SMALL RING HETERO CYCLES
Part 1
Aziridines, Azirines, Thiiranes, Thiirenes

Edited by
Alfred Hassner
DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF NEW YORK AT BINGHAMTON

AN INTERSCIENCE® PUBLICATION
JOHN WILEY AND SONS
NEW YORK · CHICHESTER · BRISBANE · TORONTO · SINGAPORE
SMALL RING HETEROCYCLES – PART 1

This is the Forty-Second Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
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Part 1
Aziridines, Azirines, Thiiranes, Thiirenes

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Preface

The chemistry of small ring compounds (three- and four-membered rings) has played a considerable role in the development of modern organic chemistry. Foremost among these reactive molecules are the small ring heterocycles. The presence of one or more heteroatoms in these strained rings imparts a measurable dipole moment to such molecules. It also adds a new dimension of intrinsic difficulty concerning the synthesis and stability of such heterocyclic analogs of cyclopropanes and cyclobutanes. If one considers the compressed bond angles (near 60° in three-membered rings and near 90° in four-membered rings), the mere synthetic challenge, especially for the unsaturated analogs of these heterocycles, seems enormous. Indeed, the small ring heterocycles possess much greater reactivity toward a variety of reagents than do their five- or six-membered ring analogs.

It is only since the mid-1960s that an explosive expansion in the chemistry of some of these heterocycles has taken place. In 1964, when the first volume of this series on three- and four-membered heterocycles was published, three pages were devoted to azirines, the unsaturated analogs of aziridines; in this volume the subject occupies an entire chapter. Similarly, while the chemistry of the saturated three-membered rings containing sulfur (e.g., thiiranes) has been relatively well established for some time, the analogous unsaturated compounds (thiirenes, thiirene oxides, etc.) have been known for only 10 years. A number of three-membered rings incorporating two or more heteroatoms still constitute essentially unexplored territory. Therefore the field of small ring heterocycles not only holds current intense interest but also provides a challenge for further investigations.

Because of the overwhelming amount of material to be covered, more than two volumes in this series are necessary. The first is devoted to three-membered rings containing nitrogen and sulfur. It also covers the 3-membered rings containing Sulfur and another hetero atom, such as Thiaziridine-dioxide. It consists of three chapters: Aziridines, Azirines, and Three-Membered Rings Containing Sulfur. This is an area in which considerable progress has been made over the past 18 years and which is of importance, not only from the synthetic and mechanistic points of view, but also from considerations of theoretical calculations and orbital symmetry considerations. For instance, there has been a great deal of recent progress on regio- and stereoselectivity, as well as on photochemistry of these three-membered rings. What is even more intriguing is their use as synthons for other functional groups as well as for larger ring heterocycles. Furthermore, there has been increasing interest in the biological properties and polymerization behavior of such molecules.

Editing this volume is especially meaningful to me, because I had the privilege of being involved firsthand in the exciting explorations of some of these heterocycles (in particular of azirines) during the past 20 years.

An effort was made to update the chapters since the appearance of the last review in this series edited by Weissberger in 1964. Hence, this volume cannot
possibly be all-inclusive but must be selective. Each chapter attempts to build on a previous chapter or review on this subject but from that point stands on its own.

I am grateful to the authors of the chapters for their splendid cooperation and to my secretary, Joyce Scotto, for her help and encouragements.

Most of all, this book is devoted to my family with love and appreciation and to the memory of our 16-year-old daughter Erica, who was torn from us so prematurely during the time this volume was being completed.

ALFRED HASSNER

Binghamton, New York
January 1983
Contents

1. AZIRIDINES 1
   James A. Deyrup

2. AZIRINES 215
   Vasu Nair

3. THREE-MEMBERED RINGS CONTAINING SULFUR 333
   Uri Zoller

Author Index 631
Subject Index 673
# CHAPTER I

## Aziridines

JAMES A. DEYRUP

*Department of Chemistry, University of Florida, Gainesville, Florida*

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>II.</td>
<td>Physical Properties</td>
<td>3</td>
</tr>
<tr>
<td>1.</td>
<td>Nuclear Magnetic Resonance Spectroscopy: Structure and Stereochemistry at Carbon</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Nuclear Magnetic Resonance Spectroscopy: Conformation and Nitrogen Configuration</td>
<td>5</td>
</tr>
<tr>
<td>3.</td>
<td>Configurational Stability at Nitrogen: Optically Active Aziridines</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>Ultraviolet Spectroscopy</td>
<td>8</td>
</tr>
<tr>
<td>5.</td>
<td>Mass Spectroscopy</td>
<td>8</td>
</tr>
<tr>
<td>6.</td>
<td>X-ray Crystallography</td>
<td>9</td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Other Physical Studies</td>
<td>10</td>
</tr>
<tr>
<td>III.</td>
<td>Synthesis of Aziridines</td>
<td>11</td>
</tr>
<tr>
<td>1.</td>
<td>Aziridines via Intramolecular Cyclization</td>
<td>11</td>
</tr>
<tr>
<td>A.</td>
<td>Aziridines from Amino Alcohols</td>
<td>11</td>
</tr>
<tr>
<td>B.</td>
<td>Aziridines from β-Haloamines</td>
<td>16</td>
</tr>
<tr>
<td>C.</td>
<td>Aziridines from Latent β-Amino Halides</td>
<td>20</td>
</tr>
<tr>
<td>D.</td>
<td>Aziridines from β-Iodoisocyanates</td>
<td>21</td>
</tr>
<tr>
<td>E.</td>
<td>Reductive Cyclization Routes to Aziridines</td>
<td>22</td>
</tr>
<tr>
<td>F.</td>
<td>Aziridines from N-halo- and N,N-dihihaloamines</td>
<td>29</td>
</tr>
<tr>
<td>G.</td>
<td>Aziridines via Nucleophilic Addition to Vinyl Halides</td>
<td>30</td>
</tr>
<tr>
<td>2.</td>
<td>Aziridines from Azirines</td>
<td>34</td>
</tr>
<tr>
<td>A.</td>
<td>Conversion of Azirines to Aziridines</td>
<td>34</td>
</tr>
<tr>
<td>B.</td>
<td>Aziridines from Oximes and Related Reactions</td>
<td>42</td>
</tr>
<tr>
<td>C.</td>
<td>The Reaction of Oximes with Hydrides</td>
<td>47</td>
</tr>
<tr>
<td>3.</td>
<td>Aziridines via Cycloadditions to Alkenes</td>
<td>51</td>
</tr>
<tr>
<td>A.</td>
<td>Aziridine Synthesis via Triazolines</td>
<td>52</td>
</tr>
<tr>
<td>B.</td>
<td>Aziridines Formed via Nitrene Additions to Alkenes</td>
<td>55</td>
</tr>
<tr>
<td>a.</td>
<td>Aziridines from Carbonyl Nitrene</td>
<td>61</td>
</tr>
<tr>
<td>b.</td>
<td>Aziridines from Aminonitrene Additions to Alkene</td>
<td>62</td>
</tr>
<tr>
<td>c.</td>
<td>Aziridines from Oxynitrene Addition to Alkenes</td>
<td>69</td>
</tr>
<tr>
<td>d.</td>
<td>Intramolecular Addition of Unstabilized Nitrenes</td>
<td>69</td>
</tr>
<tr>
<td>4.</td>
<td>Aziridines from Carbenoid Addition to Imines</td>
<td>71</td>
</tr>
<tr>
<td>5.</td>
<td>Other Aziridine Syntheses</td>
<td>74</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Eighteen years have elapsed between the original aziridine review in this series and the publication of this book. During this time span the quantity and diversity of aziridine chemistry underwent enormous expansion. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines, and the reactions of aziridines have received particular attention. As a result, applications of aziridine chemistry to synthesis, mechanistic studies, and biological investigations have become increasingly numerous. Space restrictions have made it impossible to include all publications or to cover all areas in optimum depth. It is hoped, however, that the most useful and promising developments are covered.
A number of reviews have appeared during this period. The most important is the comprehensive book by Dermer and Ham published in 1969. Synthesis of aziridines were summarized in 1967. A particularly useful review of aziridine polymers appeared in 1976, and that subject is not discussed here. Two reviews of the Russian literature have appeared. The rearrangements of aziridines have been discussed in detail in 1971 and in an earlier reference. Other more specialized reviews are mentioned in subsequent sections.

This chapter is organized along lines parallel to the original chapter. A discussion of physical properties is followed by aziridine syntheses and aziridine transformations (with and without ring destruction). Subsequent sections treat aziridinium salts, α-lactams, methyleneaziridines, biological applications, and so on.

II. PHYSICAL PROPERTIES

1. Nuclear Magnetic Resonance Spectroscopy: Structure and Stereochemistry at Carbon

Applications of proton nuclear magnetic resonance $^1$H nmr spectroscopy have been especially useful in aziridine structure and stereochemical assignments. A particularly useful review summarizes pertinent work through 1969. The large (5-9 Hz) coupling constant for the coplanar vicinal cis hydrogens compared to the smaller (2-6 Hz) trans value allows configurational assignment to many aziridines. The geminal coupling constant decreases from approximately 2 to $-7$ Hz as the electronegativity of the aziridine substituents increases.

The aziridine ring exerts anisotropic effects on adjacent groups. The chemical shifts (relative to the corresponding alkene) of 1 and 2 are indicative of shifts caused by the aziridine ring. A detailed theoretical study of these effects and their origin has been published. The effect seems to be the result of anisotropy of the nitrogen atom.

Applications of $^{13}$C nmr to aziridines have become more frequent. An extensive study of diverse N-unsubstituted structures has allowed development of an empirical formula for shift prediction. Three bond $^{13}$J$^\text{CH}$ coupling constants have been determined for aziridines and the s character of C in 3 (30%) and 4 (34%) assigned from $^{13}$C-H coupling constants. A complete $^{13}$C analysis of mitomycin C (5) has been published.
A variety of aziridines with general structure 6 have been examined by $^1$H\textsuperscript{193} as well as by $^{15}$N nmr spectroscopy\textsuperscript{24} and $^{15}$N–$^{13}$C coupling constants have been correlated with stereochemistry in arylaziridines.\textsuperscript{25} The $^{13}$C nmr spectra of various cis- and trans-aziridines (7 and 8) have revealed important differences between the chemical shifts of the two ring carbons.\textsuperscript{26}

In the former case, the $\alpha$-carbon is more deshielded than the $\beta$. In the isomer, 8, the reverse is true. This difference is explained on the basis of hyperconjugative delocalization between the aziridine ring and the carbonyl (structure 9) for the trans isomer. Apparently, the trans isomer allows a bisected geometrical relationship between carbonyl and ring that is favorable to structure 9. In contrast, steric constraints force the carbonyl of 7 into a conformation that prohibits such delocalization. Similar conclusions about cis vs. trans differences had previously been identified via infrared (ir) and ultraviolet (uv) spectroscopy (see Section II, 3).\textsuperscript{27}
Although less reliable than coupling constants, chemical shifts have also generated useful structural data. In one such study, solvent effects were employed to measure electronic transmission by the aziridine ring. It was concluded that the aziridine ring was less effective in such transmissions than cyclopropane and epoxide rings. Other studies on chemical shifts vs. structure and solvent effects have been published.

2. Nuclear Magnetic Resonance Spectroscopy: Conformation and Nitrogen Configuration

In addition to structural-stereochemical assignments, nmr spectroscopy has been able to address intriguing questions of side chain conformation and nitrogen stereochemistry. Both considerations are important because of their relationships to the chemical properties of aziridines.

The conformations of some aziridine aldehydes have been studied, and trans conformation 10 is both less polar and more stable than the s-cis form 11. The former is favored (based on coupling constant analysis) by a 75:25 ratio. Long-range coupling between the N-methyl group and the trans hydrogen of 12 is larger than with the cis hydrogen and, as a result, the former is broader. Studies on 15N-H coupling in structures of type 13 have revealed that the coupling constants are dependent on the orientation of the lone pair. Similar effects have been noted in N-chloroaziridines.

In contrast to most amines, the bonding constraints of the aziridine ring usually depress inversion rates until they are at least observable by nmr spectroscopy. When the substituent bulk of A and A' (Eq. 1) is unequal, the population of the two configurations is different. This fact has been used in an ingenious manner to differentiate between cis and trans isomers. The trans isomer (14) displays a more complex spectrum at low temperatures because of slow interconversion between the two configurations. In contrast, the cis isomer (15) spectrum is essentially temperature invariant because the all-cis configuration is so unfavorable.
When $A = A'$ (as in Eq. 1), the analysis of the nmr spectra, the extraction of rate constants, and the determination of energies of activation are relatively straightforward. In general, conjugative effects (16 and 17) stabilize the transition state and accelerate inversion. Electron-withdrawing groups on nitrogen hinder rehybridization (18), and bulky groups on nitrogen and on the ring (19) facilitate inversion.36–39

Subsequent work has added numerous examples of these principles.13, 15, 34, 40–47

3. Configurational Stability at Nitrogen: Optically Active Aziridines

The results described in the preceding section suggested the possibility that configuration stability at nitrogen might be attainable. In fact, a number of isomeric
pairs of type 20 have been separated\textsuperscript{48-53} and a $\Delta F^\ddagger$ for inversion in excess of 21 kcal/mole has been estimated.\textsuperscript{38}

![Diagrams of compounds 20, 21, 22, 23, 24, and 25.]

Configuration has also been imposed on an aziridine nitrogen by incorporation of the ring into bicyclic structure 21.\textsuperscript{54} Since 21 was formed from an optically active precursor (22), its optical rotatory dispersion (ORD) spectrum could be used to assign configuration to the $N$-chlorocompounds 23 and 24, which were, in turn, separable by gas-liquid chromatography (glc).\textsuperscript{55-57}

Finally, it has been possible to achieve synthesis of optically active aziridines in which nitrogen is the only chiral center. Chlorination of an aziridine with an optically active hypochlorite yielded aziridine 25. This aziridine racemized in 4 days at 0$^\circ$.\textsuperscript{58} It has also been possible to prepare optically active 26 either by resolution of the half-ester with subsequent esterification\textsuperscript{59, 60} or by partial destruction of one antipode via aminolyses with 1-ephedrine.\textsuperscript{61}
4. Ultraviolet Spectroscopy

It has been known for a long time that cis-aziridinyl ketones (7) have uv maxima at shorter wavelengths and lower extinction coefficient $\epsilon$ than their trans analogs (8).\textsuperscript{27, 62, 63} Even with the advent of sterochemical assignments by nmr spectroscopy, this application of uv spectroscopy remains useful.\textsuperscript{64} More recently, semiempirical calculations have confirmed that the preferred conformation of aryl- (and presumably carbonyl-) substituted aziridines is the bisected conformation 27.\textsuperscript{65} As previously mentioned, steric factors prohibit this conformation in the cis isomer.

5. Mass Spectroscopy

Although routine mass spectra are common in most recent publications, the technique has not been especially important in structural assignment. Not surprisingly, little difference exists between cis and trans isomers.\textsuperscript{66} A few additional studies contain useful information.\textsuperscript{57, 68}

6. X-ray Crystallography

A significant number of aziridines with general structure 28 have been analyzed by x-ray crystallographic techniques.\textsuperscript{69-75} In all cases the nitrogen is pyrimidal. Bond lengths of 1.48 Å (C=N) and 1.46 Å (C=C) are typical. Other structures determined include 29,\textsuperscript{76} 30,\textsuperscript{77} 31,\textsuperscript{78} and mitomycin A, 32.\textsuperscript{79}
The originally cited range (8-9.5) for aziridine pKₐ's was based on relatively simple aziridine structures. A number of more complex systems have been studied and they also fall within this range. The pKₐ's of structures 33, 34, and 35 illustrate this point. Compound 36 is only slightly outside this range.

The novel triimine 37, however, falls outside this range for all three of its pKₐ's (6.42, 2.71, and ca. -1.0). These values, however, are within good agreement of those calculated on the basis of inductive effects. Somewhat less obvious are the pKₐ's of mitomycins. Values of 3.2 for mitomycin C (5) and 4.3 for mitomycin B (38) have been reported. It does not seem that inductive factors alone could be responsible for this effect. The answer is worth seeking, since the bioalkylating ability of the mitomycin aziridine rings is preserved under physiological conditions by these low pKₐ's.
8. Other Physical Studies

A dipole moment study has allowed assignment of the trans configuration to the phenyl groups of 39.\textsuperscript{87} Dipole moment studies\textsuperscript{88} and electron diffraction\textsuperscript{89} demonstrated that the N-phenyl group assumes the orientation of 40. This conformation is also found in crystallographic studies. Electron spin resonance (esr) spectroscopy studies of 41 have shown conformations 41\textsuperscript{a}\textsuperscript{90} and 41\textsuperscript{b}\textsuperscript{91} to be the most stable for these radicals.

The structure 42, which was assigned on the basis of esr spectral evidence,\textsuperscript{92} has been shown to be incorrect.\textsuperscript{93,94}
III. SYNTHESIS OF AZIRIDINES

1. Aziridines via Intramolecular Cyclization

The most obvious and oldest approach to aziridine synthesis involves internal (neighboring group) cyclization of an amino group situated beta to a leaving group. The best known of these procedures are the so-called Gabriel and Wenker synthesis (Eq. 2).

\[ \begin{align*}
\text{N} & \quad \text{H} \\
\text{X} & \quad \rightarrow \quad \text{N} \\
\text{X} & \quad \rightarrow
\end{align*} \]

\[ X = \text{Br, Cl, I (Gabriel)} \]
\[ X = \text{OSO}_3^- \text{(Wenker)} \]

Such reactions show the expected stereospecificity and generally fail when the appropriate trans coplanar geometry cannot be assumed.\textsuperscript{95, 96} Side reactions include dimerization, polymerization, and elimination. Most of the recent developments in this synthetic approach have been in the routes to the cyclization precursor (new reagents, higher yields, greater stereospecificity, more convenient techniques, etc.) and in the cyclization step (ease of isolation, milder conditions, etc.). The sections that follow are organized on the basis of the precursor employed for cyclization.

A. Aziridines from Amino Alcohols

Amino alcohols suitable for aziridine synthesis are readily available from epoxides and occasionally from the reduction of α-amino ketones. The Wenker procedure for converting amino alcohols to aziridines has been reviewed thoroughly.\textsuperscript{95, 96} Early workers utilized sulfuric acid to form the hydrogen sulfate ester. This approach remains applicable for a remarkable number of systems. The alternative use of \text{ClSO}_3\text{H} offers advantages with more sensitive systems.\textsuperscript{97–99} Some of the more interesting structures prepared by this method are found in Table 1. The Wenker-type synthesis has even been identified in the enzymatic synthesis of aziridine 43. Apparently the enzymatic synthesis of the hydrogen sulfate ester is followed by nonenzymatic cyclization.\textsuperscript{105}
Aziridines

<table>
<thead>
<tr>
<th><img src="image" alt="Aziridine Structures" /></th>
<th><img src="image" alt="Aziridine Structures" /></th>
<th><img src="image" alt="Aziridine Structures" /></th>
<th><img src="image" alt="Aziridine Structures" /></th>
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<td><img src="image" alt="Aziridine Structures" /></td>
<td><img src="image" alt="Aziridine Structures" /></td>
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</table>

**TABLE 1. AZIRIDINES FROM AMINO HYDROGEN SULFATE CYCLIZATIONS**

<table>
<thead>
<tr>
<th><img src="image" alt="Aziridine Structures" /></th>
<th><img src="image" alt="Aziridine Structures" /></th>
<th><img src="image" alt="Aziridine Structures" /></th>
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<td><img src="image" alt="Aziridine Structures" /></td>
<td><img src="image" alt="Aziridine Structures" /></td>
</tr>
</tbody>
</table>

*Wavy line indicates the new C–N bond formed in the cyclization step.*

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<thead>
<tr>
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<th><img src="image" alt="Aziridine Structures" /></th>
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<td><img src="image" alt="Aziridine Structures" /></td>
<td><img src="image" alt="Aziridine Structures" /></td>
</tr>
</tbody>
</table>

It is also possible to convert an amino alcohol to the corresponding tosylate or methanesulfonate ester (Eq. 3). This variation has most often been applied to compounds that have bulky or electron-attracting groups on nitrogen because such groups inhibit reaction on nitrogen. Some representative structures and yields are found in Table 2. This approach has been applied to the synthesis of 44 and to a wide variety of epimino sugars.

```
HN OTs
\[\text{R}\]
\[\text{R}\]
```

```
HN OH
\[\text{R}\]
```

```
HN OSO\(_2\)CH\(_3\)
\[\text{R}\]
```

(3)
### Table 2. Aziridines from Amino Tosylate Cyclization

<table>
<thead>
<tr>
<th>X</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ts</td>
<td>H</td>
<td>CO₂C₅H₅</td>
<td>Ts</td>
<td>90</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>H</td>
<td>CO₂C₅H₅</td>
<td>COCH₃C₆H₅</td>
<td>63</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>H</td>
<td>CO₂C₅H₅</td>
<td>COCH₃NHCO₂CH₂C₅H₅</td>
<td>95</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>H</td>
<td>CONHCH₃CO₂C₅H₅</td>
<td>COCH₃NHCO₂CH₂C₅H₅</td>
<td>67</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>CH₃</td>
<td>CO₂C₅H₅</td>
<td>Ts</td>
<td>29</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>CH₃</td>
<td>CO₂C₅H₅</td>
<td>COCH₃NHCO₂CH₂C₅H₅</td>
<td>88</td>
<td>106</td>
</tr>
<tr>
<td>Ts</td>
<td>CH₃</td>
<td>CONHCH₃CO₂C₅H₅</td>
<td>COCH₃NHCO₂CH₂C₅H₅</td>
<td>94</td>
<td>107</td>
</tr>
<tr>
<td>CH₃SO₂</td>
<td>H</td>
<td>CH₃Cl</td>
<td>t-Bu</td>
<td>55</td>
<td>108</td>
</tr>
<tr>
<td>CH₃SO₂</td>
<td>H</td>
<td>CH₂O₂CCH₃</td>
<td>t-Bu</td>
<td>32</td>
<td>108</td>
</tr>
</tbody>
</table>

Reaction of dimesylates with hydrazine has been used to make 1-aminoaziridine sugar derivatives (Eq. 4).¹²⁰,¹²¹

\[
\text{MsO} + \text{MsO} \xrightarrow{\text{H₂NNH₂}} \text{H₂NN} + \text{O} \tag{4}
\]

Several more recent publications have resulted in a superior route from amino alcohols to aziridines based on the driving force furnished by the strength of the phosphorus-oxygen bond. These reactions utilize reagents formed from \((\text{C}_₆\text{H}_₅)_₃\text{P}\) and \(\text{Br}_₂\), \(\text{Cl}_₂\), or \(\text{CCl}_₄\) in the presence of base. Examples of the products formed are listed in Table 3. As can be seen, the reactions are general and the yields are high. The reactions often proceed below \(0^°\) and are stereospecific (ring closure with inversion). The final step probably involves nitrogen assisted \(\text{C-O}\) rupture with formation of the \(\text{P-O}\) bond. A similar reaction (Eq. 5) may also become useful.¹³⁰

Intermediates 45 and 46 were postulated.
### TABLE 3. AZIRIDINES FROM PHOSPHINE-HALIDE-MEDIATED RING CLOSURE OF AMINO ALCOHOLS

![Diagram](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Reagent</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>n-C₆H₅</td>
<td>60</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>r-Bu</td>
<td>66</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₁₁</td>
<td>50</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₂CH₂</td>
<td>54</td>
<td>122</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₁₁</td>
<td>11</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₂CH₂</td>
<td>51</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₂CH₂</td>
<td>51</td>
<td>122</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>74</td>
<td>122</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>CO₂CH₃</td>
<td>76</td>
<td>123</td>
</tr>
</tbody>
</table>

| CH₃=C | H    | H    | CH₃  | C₆H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | CH₃  | C₆H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | C₂H₅ | C₆H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | H    | C₆H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | CH₃  | CH₂C₆H₅     | 50–60     | 124, 125 |
| CH₃=C | H    | H    | CH₃  | C₂H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | CH₃  | C₆H₅         | 50–60     | 124, 125 |
| CH₂=C | H    | H    | CH₃  | C₆H₅         | 50–60     | 124, 125 |

| H     | CH₂=CH| H    | CH₂=CH | CH₃  | (C₆H₅)₂PBr₂ | –         | 126  |
| H     | H     | H    | H      | H    | (C₆H₅)₂PCCl₂| 52        | 127  |
| H     | H     | H    | H      | C₆H₁₁| (C₆H₅)₂PCCl₂| 58        | 127  |
| H     | H     | H    | H      | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 66        | 127  |
| CH₃   | H     | H    | H      | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 80        | 127  |
| CH₃   | H     | H    | H      | C₆H₁₁ | (C₆H₅)₂PCCl₂| 68        | 127  |
| C₂H₅  | H     | H    | H      | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 73        | 127  |
| C₂H₅  | H     | H    | H      | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 86        | 127  |
| C₂H₅  | H     | H    | H      | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 91        | 127  |
| H     | (CH₃)₆| H    | n-Bu   | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 74        | 127  |
| H     | (CH₃)₆| H    | CH₂C₆H₅| (C₆H₅)₂PCCl₂| 89        | 127  |
| CH₃=CH | –     | C≡CH | –      | t-Bu  | (C₆H₅)₂PCCl₂| 31        | 128  |

76% \((\text{C₆H₅})₃\text{P, CCl}_4\)
The reduction of azidotosylates or methanesulfonates under conditions that cause immediate cyclization (Eq. 6) has been used to advantage in certain cases.

\[
\begin{align*}
\text{N}_3 \quad \text{OTs} & \quad \rightarrow \quad \left[ \begin{array}{c}
\text{NH}_2 \\
\text{OTs}
\end{array} \right] \quad \rightarrow \quad \text{N} \quad \text{H}
\end{align*}
\]

This approach is particularly useful for N-unsubstituted aziridines, where selective esterification of the amino alcohol would not be possible. The azidoalcohols are available from the corresponding epoxide or via the sequence of Eq. 7. The latter route has been used to synthesize epimino derivatives of the juvenile hormone.\(^{131}\)

\[
\text{Cl} \quad \text{O} \quad 1. \text{NaN}_2 \quad 2. \text{NaBH}_4 \quad \text{OH} \quad \text{N}_3
\]

Although NaBH\(_4\) is the usual reducing agent for azidotosylates, nickel-catalyzed hydrogenations have also been employed.\(^ {132-134}\) This type of aziridine synthesis has been utilized in the preparation of epimino sugars and sugar derivatives.\(^ {134-137}\) Structures 47,\(^{133}\) 48,\(^{138}\) 49,\(^{139}\) 50,\(^{83}\) and 51\(^{140}\) are among the more interesting molecules made by these reductive cyclizations.

A new route to aziridines from azidoalcohols has been developed recently. In this reaction the azidoalcohol is reacted with triphenylphosphine. The reaction is stereospecific, as exemplified by the formation of 52.\(^ {141}\) The details of the reaction mechanism are unclear. The yields of 53, 54, 55,\(^ {141}\) 56, and 57\(^ {142}\) are good.
A related reaction has been employed in the recent, total synthesis of dl-porfiromycin.\textsuperscript{143}

**B. Aziridines from $\beta$-Haloamines**

The synthesis of aziridines from $\beta$-haloamines (Gabriel synthesis) is very general and has been used extensively. The following discussion emphasizes some of the more interesting recent examples. The preparation of various $N$-arylaziridines (Eq. 8) via NaH-DMSO treatment takes place in approximately 80\% yield.\textsuperscript{144}

$$
\begin{align*}
\text{R-} & \text{NHCH}_{2}\text{CH}_{2}\text{X} & \text{NaH} & \text{DMSO} & \text{R-} \text{N} & \text{NH} \\
\text{Dihaloaziridines (Eq. 9) can also be prepared by this approach when the nitrogen substituent is strongly electron attracting.}\textsuperscript{145} \text{ A novel biaziridine has been obtained (both $dl$ and meso forms) as shown in Eq. 10.}\textsuperscript{146} \text{ Aziridines with a functional group on nitrogen (Eq. 11) result from the appropriate dihalide.}\textsuperscript{147} \text{ A different type of dihalide provides a useful route to the bicyclic aziridines 58 (Eq. 12).}\textsuperscript{148}
\end{align*}
$$
Synthesis of Aziridines

\[ C_{6}H_{5}CONH-\text{CH-CHCl}, \xrightarrow{\text{NaNH}} DMSO C_{6}H_{5}CO-N_{\text{HCH-CH-CI}} \]  \hspace{1cm} (9)

R = CH\, (52%)
R = C\,_6H\, (62%)
R = C(CH\,)\,_2CHO (45%)

Intramolecular alkylation (Eq. 13) results in aziridine synthesis via ring contraction. Presumably a bicyclic intermediate 59 is formed.

The synthesis of a silicon derivative of an aziridine has been achieved via a Gabriel-type reaction (Eq. 14).
Aziridines

Steroids bearing an aziridine ring have potential biological activity. In addition to cyclization of steroidal iodoamines, Eqs. 15, 16, 17 have been successful procedures for attaching the aziridine ring to the steroid nucleus.

A number of unusual bicyclic aziridines have been prepared from amino halides. These are summarized in Table 4. Cyclization is also possible when the nitrogen has a heteroatom substituent. Examples are depicted in Eq. 18 and Eq. 19.

\[
(C_6H_{13})_2SiCH-CH_2-NHCO_2CH_3 \xrightarrow{31\% \text{ OH}} (C_6H_{13})_2Si\begin{array}{c} \text{N} \\ \text{H} \end{array} \quad (14)
\]

\[
\xrightarrow{\text{NHCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{LiAlH}_4} \text{NHCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{NBS}} \text{NHCH}_2\text{CH}_2\text{N}_2 \quad (15)
\]

\[
\xrightarrow{\text{H}_2\text{NCN} \xrightarrow{\text{NBS}} \text{Br} \quad \text{N} \quad \text{CN} \quad (17)
\]

\[
\xrightarrow{\text{CH}_2\text{ONH}_2 \xrightarrow{\text{NCl}} \text{ClNH} \quad \text{OCH}_3 \quad (18)
\]

\[
\text{ClNHNO}_2 \quad \text{AcO} \quad (19)
\]
TABLE 4. BICYCLIC AZIRIDINES PREPARED VIA AMINO HALIDE CYCLIZATION

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Synthesis of Aziridines" /></td>
<td></td>
</tr>
</tbody>
</table>

20% | 154 |

Wavy line indicates bond generated via cyclization.

The cyclizations described so far have been displacements by nitrogen on carbon. This can be reversed with appropriate substituents on nitrogen as depicted in Eqs. 20 and 21. Specific examples of Eq. 20 are located in Table 5.

![Synthesis of Aziridines](image) (20)

![Synthesis of Aziridines](image) (21)

TABLE 5. AZIRIDINE VIA DISPLACEMENT ON NITROGEN

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON(i-Pr)C₆H₅</td>
<td>57</td>
<td>163</td>
</tr>
<tr>
<td>CON(CH₃)C₆H₅</td>
<td>35</td>
<td>163</td>
</tr>
<tr>
<td>CO₂C₆H₅</td>
<td>5</td>
<td>164</td>
</tr>
<tr>
<td>CO₂CH₃</td>
<td>30</td>
<td>164</td>
</tr>
<tr>
<td>CON(C₂H₅)₂</td>
<td>56</td>
<td>164</td>
</tr>
<tr>
<td>CN</td>
<td>5</td>
<td>164</td>
</tr>
</tbody>
</table>
Aziridines

The contraction of $\alpha$-chloro-$\beta$-lactams to aziridines by certain nucleophiles (Nu) has been reported (Eq. 22). The conversion is stereospecific, and although more exotic mechanisms can be considered, the intermediate shown is more reasonable. These reactions are found in Table 6. The extension of the Darzen's synthesis to aldimines produces aziridines (Eq. 23) and is mechanistically similar to the ring closures of this section. The reaction requires low temperatures and aprotic solvents. The stereochemical course of the reaction depends on the substituents and the base-cation pair employed. Although attempts have been made to rationalize the stereochemical outcome on the basis of these parameters, it is not clear that a satisfactory explanation is available. These results are given in Table 7.

C. Aziridines from Latent $\beta$-Amino Halides

Although the direct closure of $\beta$-haloamines usually proceeds without problems, attempts to prepare and purify these precursors can prove to be unsatisfactory. For this reason a number of alternative approaches have been developed in which

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>X</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>t-Bu</td>
<td>O⁻</td>
<td>94</td>
<td>165,166</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>t-Bu</td>
<td>O⁻</td>
<td>83</td>
<td>165,166</td>
</tr>
<tr>
<td>H</td>
<td>C₆H₅</td>
<td>t-Bu</td>
<td>O⁻</td>
<td>30</td>
<td>165,166</td>
</tr>
<tr>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>NC₆H₆</td>
<td>100</td>
<td>167</td>
</tr>
<tr>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>NC₆H₆</td>
<td>90</td>
<td>167</td>
</tr>
<tr>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>N(CH₂CH₂)₂O</td>
<td>20</td>
<td>167</td>
</tr>
<tr>
<td>H</td>
<td>p-CH₃OC₆H₄</td>
<td>C₆H₅</td>
<td>C₆H₁₀N</td>
<td>62</td>
<td>167</td>
</tr>
<tr>
<td>H</td>
<td>p-CH₃OC₆H₄</td>
<td>C₆H₅</td>
<td>C₆H₁₀N</td>
<td>37</td>
<td>167</td>
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