroleum ether (bp 65-110 °C) to afford 29b as colorless prisms (16.6 g, 63%), mp 77-78 °C (lit. 36 mp 77-78.5 °C). The ir (KBr) and nmr (CDCl₃) spectra of this material were identical to the spectra of the material prepared by the modified Ritter reaction (except the chemical shifts of the OH and NH differed, presumably due to a concentration effect).

**Attempted Cyclization of N-t-Butylmandelamide (29a) with Thionyl Chloride (Chupp's² Conditions). N-t-Butyl-2-chlorophenylacetamide (30a)**

A solution of N-t-butylmandelamide (2.07 g, 10.0 mmol) in thionyl chloride (10 mL) was allowed to stir at room temperature for 1 hour. The reaction mixture was then concentrated at room temperature at reduced pressure. The residue was diluted with anhydrous ether and again concentrated at reduced pressure. This process was repeated several times (until excess thionyl chloride had been removed) to give an off-white solid, which was recrystallized from petroleum ether (bp 65-110 °C) to afford fine, colorless needles (2.16 g, 96%), mp 126-127 °C (lit. 42 mp 127-128 °C), which were identified as N-t-butyl-2-chlorophenylacetamide (30a) by comparing the ir (KBr) and nmr (CDCl₃) spectra with those of an authentic
sample prepared from 2-chlorophenylacetyl chloride and t-butylamine. Examination of the residue obtained upon concentration of the petroleum ether mother liquor by nmr spectroscopy revealed the presence of a trace of 2-oxo-3-t-butyl-5-phenyl-1,2,3-oxathiazolidin-4-one (31a) diastereomers, characterized by a t-butyl singlet at δ 1.58 and two benzylic singlets of equal intensity at δ 5.52 and 5.87.

Attempted Cyclization of N-t-Butylglycolamide (29b) with Thionyl Chloride (Chupp's Conditions). N-t-Butyl-2-chloroacetamide (30b)

A solution of N-t-butylglycolamide (1.31 g, 10.0 mmol) in thionyl chloride (10 mL) was allowed to stir at room temperature for 1 hour. The reaction mixture was then concentrated at room temperature at reduced pressure. The residue was diluted with anhydrous ether and again concentrated at room temperature at reduced pressure. This process was repeated several times (until the excess thionyl chloride had been removed) to give an off-white solid, which was recrystallized from petroleum ether (bp 65-110°) to afford colorless plates (0.92 g, 61%), mp 81-83° (lit. 43 mp 82-83°), which were identified as N-t-butyl-2-chloroacetamide (30b) by comparing the ir (KBr) and nmr (CDCl₃) spectra with those of an authentic sample prepared from 2-chloroacetyl chloride and t-butylamine. 42

A second crop of crystals (0.22 g) was obtained from a smaller volume of petroleum ether. However, the broad, depressed melting point and nmr (CDCl₃) spectrum of this material suggested contamination by starting material 29b. Finally
examination by nmr spectroscopy of the residue obtained upon concentration of the petroleum ether mother liquor of the second crop of crystals indicated a mixture of residual 30b, unreacted 29b, and 2-oxo-1,2,3-oxathiazolidin-4-one 31b. Heterocycle 31b was characterized by a t-butyl singlet at δ 1.58 and an AB quartet centered at δ 4.78 (J\(_{\text{AB}}\) = ca. 14.5 Hz, δ\(_{\text{AB}}\) = ca. 20.6 Hz).

2-Oxo-3-t-butyl-5-phenyl-1,2,3-oxathiazolidin-4-one (31a) (Diastereomeric Mixture)\(^\text{130}\)

A solution of thionyl chloride (7.14 g, 4.31 mL, 60.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise to a stirred solution of imidazole (16.3 g, 240 mmol) in anhydrous tetrahydrofuran (100 mL) chilled with an ice water bath. Upon completion of this addition and after stirring at room temperature for 10 minutes, the imidazole hydrochloride precipitate was removed by rapid suction filtration. A solution of N-t-butylmandelamide (8.29 g, 40.0 mmol) in anhydrous tetrahydrofuran (100 mL) was added dropwise at room temperature to the stirred solution of 1,1'-thionyldiimidazole prepared above. Following this addition, the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated at reduced pressure. The residue was taken up in dichloromethane (200 mL) and washed with water (2 x 100 mL) to remove the imidazole by-product. The dried (MgSO\(_4\)) dichloromethane layer was evaporated at reduced pressure to give a pale yellow oil. The presence of the desired 2-oxo-1,2,3-oxathiazolidin-
4-one 31a as a diastereomeric mixture (ca. 50:50) was shown by nmr spectroscopy. The cis isomer was characterized by a benzylic singlet at $\delta$ 5.62, while the trans isomer was characterized by a benzylic singlet at $\delta$ 5.93. This oil was chromatographed over a column of silica gel (ca. 200 g) eluting with benzene to separate the diastereomers from slower moving material. Combination and evaporation at reduced pressure of the fractions showing a spot with $R_f = 0.75$ afforded a pale yellow oil (7.79 g, 77%), which was shown by nmr spectroscopy to be an almost pure mixture (ca. 50:50) of diastereomers 31a. This oil was crystallized from hexanes upon refrigeration to afford colorless crystals in two crops: crop A (5.00 g, 49%), crop B (1.42 g, 14%). Crop A was shown by nmr spectroscopy to be enriched slightly in favor of the cis isomer (cis:trans, 3:2), while crop B was shown to be enriched in favor of the trans isomer (trans:cis, 5:1). Crop A afforded, after three additional recrystallizations from hexanes at room temperature, the pure cis isomer of 31a as fine, colorless needles (1.44 g, 14%): mp 97-98\(^\circ\); ir (KBr) 1715 cm\(^{-1}\) (C=O stretch); nmr (CDCl\(_3\)) $\delta$ 1.59 (s, 9H, t-Bu), 5.59 (s, 1H, ArCH), 7.21-7.66 (m, 5H, ArH); ms m/e (rel intensity) 253 ($M^+_{1}$), 154 ($M^+_{t-BuNCO, 100}$), 126 (36), 106 (35), 105 (PhCO, 83), 78 (49), 77 (41), 57 ($C_4H_9$, 55).


Attempts to obtain the pure trans isomer from crop B by further fractional recrystallizations were unsuccessful:
nmr (trans isomer in crop B) (CDCl$_3$) $\delta$ 1.58 (s, 9H, t-Bu), 5.90 (s, 1H, ArCH), 7.34 (s, 5H, ArH).

2-Oxo-3-t-butyl-1,2,3-oxathiazolidin-4-one (31b)

A solution of thionyl chloride (3.57 g, 2.16 mL, 30.0 mmol) in anhydrous tetrahydrofuran (25 mL) was added dropwise to a stirred solution of imidazole (8.17 g, 120 mmol) in anhydrous tetrahydrofuran (50 mL) chilled with an ice water bath. Upon completion of this addition and after stirring at room temperature for 10 minutes, the imidazole hydrochloride precipitate was removed by rapid suction filtration. A solution of N-t-butylglycolamide (2.62 g, 20.0 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise over a period of 40 minutes at room temperature to the stirred solution of 1,1'-thionyl-diimidazole prepared above. Following this addition, the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated at reduced pressure. The residue was taken up in dichloromethane (100 mL) and washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO$_4$) dichloromethane layer was evaporated at reduced pressure to give a yellow oil (4.01 g), which was shown by nmr spectroscopy to be a mixture of the desired 2-oxo-1,2,3-oxathiazolidin-4-one 31b and the linear sulfite 34b in a ratio of ca. 77:23, respectively. This oil was chromatographed over a 2.6 x 27 cm column of silica gel (ca. 50 g) eluting with benzene to separate 31b from slower moving material.
Combination and evaporation at reduced pressure of the fractions showing a spot with \( R_F = 0.65 \) gave a pale yellow crystalline solid (1.35 g), which was recrystallized from hexanes to afford 31b as a colorless crystalline solid (1.16 g, 33\%): mp 66-67.5\(^\circ\)C; ir (KBr) 1710 (C=O stretch), 1175 cm\(^{-1}\) (S=O stretch); nmr (CDCl\(_3\)) \( \delta \) 1.60 (s, 9H, t-Bu), 4.82 (AB \( q \), \( J_{AB} \)=14.6 Hz, \( \delta_{AB} \)=19.7 Hz, 2H, CH\(_2\)); ms m/e (rel intensity) 177 (M\(^+\),0.2), 162 (M\(^+\)-CH\(_3\),18), 122 (50), 104 (26), 98 (39), 76 (20), 70 (41), 57 (C\(_4\)H\(_9\), 72), 56 (51), 44 (25), 42 (25), 41 (100), 39 (37), 32 (32), 30 (20), 29 (63).

**Anal.** Calcd for C\(_{6}\)H\(_{11}\)NO\(_3\)S: C, 40.66; H, 6.26; N, 7.90.

**Found:** C, 40.55; H, 6.29; N, 7.89.

**Linear Sulfite (34b) of N-t-Butylglycolamide (29b)**

A solution of thionyl chloride (1.78 g, 1.08 mL, 15.0 mmol) in anhydrous tetrahydrofuran (15 mL) was added dropwise to a stirred solution of imidazole (4.08 g, 60.0 mmol) in anhydrous tetrahydrofuran (25 mL) chilled in an ice water bath. Upon completion of this addition and after stirring at room temperature for 10 minutes, the imidazole hydrochloride precipitate was removed by rapid suction filtration. The resulting tetrahydrofuran solution of 1,1'-thionyldiimidazole was added dropwise to a stirred solution of N-t-butylglycolamide (2.62 g, 20.0 mmol) in anhydrous tetrahydrofuran (50 mL) at room temperature. Following this addition, the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated at
reduced pressure. The residue was taken up in dichloromethane (100 mL) and washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO₄) dichloromethane layer was evaporated at reduced pressure to give an off-white solid (3.31 g), which was shown by nmr spectroscopy to be a mixture of 2-oxo-1,2,3-oxathiazolidin-4-one 31b and linear sulfite 34b in a ratio of ca. 16:84. Recrystallization from benzene: hexanes afforded 34b as fine, colorless plates (2.41 g, 78%): mp 103-105°; ir (KBr) 3390 and 3375 (N-H stretch), 1675 (C=O stretch), 1530 (N-H bend), 1200 cm⁻¹ (S=O stretch); nmr (CDCl₃) δ 1.38 (s, 18H, t-Bu), 4.38 (s, 4H, CH₂), 6.32 (br, 2H, NH); ms m/e (rel intensity) 293 (M⁺-CH₃,1.5), 180 (13), 179 (29), 162 (23), 122 (39), 115 (35), 98 (13), 59 (27), 58 (25), 57 (C₄H₉, 100).

Anal. Calcd for C₁₂H₂₄N₂O₅S: C, 46.74; H, 7.84; N, 9.08. Found: C, 46.70; H, 7.84; N, 9.10.

3-(3',4'-Dichlorophenyl)-5-methyl-2,4-oxazolidinedione (37a)

A mixture of 3',4'-dichlorolactanilide² (2.34 g, 10.0 mmol) and 1,1'-carbonyldiimidazole (2.23 x 80%, 11.0 mmol) in benzene (100 mL) was heated at reflux with stirring for 2 hours. Upon cooling, the reaction mixture was washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO₄) benzene layer was evaporated at reduced pressure to give a colorless solid (2.56 g), which was recrystallized from ethyl acetate, to afford 37a as a colorless crystalline solid (2.30 g, 88%): mp 154-155° (lit. 151 mp 156°); ir (KBr)
1840 and 1800 (C=O stretch, w), 1735 cm⁻¹ (C=O stretch, s); nmr (Me₂SO-d₆) δ 1.59 (d, J=7 Hz, 3H, CH₃CH), 5.23 (q, J=7 Hz, 1H, CH₃), 7.47 (d of d, J₅,₆=8.5 Hz, J₂,₆=2.1 Hz, 1H, ArH₆), 7.78 (d, J₂,₆=2.1 Hz, 1H, ArH₂), 7.79 (d, J₅,₆=8.5 Hz, 1H, ArH₅); ms m/e (rel intensity) 261 (M⁺+2,23), 259 (M⁺,35), 189 (60), 187 (M⁺-CO₂-CO,100), 174 (24), 172 (M⁺-CO₂-CO-CH₃, 37), 161 (9), 159 (10), 147 (6), 145 (C₆H₃Cl₂, 9), 126 (8), 124 (26), 55 (10).

3-t-Butyl-5-phenyl-2,4-oxazolidinedione (37b)

A mixture of N-t-butylmandelamide (2.07 g, 10.0 mmol) and 1,1'-carbonyldiimidazole (2.07 g x 98%, 12.5 mmol) in benzene (100 mL) was heated at reflux with stirring for 2 hours. Upon cooling, the reaction mixture was washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO₄) benzene layer was then evaporated at reduced pressure to give a pale yellow oil, which was passed through a short column of silica gel eluting with benzene to remove a small amount of tar. The benzene eluent was evaporated at reduced pressure to give a pale yellow oil (2.44 g), which was crystallized from hexanes to afford 37b as colorless crystals (2.18 g, 94%): mp 56.5-57.5° (lit. 52 mp 89-90°); ir (KBr) 1820 and 1795 (C=O stretch, m), 1730 cm⁻¹ (C=O stretch, s); nmr (CDCl₃) δ 1.60 (s, 9H, t-Bu), 5.45 (s, 1H, ArCH), 7.34 (s, 5H, ArH); ms m/e (rel intensity) 233 (M⁺,3), 178 (21), 160 (4), 146 (5), 105 (9), 90 (7), 86 (9), 77 (8), 70 (8), 57 (C₄H₉, 100), 56 (29).
Anal. Calcd for C_{13}H_{15}NO_3: C, 66.94; H, 6.48; N, 6.00.
Found: C, 66.92; H, 6.50; N, 6.04.

N-t-Butyl Carbamate (38) of Ethyl Mandelate

A solution of ethyl mandelate^{131} (18.0 g, 0.100 mole) and t-butyl isocyanate (19.8 g, 0.200 mole) in toluene (75 mL) was heated at reflux with stirring for 24 hours. Upon cooling, the reaction mixture was diluted with ether (75 mL) and washed with water (100 mL). The dried (MgSO_4) organic layer was then concentrated at reduced pressure to give a yellow oil, which was crystallized from petroleum ether (bp 65-110°) to afford 38 as fine, colorless needles (26.5 g, 95%): mp 61-62° (lit. {52} mp 60-61°); ir (KBr) 3360* (N-H stretch), 1755 (C=O stretch, ester), 1705 (C=O stretch, carbamate), 1525 cm^{-1} (N-H bend); nmr (CDCl_3) δ 1.17 (t, J=7 Hz, 3H, CH_3CH_2O), 1.32 (s, 9H, t-Bu), 4.16 (q, J=7 Hz, 2H, CH_3CH_2O), 5.16 (br, 1H, NH), 5.88 (s, 1H, ArCH), 7.13-7.62 (m, 5H, ArCH).

Authentic 3-t-Butyl-5-phenyl-2,4-oxazolidinedione (37b)

A mixture of the N-t-butyl carbamate of ethyl mandelate (5.59 g, 20.0 mmol) and sodium metal (0.10 g) in toluene (15 mL) was heated at reflux with stirring for 6 hours. Upon cooling, the reaction mixture was diluted with ether (15 mL) and washed with water (2 x 15 mL). The dried (MgSO_4) organic layer was then concentrated at reduced pressure to give an orange oil (4.85 g), which was chromatographed over a 2.5 x
24 cm column of silica gel (ca. 40 g) eluting with benzene. Combination and evaporation at reduced pressure of the fractions showing a spot with $R_f = 0.7$ afforded a yellow-green oil (2.67 g), which was crystallized from hexanes to afford 37b as fine, colorless needles (2.23 g, 48%), mp 56-57.5° (lit. mp 89-90°). The nmr (CDCl$_3$) and ir (KBr) spectra of this material were identical to the spectra of the material prepared from the reaction of N-t-butylmandelamide (29a) and 1,1'-carbonyldiimidazole.

l-t-Butyl-3-o-tolylhydantoin (14a)

A mixture of 2-t-butylamino-o-acetotoluidide$^1$ (2.20 g, 10.0 mmol), 1,1'-carbonyldiimidazole (2.23 g x 80%, 11.0 mmol), and potassium t-butoxide (0.056 g, 0.500 mmol) in anhydrous tetrahydrofuran (100 mL) was heated at reflux with stirring for 2 hours. Upon cooling, the reaction mixture was concentrated at reduced pressure. The residue was taken up in dichloromethane (100 mL) and washed with water (2 x 50 mL) to remove the imidazole by-product. The dried (MgSO$_4$) dichloromethane layer was evaporated at reduced pressure to give a pale yellow oil, which was crystallized from ethyl acetate:hexanes to afford 14a as fine colorless needles (1.85 g, 75%): mp 137.5-138.5°; ir (KBr) 1760 (C=O stretch, m), 1700 cm$^{-1}$ (C=O stretch, s); nmr (CDCl$_3$) δ 1.40 (s, 9H, t-Bu), 2.17 (s, 3H, ArCH$_3$), 3.97 (s, 2H, CH$_2$), 6.93-7.35 (m, 4H, ArH); ms m/e (rel intensity) 246 (M$^+$, 15), 231 (M$^+$-CH$_3$, 55), 134 (29), 133 (20), 70 (M$^+$-CH$_3$-CH$_3$PhNCO-CO,100),
l-Phenyl-3-o-tolylhydantoin (14b)

A mixture of 2-anilino-o-acetotoluidide\(^1\) (2.40 g, 10.0 mmol), 1,1'-carbonyldiimidazole (2.23g x 80%, 11.0 mmol), and potassium t-butoxide (0.056 g, 0.500 mmol) in anhydrous tetrahydrofuran (100 mL) was heated at reflux with stirring for 3 hours. Upon cooling, the reaction mixture was concentrated at reduced pressure. The residue was taken up in dichloromethane (100 mL) and washed with 10% hydrochloric acid (2 x 50 mL) to remove the imidazole by-product and unreacted 2-anilino-o-acetotoluidide. The dried (MgSO\(_4\)) dichloromethane layer was evaporated at reduced pressure to give a yellow oil, which was crystallized from ethyl acetate: hexanes to afford 14b as a colorless, crystalline solid (1.65 g, 62%): mp 129.5-131° (lit.\(^54\) mp 126°); ir (KBr) 1765 (C=O stretch, m), 1715 cm\(^{-1}\) (C=O stretch, s); nmr (CDCl\(_3\)) \(\delta\) 2.20 (s, 3H, ArCH\(_3\)), 4.34 (s, 2H, CH\(_2\)), 6.94-7.73 (m, 9H, ArH); ms m/e (rel intensity) 267 (M\(^+\)+1,10), 266 (M\(^+\),52), 133 (M\(^+\)-CH\(_3\)PhNCO,9), 106 (31), 105 (M\(^+\)-CH\(_3\)PhNCO-CO,100), 104 (33), 77 (27), 51 (10).

Benzyloxyacetaldehyde Diethyl Acetal (60)

Benzyloxyacetaldehyde diethyl acetal was prepared in 79% yield from sodium benzoic acid and bromoacetaldehyde diethyl acetal according to the procedure of Parham and Reiff.\(^77\)
bp 85°/ca. 0.4 mm Hg (lit. 77 bp 99-100°/0.55 mm Hg); nmr
(CDCl₃) δ 1.18 (t, J=7 Hz, 6H, CH₃CH₂O), 3.25-3.99 (m, 6H,
CH₃CH₂O and CHCH₂O), 4.53 (s, 2H, ArCH₂), 4.65 (t, J=5 Hz,
1H, CHCH₂O); 7.28 (s, 5H, ArH).

Hydroxyacetaldehyde Diethyl Acetal (61)

Hydroxyacetaldehyde diethyl acetal was prepared in 78% yield by the sodium/liquid ammonia hydrogenolysis of benzyl-
 oxyacetaldehyde diethyl acetal according to the procedure of Parham and Reiff: 77 bp 79-80°/17 mm Hg (lit. 77 bp 69-
70.5°/10 mm Hg); nmr (CDCl₃) δ 1.17 (t, J=7 Hz, 6H, CH₃CH₂O),
3.11 (d of d, J=5.5 Hz, J=7 Hz, 1H, CHCH₂OH), 3.23-3.99
(m, 6H, CH₃CH₂O and CHCH₂OH), 4.64 (t, J=5 Hz, 1H, CHCH₂OH).

2,2-(Diethoxy)ethyl Carbamate (62a)

A solution of hydroxyacetaldehyde diethyl acetal (13.4 g,
0.100 mole) in anhydrous tetrahydrofuran (75 mL) was added
dropwise to a stirred suspension of 1,1'-carbonyldiimidazole
(18.2 g x 98%, 0.110 mole) in anhydrous tetrahydrofuran
(250 mL) at room temperature. Upon completion of this addi-
tion, the reaction mixture was allowed to stir at room temper-
ature for 30 minutes. Concentrated ammonium hydroxide (40
mL) was then added dropwise to the stirred reaction mixture
which had been chilled with an ice water bath. Following
this second addition, the reaction mixture was allowed to
stir at room temperature for an additional 30 minutes. The
reaction mixture was then concentrated at reduced pressure.
The residue was partitioned between dichloromethane (100 mL) and water (50 mL). The phases were separated, and the aqueous phase was extracted with additional dichloromethane (50 mL). The combined, dried (MgSO$_4$) dichloromethane extracts were then evaporated at reduced pressure to give a pale yellow oil (22.4 g). This oil was chromatographed over a 2.5 x 53.5 cm column of neutral alumina (ca. 300 g) eluting with chloroform to remove the residual imidazole by-product. The purification was monitored by nmr spectroscopy. The fractions collected between 200 and 1000 mL of eluted chloroform were combined and evaporated at reduced pressure to afford 62a as a pale yellow oil (17.0 g x 96%, 92%), which was used without further purification: ir (CHCl$_3$) 3530* and 3425* (N-H stretch), 1725 (C=O stretch), 1585 (N-H bend), 1080 cm$^{-1}$ (C-O stretch); nmr (CDCl$_3$) $\delta$ 1.22 (t, J=7 Hz, 6H, CH$_3$CH$_2$O), 3.29-4.07 (m, 4H, CH$_3$CH$_2$O), 4.06 (d, J=5 Hz, 2H, CHCH$_2$O), 4.71 (t, J=5 Hz, 1H, CHCH$_2$O), 5.72 (br, 2H, NH$_2$).

4-Oxazolin-2-one (47a) and Dimer 68

A solution of 2,2-(diethoxy)ethyl carbamate (7.16 g x 99%, 40.0 mmol) in glacial acetic acid (45 mL) was heated at reflux with stirring for 6 hours. Concentration of the reaction mixture at reduced pressure gave an orange oil, which crystallized upon cooling to room temperature. This crystalline residue was recrystallized twice from ethyl acetate:hexanes to afford 47a as fine, colorless needles
(1.39 H, 41%): mp 105-107° (lit. 105-107°); ir (KBr) 3200* (N-H stretch), 1760 and 1740 cm⁻¹ (C=O stretch); nmr (Me₂SO-d₆) δ 6.81 (d, J=2 Hz, 1H, OCH=CHN), 6.95 (d, J=2 Hz, 1H, OCH=CHN), 10.4 (br, 1H, NH); ms m/e (rel intensity) 85 (M⁺,100), 57 (M⁺-CO,22); m/e (calcd for C₃H₃NO₂) 85.0163, (found) 85.0162.

Anal. Calcd for C₃H₃NO₂: C, 42.36; H, 3.56; N, 16.47. 
Found: C, 42.17; H, 3.62; N, 16.57.

Concentration of the ethyl acetate-hexanes mother liquor of 47a gave a yellow oil. This oil was shown by nmr spectroscopy to be a mixture of residual 47a, 4-oxazolin-2-one dimer (68), 4-ethoxy-2-oxazolidinone (64a), and BHT (2,6-di-t-butyl-p-cresol), the stabilizer in tetrahydrofuran, which was a contaminant in the 2,2-(diethoxy)ethyl carbamate starting material. Upon sitting at room temperature overnight, a dichloromethane solution of this oil deposited a small amount of dimer 68 as a colorless solid (62 mg): mp 134-136°; ir (KBr) 3285* (N-H stretch), 3145* (vinyl C-H stretch), 1750 cm⁻¹ (C=O stretch); nmr (Me₂SO-d₆) δ 4.31 (d of d, J_AB=9.9 Hz, J_BX= 3.1 Hz, 1H, H_B), 4.58 (d of d, J_AB=9.9 Hz, J_Ax=7.9 Hz, 1H, H_A), 5.68 (d of d, J_Ax=7.9 Hz, J_BX=3.1 Hz, 1H, HX, sharpens with D₂O), 7.07 (d, J=2 Hz, 1H, OCH=CHN), 7.14 (d, J=2 Hz, 1H, OCH=CHN), 8.51 (br, 1H, NH, washes out with D₂O), see Appendix NMR No. 7; ms m/e (rel intensity) 86 (16), 85 (100), 57 (29).

Anal. Calcd for C₆H₆N₂O₄: C, 42.36; H, 3.56; N, 16.47. 
Found: C, 42.46; H, 3.60; N, 16.41.
Catalytic Hydrogenation of 4-Oxazolin-2-one (47a). 2-Oxazolidinone (63)

A solution of 4-oxazolin-2-one (170 mg, 2.00 mmol) in glacial acetic acid (20 mL) was hydrogenated in the presence of 10% palladium on charcoal (50 mg) for 5 hours at 60 psi initial pressure in a Parr apparatus. Most of the hydrogen was taken up in the first few minutes of the hydrogenation period. The catalyst was removed by filtration through a Celite 545 bed. The acetic acid filtrate was then concentrated at reduced pressure to give an off-white solid (200 mg), which was recrystallized from a small volume of chloroform to afford a colorless crystalline solid (103 mg, 59%), mp 85.5-87.5°. This material was shown to be 2-oxazolidinone (63) by comparison of its ir (KBr) and nmr (CDCl₃) spectra with those of an authentic sample.

Authentic 2-Oxazolidinone (63)

2-Oxazolidinone was prepared in 70% yield by the sodium methoxide catalyzed condensation of 2-aminoethanol and diethyl carbonate according to the procedure of Homeyer: mp 86.5-88.5° (lit. mp 87-89°); ir (KBr) 3150 (N-H stretch), 1730 cm⁻¹ (C=O stretch); nmr (CDCl₃) δ 4.03 (AA'BB' m, 4H, OCH₂CH₂N, BB' system sharpens with D₂O), 6.69 (br, 1H, NH, washes out with D₂O).

β-Chloroethylidenebisbenzyl Carbamate

β-Chloroethylidenebisbenzyl carbamate was prepared in 58% yield from chloroacetaldehyde diethyl acetal and benzyl
carbamate according to the procedure of Strumza and Ben-Ishai: mp 142.5-143.5° (lit. mp 140°); ir (KBr) 3200 (N-H stretch), 1700 (C=O stretch), 1545 cm\(^{-1}\) (N-H bend); nmr (CDCl\(_3\)) \(\delta\) 3.71 (d, J=5 Hz, 2H, CH\(_2\)Cl), 5.07 (s, 4H, ArCH\(_2\)), 5.25-6.12 (m, 3H, CH\(_2\)Cl and NH), 7.28 (s, 10H, ArH).

4-Carbobenzyloxymino-2-oxazolidinone (65)

4-Carbobenzyloxymino-2-oxazolidinone was prepared in 37% yield from \(\beta\)-chloroethylidenebisbenzyl carbamate according to the procedure of Strumza and Ben-Ishai: mp 135-136.5° (lit. mp 126°); ir (KBr) 3290* and 3245* (N-H stretch), 1775 (C=O stretch, oxazolidinone), 1685 (C=O strech, carbamate), 1530 cm\(^{-1}\) (N-H bend); nmr (\(\text{Me}_2\text{SO-d}_6\)) \(\delta\) 4.05 (d of d, \(J_{AB}=9.2\) Hz, \(J_{BX}=3.4\) Hz, 1H, \(H_B\)), 4.45 (d of d, \(J_{AB}=9.2\) Hz, \(J_{AX}=8.0\) Hz, 1H, \(H_A\)), 5.06 (s, 2H, ArCH\(_2\)), 5.38 (t of d, \(J_{AX}=J_{XY}=8.0\) Hz, \(J_{BX}=3.4\) Hz, 1H, \(H_X\)), 7.33 (s, 5H, ArH), 8.14 (br d, \(J_{XY}=8.0\) Hz, 1H, carbamate NH), 8.25 (br, 1H, oxazolidinone NH).

4-Amino-2-oxazolidinone Hydrochloride (66)

4-Amino-2-oxazolidinone hydrochloride was prepared in 66% yield by the catalytic hydrogenolysis of 4-carbobenzyloxymino-2-oxazolidinone according to the procedure of Strumza and Ben-Ishai: mp 154-155° (lit. mp 153-154°); ir (KBr) 3200, 2960, 2880, 2550, and 1940 (NH\(_3^+\) stretches and overtones), 1755 cm\(^{-1}\) (C=O stretch); nmr (\(\text{Me}_2\text{SO-d}_6\)) \(\delta\) 4.21-
4.78 (AB m of ABX system, 2H, H_A and H_B), 5.00-5.30 (X m of ABX system, 1H, H_X), 8.70 (s, 1H, oxazolidinone NH), 8.93 (br, 3H, NH_3^+).

4-Ethoxy-2-oxazolidinone (64a)

4-Ethoxy-2-oxazolidinone was prepared in 82% yield from 4-amino-2-oxazolidinone hydrochloride according to the procedure of Strumza and Ben-Ishai: mp 49-51° (lit. 67 mp 45°); ir (KBr) 3150 (N-H stretch), 1750 cm^{-1} (C=O stretch); nmr (CDCl_3) δ 1.17 (t, J=ca. 7 Hz, 3H, CH_3CH_20), 3.15-3.89 (m, 2H, CH_3CH_2O), 4.21 (d of d, J_AB=9.8(5) Hz, J_BX=1.9 Hz, 1H, H_B), 4.40 (d of d, J_AB=9.8(5) Hz, J_AX=6.0 Hz, 1H, H_A), 5.08 (d of d, J_AX=6.0 Hz, J_BX=1.9 Hz, 1H, H_X, sharpens with D_2O), 7.82 (br, 1H, NH, washes out with D_2O), see Appendix NMR No. 8.

Conversion of 4-Ethoxy-2-oxazolidinone (64a) to 4-Oxazolin-2-one (47a)

A solution of 4-ethoxy-2-oxazolidinone (262 mg, 2.00 mmol) in glacial acetic acid (2 mL) was heated at reflux with stirring for 3 hours. Concentration of the reaction mixture at reduced pressure gave an off-white solid, which was recrystallized from ethyl acetate:hexanes to afford fine, colorless needles (70.4 mg, 41%). This material was shown to be 4-oxazolin-2-one (47a) by comparison of melting point and ir (KBr) spectrum with those of an authentic sample.
Conversion of 4-Amino-2-oxazolidinone Hydrochloride (66) to 4-Oxazolin-2-one (47a)

A suspension of 4-amino-2-oxazolidinone hydrochloride (624 mg, 4.50 mmol) in glacial acetic acid (15 mL) was heated at reflux with stirring for 5 hours. Upon cooling, the ammonium chloride by-product was removed by suction filtration. Concentration of the filtrate at reduced pressure gave a yellow-brown solid, which was recrystallized twice from ethyl acetate:hexanes to afford fine, colorless needles (113 mg, 29%). This material was shown to be 4-oxazolin-2-one (47a) by comparison of its nmr (Me$_2$SO-d$_6$) spectrum with the spectrum of an authentic sample.

Ureidoacetaldehyde Diethyl Acetal (54)

Ureidoacetaldehyde diethyl acetal was prepared in 61% yield from aminoacetaldehyde diethyl acetal according to the procedure of Duschinsky and Dolan: mp 104-105.5° (lit. mp 104-107°); ir (KBr) 3240 and 3100 (N-H stretch), 1655 (C=O stretch), 1560 cm$^{-1}$ (N-H bend); nmr (CDCl$_3$) δ 1.18 (t, J=ca. 7 Hz, 6H, CH$_3$CH$_2$O), 3.25 (t, J=5.5 Hz, 2H, CHCH$_2$NH), 3.22-3.98 (m, 4H, CH$_3$CH$_2$O), 4.47 (t, J=5.5 Hz, 1H, CHCH$_2$NH), 5.12 (br, 2H, NH$_2$) 5.92 (br t, J=5.5 Hz, 1H, CHCH$_2$NH).

4-Imidazolin-2-one (52)

4-Imidazolin-2-one was prepared in 56% yield from ureidoacetaldehyde diethyl acetal according to the procedure of Duschinsky and Dolan: mp 245-248° (lit. mp 250-251°); ir (KBr) 3050 (N-H stretch), 1655 cm$^{-1}$ (C=O stretch);
ms m/e (rel intensity) 84 (M⁺100), 56 (M⁺-CO, 33).

4-Imidazolin-2-one Dimer. 4-(2-Oxo-4-imidazolin-4-yl)-2-imidazolidinone(57)

4-(2-Oxo-4-imidazolin-4-yl)-2-imidazolidinone was prepared in 51% yield upon the acid catalyzed dimerization of 4-imidazolin-2-one according to the procedure of Zigeuner and Rauter: 75 mp 309-310° (lit. 74 mp 308-310°; lit. 75 mp 310°); ir (KBr) 3190* (N-H stretch), 1675 cm⁻¹ (C=O stretch); nmr (CF₃CO₂H) δ 3.76 (d of d, J_AB=10.0 Hz, J_BX=7.0 Hz, 1H, H_B), 4.11 (d of d, J_AB=10.0 Hz, J_AX=9.6 Hz, 1H, H_A), 5.14 (d of d, J_AX=9.6 Hz, J_BX=7.0 Hz, 1H, H_X), 6.73 (s, 1H, NCH=CN); ms m/e (rel intensity) 168 (M⁺52), 139 (100), 112 (61), 111 (37), 85 (31), 84 (43), 83 (22), 56 (42), 54 (21).

3-Acetyl-4-oxazolin-2-one (47b)

A solution of 2,2-(diethoxy)ethyl carbamate (17.0 g x 96%, 92.0 mmol) in glacial acetic acid (90 mL) was heated at reflux with stirring for 6 hours. The reaction mixture was then concentrated at reduced pressure. Acetic anhydride (90 mL) was added to the residue, and the mixture was heated at reflux with stirring for an additional hour. The reaction mixture was then fractionated under vacuum to afford 47b as a colorless liquid (8.91 g, 76%), bp 103-104°/16 mm Hg (lit. 88 bp 110°/24 mm Hg), which crystallized upon refrigeration, mp 37.5-39° (lit. 88 mp 35-37°): ir (CHCl₃) 1780 (C=O stretch, oxazolinone), 1725 cm⁻¹ (C=O stretch, acetyl);
nmr 60-MHz (CDCl$_3$) $\delta$ 2.63 (s, 3H, CH$_3$), 6.95 (d, $J=2.3$ Hz, 1H, OCH=CHN), 7.30 (d, $J=2.3$ Hz, 1H, OCH=CHN); nmr 100-MHz (CDCl$_3$) $\delta$ 2.59 (s, 3H, CH$_3$), 6.89 (d, $J=2.3$ Hz, 1H, OCH=CHN), 7.25 (d, $J=2.3$ Hz, 1H, OCH=CHN); $^{13}$C nmr (CDCl$_3$) $\delta$ 23.1 (q, $^1J_{CH}_3=131.1$ Hz, CH$_3$), 111.8 (d of d, $^1J_{C-4,H}=204.7$ Hz, $^2J_{C-4,H}=15.2$ Hz, C-4), 130.0 (d of d, $^1J_{C-5,H}=216.2$ Hz, $^2J_{C-5,H}=11.7$ Hz, C-5), 151.9 (t, $^3J_{C-2,H}=7.0$ Hz, C-2), 167.5 (q, $^2J_{COCH}_3=7.2$ Hz, CH$_3$CON); ms m/e (rel intensity) 127 (M$^+$,20), 85 (M$^+$-CH$_2$CO,30), 57 (6), 43 (CH$_3$CO,100); m/e (calcd for C$_5$H$_5$NO$_3$) 127.0269, (found) 127.0271.

Anal. Calcd for C$_5$H$_5$NO$_3$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.34; H, 3.96; N, 11.04.

**N-Methyl 2,2-(Diethoxy)ethyl Carbamate (62c)**

A solution of hydroxyacetaldehyde diethyl acetal (6.71 g, 50.0 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise to a stirred suspension of 1,1'-carbonyldiimidazole (9.10 g x 98%, 55.0 mmol) in anhydrous tetrahydrofuran (125 mL) at room temperature. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 30 minutes. A solution of 40% aqueous methylamine (20 mL) was then added dropwise to the stirred reaction mixture which had been chilled with an ice water bath. Following this second addition, the reaction mixture was allowed to stir at room temperature for an additional 30 minutes. The reaction mixture was then concentrated at reduced pressure. The residue was partitioned between dichloromethane (50 mL)
and water (25 mL). The phases were separated, and the aqueous phase was extracted with additional dichloromethane (25 mL). The combined, dried (MgSO$_4$) dichloromethane extracts were then evaporated at reduced pressure to give a pale yellow oil (12.3 g). This oil was chromatographed over a 2.5 x 25.5 cm column of neutral alumina (ca. 125 g) eluting with chloroform to remove the residual imidazole by-product. The purification was monitored by nmr spectroscopy. The fractions collected between 60 and 390 mL of eluted chloroform were combined and evaporated at reduced pressure to afford as a pale yellow oil (9.83 g x 95%, 98%), which was used without further purification: ir (CHCl$_3$) 3460* (N-H stretch), 1725 (C=O stretch), 1525 (N-H bend), 1130 or 1070 cm$^{-1}$ (C-O stretch); nmr (CDCl$_3$) $\delta$ 1.21 (t, J=7 Hz, 6H, CH$_3$CH$_2$O), 2.77 (d, J=5 Hz, 3H, CH$_3$NH), 3.28-4.02 (m, 4H, CH$_3$CH$_2$O), 4.05 (d, J=5 Hz, 2H, CHCH$_2$O), 4.68 (t, J=5 Hz, 1H, CHCH$_2$O), 5.57 (br, 1H, CH$_3$NH).

3-Methyl-4-oxazolin-2-one (47c)

A solution of N-methyl 2,2-(diethoxy)ethyl carbamate (9.06 g x 95%, 45.0 mmol) in glacial acetic acid (45 mL) was heated at reflux with stirring for 6 hours. Concentration of the reaction mixture at reduced pressure gave a yellow-brown liquid. This liquid was dissolved in ethyl acetate (100 mL) and washed with a saturated aqueous solution of sodium carbonate (50 mL). The dried (MgSO$_4$) ethyl acetate layer was then evaporated at reduced pressure to give an
off-white solid (4.51 g), which was recrystallized twice from benzene:hexanes to afford a colorless crystalline solid (2.47 g), mp 63.5-66º. This material was shown by nmr spectroscopy to be contaminated by a trace impurity characterized by a singlet at δ ca. 2.95. Vacuum sublimation of this material at 40-45º/23 mm Hg afforded 47c as a colorless sublimate (2.01 g, 45%): mp 68-69º (lit. 88 mp 78-80º); ir (KBr) 1735 cm⁻¹ (C=O stretch); nmr 60-MHz (CDCl₃) δ 3.27 (s, 3H, CH₃), 6.67 (d, J=2 Hz, 1H, OCH=CHN), 6.87 (d, J=2 Hz, 1H, OCH=CHN); nmr 100-MHz (CDCl₃) δ 3.25 (s, 3H, CH₃), 6.71 (d, J=2 Hz, 1H, OCH=CHN), 6.90 (d, J=2 Hz, 1H, OCH=CHN); ¹³C nmr (CDCl₃) δ 30.5 (q, ¹³JC-4,H=197.5 Hz, ²JC-4,H=15.0 Hz, ³JC-4,CH₃=2.8 Hz, C-4), 127.5 (d of d, ¹JC-5,H=214.9 Hz, ²JC-5,H=11.1 Hz, C-5), 156.0 (br, C-2); ms m/e (rel intensity) 99 (M⁺, 77), 71 (M⁺-CO, 4), 44 (19), 42 (M⁺-CH₃NCO, 100); m/e (calcd for C₄H₅NO₂) 99.0320, (found) 99.0327.


Found: C, 48.56; H, 5.11; N, 14.13.

A brown oil remained in the sublimation apparatus after sublimation of 47c. This oil was shown by nmr spectroscopy to be a mixture of unsublimed 47c and the above-mentioned impurity, which was tentatively identified as 3-methyl-4-hydroxy-2-oxazolidinone (75): nmr ⁹¹ (CDCl₃) δ 2.90 (s, 3H, CH₃), 4.10 (d of d, JAB=9.8 Hz, JBX=2.3 Hz, 1H, Hₐ), 4.40 (d of d, JAB=9.8 Hz, JAX=6.5 Hz, 1H, Hₐ), 5.32 (d of d, JAX=6.5 Hz, JBX=2.3 Hz, 1H, Hₓ), 5.57 (br, 1H, OH).
Finally, concentration of the combined benzene:hexanes mother liquor of crude 47c (prior to sublimation) gave a yellow oil. This oil was chromatographed over a 1.2 x 22.5 cm column of silica gel (ca. 11g) eluting with benzene. This attempted purification was monitored by nmr spectroscopy. The fractions collected between 80 and 380 mL of eluted benzene were combined and evaporated at reduced pressure to give a pale yellow crystalline solid (0.61 g). Recrystallization from benzene:hexanes afforded colorless plates (0.30 g, 6.7%), mp 67.5-69°, which were shown by ir spectroscopy to be additional 47c. Concentration of this benzene:hexanes mother liquor again gave a yellow oil, which was shown by nmr spectroscopy to be a mixture of 47c and a compound tentatively identified as 3-methyl-4-ethoxy-2-oxazolidinone (64c): 

\[
\begin{align*}
nmr^{91} (CDCl_3) & \delta 1.23 (t, J=7 Hz, 3H, CH_3CH_2O),
2.92 (s, 3H, CH_3),
3.59 (q, J=7 Hz, 2H, CH_3CH_2O),
4.17 (d of d, J_{AB}=9.8(5) Hz, J_{BX}=1.7 Hz, 1H, H_B),
4.35 (d of d, J_{AB}=9.8(5) Hz, J_{AX}=6.1 Hz, 1H, H_A),
5.12 (d of d, J_{AX}=6.1 Hz, J_{BX}=1.7 Hz, 1H, H_A).
\end{align*}
\]

\[\alphaBromophenylacetaldehyde Dimethyl Acetal\]

\[\alphaBromophenylacetaldehyde dimethyl acetal was prepared in 84% yield from styryl acetate^{134} according to the general procedure of Bedoukian^{134-136} bp 90-91.5°/ca. 1 mm Hg (lit.\textsuperscript{134} bp 133-135°/10 mm Hg; lit.\textsuperscript{135} bp 138-140°/14 mm Hg; lit.\textsuperscript{136} bp 84-86°/0.4 mm Hg); nmr (CDCl\textsubscript{3}) \delta 3.15 (s, 3H, OCH\textsubscript{3}), 3.36 (s, 3H, OCH\textsubscript{3}), 4.78 (AB q, J_{AB}=6.7 Hz, \delta_{AB}=13.3 Hz, 2H, CH\textsubscript{2}-CH\textsubscript{2}), 7.05-7.53 (m, 5H, ArH).\]
**β-Bromo-β-phenylethylidenebisethyl Carbamate**

β-Bromo-β-phenylethylidenebisethyl carbamate was prepared in 57% yield from α-bromophenylacetaldehyde dimethyl acetal and ethyl carbamate according to the procedure of Strumza and Ben-Ishai: 67 mp 123.5-125°137 (lit. 67 mp 136°); ir (KBr) 3200 (N-H stretch), 1700 (C=O stretch), 1540 cm⁻¹ (N-H bend); nmr (CDCl₃) δ 1.17 (t, J=7 Hz, 3H, CH₃CH₂O), 1.23 (t, J=7 Hz, 3H, CH₃CH₂O), 4.08 (q, J=7 Hz, 2H, CH₃CH₂O), 4.14 (q, J=7 Hz, 2H, CH₃CH₂O), 5.35-6.20 (m, 4H, CH-CH and NH), 7.23-7.63 (m, 5H, ArH).

4-Carboethoxyamino-5-phenyl-2-oxazolidinone (77)

A solution of β-bromo-β-phenylethylidenebisethyl carbamate (22.63 g, 63.0 mmol) in o-xylene (500 mL) was heated at reflux with stirring for 4 hours. The solution was then allowed to cool to room temperature and left overnight in the refrigerator. The crude product was obtained upon suction filtration as fine, colorless needles (14.03, 89%), mp 168-171°. Recrystallization from ethyl acetate:hexanes afforded trans-77 as fine, colorless needles (8.15 g, 52%): mp 174.5-176° (lit. 67 mp 178°); ir (KBr) 3295* (N-H stretch), 1775 and 1740 (C=O stretch, oxazolidinone), 1690 (C=O stretch, carbamate), 1535 cm⁻¹ (N-H bend); nmr (Me₂SO-d₆) δ 1.19 (t, J=7 Hz, 3H, CH₃CH₂O), 4.07 (q, J=7 Hz, 2H, CH₃CH₂O), 5.17 (d of d, Jₐᵦ=4 Hz, Jₖᵦ=8 Hz, 1H, Hₐ), collapses to a doublet with Jₐᵦ=4 Hz with D₂O), 5.33 (d, Jₐᵦ=4 Hz, 1H, Hₐ), 7.43 (s, 5H, ArH), 8.23 (br d, Jₖᵦ=8 Hz, 1H, carbamate NH, washes out.
with D$_2$O), 8.45 (br, 1H, oxazolidinone NH, washes out with D$_2$O).

Three additional crops of 77 (4.95 g, 31%) were obtained from successively smaller volumes of ethyl acetate:hexanes. These subsequent crops had progressively lower and broader melting points due to contamination by the cis isomer: nmr (cis isomer in cis:trans mixture) (Me$_2$SO-$_d_6$) $\delta$ 0.96 (t, J=7 Hz, 3H, CH$_3$CH$_2$O), 3.82 (q, J=7 Hz, 2H, CH$_3$CH$_2$O), 5.61 (d of d, $J_{AB}$=7 Hz, $J_{BX}$=8.5 Hz, 1H, H$_B$), collapses to a doublet with $J_{AB}$=7 Hz with D$_2$O), 5.83 (d, $J_{AB}$=7 Hz, 1H, H$_A$), 7.40 (s, 5H, ArH), 7.65 (br d, $J_{BX}$=8.5 Hz, 1H, carbamate NH, washes out with D$_2$O), 8.35 (br, 1H, oxazolidinone NH, washes out with D$_2$O).

5-Phenyl-4-oxazolin-2-one (47d)

5-Phenyl-4-oxazolin-2-one was prepared in 77% yield from 4-carboethoxyamino-5-phenyl-2-oxazolidinone according to the procedure of Strumza and Ben-Ishai: $^{67}$ mp 216.5-218$^\circ$ (lit. $^{67}$ mp 223-224$^\circ$; lit. $^{69}$ mp 216-217$^\circ$); ir (KBr) 3200* (N-H stretch), 3130* (vinyl C-H stretch), 1745 and 1720 cm$^{-1}$ (C=O stretch); nmr (Me$_2$SO-$_d_6$) $\delta$ 7.13-7.79 (m, 6H, ArH and OC=CH$_N$), 10.5 (br, 1H, NH); ms m/e (rel intensity) 161 (M$^+$,100), 133 (M$^+$-CO,5), 117 (M$^+$-CO$_2$,16), 106 (14), 105 (PhCO,86), 90 (23), 89 (14), 77 (56).

3-Acetyl-5-phenyl-4-oxazolin-2-one (47e)

A mixture of 5-phenyl-4-oxazolin-2-one (3.22 g, 20.0 mmol) and acetic anhydride (20 mL) was heated at reflux with
stirring for 1 hour. Concentration of the reaction mixture at reduced pressure gave an off-white solid, which was re-crystallized from benzene to afford 47e as fine, colorless prisms (3.69, 91%): mp 140-141°; ir (KBr) 1775 (C=O stretch, oxazolinone), 1720 cm⁻¹ (C=O stretch, acetyl); nmr (CDCl₃) δ 2.65 (s, 3H, CH₃), 7.25-7.70 (m, 6H, ArH and OC=CHN); ms m/e (rel intensity) 203 (M⁺,6), 161 (M⁺-CH₂CO,100), 117 (8), 106 (9), 105 (PhCO,47), 90 (6), 83 (12), 77 (25), 43 (CH₃CO,97); m/e (calcd for C₁₁H₉NO₃) 203.0582, (found) 203.0577.

Anal. Calcd for C₁₁H₉NO₃: C, 65.02; H, 4.46; N, 6.89.
Found: C, 65.06; H, 4.49; N, 6.90.

Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and 1,3-Diphenylisobenzofuran (78). Adduct 81a

A mixture of 4-oxazolin-2-one (170 mg, 2.00 mmol) and 1,3-diphenylisobenzofuran (541 mg, 2.00 mmol) in toluene (3 mL) was heated at reflux with stirring under a nitrogen atmosphere for 2 hours. Upon cooling, a pale yellow solid (424 mg, 60%) was collected by suction filtration and washed with toluene. The analytical sample of endo-81a was prepared by triturating the pale yellow solid with absolute ethanol and collecting the residual colorless solid by suction filtration: mp 254-256° (dec.); ir (KBr) 3220* and 3150* (N-H stretch), 1765 cm⁻¹ (C=O stretch); nmr (Me₂SO-d₆) δ 4.54 (br d, J=9 Hz, 1H, OCH-CHN), 5.29 (d, J=9 Hz, 1H, OCH-CHN), 7.05 (AA'BB' m, 4H, ArH), 7.31-7.76
Analytical  
Calcd for C_{23}H_{17}NO_3:  C, 77.73; H, 4.82; N, 3.94.

Found:  C, 77.47; H, 4.90; N, 3.98.

Concentration of the toluene filtrate at reduced pressure gave a yellow-green solid, which was shown by nmr (CDCl_3) spectroscopy to be largely a mixture of unreacted 47a and 78 and residual toluene. However, there was also a small amount of endo-81a and a second adduct present. The second adduct, which was characterized by a broad doublet at δ 4.19 and a sharper doublet at δ 4.96 with J = 6 Hz, was assigned as exo-81a.

**Acid Hydrolysis of Adduct 81a. 4,9-Diphenylnapth[2,3-d]-oxazolin-2-one (88)**

A suspension of adduct 81a (178 mg, 0.500 mmol) in glacial acetic acid (20 mL) and concentrated hydrochloric acid (15 mL) was heated at reflux with stirring for 4 hours. Upon cooling, 88 was obtained as a colorless solid (127 mg, 75%) upon collection by suction filtration and washing successively with water, ethanol, and ether: mp 343-345°; ir (KBr) 3100 (N-H stretch), 1750 cm^{-1} (C=O stretch); ms m/e (rel intensity) 338 (M^+1,25), 337 (M^+,100), 336 (M^+-1, 17); m/e (calcd for C_{23}H_{15}NO_2) 337.1102, (found) 337.1103.

**Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and Hexachlorocyclopentadiene (79). Adduct 82**

A solution of 4-oxazolin-2-one (255 mg, 3.00 mmol) and hexachlorocyclopentadiene (818 mg, 3.00 mmol) in ethyl
acetate (3 mL) was heated at reflux with stirring under a nitrogen atmosphere for 77 hours. Upon cooling, the reaction mixture was passed through a short column of Florex eluting with ethyl acetate. The ethyl acetate eluent was evaporated at reduced pressure to give a brown semisolid. This semisolid was triturated with hexanes, and the insoluble residue was collected by suction filtration to yield a brown solid. This solid was then recrystallized from benzene to afford 82 as fine, off-white, cubic crystals (584 mg, 54%). The analytical sample of 82 was obtained as colorless, cubic crystals upon an additional recrystallization from chloroform: mp 275-285° (dec.); ir (KBr) 3245* and 3155* (N-H stretch), 1765 cm\(^{-1}\) (C=O stretch); nmr (Me\(_2\)SO-\(d_6\)) \(\delta\) 4.77 (br d, J=8 Hz, 1H, OCH-CHN, sharpens with D\(_2\)O), 5.42 (d, J=8 Hz, 1H, OCH-CHN), 9.07 (br, 1H, NH, washes out with D\(_2\)O); ms m/e (rel intensity) 359 (M\(^+\)+4, 0.5), 357 (M\(^+\)+2, 0.6), 355 (M\(^+\), 0.3), 276 (13), 274 (29), 272 (36), 270 (C\(_5\)\(^{35}\)Cl\(_6\), 19), 241 (6), 239 (16), 237 (24), 235 (C\(_5\)\(^{35}\)Cl\(_5\), 15), 85 (C\(_3\)H\(_3\)NO\(_2\), 100), 57 (8); m/e (calcd for C\(_8\)H\(_3\)\(^{35}\)Cl\(_6\)NO\(_2\)) 354.8294, (found) 354.8284. 

Anal. Calcd for C\(_8\)H\(_3\)Cl\(_6\)NO\(_2\): C, 26.85; H, 0.85; N, 3.91. 

Found: C, 26.81; H, 0.85; N, 3.92.

Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and o-Chloranil (80). Adduct 83

A mixture of 4-oxazolin-2-one (170 mg, 2.00 mmol) and o-chloranil (492 mg, 2.00 mmol) in benzene (10 mL) was heated at reflux with stirring under a nitrogen atmosphere
for 24 hours. Upon cooling, a pale yellow solid (570 mg, 86%) was collected by suction filtration and washed with benzene. The analytical sample of 83 was obtained as fine, colorless needles upon recrystallization from absolute ethanol: mp 265-275° (dec.); ir (KBr) 3235* and 3180* (N-H stretch), 1775 and 1755 (C=O stretch), 1435 cm⁻¹ (C-O stretch); nmr¹³⁸ (Me₂SO-d₆) δ 4.92 (br, NH and H₂O in Me₂SO-d₆), 6.30 (d, J=6 Hz, 1H, OCH-CHN), 6.68 (d, J=6 Hz, 1H, OCH-CHN); ms m/e (rel intensity) 333 (M⁺+4,5), 331 (M⁺+2,11), 329 (M⁺,8), 261 (8), 259 (16), 257 (C₇H₃⁵Cl₄O₂, 12), 85 (C₃H₃NO₂,100), 57 (9), 56 (19); m/e (calcd for C₉H₃⁵Cl₄NO₄) 328.8816, (found) 328.8832.

Anal. Calcd for C₉H₃Cl₄NO₄: C, 32.66; H, 0.91; N, 4.23.

Found: C, 32.81; H, 0.94; N, 4.27.

Cycloaddition Reaction of 3-Acetyl-4-oxazolin-2-one (47b) and 1,3-Diphenylisobenzofuran (78). Adduct 81b

A solution of 3-acetyl-4-oxazolin-2-one (153 mg, 1.20 mmol) and 1,3-diphenylisobenzofuran⁶² (270 mg, 1.00 mmol) in toluene (3 mL) was heated at reflux with stirring for 3 hours. Additional 1,3-diphenylisobenzofuran (90 mg, 0.33 mmol) was added, and the reaction mixture was heated at reflux with stirring for an additional 2 hours. Concentration of the reaction mixture at reduced pressure gave a yellow solid, which was chromatographed over a column of silica gel (ca. 10 g) eluting with benzene. Combination and evaporation at reduced pressure of the fractions showing a spot with Rₛ = 0.6 gave a pale yellow solid (380 mg).
Recrystallization from benzene:hexanes afforded 81b as fine, colorless needles (312 mg, 65%): mp 185-186.5º (dec.); ir (KBr) 1775 (C=O stretch, oxazolidinone), 1705 cm⁻¹ (C=O stretch, acetyl); nmr (CDCl₃) δ 2.14 (s, 3H, CH₃), 5.31 (AB q, Jₐₕ=8.9 Hz, δₐₕ=16.3 Hz, 2H, OCH-CHN), 7.00-8.04 (m, 14H, ArH).

Anal. Calcd for C₂₅H₁₉NO₄: C, 75.55; H, 4.82; N, 3.52. Found: C, 75.47; H, 4.82; N, 3.56.

Deacetylation of Adduct 81b. Adduct 81a

A suspension of 81b (39.7 mg, 0.100 mmol) in 10% aqueous ammonia (2 mL) and 95% ethanol (4 mL) was allowed to stir at room temperature for 24 hours. The product was collected by suction filtration and washed with 50% ethanol to afford a colorless solid (27.0 mg, 76%), mp 248.5-250º. This material was identified as endo-81a by comparison of the ir (KBr) and nmr (Me₂SO-d₆) spectra with those of an authentic sample.

Cycloaddition Reaction of 3-Acetyl-4-oxazolin-2-one (47b) and Cyclopentadiene. Adduct 84b

The procedure employed here is similar to that described by Scharf and Küsters for the reaction of dichlorovinylene carbonate and cyclopentadiene. A solution of 3-acetyl-4-oxazolin-2-one (636 mg, 5.00 mmol) and freshly distilled cyclopentadiene (330 mg, 5.00 mmol) in o-xylene (3 mL) was heated at reflux with stirring for 1 hour. (A coiled reflux condenser capped with a dry ice/i-propyl alcohol cold finger
was employed to minimize loss of the cyclopentadiene.) Upon cooling to room temperature, additional cyclopentadiene (330 mg, 5.00 mmol) was added to the reaction mixture, which was then heated at reflux with stirring for an additional hour. This process was repeated three more times so that a total of 1.65 g (25.0 mmol) of cyclopentadiene was employed. After the fifth and final reflux period, concentration of the reaction mixture at reduced pressure gave a yellow liquid. This liquid was shown by nmr spectroscopy to be a mixture of unreacted 47b, the desired adduct, cyclopentadiene dimer, and residual o-xylene. The ratio of unreacted 47b to adduct was ca. 1:4, indicating that the reaction had gone ca. 80% toward completion. This yellow liquid was then chromatographed over a 1.2 x 25 cm column of silica gel (ca. 10 g) eluting initially with 50:50 benzene:hexanes (6 x 25 mL), followed by benzene (12 x 25 mL), and finally with chloroform (3 x 50 mL). This purification was monitored by nmr spectroscopy. The fractions collected between 200 and 500 mL of eluted solvent were combined and evaporated at reduced pressure to afford 84b as a pale yellow oil (613 mg, 63% based on 47b), which was used without further purification: ir (CHCl₃) 1775 (C=O stretch, oxazolidinone), 1700 cm⁻¹ (C=O stretch, acetyl); nmr (CDCl₃) δ 1.38 (d, J₇₅,₇₆=10.0 Hz, W₇=3.5 Hz, 1H, H₇₅), 1.76 (d of t, J₇₅,₇₆=10.0 Hz, J₇₅,₇₆=1.9 Hz, 1H, H₇₅), 2.42 (s, 3H, CH₃), 3.39 (br m, W₇=16.5 Hz, 2H, H₂ and H₄), 4.52 (d of d, J₂,₄=8.4 Hz, J₃,₄=3.6 Hz, 1H, H₃), 4.99 (d of d, J₂,₃=8.4 Hz,
Deacetylation of Adduct 84b. Adduct 84a.

A solution of 84b (193 mg, 1.00 mmol) in 10% aqueous ammonia (8 mL) and 95% ethanol (16 mL) was allowed to stir at room temperature for 12 hours. The reaction mixture was then concentrated at reduced pressure at room temperature (until most of the ethanol and ammonia had been removed). The aqueous residue was then extracted with dichloromethane (3 x 20 mL). The combined, dried (MgSO₄) dichloromethane extracts were evaporated at reduced pressure to give a colorless solid, which was recrystallized from benzene to afford 84a as a colorless, flocculent solid (148 mg, 98%): mp 165-166°; ir (KBr) 3265* (N-H stretch), 1735 and 1705 cm⁻¹ (C=O stretch); nmr¹³⁹ (CDCl₃) δ 1.22 (d, J₇ₛ,₇ₐ=10.0 Hz, Wₜ=3.0 Hz, 1H, H₇ₐ), 1.68 (d of t, J₇ₛ,₇ₐ=10.0 Hz, J₇ₛ,₁=7ₗₛ,₄=1.9 Hz, 1H, H₇ₙ), 3.07 (br m, Wₚ=8 Hz, 1H, H₁ or H₄), 3.30 (br m, Wₚ=8.5 Hz, 1H, H₁ or H₄), 4.09 (br d of d, J₂,₃=8.4 Hz, J₃,₄=3.8 Hz, 1H, H₃, sharpens with D₂O), 5.02 (d of d, J₂,₃=8.4 Hz, J₁,₇₄=4.1 Hz, 1H, H₂), 6.20 (t, unsymmetrical, S=3.9 Hz, 2H, H₅ and H₆), 6.52 (br, 1H, NH, washes out with D₂O).

Anal. Calcd for C₈H₉NO₂: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 6.02; N, 9.26.

Catalytic Hydrogenation of 84a. endo-3-Oxa-5-azatricyclo-[5,2,1,0²⁷°]decan-4-one (95)

A solution of 84a (83.1 mg, 0.550 mmol) in glacial
acetic acid (10 mL) was hydrogenated in the presence of 10% palladium on charcoal (25 mg) for 2 hours at 60 psi initial pressure in a Parr apparatus. Most of the hydrogen was consumed during the first few minutes of the hydrogenation period. The catalyst was removed by filtration through a Celite 545 bed. The acetic acid filtrate was then concentrated at reduced pressure. The residue was recrystallized from benzene:hexanes to afford endo-95 as fine, colorless needles (64.5 mg, 77%): mp 136-137.5° (lit.101 137-139°); ir (KBr) 3260* (N-H stretch), 1740 and 1705 cm⁻¹ (C=O stretch); nmr (CDCl₃) δ 1.12-2.00 (m, 6H, H₅, H₆, and H₇), 2.43 and 2.58 (br m, overlapping signals, 2H, H₁ and H₄), 3.91 (br d of d, J₂,₃=10.0 Hz, J₃,₄=4.5 Hz, 1H, H₃), 4.77 (d of d, J₂,₃=10.0 Hz, H₁,₂=4.6 Hz, 1H, H₂), 6.73 (br, 1H, NH).

Cycloaddition Reaction of 3-Acetyl-4-oxazolin-2-one (47b) and Anthracene. Adduct 85b

A mixture of 3-acetyl-4-oxazolin-2-one (1.91 g, 15.0 mmol) and anthracene (1.78 g, 10.0 mmol) in o-xylene (10 mL) was heated at reflux with stirring for 72 hours. Upon cooling and chilling briefly, the product was collected by suction filtration and washed with cold benzene to give a light brown crystalline solid (2.38 g). Concentration of the benzene filtrate at reduced pressure gave a brownish crystal- line solid, which was recrystallized from a smaller volume of benzene to afford off-white plates (0.40 g). Both crops of product were combined and recrystallized an additional
time from benzene to afford 85b as colorless plates (2.65 g, 87%): mp 189.5-190.5°; ir (KBr) 1780 (C=O stretch, oxazolidinone), 1700 cm⁻¹ (C=O stretch, acetyl); nmr 60-MHz (CDCl₃) δ 2.31 (s, 3H, CH₃), 4.37-4.87 (m, 3H, H₁₀, H₁₁, and H₁₂), 5.04 (d, J₉,₁₂=3 Hz, 1H, H₉), 6.96-7.53 (m, 8H, ArH); nmr 100-MHz (CDCl₃) δ 2.31 (s, 3H, CH₃), 4.49 (d of d, J₁₁,₁₂=8.2 Hz, J₉,₁₂=3.0 Hz, 1H, H₁₂), 4.64 (d, J₁₀,₁₁=3.4 Hz, 1H, H₁₀), 4.74 (d of d, J₁₁,₁₂=8.2 Hz, J₁₀,₁₁=3.4 Hz, 1H, H₁₁), 5.04 (d, J₉,₁₂=3.0 Hz, 1H, H₉), 6.99-7.49 (m, 8H, ArH), see Appendix NMR No. 10.

**Anal.** Calcd for C₁₉H₁₅NO₃: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.73; H, 4.96; N, 4.57.

**Deacetylation of Adduct 85b. Adduct 85a**

A suspension of 85b (1.53 g, 5.00 mmol) in 10% aqueous ammonia (20 mL) and 95% ethanol (40 mL) was allowed to stir at room temperature for 15 hours. The reaction mixture was then concentrated at reduced pressure at room temperature (until most of the ethanol and ammonia had been removed). The product, which was liberated during the concentration, was collected by suction filtration, washed with water, and allowed to air-dry for several hours to yield a colorless solid (1.28 g, 97%), mp 225.5-227°. Recrystallization from ethyl acetate:hexanes afforded 85a as fine, colorless needles (1.21 g, 92%): mp 231-232°; ir (KBr) 3150 (N-H stretch), 1755 cm⁻¹ (C=O stretch); nmr (CDCl₃) δ 4.00 (br d of d, J₁₁,₁₂=8.6 Hz, J₉,₁₂=3.2 Hz, 1H, H₁₂), 4.36 (d, J₉,₁₂=3.2 Hz, 1H,
Hg), 4.65 (d, J_{10,11} = 3.7 Hz, 1H, H_{10}), 4.86 (d of d, J_{11,12} = 8.6 Hz, J_{10,11} = 3.7 Hz, 1H, H_{11}), 6.10 (br, 1H, NH, washes out with D_{2}O), 7.05-7.53 (m, 8H, ArH).

**Anal.** Calcd for C_{17}H_{13}NO: C, 77.55; H, 4.98; N, 5.32.
Found: C, 77.49; H, 5.10; N, 5.30.

**Alkaline Hydrolysis of 85a. cis-11-Hydroxy-12-amino-9,10-dihydro-9,10-ethanoanthracene (96)**

A solution of 85a (527 mg, 2.00 mmol) in 2N sodium hydroxide (6 mL) and ethanol (6 mL) was heated at reflux with stirring for 14 hours. Upon cooling, the reaction mixture was concentrated at reduced pressure at room temperature (until most of the ethanol had been removed). The alkaline aqueous residue was then extracted with dichloromethane (3 x 10 mL). The combined, dried (MgSO_{4}) dichloromethane extracts were evaporated at reduced pressure to give a colorless solid, which was recrystallized from ethyl acetate: hexanes to afford 96 as colorless, flocculent needles (423 mg, 89%): mp 162-163°; ir (KBr) 3370*, 3290*, 3035*, 2940*, 2880*, 2830*, and 2730* cm\(^{-1}\) (free and H-bonded N-H and O-H stretches); nmr\(^{141}\) (CDCl_{3}) \(\delta\) 2.18 (br, 3H, OH and NH\(_{2}\), washes out with D\(_{2}\)O), 3.28 (br d, 1H, H\(_{12}\)), 3.86 (poorly resolved d of d, J\(_{11,12}\)\(\approx\) ca. 8 Hz, J\(_{10,11}\)\(\approx\) ca. 3 Hz, 1H, H\(_{11}\)), 4.16 (d, J\(_{9,12}\)\(\approx\) 3 Hz, 1H, H\(_{9}\)), 4.42 (d, J\(_{10,11}\)\(\approx\) 3 Hz, 1H, H\(_{10}\)), 6.97-7.52 (m, 8H, ArH).

**Anal.** Calcd for C_{16}H_{15}NO: C, 80.98; H, 6.37; N, 5.90.
Found: C, 80.87; H, 6.41; N, 5.88.
Alkaline Hydrolysis of 85b. cis-11-Hydroxy-12-amino-9,10-dihydro-9,10-ethanoanthracene (96)

A solution of 85b (611 mg, 2.00 mmol) in 2N sodium hydroxide (6 mL) and ethanol (6 mL) was heated at reflux with stirring for 3 hours. Upon cooling, the reaction mixture was concentrated at reduced pressure at room temperature (until most of the ethanol had been removed). The alkaline aqueous residue was then extracted with dichloromethane (3 x 10 mL). The combined, dried (MgSO₄) dichloromethane extracts were evaporated at reduced pressure to give a colorless solid, which was recrystallized from ethyl acetate: hexanes to afford colorless, flocculent needles (353 mg, 74%), mp 162-163°. This material was shown to be identical to aminoalcohol 96 by comparison of ir (KBr) and nmr (CDCl₃) spectra.

Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and 3,6-Diphenyl-1,2,4,5-tetrazine (97a). 4-Amino-3,6-diphenylpyridazine (102)

A mixture of 4-oxazolin-2-one (170 mg, 2.00 mmol) and 3,6-diphenyl-1,2,4,5-tetrazine (469 mg, 2.00 mmol) in ethyl acetate (4 mL) was heated at reflux with stirring under a nitrogen atmosphere for 80 hours. Upon cooling, a mixture of a pinkish solid and fine, blue-red needles (unreacted 97a) was collected by suction filtration and washed with ethyl acetate. This mixture was triturated with chloroform to remove the unreacted 97a. The insoluble residue was collected by suction filtration and washed with chloroform. This trituration/filtration process was repeated a second time to
finally afford a colorless solid (177 mg, 36%). The analytical sample of 102 was obtained as fine, colorless plates upon recrystallization from absolute ethanol: mp 294-295.5° (lit. 112 mp 304°); ir (KBr) 3475*, 3290*, 3085*, 3050* (N-H stretch), 1635 or 1585 cm⁻¹ (N-H bend); nmr (Me₂SO-d₆) δ 6.04 (br, 2H, NH₂), 7.19 (s, 1H, ArH₅), 7.29-7.77 (m, 8H, ArH'), 7.83-8.05 (m, 2H, ArH'); ms m/e (relative intensity) 248 (M⁺+1,18), 247 (M⁺,86), 246 (M⁺-1,100), 219 (7), 178 (27), 117 (73), 104 (10), 90 (15), 89 (19), 77 (14), 51 (12); m/e (calcd for C₁₆H₁₃N₃) 247.1109, (found) 247.1098.

**Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b). Dihydropyridazidine 107a**

A mixture of 4-oxazolin-2-one (213 mg, 2.50 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine¹¹⁴ (472 mg, 2.00 mmol) in ethyl acetate (10 mL) was allowed to stir at room temperature for 24 hours. The product, which precipitated from the solution during the course of the reaction, was collected by suction filtration and washed with ethyl acetate to afford 107a as a yellow solid (556 mg, 95%), which was used without further purification: mp 210-251° (dec.); ir (KBr) 3300* (N-H stretch), 1760 cm⁻¹ (C=O stretch).

**Anal. Calcd for C₁₅H₁₁N₅O₂:** C, 61.43; H, 3.78; N, 23.88.  
**Found:** C, 61.21; H, 3.80; N, 23.79.

A suspension of 107a in CDCl₃ was prepared in an nmr tube. Upon addition of a few drops of D₂O and a trace of...
trifluoroacetic acid vapor, solution occurred with shaking over a period of ca. 30 minutes. The predominant component in this solution was characterized by two doublets centered at δ 4.76 and 5.04 with J=ca. 8 Hz. This compound was tentatively assigned as dihydropyridazine-deuterium oxide addition product trans-123a. The pyridyl resonances in this spectrum integrated ca. 80% too high for trans-123a, which suggested the possibility of an accompanying acid catalyzed decomposition of 107a to afford 4-aminopyridazine 110a. Similarly, a few drops of absolute methanol and a trace of trifluoroacetic acid vapor were added to a suspension of 107a in CDCl₃. The nmr spectrum showed, in addition to excess methanol, a substance characterized by a methyl singlet at δ 3.01 and two doublets centered at δ 5.06 and 5.33 with J=ca. 8 Hz. This material was identified as the dihydropyridazine-methanol addition product trans-116a by spectral comparison with an authentic sample. The minor methanol addition product trans-117a could not be detected, although it may have been present.

Thermolysis of Dihydropyridazine 107a. 4-Amino-3,6-di(2'-pyridyl)pyridazine (110a) and 4-Hydroxy-3,6-di(2'-pyridyl)pyridazine (111)

A suspension of 107a (293 mg, 1.00 mmol) in toluene (10 mL) was heated at reflux with stirring for 6 hours. Upon cooling a greenish-brown solid (130 mg) was collected by suction filtration and washed with benzene. Recrystallization of this material from dimethyl sulfoxide afforded 110a
as fine, pale yellow needles (42 mg, 17%): mp 253.5-255°; ir (KBr) 3200 and 3020 (N-H stretch), 1610 and 1570 cm⁻¹ (aromatic C=C or C=N stretch and N-H bend); nmr (Me₂SO-d₆) δ 7.42-7.72 (m, 2H, ArH₅), 7.83-8.33 (m, 5H, ArH₅, ArH₄, and NH₂), 8.50-8.95 (m, 4H, ArH₃, and ArH₆); ms m/e (rel intensity) 250 (M⁺+1,18), 249 (M⁺,100), 248 (M⁺-1,94), 221 (10), 220 (37), 194 (10), 193 (23), 118 (15), 104 (12), 91 (12), 79 (14), 78 (45), 52 (13), 51 (19); m/e (calcd for C₁₄H₁₁N₅) 249.1014, (found) 249.0998.


Found: C, 67.51; H, 4.46; N, 28.03.

Concentration of the combined toluene:benzene filtrates at reduced pressure gave an orangish solid (150 mg), which was recrystallized from benzene to afford III as fine, yellow needles (37 mg, 15%): mp 218.5-220°; ir (KBr) 3440* (br O-H stretch), 1595, 1580, 1570, and 1540 cm⁻¹ (aromatic C=C or C=N stretches); nmr (CDCl₃) δ 7.23-7.60 (m, 2H, ArH₅), 7.71-8.12 (m, 2H, ArH₄), 8.10 (s, 1H, ArH₅), 8.47-9.05 (m, 4H, ArH₃, and ArH₆), 14.8 (br, 1H, OH, washes out with D₂O); ms m/e (rel intensity) 251 (M⁺+1,35), 250 (M⁺,100), 222 (17), 196 (10), 194 (43), 193 (75), 192 (16), 119 (12), 118 (19) 106 (10), 105 (C₆H₅N₂,93), 104 (24), 91 (25), 79 (27), 78 (74), 64 (21), 63 (15), 52 (22), 51 (37), 50 (13); m/e (calcd for C₁₄H₁₀N₄O) 250.0854, (found) 250.0851.

Cycloaddition Reaction of Vinylene Carbonate (50) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b). Authentic 4-Hydroxy-3,6-di(2'-pyridyl)pyridazine (111)

A mixture of vinylene carbonate (207 mg, 2.40 mmol)
and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine\textsuperscript{114} (472 mg, 2.00 mmol) in benzene (10 mL) was heated at reflux with stirring for 48 hours. Additional vinylene carbonate (207 mg, 2.40 mmol) was added to the reaction mixture at this time since the nmr spectrum of an aliquot removed from the reaction mixture indicated that the original vinylene carbonate had been consumed. The reaction mixture was heated at reflux with stirring for an additional 40 hours. Although the reaction appeared near completion as indicated by the appreciable decolorization of the reaction mixture, additional vinylene carbonate (207 mg, 2.40 mmol) was added. The reaction mixture was then heated at reflux with stirring for a final 18 hours. The product, which crystallized upon cooling, was collected by suction filtration and washed with benzene to afford \textbf{111} as fine, tannish needles (336 mg, 67%), mp 218-219.5\textdegree. Concentration of the benzene filtrates at reduced pressure gave a tannish solid, which was recrystallized from a smaller volume of benzene to give additional \textbf{111} (115 mg, 23%), mp 218.5-219.5\textdegree. The analytical sample of \textbf{111} was obtained as fine, pale yellow needles upon an additional recrystallization from benzene, mp 218.5-219.5\textdegree. The ir (KBr) and nmr (CDCl\textsubscript{3}) spectra of this material were identical to the spectra of \textbf{111} obtained upon thermolysis of dihydropyridazine \textsuperscript{107a}.

Anal. Calcd for C\textsubscript{14}H\textsubscript{10}N\textsubscript{4}O: C, 67.19; H, 4.03; N, 22.39.

Found: C, 67.09; H, 4.04; N, 22.31.
Cycloaddition Reaction of 3-Acetyl-4-oxazolin-2-one (47b) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b). 4-Acetamido-3,6-di(2'-pyridyl)pyridazine (110b)

A mixture of 3-acetyl-4-oxazolin-2-one (159 mg, 1.25 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (236 mg, 1.00 mmol) in toluene (6 mL) was heated at reflux with stirring for 46 hours. Upon cooling, the product was collected by suction filtration and washed with benzene to give 110b as a pinkish, crystalline solid (210 mg, 72%). Concentration of the toluene:benzene filtrate gave a reddish solid. This reddish solid was shown by nmr spectroscopy to be a mixture of excess 47b and the desired 110b. The reddish coloration also suggested the presence of a trace of unreacted 97b. However, there was no sign of 4-hydroxypyridazinol111. This reddish solid was recrystallized from a small volume of benzene to afford additional 110b as a pinkish, crystalline solid (24 mg, 8%). Both crops of pinkish, crystalline solid were combined and recrystallized twice from benzene (decolorization with charcoal) to afford 110b as fine, pale yellow needles (163 mg, 56%): mp 242-243°; ir (KBr) 2900 (br, C-H and H-bonded N-H stretches), 1700 (C=O stretch), 1570 or 1545 cm\(^{-1}\) (aromatic C=C or C=N stretch and N-H bend); nmr (CDCl\(_3\)) \(\delta\) 2.32 (s, 3H, CH\(_3\)), 7.13-7.55 (m, 2H, ArH\(_5\)), 7.68-8.15 (m, 2H, ArH\(_4\)), 8.53-9.07 (m, 4H, ArH\(_3\) and ArH\(_6\)), 9.71 (s, 1H, ArH\(_5\)), 13.4 (br, 1H, NH); ms m/e (rel intensity) 292 (M\(^+\)+1,8), 291 (M\(^+\)+1,37), 277 (22), 276 (M\(^+\)-CH\(_3\)+100), 248 (8), 105 (13), 78 (31), 51 (10), 43 (CH\(_3\)CO, 14); m/e (calcd for C\(_{16}\)H\(_{13}\)N\(_5\)O) 291.1119, (found) 291.1118.
Anal. Calcd for C_{16}H_{13}N_{5}O: C, 65.97; H, 4.50; N, 24.04.
Found: C, 66.08; H, 4.55; N, 23.97.

Authentic 4-Acetamido-3,6-di(2'pyridyl)pyridazine (110b)

A mixture of 4-amino-3,6-di(2'-pyridyl)pyridazine (74.8 mg, 0.300 mmol) and acetic anhydride (1 mL) was heated at reflux with stirring for 1 hour. Concentration of the reaction mixture at reduced pressure gave a dark brown solid, which was recrystallized from benzene (decolorization with charcoal) to afford 110b as dark yellow needles (55.8 mg, 64%), mp 241-243°. The ir (KBr) and nmr (CDCl₃) spectra of this material were identical to the spectra of the material prepared from 3-acetyl-4-oxazolin-2-one (47b) and 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (97b).

Cycloaddition Reaction of 3-Methyl-4-oxazolin-2-one (47c) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b) in Ambient Chloroform. Dihydropyridazine-Ethanol Addition Products 
trans-120c and trans-121c

A solution of 3-methyl-4-oxazolin-2-one (238 mg, 2.40 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (472 mg, 2.00 mmol) in chloroform (Mallinckrodt AR, containing 0.75% ethanol as preservative) (10 mL) was allowed to stir at room temperature for 18 days. The reaction was terminated at this time even though decolorization had not occurred. (In fact, the reaction probably could have been terminated much earlier with essentially the same results. The reaction appeared to have a t_{1/2} of ca. 2.5 days as determined by
by nmr spectroscopy and had gone ca. 80-85% toward completion after 7 days.) Concentration of the reaction mixture at reduced pressure at room temperature gave a reddish oil, which was shown by nmr $\text{(CDCl}_3$) spectroscopy to be largely a mixture of excess 3-methyl-4-oxazolin-2-one and two dihydro-pyridazine-ethanol addition products. The predominant isomer trans-120c was characterized by a methyl triplet at $\delta$ 0.92, a methyl singlet at $\delta$ 2.71, a doublet of doublets centered at $\delta$ 5.29 ($J$=ca. 9 Hz and $J$=ca. 2.5 Hz), and a doublet centered at $\delta$ 5.66 ($J$=ca. 9 Hz). The minor isomer trans-121c was characterized by a methyl triplet at $\delta$ 0.97, a methyl singlet at $\delta$ 2.10, a doublet of doublets centered at $\delta$ 4.56 ($J$=ca. 9 Hz and $J$=ca. 2.5 Hz), and a doublet centered at $\delta$ 6.18 ($J$=ca. 9 Hz). The ratio of trans-120c to trans-121c was ca. 80:20.

Approximately half of the reddish oil was chromatographed over a 1.2 x 20 cm column of silica gel (ca. 9.5 g) eluting with chloroform. The purification was monitored by nmr spectroscopy. The fractions collected between 100 and 180 mL of eluted chloroform were combined and evaporated at reduced pressure at room temperature to give a pinkish solid. This solid was shown by nmr spectroscopy to be largely trans-120c contaminated with trans-121c. Since trans-120c appeared to be stable to column chromatography, the other half of the reddish oil was likewise chromatographed over a 1.2 x 21 cm column of silica gel (ca. 10 g) eluting with chloroform. The materials obtained from each of these
chromatographic separations were combined and rechromatographed over a 1.2 x 21 cm column of silica gel (ca. 10 g) eluting with chloroform. The fractions collected between 100 and 260 mL of eluted chloroform were combined and evaporated at reduced pressure at room temperature to give a pale yellow solid (300 mg). This yellow solid was recrystallized from a small volume of chloroform:hexanes upon refrigeration to afford trans-120c as a colorless, granular solid (209 mg, 30%): mp ca. 165° (dec.); ir (KBr) 3340* (N-H stretch), 1750 cm\(^{-1}\) (C=O stretch); nmr (CDCl\(_3\)) \(\delta\) 0.93 (t, J=7 Hz, 3H, CH\(_3\)CH\(_2\)O), 2.73 (s, 3H, NCH\(_3\)), 2.83-3.45 (m, 2H, CH\(_3\)CH\(_2\)O), 5.29 (d of d, J\(_{AB}\)=9.5 Hz, J\(_{BX}\)=2.5 Hz, 1H, H\(_B\)), 5.67 (d, J\(_{AB}\)=9.5 Hz, 1H, H\(_A\)), 7.15-8.18 (m, 7H, ArH and NH), 8.52-8.74 (m, 2H, ArH).

**Anal.** Calcd for C\(_{18}\)H\(_{19}\)N\(_5\)O\(_3\): C, 61.18; H, 5.42; N, 19.82.

**Found:** C, 61.21; H, 5.43; N, 19.80.

Addition of a trace of trifluoroacetic acid vapor to an nmr solution of trans-120c in CDCl\(_3\) failed to catalyze the rapid exchange of the NH proton. As a result, the H\(_B\) doublet of doublets failed to collapse to a doublet. However, addition of the trifluoroacetic acid vapor did result in the immediate appearance of trans-121c, as indicated by a methyl singlet at \(\delta\) 2.10 and a doublet centered at \(\delta\) 6.23 (J=ca. 9 Hz). The ratio of trans-120c to trans-121c was ca. 80:20. Additionally, signals due to free ethanol appeared, i.e., a triplet at \(\delta\) 1.22 and a quartet at \(\delta\) 3.73 (J=7 Hz). Upon allowing the nmr solution to sit at room temperature
for 24 hours, the signals due to ethanol increased in intensity, while the signals due to trans-120c and trans-121c diminished. Also, a doublet centered at δ 3.09 (J=5 Hz), which was attributed to 4-methylaminopyridazine 110c, and a singlet at δ 8.07, which was attributed to 4-hydroxypyridazine 111, appeared.

In a related nmr (CDCl₃) experiment, the NH proton of trans-120c failed to wash out with D₂O until a trace of trifluoroacetic acid vapor was added. Thus, the doublet of doublets centered at δ 5.29 collapsed to a doublet (J_AB = ca. 9.5 Hz), while the complex multiplet at δ 7.15-8.18 integrated for only six protons relative to the two-proton multiplet at δ 8.52-8.74. This acid catalyzed deuterium exchange was accompanied by the liberation of ethanol and the apparent formation of trans-121c, as indicated by the appearance of a weak methyl singlet at δ 2.10. However, the major change in the spectrum was the appearance of a major, new product, characterized by a methyl singlet at δ 2.77 and two doublets centered at δ 4.80 and δ 5.70 with J_AB = ca. 9Hz. This new product was tentatively identified as dihydropyridazine-deuterium oxide addition product trans-123c.

Cycloaddition Reaction of 3-Methyl-4-oxazolin-2-one (47c) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b) in Refluxing Methanol. Dihydropyridazine-Methanol Addition Products trans-116c and trans-117c

A mixture of 3-methyl-4-oxazolin-2-one (119 mg, 1.20 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine 114 (236 mg, 1.00 mmol) in absolute methanol (5 mL) was heated at reflux
with stirring for 32 hours. Concentration of the reaction mixture at reduced pressure at room temperature gave a pinkish oil. This oil was shown by nmr (CDCl$_3$) spectroscopy to be largely a mixture of residual methanol, excess 3-methyl-4-oxazolin-2-one, and two dihydropyridazine-methanol addition products. The major isomer trans-116c was characterized by an N-methyl singlet at $\delta$ 2.70, an O-methyl singlet at $\delta$ 2.92, a doublet of doublets centered at $\delta$ 5.31 (J=ca. 9 Hz and J=ca. 2.5 Hz), and a doublet centered at $\delta$ 5.67 (J=ca. 9 Hz). The minor isomer trans-117c was characterized by an N-methyl singlet at $\delta$ 2.08, an O-methyl singlet at $\delta$ 2.86, a doublet of doublets centered at $\delta$ 4.63 (J=ca. 9 Hz and J=ca. 2.5 Hz), and a doublet centered at $\delta$ 6.18 (J=ca. 9 Hz). The ratio of trans-116c to trans-117c was ca. 67:33.

This pinkish oil was chromatographed over a 1.2 x 21 cm column of silica gel (ca. 10 g) eluting with ether containing 2% (v/v) methanol. The purification was monitored by nmr spectroscopy. The fractions collected between 70 and 120 mL of eluted solvent were combined and concentrated at reduced pressure at room temperature to give a small amount of a pale yellow oil. This oil was crystallized from a small volume of ether:methanol upon refrigeration to afford trans-116c as colorless prisms (112 mg, 33%): mp 151.5-153$^\circ$ (dec.); ir (KBr) 3335* (N-H stretch), 1750 (C=O stretch), 1580 cm$^{-1}$ (N-H bend); nmr (CDCl$_3$) $\delta$ 2.71 (s, 3H, NCH$_3$), 2.91 (s, 3H, OCH$_3$), 5.26 (d of d, J$_{AB}$=9.4 Hz, J$_{BX}$=2.5 Hz, 1H, H$_B$), 5.64 (d, J$_{AB}$=9.4 Hz, 1H, H$_A$), 7.11-8.16 (m, 7H, ArH and
NH), 8.48-8.71 (m, 2H, ArH), see Appendix NMR No. 11.

Anal. Calcd for C_{17}H_{17}N_{5}O_{3}: C, 60.17; H, 5.05; N, 20.64.

Found: C, 60.28; H, 5.08; N, 20.59.

The fractions collected between 130 and 210 mL of eluted solvent were likewise combined and concentrated at reduced pressure at room temperature to give a smaller amount of pale yellow oil. This oil was also crystallized from a small volume of ether:methanol upon refrigeration to afford trans-117c as finer, colorless prisms (65.5 mg, 19%): mp 160.5-162° (dec.); ir (KBr) 3395* (N-H stretch), 1740 (C=O stretch), 1580 cm^{-1} (N-H bend); nmr (CDCl_{3}) δ 2.10 (s, 3H, NCH_{3}), 2.85 (s, 3H, OCH_{3}), 4.54 (d of d, J_{AB}=9.3 Hz, J_{BX}=2.3 Hz, 1H, H_{B}), 6.17 (d, J_{AB}=9.3 Hz, 1H, H_{A}), 7.06-8.07 (m, 7H, ArH and NH), 8.49-8.77 (m, 2H, ArH), see Appendix NMR No. 12.

Anal. Calcd for C_{17}H_{17}N_{5}O_{3}: C, 60.17; H, 5.05; N, 20.64.

Found: C, 60.14; H, 5.08; N, 20.65.

Cycloaddition Reaction of 3-Methyl-4-oxazolin-2-one (47c) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b) in Refluxing Chloroform. 4-Methylamino-3,6-di(2'-pyridyl)pyridazine (110c) and 4-Hydroxy-3,6-di(2'-pyridyl)pyridazine (111)

A solution of 3-methyl-4-oxazolin-2-one (119 mg, 1.20 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (236 mg, 1.00 mmol) in chloroform (Mallinckrodt AR, containing 0.75% ethanol as preservative) (5 mL) was heated at reflux with stirring for 31 hours. Although the reaction mixture had completely decolorized after heating overnight, i.e., 14 hours, it was necessary to heat the reaction mixture for an additional
17 hours to destroy the last traces of the dihydropyridazine-ethanol addition products trans-120c and trans-121c. Concentration of the reaction mixture at reduced pressure gave a greenish solid. This solid was chromatographed over a 1.2 x 18 cm column of neutral alumina (ca. 22 g) eluting initially with 75:25 benzene:chloroform (10 x 10 mL), followed by 50:50 benzene:chloroform (20 x 10 mL), 25:75 benzene:chloroform (10 x 10 mL), chloroform (10 x 10 mL), and finally 75:25 chloroform:methanol (10 x 10 mL). The purification was monitored by nmr spectroscopy. The fractions collected between 160 and 230 mL of eluted solvent were combined and evaporated at reduced pressure to give a greenish-yellow solid (100 mg). This solid was shown by nmr spectroscopy to be a mixture of excess 3-methyl-4-oxazolin-2-one and the 4-methylaminopyridazine 110c. The fractions collected between 510 and 550 mL of eluted solvent were combined and evaporated at reduced pressure to afford a brownish solid (80 mg, 32%). This solid was identified by nmr spectroscopy as the 4-hydroxy-pyridazine 111.

The mixture of unreacted 3-methyl-4-oxazolin-2-one and 4-methylaminopyridazine 110c was rechromatographed over a 1.2 x 10 cm column of silica gel (ca. 5 g) eluting with chloroform. This separation was also monitored by nmr spectroscopy. The fractions collected between 80 and 160 mL of eluted chloroform were combined and evaporated at reduced pressure to give 110c as a yellow solid (45 mg, 17%). The analytical sample of 110c was obtained as a fine, granular, yellow solid upon recrystallization from benzene: mp 210-
Cycloaddition Reaction of 3-Methyl-4-oxazolin-2-one (47c) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b) in Refluxing Benzene. Mixture of 2:1 Adducts exo,exo-124 and exo,exo-125 and Dihydropyridazine 107c

A mixture of 3-methyl-4-oxazolin-2-one (238 mg, 2.40 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (472 mg, 2.00 mmol) in benzene (10 mL) was heated at reflux with stirring for 8 hours. Upon cooling, a colorless solid (164 mg, 34% based on 47c) was collected by suction filtration and washed with benzene. This mixture of 2:1 adducts, exo,exo-124 and exo,exo-125, was characterized as a mixture without further purification: mp ca. 290° (dec.); ir (KBr) 1760 cm⁻¹ (C=O stretch); nmr (2:1 mixture of 124 and 125) (CF₃CO₂H) δ 2.40 (s, 2H, CH₃, 125), 2.49 (s, 4H, CH₃, 124), 5.31 (d, J_AB=ca. 9 Hz, 0.7H, OCH-CHN, 125), 5.41 (d, J_AB=ca. 9 Hz, 2H, OCH-CHN, 124 and 125), 8.25-9.50 (m, 8H, ArH, 124 and 125); ms m/e (rel intensity) 406 (M⁺, 0.1), 378 (M⁺-N₂, 0.9),
349 (0.7), 334 (M^+-N_2-CO_2, 2.4), 333 (1.0), 321 (0.7), 320 (1.8), 319 (1.4), 304 (19), 290 (M^+-N_2-CO_2-CO_2, 12), 260 (28), 249 (21), 243 (31), 235 (C_{15}H_{13}N_3, 43), 234 (C_{15}H_{12}N_3, 66), 207 (23), 189 (C_{10}H_9N_2O_2, 79), 161 (24), 117 (22), 104 (C_6H_4N_2, 35), 99 (C_4H_5NO_2, 32), 79 (31), 78 (C_5H_4N, 67), 51 (26), 44 (53), 42 (C_2H_2O, 100).

Anal. Calculated for C_{20}H_{18}N_6O_4: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.96; H, 4.49; N, 20.58.

Concentration of the benzene filtrate of 124 and 125 at reduced pressure at room temperature gave an orangish oil. The nmr spectrum of this oil indicated that it was largely a mixture of unreacted 3-methyl-4-oxazolin-2-one and a product characterized by a methyl singlet at \( \delta = 2.68 \) and two doublets centered at \( \delta = 5.77 \) and 6.19 with \( J = 10.3 \) Hz (see Appendix NMR No. 13).\(^{121}\) This substance was assigned as dihydropyridazine 107c. No attempt was made to isolate 107c from this mixture. This structural assignment was confirmed indirectly. Accordingly, one drop of absolute methanol was added to the nmr sample containing 107c. This resulted in the immediate disappearance of the signals attributed to 107c and the appearance of new signals due to the dihydropyridazine-methanol addition product trans-116c; i.e., methyl singlets at \( \delta = 2.67 \) and 2.82, a doublet of doublets centered at \( \delta = 5.22 \) (\( J = \text{ca.} 9.5 \) Hz and \( J = \text{ca.} 2.5 \) Hz), and a doublet centered at \( \delta = 5.60 \) (\( J = \text{ca.} 9.5 \) Hz).\(^{121}\) The presence of the minor dihydropyridazine-methanol addition product trans-117c was inferred from the presence of a new,
weak singlet at δ 2.00. The spectrum was not clean enough to discern the other signals characteristic of trans-117c.

**Cycloaddition Reaction of 4-Oxazolin-2-one (47a) and 3,6-Di(2'-pyridyl)-1,2,4,5-tetrazine (97b) in Ambient Methanol. Dihydropyridazine-Methanol Addition Products trans-116a and trans-117a**

A mixture of 4-oxazolin-2-one (102 mg, 1.20 mmol) and 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine (236 mg, 1.00 mmol) in absolute methanol (5 mL) was allowed to stir at room temperature for 46 hours. Concentration of the reaction mixture at reduced pressure at room temperature gave a pale yellow oil. Examination of this oil by nmr (CDCl$_3$) spectroscopy indicated the presence of residual methanol and excess 4-oxazolin-2-one, as well as a mixture of two dihydropyridazine-methanol addition products. The major isomer trans-116a was characterized by a methyl singlet at δ 2.97, a doublet centered at δ 5.09 (J=ca. 8.5 Hz), and a doublet of doublets centered at δ 5.34 (J=ca. 8.5 Hz and J=ca. 2 Hz). The minor isomer trans-117a was characterized by a methyl singlet at δ 2.91 and a doublet at δ 6.16 (J=ca. 9 Hz). The doublet of doublets expected for trans-117a was obscured by the broad methanol OH signal. The ratio of trans-116a to trans-117a was ca. 80:20. No attempt was made to isolate or separate these isomers.
3,6-di(2'pyridyl)-1,2,4,5-tetrazine \(^{114}\) (236 mg, 1.00 mmol) in absolute ethanol (5 mL) was allowed to stir at room temperature for 46 hours. The product, which precipitated from the solution during the course of the reaction, was collected by suction filtration and washed with ethanol to afford a yellow solid (198 mg, 68%), mp 220–250°. This solid was identified as dihydropyridazine \(^{107a}\) by comparison of its IR (KBr) spectrum with the spectrum of an authentic sample.

Concentration of the ethanol filtrate at reduced pressure at room temperature gave a small amount of a pale yellow oil. Examination of this oil by nmr (CDCl\(_3\)) spectroscopy revealed the presence of residual ethanol and excess 4-oxazolin-2-one, as well as a mixture of two dihydropyridazine-ethanol addition products. The major isomer trans-120a was characterized by a doublet centered at \(\delta\ 5.06\) (\(J=ca.\ 8.5\ Hz\)) and a doublet of doublets centered at \(\delta\ 5.33\) (\(J=ca.\ 8.5\ Hz\) and \(J=ca.\ 2\ Hz\)). The minor isomer trans-121a was characterized by a doublet at \(\delta\ 6.17\) (\(J=ca.\ 9\ Hz\)). The expected doublet of doublets for trans-121a was obscured by the broad ethanol OH signal. No attempt was made to isolate or separate these isomers.

Cycloaddition Reaction of 3-Acetyl-5-phenyl-4-oxazolin-2-one (47e) and Anthracene. Adduct 85e

A mixture of 3-acetyl-5-phenyl-4-oxazolin-2-one (406 mg, 2.00 mmol) and anthracene (535 mg, 3.00 mmol) in p-cymene (4 mL) was heated at reflux with stirring for 60
hours. Upon cooling, the reaction mixture was chromatographed over a 2.4 x 16 cm column of silica gel (ca. 30 g) eluting with benzene. The progress of this separation was followed initially by TLC (for the excess anthracene) and ultimately by nmr spectroscopy. The fractions collected between 150 and 900 mL of eluted benzene were combined and evaporated at reduced pressure to afford a pale yellow solid (634 mg). Recrystallization from toluene afforded 85e as a colorless crystalline solid (514 mg, 67%): mp 210.5-211.5°; ir (KBr) 1775 (C=O stretch, oxazolidinone), 1695 cm⁻¹ (C=O stretch, acetyl); nmr (CDCl₃) δ 2.35 (s, 3H, CH₃), 4.55 (s, 1H, H₁₀), 4.84 (d, J₉,₁₂=3.2 Hz, 1H, H₉ or H₁₂), 5.16 (d, J₉,₁₂=3.2 Hz, 1H, H₉ or H₁₂), 6.68-7.68 (m, 13H, ArH).

Anal. Calcd for C₂₅H₁₉NO₃: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.68; H, 5.03; N, 3.67.

Deacetylation of Adduct 85e. Adduct 85d.

A suspension of 85e (191 mg, 0.500 mmol) in 10% aqueous ammonia (4 mL) and 95% ethanol (8 mL) was allowed to stir at room temperature for 17 hours. The reaction mixture was then concentrated at reduced pressure at room temperature (until most of the ammonia and ethanol had been removed). The product, which precipitated during the concentration, was collected by suction filtration, washed with water, and allowed to air-dry for several hours to give a colorless solid (166 mg, 98%), mp 287-289°. Recrystallization from
absolute ethanol afforded 85\(^{\text{d}}\) as fine, colorless, cubic crystals (147 mg, 86%): mp 282-283\(^{\circ}\); ir (KBr) 3120 (N-H stretch), 1750 cm\(^{-1}\) (C=O stretch); nmr (Me\(_2\)SO-d\(_6\)) \(\delta\) 4.28 (br d, \(\text{J}_{9,12}=3.2 \text{ Hz}, 1\text{H}, \text{H}_{12}\)), 4.60 (d, \(\text{J}_{9,12}=3.2 \text{ Hz}, 1\text{H}, \text{H}_{9}\)), 4.78 (s, 1H, \text{H}_{10}), 6.77-7.63 (m, 13H, ArH), 7.97 (br, 1H, NH).

**Anal. Calcd for C\(_{23}\)H\(_{17}\)NO\(_2\):** C, 81.40; H, 5.05; N, 4.13.

**Found:** C, 81.26; H, 5.07; N, 4.13.
REFERENCES AND NOTES


10. A. Michaelis, ibid., 24, 753 (1891).


24. The percentage of Z isomer for 10a as determined from the $^{13}$C peak heights was ca. 5% lower than the value reported by Saito and Nukada$^4$ for neat 10a and by Sauers and Relles$^{2,3}$ for a CCl$_4$ solution of 10a (as determined by 100-MHz $^1$H nmr). This 5% difference may simply be due to a solvent effect since the $^{13}$C spectrum of 10a was obtained for a CDC$_3$ solution. Unfortunately, the sample of 10a employed in this study became contaminated with 4-butyrolactone and aniline, hydrolysis products of 10a,$^3$ upon prolonged standing at room temperature (while the Varian XL-100-15 nmr spectrometer was down). While this did not affect the $^{13}$C analysis since the $^{13}$C spectra of both 4-butyrolactone$^{2,5}$ and aniline$^8$ have been reported, the isomer distribution (i.e., 55% Z) as determined by 100-MHz $^1$H nmr was inherently unreliable due to the presence of the 4-butyrolactone contaminant.


27. See, for example, the $^{13}$C spectrum of aniline.$^8$


31. 1,1'-Carbonyldiimidazole is commercially available in 98% purity from Aldrich Chemical Co., Inc.


45. This product ratio is strongly dependent upon the rate of addition. When 29b was added to 24 over a period appreciably shorter than 40 minutes, 31b and 34b were formed in a ratio of ca. 39:61, respectively.
46. Inverse addition of the reagents (i.e., addition of 24 to 29a) in tetrahydrofuran still afforded largely 31a. Curiously, this was not the case in dichloromethane as inverse addition resulted in the formation of a mixture of 31a and linear sulfite 34a in a ratio of ca. 32:68, respectively, as determined by nmr spectroscopy. Since linear sulfite 34a has three centers of
asymmetry, \(2^3=8\) isomers are expected. However, due to the symmetry of the molecule, this reduces to two meso isomers and one d,l pair. The nmr spectrum of the crude sulfite mixture exhibited three t-butyl singlets at \(\delta \) 1.27, 1.30, and 1.35 in a ratio of ca. 18:17:32, respectively. Although the linear sulfite mixture was separated from 3a by recrystallization, no attempt was made to separate the individual linear sulfite isomers.


57. (a) M. S. Newman and R. W. Addor, J. Am. Chem. Soc., 75,
1263 (1953); (b) M. S. Newman and R. W. Addor, ibid., 77, 3789 (1955).


68. Huisgen and Blaschke were actually the first workers to prepare 5-phenyl-4-oxazolin-2-one. However, they were not certain if they had prepared the 4-phenyl or 5-phenyl isomer. Botari et al. subsequently prepared the 4-phenyl isomer and concluded that Huisgen and Blaschke's material was the 5-phenyl isomer.


80. Vinylene carbonate was obtained from Aldrich Chemical Co., Inc.


82. The NH proton of dimer 57 underwent rapid exchange with the trifluoroacetic acid solvent to give an intense absorption at ca. δ 9.9. The sample was recovered unchanged upon evaporation of the trifluoroacetic acid and trituration of the residue with water.


84. Saettone and co-workers have reported the preparation of 4-hydroxy-2-oxazolidinones and their conversion to 4-oxazolin-2-ones upon heating in glacial acetic acid.85


90. Reference 89, pp 234-237.

91. Analysis of nmr spectra containing ABX spin systems were performed according to the procedure of E. W. Garbisch, *J. Chem. Educ.*, 45, 402 (1968).
92. Most of the reactions described in this section were performed only once and, as such, no attempt was made to maximize yields.


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118. Presumably both pyridyl nitrogens of 124 and 125 were protonated by the trifluoroacetic acid solvent. The deshielded pyridyl signals were consistent with such protonation. The sample was recovered unchanged upon evaporation of the trifluoroacetic acid and trituration of the residue with water.


121. These chemical shifts are dependent on the amount of residual benzene present in the nmr sample.


123. When this reaction mixture was quenched with excess methanol after stirring at room temperature for only 1 hour, work-up afforded a mixture, which was shown by nmr spectroscopy to consist of 1a, 4a, and 12, with 4a constituting ca. 40% of the mixture. Quenching the reaction mixture after 8 hours again gave
a mixture of 1a, 4a, and 12, with 4a now constituting ca. 70% of the mixture. Finally, quenching the reaction mixture after 15 hours afforded only 4a. By comparison, the corresponding reaction using 1,1'-thionyl diimidazole, described in procedure B, had gone to completion after stirring at room temperature for only 2 hours.


129. This preparation was carried out by J. N. Shuster.

130. This reaction was initially investigated by S. K. Holloway.


132. Most of the imidazole by-product can be removed by washing the crude reaction mixture with larger volumes of water; however, only at the expense of 20-30% of the carbamateacetal, which has some water solubility.

133. The melting point of 65 appeared to depend upon the rate at which the sample was heated. If the rate of heating was rapid, then the reported melting point was observed.


137. The melting point of this compound did not appear to be a valid criterion of purity. That is, the melting point depended upon the rate of heating, as well as the temperature at which the sample was inserted into the melting point apparatus. This behavior may be a result
of the thermal instability of this biscarbamate toward 2-oxazolidinone (77) formation, traces of which would serve to depress the melting point of the biscarbamate.

138. The NH proton underwent rapid exchange with the water present in the Me$_2$SO-d$_6$ solvent in the nmr spectrum of recrystallized 83. However, this was not the case for unrecrystallized 83 as the NH proton appeared as a broad signal centered at $\delta$ 9.55 and the C-4 proton at $\delta$ 6.30 appeared as a doublet of doublets with $J=6$ Hz and $J=\text{ca.} 1.5$ Hz. The smaller coupling constant was presumably due to coupling with the adjacent NH proton.

139. The assignments of H$_7^a$ and H$_7^b$ were made by analogy to the spectral assignments of 2,3-dihalobicyclo-[2.2.1]hept-5-enes reported by Laszlo and Schleyer$^{101a}$ and Subramanian, Emerson, and LeBel.$^{101b}$ Coupling constants $J_{7s,1}$, $J_{1,2}$, and $J_{3,4}$ were measured directly from the spectrum and, as such, are only first order approximations.

140. Coupling constants $J_{1,2}$ and $J_{3,4}$ were measured directly from the spectrum and, as such, are only first-order approximations. The chemical shifts and coupling constants agree favorably with the partial 100-MHz nmr spectrum reported for endo-$^9_5$ by Hohenlohe-Oehringen.$^{102}$

141. Curiously, although the combined OH and NH nmr signal of aminoalcohol 96 washed out with D$_2$O, the broadened signals for H$_{11}$ and H$_{12}$ failed to sharpen perceptibly. It was also interesting to note that for unrecrystallized 96, H$_{11}$ and H$_{12}$ each appeared as well-resolved doublet of doublets with $J_{11,12}=8$ Hz and $J_{9,12}=J_{10,11}=3$ Hz.
NMR No. 1. $^{13}$C Spectrum of 1-Oxo-2-o-toly-5-t-butyl-1,2,5-thiadiazolidin-3-one (4a) in CDCl$_3$. 

4a
NMR No. 2. $^{13}$C Spectrum of trans-2-Oxo-3-(3',4'-dichlorophenyl)-5-methyl-1,2,3-oxathiazolidin-4-one (8a) in CDCl$_3$. 
NMR No. 3. $^{13}$C Spectrum of 1-p-Tolyl-2-pyrrolidinone (10b) in CDCl$_3$. 
NMR No. 4. 13C SORD Spectrum of 1-p-Tolyl-2-pyrrolidinone (10b) in CDCl₃.
NMR No. 5. 100-MHz $^1$H Spectrum of 2-p-Tolyliminotetrahydrofuran (11b-Z) and (11b-E) in CDCl$_3$. 
NMR No. 6. $^{13}$C Spectrum of 2-p-Tolyliminotetrahydrofuran (llb-Z) and (llb-E) in CDCl$_3$. 
NMR No. 7. 60-MHz $^1$H Spectrum of Dimer 68 in Me$_2$SO-d$_6$. 
NMR No. 8. 60-MHz $^1$H Spectrum of 4-Ethoxy-2-oxazolidinone (64a) in CDCl$_3$. 
NMR No. 9. 60-MHz $^1$H Spectrum of Adduct 84b in CDCl$_3$. 
NMR No. 10. 100-MHz $^1H$ Spectrum of Adduct 85b in CDCl$_3$. 
NMR No. 11. 60-MHz $^1$H Spectrum of Dihydropyridazine-Methanol Addition Product trans-116c in CDCl$_3$. 
NMR No. 12. 60-MHz $^1$H Spectrum of Dihydropyridazine-Methanol Addition Product trans-117c in CDCl$_3$. 

Trans-117c
NMR No. 13. 60-MHz $^1H$ Spectrum of Mixture Containing Dihydropyridazine $^{107c}$ in CDCl$_3$. 
Henry Lee Gingrich was born on November 11, 1949, in Philadelphia, Pennsylvania. Shortly thereafter, his family moved to Elizabethtown, Pennsylvania, where in June, 1967, he graduated from Elizabethtown Area High School. In June, 1971, he graduated with honors from Elizabethtown College with a Bachelor of Science degree in Chemistry. In September, 1971, Mr. Gingrich enrolled in the Graduate School of the University of Florida to pursue doctoral studies in the Department of Chemistry. During his graduate studies, he was awarded a University of Florida Graduate School Fellowship (1971-1972) and a Proctor & Gamble Co. Fellowship (1974-1975). He also held a teaching assistantship from June, 1972 to August, 1973, and an interim graduate teaching assistantship from September, 1973 to March, 1974. Mr. Gingrich received the Dupont Award for Excellence in Teaching in 1973. Upon graduation, he will begin postdoctoral studies at the State University of New York at Buffalo with Professor Albert Padwa.
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Immunology and Medical Microbiology

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1977

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