SMALL RING HETEROCYCLES - PART 2

This is the Forty-Second Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

Editors



SMALL RING HETEROCYCLES—
Part 2

Azetidines, β-Lactams, Diazetidines, and Diaziridines

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

An Interscience® Publication

Copyright © 1983 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Main entry under title:

Small ring heterocycles.

(The Chemistry of heterocyclic compounds, ISSN 0069 3154; v. 42, pt. 1-)

"An Interscience publication".

Includes indexes.

1. Heterocyclic compounds. 2. Ring formation (Chemistry) I. Hassner, Alfred, 1930- .

II. Series: Chemistry of Heterocyclic compounds; v. 42, pt. 1, etc.

QD400.S5115 547'.59 82-4790

ISBN 0-471-05625-1

ISBN 13: 978-0-471-05625-6

10 9 8 7 6 5 4 3 2 1

To my wife Cyd

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

ARNOLD WEISSBERGER

Research Laboratories
Eastman Kodak Company
Rochester, New York

EDWARD C. TAYLOR

Princeton University
Princeton, New Jersey

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.

The overwhelming amount of recent research literature in this field has made it necessary to divide this treatise on small ring heterocycles into several parts, with three- and four-membered rings sometimes interspersed. The current volume constitutes Part 2 in the series.

Part 1 includes the three-membered rings containing one nitrogen or sulfur; thus it consists of chapters on *Aziridines*, *Azirines*, and *Three-Membered Rings Containing Sulfur*, which includes *Thiiranes*, *Thiirenes*, as well as their respective *Oxides*, *Dioxides*, and *Onium* salts.

Part 2 contains four chapters. Three of these cover the chemistry of four-membered rings containing nitrogen, namely *Azetidines* (and *Azetines*), *β-Lactams*, and *Four-Membered Rings Containing Two Nitrogens* (*Diazetidines* and *Diazetines*). To tie in with the latter subject, a chapter on three-membered rings containing two nitrogens (*Diaziridines*, *Diazirines*, *Diaziridinones*) is included.

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 review of this series on three- and four-membered heterocycles, edited by Weissberger, was published, azetines were unknown, while β-lactams and diazetidines were covered as part of the azetidines (trimethyleneimines) chapter and little was known about diaziridines. Most of these topics are now covered in separate chapters of the current volume.

The recent interest in β-lactams, largely due to the pharmacological properties of penam (e.g., penicillin) and cepham (e.g., cephalosporin) antibiotics, has necessitated a chapter devoted to synthesis of β-lactams (azetidinones), separate from the azetidine chapter. Even so, coverage here had to be limited to general synthetic approaches to the β-lactam ring system. Since β-lactam antibiotics rightfully require a separate volume, only a few illustrative references to their synthesis are included.

There has been a great deal of recent progress on regio- and stereoselectivity, as well as on photochemistry of these three and four-membered rings. What is even 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.

An effort was made to briefly present the general state of the art and to emphasize research results of the past 15–20 years. Such an undertaking makes it necessary to be more selective than all-inclusive. Often it became more realistic to build on existing reviews of the subject.

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 during the past 20 years.

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

Most of all, this book is devoted to my family, whose love has sustained me through this effort, and to the loving memory of my daughter, Erica, cruelly torn from us at a tender age.

ALFRED HASSNER

Binghamton, New York
February 1983

Contents

1. **AZETIDINES** 1

   James A. Moore and
   Rita Seelig Ayers

2. **THE SYNTHESIS OF THE β-LACTAM FUNCTION** 219

   Gary A. Koppel

3. **FOUR-MEMBERED RINGS CONTAINING TWO NITROGEN HETEROATOMS** 443

   Reinhard Richter and
   Henri Ulrich

4. **DIAZIRIDINES, 3H-DIAZIRINES, DIAZIRIDINONES, AND DIAZIRIDINIMINES** 547

   Harold W. Heine

Author Index 629

Subject Index 651

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

CHAPTER I

Azetidines

JAMES A. MOORE

Department of Chemistry, University of Delaware, Newark, Delaware

RITA SEELIG AYERS

E. I. du Pont de Nemours and Co., Central Research and Development Department, Experimental Station, Wilmington, Delaware

I. Introduction 3
II. Physical Properties 4
1. Thermodynamic Data and Basicity. 4
2. Vacuum Ultraviolet and Photoelectron Spectra 5
3. Infrared and Raman Data 5
4. NMR Spectra 6
5. Diffraction Data and Molecular Structure. 7
6. Mass Spectra 8
7. ESR Spectra 9
III. Synthesis of the Azetidine Ring 10
1. Formation of the N–C_2 Bond 10
A. Secondary Azetidines 11
B. *N*-Alkylazetidines 12
C. Quaternary Azetidinium Compounds 14
D. *N*-Arylazetidines 15
E. *N*-Sulfonylazetidines 16
F. *N*-Alkyl-3-azetidinols and Azetidinones 17
G. *N*-Alkylazetidine-2-carboxylates and Related Compounds 19
H. *N*-Alkyl-2-aryl-3-acylazetidines. 20
2. Formation of the C_2–C_3 Bond 21
A. Photochemical Cyclization 21
B. Other Methods 22
3. Cycloaddition. 22
A. Thermal [2+2] Cycloaddition 23
B. Photochemical [2+2] Cycloaddition 25
C. [3+1] Cycloaddition 28
4. Formation of Azetidines from Other Ring Systems 30

IV. Introduction and Transformation of Substituents 32
1. Reduction of 2-Azetidinones and Malonimides 33
2. Substituents at N_1 33
A. *N*-Alkylation 34
B. *N*-Arylation 36
C. Quaternization 36
D. Removal of Groups at N_1 37
E. *N*-Acylation and Carbamylation 38
F. Nitrogen Substituents at N_1 39
G. Oxygen Substituents at N_1 41
H. Substitution at N_1 with Other Elements 43
3. Substituents at C_2 44
A. 2-Alkyl- and 2-Alkylideneazetidines 44
B. 2-Alkoxyazetidines 45
C. Azetidine-2-alkanols and -amines 45
D. 2-Acyl- and 2-Alkylideneazetidines 47
E. Azetidine-2-carboxylates 47
F. Azetidine-2-carboxamides, Hydrazides, and Nitriles. 48
G. Azetidine-2-carboxylic Acid 49
4. Substituents at C_3 52
A. 3-Azetidinols and Derivatives 52
B. Mechanistic Considerations in Nucleophilic Substitution 53
C. 3-Amino-, Alkoxy- and Alkylthioazetidines 55
D. 3-Cyano- and 3-Carboxyazetidines. 56
E. 3-Substituted Azetidines from 1-Azabicyclo[1.1.0]butanes 56
F. 3-Azetidinones 57
G. 3-Alkylideneazetidines 58
H. 1,2-Diazabicyclo[3.2.0]heptanones 59
V. Ring-Opening and Rearrangement Reactions of Azetidines. 62
1. Thermal Ring Cleavage 62
2. Ring Opening with Nucleophiles 64
3. Polymerization 68
4. Rearrangements 69
5. Photochemistry 74
VI. Naturally Occurring Azetidines. 77
1. L-Azetidine-2-carboxylic Acid 77
2. Polyoximic Acid 79
VII. Azetines (Dihydroazetes) 80
1. 1-Azetines. 81
A. Cyclization Methods. 81
B. Elimination Methods 81
C. Rearrangement of Cyclopropyl Azides 82
D. Ring Expansion of Trichloromethylaziridines 84
E. Azetine-1-oxides from Nitroalkenes and Ynamines 85
F. [2+2] Cycloaddition 86
G. Intramolecular Cycloaddition 88
H. [1+3] Cycloaddition 90
2. 2-Alkoxy- and Alkylthio-, and Amino-1-azetines. 90
A. Thermal Stability and Valence Isomerization 91
B. Oxidation. 92
C. Cycloaddition 93
3. 2-Azetines. 95
A. Elimination 95
B. Cycloaddition 95

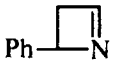
C. Intramolecular Cycloaddition 98
D. Enolic Azetidinones and Imines 99
4. Benzazetines 100
5. Dewar Pyridines, Azaprismanes, and Benzvalenes 103
VIII. Azetes and Benzazetes 106
1. Azetes 106
2. Benzazetes 109
IX. Tables 110
X. References 202

I. INTRODUCTION

This chapter is an extension of a part of the monograph presented about 20 years ago in this series entitled "Trimethyleneimines".[324a] In the earlier volume, a chapter of some 90 pages dealt with the entire series of four-membered nitrogen heterocycles, including simple imines or azetidines, β-lactams, and also rings with two nitrogen atoms. The chemistry of β-lactams now comprises Chapter 2 in this volume, and the present chapter treats only four-membered heterocycles with one nitrogen, exclusive of β-lactams, which are mentioned only incidentally in connection with the chemistry of the azetidines. The general nomenclature of this ring system is illustrated below:



Azetidine



4-Phenyl-1-azetine



Azete

Since the earlier volume in this series, a monograph by Testa et al. on the chemistry and pharmacology of azetidines appeared in 1964,[442] and a more recent review of ring syntheses of azetidines has been prepared by Cromwell and Phillips.[97] A brief review covering stereochemical aspects of azetidine synthesis has been presented by Armarego.[14] In this chapter we have attempted a comprehensive review of the literature dealing with the preparation and reaction of azetidines and the unsaturated rings, azetines and azetes.

The chemistry of azetidines has kept pace, more or less, with the rapid growth of heterocyclic chemistry in general in the past two decades, but azetidines are nevertheless not a ubiquitous class of compounds. Presently, no natural products or industrial processes provide a source of azetidines as starting materials for synthesis. A few groups – notably Testa and co-workers in Milan and Cromwell and his students in Nebraska – have systematically investigated certain facets of azetidine chemistry. Some of the interest in azetidines has involved bridging the gap between the chemistry of the highly strained aziridines and the "normal" behavior of larger rings. A number of azetidines have been prepared for pharmacological evaluation as "tied back" analogs of diethylamino-substituted compounds, but no effort has been made to cover this topic. Earlier work on medicinal and pharmacological properties of azetidines has been treated comprehensively.[442]

One compound that has attracted much attention is L-2-azetidinecarboxylic acid, found in free and combined form in numerous plants. This amino acid can replace L-proline in protein-synthesizing systems, and there is ongoing interest in synthetic peptides containing this acid.

The most notable recent advances among the topics in this chapter have been made in the synthesis and exploration of the unsaturated rings. Azetines of several types have become available in the past decade, and a few unstable azetes have been characterized.

II. PHYSICAL PROPERTIES

Azetidine and various substituted azetidines have been probed and palpated by nearly every physical method available. Much of this effort has been directed to examining the geometry of the azetidine ring and comparing the properties with those of aziridines and pyrrolidines. The azetidine ring is puckered, with an angle of 10–20° from planarity. Some comparative data on the geometry of azetidines and other four-membered ring heterocycles have been reviewed.[335]

In general, properties such as basicity, nmr coupling constants, and ionization potentials, which reflect orbital hybridization, closely resemble those of pyrrolidine. Although the ring is somewhat strained, it has little of the special characteristics exhibited by aziridines. On the other hand, because of their small ring size, azetidines and aziridines show certain resemblances in the high barriers of *N*-inversion and other kinetic criteria. In the acylation by phenyl acetate, azetidines (3,3-disubstituted) and aziridines are both "super nucleophiles"; the enhanced nucleophilicity is attributed to lesser crowding in the transition state rather than to increased *s*-character of the electron pair.[131]

In this section data from a number of physical and spectroscopic measurements for azetidine and a few representative substituted azetidines are summarized.

1. Thermodynamic Data and Basicity

Thermodynamic data for solution and protonation of azetidine and other cyclic amines have been measured[64] and collated with data for other amines.[239] The enthalpy of solution of the liquid amine in water ($-\Delta H_s^1$ at 25°C) is 6087 ± 28 cal/mole; the heat of vaporization (ΔH_v) is 8172 cal/mole; $-\Delta H_s^0 = 14259 \pm 47$ cal/mole. The partial molal volume $\bar{V}_2^0$ in H_2O at 25°C is 63.71 ml/mol.[63]

Phase equilibria for the azetidine–water system reveal the formation of a clathrate of composition $Az \cdot 5.75H_2O$, mp −7.0°C, with two eutectics at −9 and −80°C.[383] The mp of pure azetidine from this diagram is −70°C ± 1.

Parameters (molal) for the dissociation of azetidinium ion in water at 25°C are: pK_a, 11.29;[396] ΔG_i^0 15402 cal/mole; ΔH_i^0 12580 cal/mole; ΔS_i^0 9.47 cal/mole-degree. The pK_a of azetidine is very close to that of pyrrolidine (11.31), although the entropy change is larger.

The pK_a values reported for other azetidines are: 3-methyl-3-phenyl, 10.38;[131] 1-methyl, 10.40;[396] 1,3,3-trimethyl, 11.30;[165] 1-phenyl, 4.08,[48] 3.62;[387a] 1-*o*-tolyl, 3.97; 1,2,4-xylyl, 4.31; 1,2,6-xylyl, 4.64;[387a] *p*-nitrophenyl, 0.34.[241] The solution basicity of *N*-phenylazetidine is slightly greater than that of *N*-phenylpyrrolidine but this relationship is reversed when *o*-methyl groups are present in the aryl substituent.[387a]

The gas-phase basicity of azetidine obtained from equilibrium measurements by ion cyclotron resonance is slightly lower than that of the larger cyclic imines. The proton affinity of azetidine is 227.5 kcal/mole, compared to 230.5 for piperidine, 229 for pyrrolidine, and 220.1 kcal/mole for aziridine.[16,23] The vertical ionization potential for azetidine is given as 208 kcal/mole.[23,484] The vIP values for the series of cyclic imines from aziridine to hexamethylene imine are linearly related to the J_{C-H} values of the corresponding cycloalkanes, reflecting the dependence of vIP on the hybridization of the electron pair.[484]

2. Vacuum Ultraviolet and Photoelectron Spectra

In the region between 49,200 and 55,800 cm^{-1} the band maximum for azetidine is 6.44 eV (f value 0.047), compared to 6.38 eV calculated by CNDO/2 for the first transition.[91] Values for the ionization energies of azetidine from the photoelectron spectrum are 8.93 ($b_1 - \pi$), 11.40 (a_1), 12.03 (b_2), 12.9, 14 (three bands), 16.1, 17, and 18.6 eV. These energies were compared with values derived from *ab initio* calculations of MO energy levels for azetidine and other three- and four-membered heterocyclic systems.[316] Ionization potentials for *N*-arylazetidines and other *N*-arylazacycloalkanes have been correlated with differing conformer populations which vary with ring size.[387a]

3. Infrared and Raman Data

Kirste has presented a detailed analysis of the infrared spectrum of azetidine in the vapor and liquid phases.[244] A qualitative survey of infrared absorption bands for azetidine and several *N*-alkyl and *N*-aryl derivatives as liquid films has been presented.[273] The medium intensity band at 1233–1238 cm^{-1} in several azetidine spectra, attributed to CH_2 twisting, was suggested as a characteristic indicator of a simple azetidine structure. Lippert and Prigge reported detailed infrared and Raman data for cyclic amines.[291] For azetidine, ν_{CH} is 2966 cm^{-1} and ν_{NH} is 3346 (1% in CCl_4) and 3266 cm^{-1} (liquid). In the series of three- to six-membered cyclic amines the C–H stretching frequency increases with monotonically decreasing ring size because of the higher force constant associated with greater *s*-character of the C–H bonds. The N–H stretching frequencies show a more complex dependence on ring size, since hybridization of both the N–H bond and the unshared electron pair are involved. In a related study, azetidine was found to form the strongest hydrogen bonds with phenol (K_{assoc} = 200 liter/mole, compared to 195 liter/mole for pyrrolidine and 110 liter/mole for aziridine.[289]

Far infrared and Raman spectra of azetidine have been recorded, and the potential functions for ring inversion have been calculated.[71,72] It was concluded from these studies that the puckered azetidine molecule is present in two conformations, with an energy difference of 95 cm^{-1} (0.27 kcal/mole) and an inversion barrier of 1.26 kcal/mole; however, these conclusions are contradicted by MO calculations.[74] Low temperature Raman scattering from 40 to 4000 cm^{-1} indicate a phase transition in the solid at 172°K.[274]

4. Nmr Spectra

Nmr spectra have been recorded for many azetidines, and no attempt will be made to present all of these data. For the parent azetidine, the ^1H chemical shifts are: $\delta_{NH} = 2.38$, $\delta_{H_2} = 3.54$, and $\delta_{H_3} = 2.23$ ppm.[290] The position of H_2 is quite deshielded for a $-CH_2N$ proton and is at lower field than that for the α protons in either aziridine ($\delta = 1.36$ ppm) or pyrrolidine ($\delta = 2.75$ ppm). The presence of a *t*-butyl group at N_1 shifts δ_{H_2} upfield to 3.16 ppm and δ_{H_3} to 1.16 ppm.[209] In the 1-benzyl-2,2,3-trimethylazetidinium ion, the α-CH_2 is strongly deshielded (to $\delta = 4.17$ ppm).[281] The ^{13}C chemical shifts for 1-methylazetidine are: $\delta_{N-CH_3} = 46.4$, $\delta_{C_2} = 57.3$, and $\delta_{C_3} = 17.5$ ppm (very close to the chemical shifts of the corresponding carbons in pyrrolidine).[293]

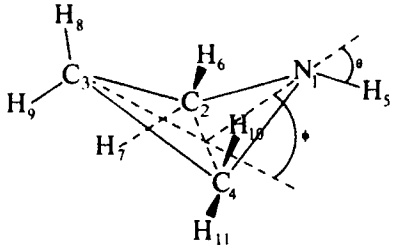
Values for the coupling constant $J_{H_{2,3}}$ are generally in the range of 6 to 7 Hz,[209,211] and those for $J_{H_{2,2}}$ are in the range of -5.5 to -7 Hz. Values for $J_{cis\text{-}H_{2,4}}$ range from -1.1 to -0.4 Hz; those for $J_{trans\text{-}H_{2,4}}$ range from -1.3 to -0.02 Hz.[401] Application of the Karplus relationship to values for $J_{H_{2,3}}$ were used to derive puckering angles of 10–15° for the C_4–N–C_2 and C_2–C_3–C_4 planes in 2-substituted azetidines.[137] The J_{C-H} values for azetidines are $J_{C_2-H} = 140.0$ and $J_{C_3-H} = 134$ Hz, again very close to those for pyrrolidine ($J_{C_2-H} = 139$ Hz).

Several dynamic nmr studies have been made of pyramidal *N*-inversion in azetidines. Temperature-dependent spectra are observed for 3,3-dimethylazetidines with *N*-alkyl, -halo and -thio substituents: for N–CH_3 $T_c = -98°$, $\Delta G^{\ddagger} = 8.8$; for N–Cl or N–Br $T_c = -54°C$, $\Delta G^{\ddagger} = 11.5$; for N–$SCCl_3$ $T_c = -45°C$, $\Delta G^{\ddagger} = 12$.[279,280] The coalescence temperature observed in the last case is probably due not to *N*-inversion, but to rotation. Inversion processes are also observed for simple 1-substituted azetidines: for N–CH_3 $T_c = -69°$, $\Delta G^{\ddagger} = 10.0$; for N–Cl $T_c = -20°$, $\Delta G^{\ddagger} = 13.4$.[268] The activation energies are substantially higher than those for the corresponding pyrrolidines, showing a clear-cut effect of ring strain in the azetidines. The higher barrier with the *N*-chloro compounds compared to *N*-methyl is consistent with inductive retardation. On the other hand, the inversion process for *N*-tosylazetidine is quite rapid ($T_c = -150°$, $\Delta G^{\ddagger} \cong 6.2$), indicating acceleration by a conjugative effect.[269]

The effect of ring size on hybridization and rotational processes in enamines or aminoacrylates of azetidine and homologous cyclic amines has also been studied by nmr. In general, azetidine and pyrrolidine derivatives show similar effects.[351,395,445]

5. Diffraction Data and Molecular Structure

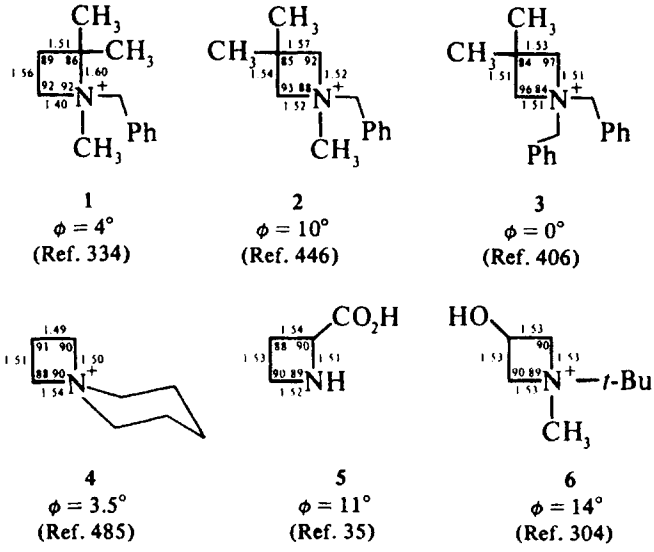
An electron diffraction study of azetidine indicated a complete set of molecular parameters fitting a model having a dihedral or puckering angle (ϕ) of 33.1°.[298] *Ab initio* geometry optimization of the equatorial isomer led to a model with a smaller puckering angle of 23.5°.[74] This angle is very sensitive to small variations (± 0.01–0.05 Å) in bond lengths. More recent computations with a 6-31G* basis set lead to a puckering angle of 25–28°, depending on correlation corrections, indicating that the azetidine ring is somewhat more puckered than cyclobutane.[95a] Geometric parameters for azetidine in the minimum-energy conformation (calculated and obtained from diffraction data) are listed below. An important conclusion from this



	Calculated	Diffraction
Bond Lengths (Å)		
N–C	1.486	1.482
C–C	1.555	1.553
C–H	1.090	1.107
N–H	1.035	1.022
Nonbonded Distances (Å)		
N_1–C_3	2.134	2.066
C_2–C_4	2.121	2.137
N_1–H_6	2.177	2.189
C_2–H_5	2.126	2.010
C_2–H_8	2.225	2.249
C_2–H_9	2.264	2.249
C_3–H_6	2.273	2.252
N_1–H_8	2.729	2.644
N_1–H_9	3.041	3.030
C_2–H_{10}	3.033	3.074
C_2–H_{11}	2.719	2.705
C_3–H_5	2.980	2.830
Angles (degrees)		
CNC	91.1	92.2
CCC	85.9	86.9
CCN	89.0	85.8
HCH	109.5	110.0
ϕ	23.5	33.1
θ	56.8	67.6
β (2-CH_2 rocking)	13.1	15.6
τ (3-CH_2 rocking)	2.5	0

study is that there is no stable axial conformer and no equatorial⇌axial ring inversion as inferred from far infrared spectra.[72] The only inversion process would be at nitrogen; for this, the energy barrier was calculated to be about 15 kcal/mole.

Structures for a number of azetidine derivatives have been determined by x-ray crystallographic diffraction methods. Bond lengths (Å) and angles for the azetidine rings and the angle of pucker ϕ (180° dihedral angle) for several of these crystals are given in Scheme 1.



1
$\phi = 4°$
(Ref. 334)

2
$\phi = 10°$
(Ref. 446)

3
$\phi = 0°$
(Ref. 406)

4
$\phi = 3.5°$
(Ref. 485)

5
$\phi = 11°$
(Ref. 35)

6
$\phi = 14°$
(Ref. 304)

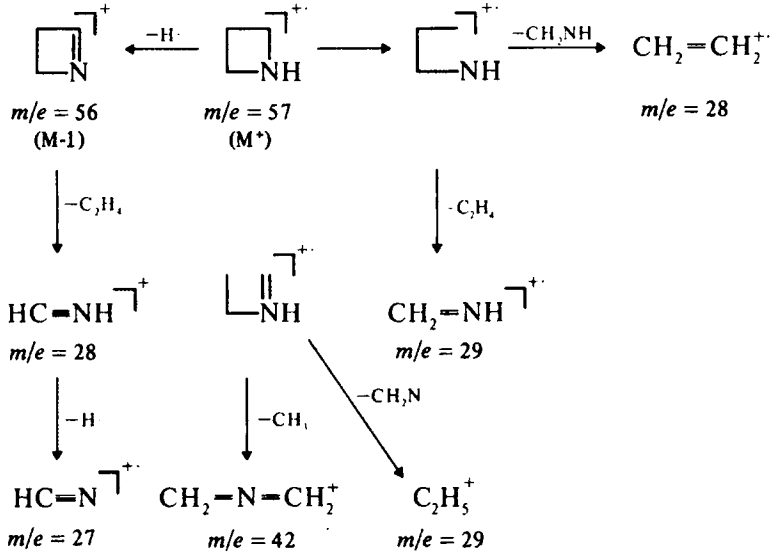
Scheme 1.

As seen from these data, the presence of substituents at the 1,1,3,3-positions imparts a lozenge shape. The only noteworthy bond length is the relatively long $N-C_2$ bond in the 1,1,2,2-tetrasubstituted azetidinium cation, which readily undergoes ring opening on solvolysis (Section V.2). The 1,1-dibenzyl-3,3-dimethyl cation (**3**) has a planar ring, evidently because of minimized 1,3-diaxial repulsions; all the other compounds contain puckered rings, although the angles in the crystal are significantly smaller than that seen in azetidine itself in the gas phase.

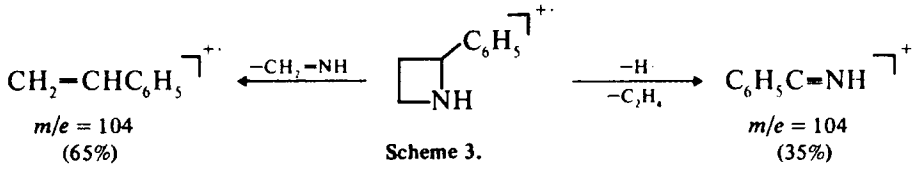
6. Mass Spectra

Electron impact mass spectra have been reported for a number of azetidines, and fragmentation schemes have been worked out with appropriate deuterium labeling for azetidines with several representative substitution patterns.[235] The spectra of the parent azetidine[160] and other secondary azetidines contain M and M-1 peaks. The latter, resulting from α-H loss, is relatively weaker than for the pyrrolidine spectrum, indicating less stabilization in the four-membered rings and suggesting that the open-chain forms contribute significantly to the M and M-1 ions.[259]

The major fragmentation in azetidine is shown in Scheme 2. The base peak ($m/e = 28$) is a doublet, and this is true also in the case of 2-phenylazetidine (Scheme 3).[259] The doublets are presumably due to the slight mass differences between NH and CH_3 masses in the fragments.



Scheme 2.

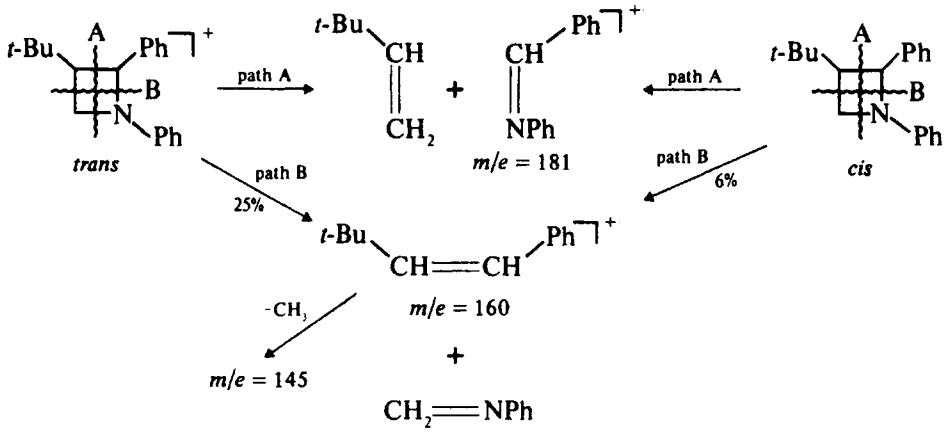


Scheme 3.

The mass spectra of more highly substituted azetidines, including azetidine-3-ols, are dominated by cleavage to an alkene (or enol) and the more stable azomethine cation radical (Scheme 4).[90,235] The relative intensities of the fragment ions differentiate the spectra of geometrical isomers.[235]

7. ESR Spectra

The paramagnetic resonance spectrum of the azetidinyl radical, generated by irradiation of a solution of azetidine and di-*t*-butylperoxide, shows values of $a^N = 13.99$ and $a_\beta^H = 38.25$, with a g value of 2.0045 ± 0.0001. These values are quite similar to those for the aziridinyl radical and indicate that the unpaired electron is in a $2p$ orbital. The splitting a_β^H is quite close to that of the cyclobutyl radical ($a_\beta^A = 36.7$).[101] The radical generated by low-temperature radiolysis of azetidine and larger cyclic imines is said to arise from C−H bond breaking.[447]



Scheme 4.

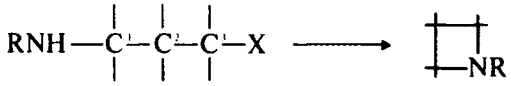
III. SYNTHESIS OF THE AZETIDINE RING

The most important method of azetidine synthesis is cyclization of open-chain compounds, most generally by formation of the C–N bond. A few azetidines have been obtained by cycloaddition methods, and occasionally by rearrangement of larger rings. Another general method for azetidine synthesis is reduction of β-lactams, discussed in Section IV.1.

1. Formation of the N–C_2 Bond

Cyclization of a 3-substituted propylamine provides the most general approach for the preparation of azetidines. Despite several limitations, a large number of simple azetidines and functionally substituted derivatives have been obtained by variations of this method. The most common substrates are γ-haloamines or dihalides and γ-amino alcohols or sulfonates.

Two generalizations can be made regarding cyclization reactions leading to azetidines. In the first place, the rates are slower (and yields frequently lower) than in the corresponding reactions involving the formation of three- or five-membered cyclic imines. These points are borne out by several kinetic studies and comparative data on the preparative efficiency of various methods. The second observation is that the formation of azetidines is quite generally facilitated by the presence of substituents in the chain or by a bulky group (R) on the nitrogen.



Systematic studies on the role of substituents are scanty, and this generalization is based largely on yields of azetidines in a variety of cyclizations. The beneficial effect of substituents, including groups of different types, cannot be attributed to a single steric or conformational factor. The rate enhancement caused by geminal substitution at C_2 of the three-carbon chain (Thorpe–Ingold effect) is due largely to more favorable entropy requirements for the cyclization. However, erythro substituents at C_1 and C_2 of the chain may retard cyclization because of an eclipsing interaction. Both alkoxycarbonyl groups at C_1 and OH at C_2 in the chain appear to strongly enhance cyclization; it seems unlikely that the effects in these cases are due entirely to conformational factors. The importance of a sterically demanding alkyl group on nitrogen has been noted with several leaving groups and is probably due in most instances to suppression of competing intermolecular reactions, although this has not been clearly demonstrated.

A. *Secondary Azetidines*

The cyclization of 3-substituted primary propylamines has found relatively little use in the preparation of simple secondary azetidines. More generally useful methods are reduction of 2-azetidinones with $LiAlH_4$ (Section IV.1) and cyclization to a tertiary azetidine or 1-sulfonyl derivative followed by removal of the substituent on nitrogen (Section IV.2).

In early work the parent azetidine was obtained in yields of 4–25%,[324a] but the purity of these preparations is very doubtful. In more recent literature, 2-bromoethylazetidine has been isolated in high yields as the picrate by cyclization of 3-amino-1,5-dibromopentane.[183] Azetidine-2-carboxylic acid has been obtained from γ-amino-α-bromobutyric acid (cf. Section IV.3).

Cyclizations of *cis*- and *trans*-2-bromomethylcycloalkyl amines to give azetidines fused to five-, six-, and seven-membered cycloalkanes have been studied in detail.[178] The three azetidines with *cis*-fused five-, six-, and seven-membered rings and the *trans*-fused seven-membered ring compound were obtained in high yields. The azetidine with *trans*-fused six-membered rings ($n = 2$) was isolated in very low yield, accompanied by 2-amino-2-methylenecyclohexane as the major product. The *trans*-fused five-membered ring product ($n = 1$) was not observed.



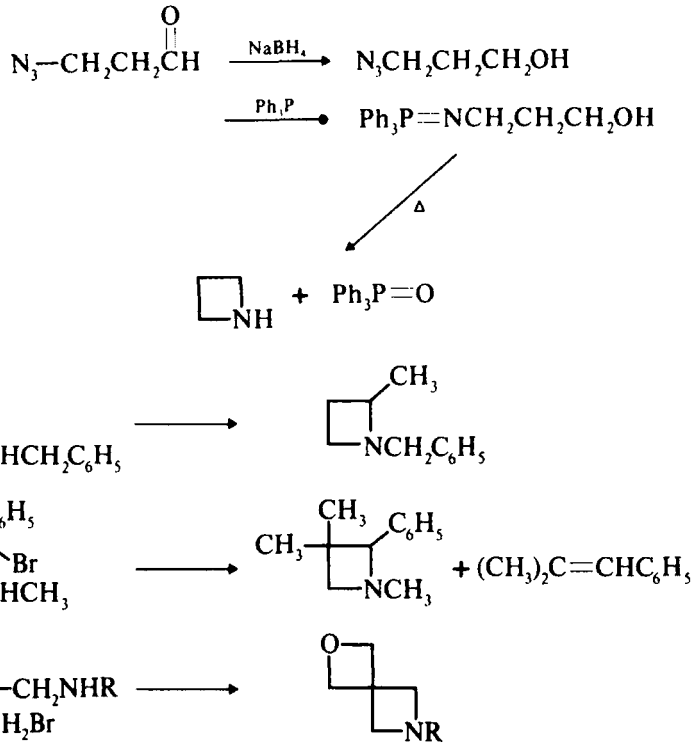
The relative rates of cyclization were *cis*-7 > *cis*-5 > *trans*-7 > *cis*-6 > *trans*-6. An isokinetic plot showed similar transition states for the three *cis*-fused and the *trans*-fused seven-membered ring cyclizations, although the reaction leading to the azetidine with a *cis*-fused five-membered ring had a positive entropy of activation and the other cyclizations had negative entropies.

B. *N-Alkylazetidines*

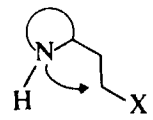
1-Alkyl derivatives of azetidine and simple ring-alkylated azetidines can be obtained by cyclization of 3-alkylaminopropyl halides, alcohols, sulfonates, and also dihalides, although alkylation of azetidines obtained by azetidinone reduction has been more widely used. Many of the simple azetidines prepared by these cyclization methods are described in the earlier literature and have been summarized.[324a]

More recent examples of bromoamine cyclizations are preparations of 1-benzyl-2-methylazetidine[448] and 1,3,3-trimethyl-2-phenylazetidine.[9] In the latter case, fragmentation of the benzylic bromide, leading to β,β-dimethylstyrene, was a side reaction. The *O*-sulfate gave similar results. A number of *N*-alkyl-2-oxa-6-azaspiro[3.3]heptanes and related 3,3-bis(hydroxymethyl)azetidines have been reported from cyclization of bromoamines or reactions of dihalides with primary amines.[308]

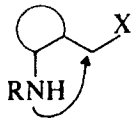
An interesting cyclization method for secondary azetidines begins with the addition of azide ion to acrolein. Reduction to the azido alcohol and reaction with triphenylphosphine lead to the phosphazine which on pyrolysis gives the parent azetidine, contaminated with benzene, in 33% yield.[421a] This method provides a useful alternative to other methods for azetidine which require removal of an *N*-substituent.



The formation of fused bicyclic azetidines by ring closure of cyclic γ-haloamines has been accomplished in three ways; examples of each have been reported:



(Refs. 307, 342)



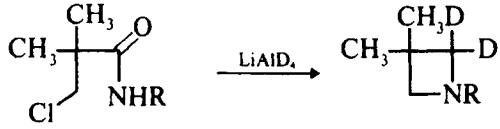
(Ref. 162)



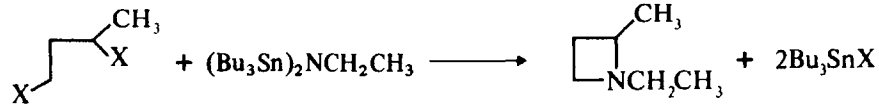
(Ref. 178)

An effective technique used for cyclization of 1-alkylamino-1,1-dialkyl-3-chloropropanes, and probably more widely applicable, is reaction with silver perchlorate, removal of silver chloride, and isolation of the 1,2,2-trisubstituted azetidine as the perchlorate salt. Quaternary azetidinium salts can be obtained by the same procedure from tertiary amines.[472]

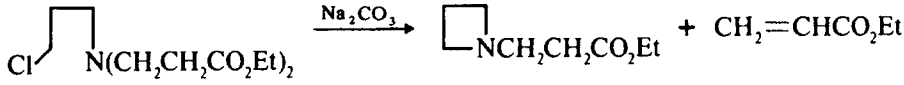
A convenient approach to 1-substituted-3,3-dimethylazetidines is the reduction of β-chloropivalamides with lithium aluminum hydride.[218,219,476] The azetidine is isolated directly after basic hydrolysis of the reaction mixture. Reduction of the *N*-methyl amide with $LiAlD_4$ gave the 2-d_2-azetidine.[476]



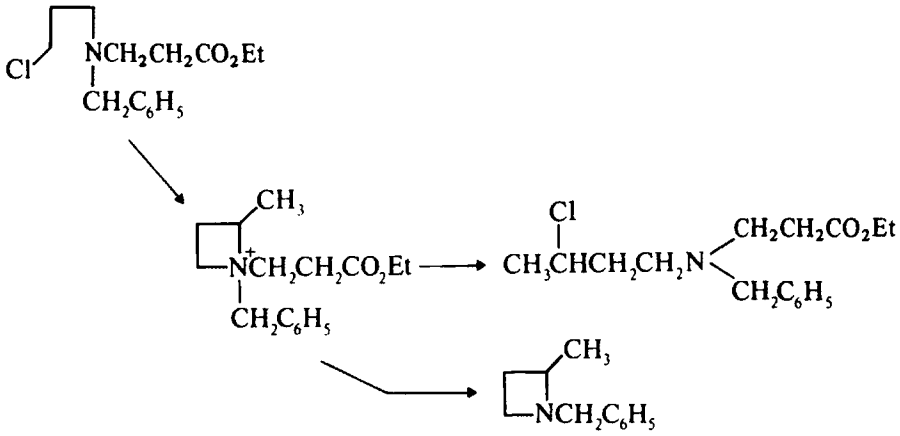
An improved method for cyclization of dihalides is metathesis with *N*-ethylhexabutyldistannazane at 150°C, which gives 1-ethyl-2-methylazetidine in 50–60% yields from either 1,3-dichloro- or 1,3-dibromobutane. The product from 1,3-dibromopropane could not be isolated.[386]



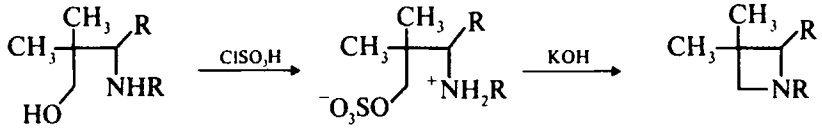
Wadsworth has reported a novel and very useful approach to azetidine synthesis by cyclization of *N*-(γ-chloropropyl)iminodipropionate esters with simultaneous loss of a β-carboethoxyethyl group to give the *N*-(ethoxycarbonylethyl)azetidines in 50–75% yields.[461,462] This method couples the advantage of high efficiency in cyclization to the quaternary azetidinium derivative with the facile β-elimination of the acrylic ester group.



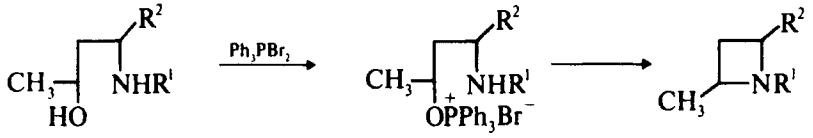
The procedure was applied to the preparation of several ring-alkylated carboethoxyethylazetidines and two *N*-benzylazetidines. The yield of 1-benzyl-2-methylazetidine was very low because of ring opening of the quaternary intermediate to the secondary chloride.



Alkylamino sulfonate or sulfate esters are often more readily accessible than the halides from 2-aminopropanols, and cyclization of these esters has been used in azetidine synthesis with varying success. *N*-Benzylazetidine, with no alkyl groups in the ring, was obtained in 5–10% yields by cyclization of the sulfate ester and in 26% yield from the sulfonate.[455] Anderson and Wills prepared 1-alkyl-3,3-dimethylazetidines and 1,2,4,4-tetramethylazetidine in 60–90% yields from the sulfates.[10,47]



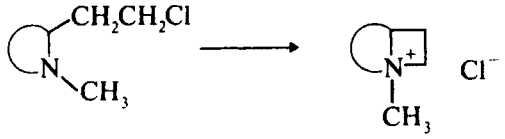
3,3-Dimethylazetidine has been obtained in 37% yield simply by heating the aminopropanol with aqueous sulfuric acid.[203] Another approach that uses the alcohol directly is the one-step reaction of *t*-alkyl- or benzylamino alcohols with triphenylphosphine dibromide followed by triethylamine.[144,167] *N*-Methylazetidines are obtained in 40–60% yields by cyclization of methylamino alcohols with triphenylphosphine, carbon tetrachloride, and triethylamine.[408]



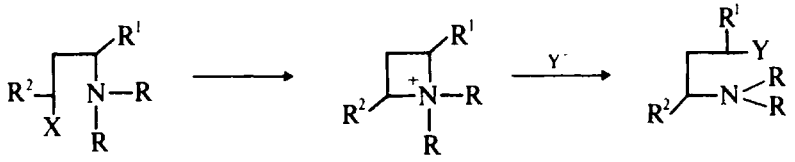
C. *Quaternary Azetidinium Compounds*

Cyclization of a dialkylaminopropyl halide or sulfonate is generally a facile process; examples and limitations have been described in earlier reviews.[324a,442] In the case of γ-dimethylamino-α,α-dimethyl halides, fragmentation of the tertiary

carbenium ion, substitution, and elimination are the major processes; the azetidinium salt is formed to the extent of a few percent.[184] The rates of cyclization of ω-bromoalkyldimethylamines to four-, six-, and seven-membered rings were found to be 5.3, 1130, and 1.7×10^5 sec^{-1}, respectively. These relative rates, which parallel closely those reported for primary bromoalkylamines, diverge greatly from those predicted on the basis of ring strain in the product.[107] The ring closure of 1-alkyl-2-β-chloroethylpyrrolidines and piperidines is usually very rapid; numerous examples have been reported.[121,136,249,307,324,389]



Quaternary azetidinium ions readily undergo ring opening (Section V.2) and are intermediates in reactions of γ-aminopropyl halides with nucleophiles, which may lead to rearranged products. The equilibrium between open-chain precursors and azetidinium salts has been studied with 3-hydroxy derivatives (Section V.2).[153]



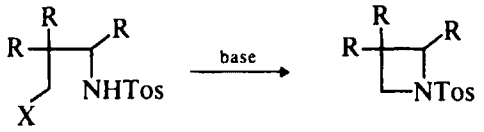
D. *N-Arylazetidines*

N-Phenylazetidine has been prepared in high yield by cyclization of *N*-3-bromopropylaniline with carbonate in very dilute (0.03 *M*) solution.[36] In aqueous ethanolic hydroxide, arylazetidines are obtained in very low yields, together with the allylaniline and γ-ethoxypropylaniline.[102] Knipe and Stirling have compared the kinetics of ω-bromoalkylaniline cyclizations and found the relative rates for three-, four- and six-membered cyclic amines to be 1:0.02:9.5. The slower rate of azetidine formation is attributed to the less favorable enthalpy of activation; the entropy of activation is the same for three- and four-membered amines. *N*-2-Fluorenylazetidine was obtained in 62% yield by reaction of the aromatic amine with 1,3-dibromopropane.[29]

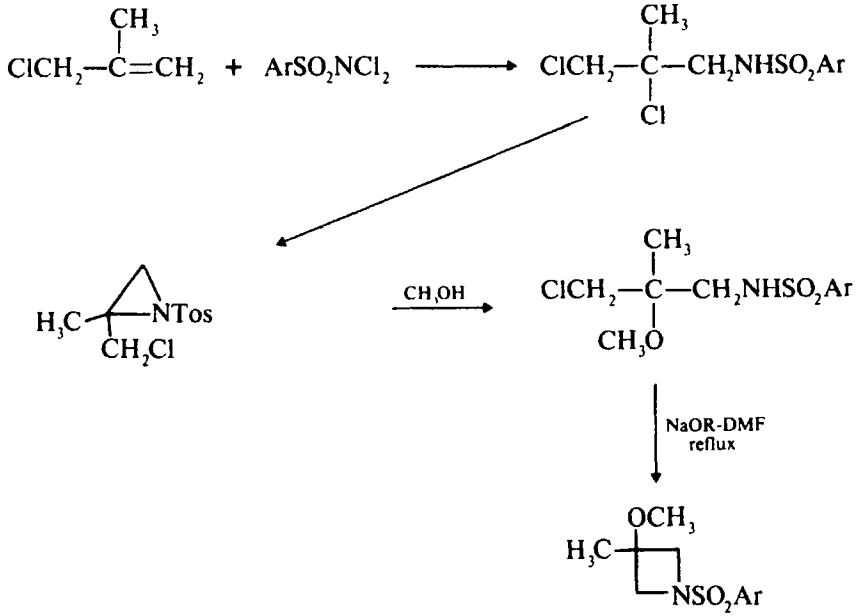
The preparation of *N*-arylazetidines from the arylamino alcohol can be accomplished with 70% sulfuric acid, but the yields are low because of subsequent rearrangement to tetrahydroisoquinolines.[125,166,168] A better method is cyclization with Ph_3PBr_2.[167,444] The reaction of arylaminopropyl phenyl ethers with 1.3 equivalents of aluminum chloride gives azetidines in 20–25% yields together with quinoline by-products.[103]

E. *N-Sulfonylazetidines*

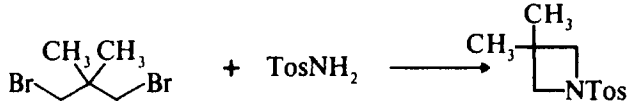
One of the most frequently used methods for azetidine formation is cyclization of a γ-sulfonamidopropyl halide or tosylate. Yields are generally higher than in cyclization of amines, and the *N*-tosyl group can be removed reductively to provide secondary azetidines (Section IV.2.D). 1-Tosylazetidines with 2-bromoethyl[423]



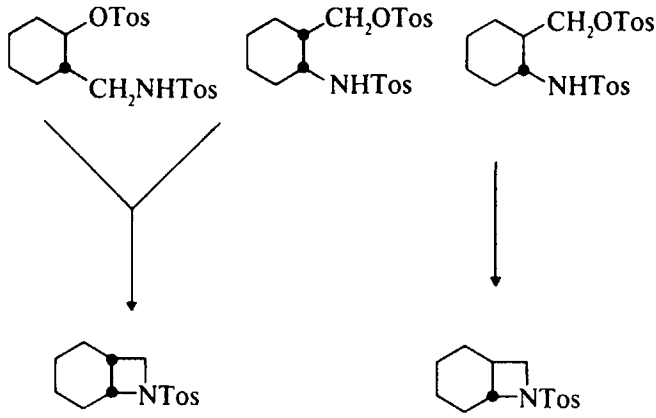
and 2-ethoxycarbonyl[89,313] groups have been prepared by this method. 3-Methoxy-3-methyl-1-sulfonylazetidines are obtained in low yields by cyclization (under vigorous conditions) of the chlorides, which are available via the aziridines.[297]



Direct cyclization of 1,3-dibromopropane with toluenesulfonamide followed by removal of the tosyl group was one of the earliest methods used for the preparation of azetidine.[324a] The care required to remove 1,5-diazocine and other impurities from azetidine prepared in this way has been emphasized.[133] Several applications of this direct cyclization method have been described for 3,3-disubstituted azetidines, including spiro systems.[34]



Tosylamido tosylates, which are readily obtained from aminopropanols, have been widely used as 1-tosylazetidine precursors. This method was developed by Vaughn et al.,[455] who used prolonged refluxing with sodium ethoxide in ethanol for the cyclization to prepare 1-tosylazetidine and the 2-methyl derivative in 80–90% yields. These conditions have been applied to the stereospecific formation of *cis*- and *trans*-2,4-dimethyl-1-tosylazetidines from the *threo*- and *erythro*-tosylamido tosylates, respectively.[145] Moriconi and Mazzochi described both *cis* and *trans* isomers in the 7-azabicyclo[4.2.0]octane series,[336] although later work[178] shows that the method used for the *trans* isomer leads to a stereochemically inhomogeneous product.

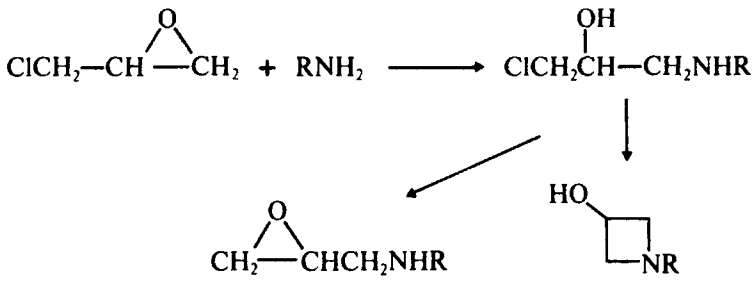


The 2- and 3-(3-pyridyl)azetidine toluenesulfonamides have been obtained in 80–90% yields by cyclization of the tosylates with potassium *t*-butoxide.[397] White and MacGillivray found that the parent toluenesulfonylazetidine can be obtained very conveniently in small scale by ring closure of the tosylate in dilute aqueous KOH.[475]

F. *N-Alkyl-3-azetidinols and azetidinones*

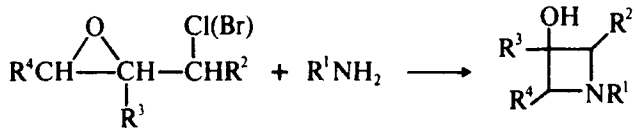
An important advance in azetidine chemistry was the finding of Gaertner that the reaction of bulky primary amines with epichlorohydrin leads to 1-alkylamino-3-chloro-2-propanols,[152,156] which cyclize readily to 3-azetidinols. Dehydrohalogenation of these amines with base leads to epoxyamines, which can be dimerized but do not furnish azetidines.[155] This development opened the way to a large variety of azetidines with functional groups at C_3, as discussed in Section IV.4.

In most examples of this azetidine synthesis, the aminochloropropanols have been cyclized *in situ* without purification. The condensation is usually carried out in polar solvents, such as water,[73] alcohols, DMSO, or DMF, at 20–60°C, but hexane has also been used for the first step.[347] It has been reported that the use of water as a solvent (rather than methanol) accelerates the cyclization to azetidine and reduces the formation of diaminopropanol as a side reaction.[146] The R group



must be of sufficient steric bulk to suppress the intermolecular side reactions.[152] Primary alkyl and benzylamines are not satisfactory, and *t*-alkyl amines have most frequently been used. Benzhydrylamine provides a satisfactory group, which can subsequently be removed by hydrogenolysis to give the *N*-unsubstituted azetidinol.[7,83,209] Cyclization of epichlorohydrin with secondary amines gives 3-hydroxyazetidinium salts directly.[153,382]

Alkyl groups at other positions in the azetidine can be provided by use of other epoxides; epibromohydrins appear to offer no advantage. Cis–trans mixtures are formed when R^2 or $R^4 \neq H$. In the preparation of 2-phenyl-3-azetidinol ($R^4 = Ph$, $R^2 = H$), a much higher yield of the predominant *trans*-azetidinol was obtained directly from the chloromethylbromohydrin precursor than from the preformed epichlorohydrin.[347]

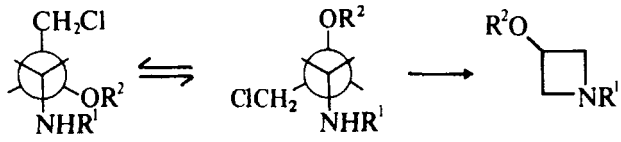


R^2	R^3	R^4	Ref.
CH_3	H	H	152, 156, 436
H	H	C_6H_5	347
H	CH_3	H	209
H	C_6H_5	H	170, 171, 309

The aminochloropropanol intermediates in these reactions have been isolated in some cases,[152] and the cyclization has been carried out in a separate step, although this is generally not advantageous for preparative purposes. In the original procedure, reaction times of several days at 25°C were used for the cyclization.[152] A sequence in which the epichlorohydrin step is carried out in hexane and the crude chloroamine then cyclized by brief refluxing in acetonitrile is stated to give better yields (50–70%) of azetidinols as the hydrochlorides.[347]

The acetate esters of aminochloropropanols ($R^1 = Ac$) undergo cyclization more slowly than the alcohols, the effect being more pronounced with the larger *N*-alkyl group (R = *t*-octyl).[152] Cyclization of 1,3-dihalo-2-methoxymethylpropanes to the *O*-methoxymethylazetidinols ($R^1 = CH_2OCH_3$) is reported by Gaj and Moore to be more efficient with methylamine than with larger amines, although the methyl group is too small to permit azetidinol formation with epichlorohydrin via

the amino alcohol.[159] From these findings, it was suggested that intermolecular reactions occur via conformation A and cyclization occurs via B. The steric bulk necessary to disfavor conformation A can be supplied by either OR^2 or NR^1, with an optimum for cyclization in the combined bulk of both groups.

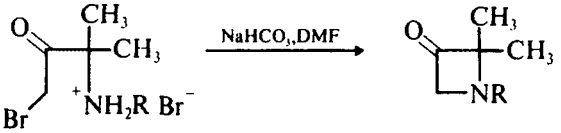


A B

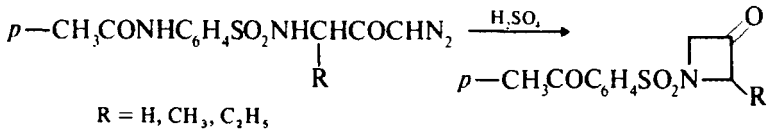
R^1	R^2	Yield (%)
t-Butyl	H	78
t-Octyl	H	68
t-Butyl	$COCH_3$	30
t-Octyl	$COCH_3$	13
CH_3	CH_2OCH_3	40–50
n-Butyl	CH_2OCH_3	23
Benzyl	CH_2OCH_3	13–15
Phenethyl	CH_2OCH_3	4

Conversion of 1,3-dichloro-2-propanol to the benzyloxy or benzhydryl ether, followed by cyclization with methyl- or ethylamine and hydrogenolysis of the bulky ether, is described as a convenient route to the 1-methyl- or 1-ethyl-3-azetidinols.[237]

The preparation of a number of 2,2-dialkyl-3-azetidinones by cyclization of 1-alkylamino-3-bromo ketones has been claimed in patents.[188,189,190,287] The ring closure was carried out at room temperature under nitrogen, and the products were isolated as hydrochlorides. The primary amine was stated to cyclize in the presence of cyanide and DMF to give the 3-cyano-3-dimethylaminoazetidine.



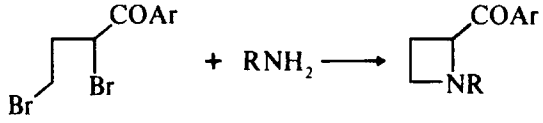
1-Arylsulfonyl-3-azetidinones are produced in 30–70% yields by cyclization of 3-sulfonamido-1-diazoketones with sulfuric acid in chloroform solution.[228a]



G. *N-Alkylazetidine-2-carboxylates and Related Compounds*

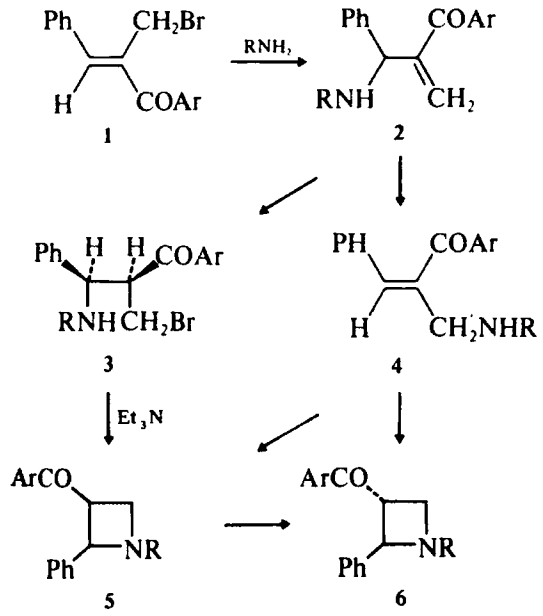
The reaction of α,γ-dibromobutyryl derivatives with primary amines provides a simple and general approach to azetidine-2-carboxylates, nitriles, and ketones, and

thence to azetidines with other functional substituents at C_2. The double alkylation of amines with 1,3-dihalo compounds has not been widely used for other azetidines, but it is a very effective method in this series. As usual, amines with rather bulky alkyl substituents are required. Methyl or benzyl esters are obtained in 35–80% yields.[173,260,266,375,376,380,470] 1-Alkyl-2-aroylazetidines[377,380] and 2-carbonitriles[175] have also been prepared (Section IV.3).



H. *N-Alkyl-2-aryl-3-acylazetidines*

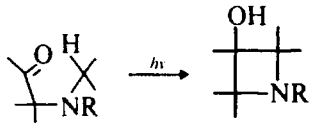
Cromwell and co-workers have obtained a number of 2-aryl-3-acylazetidines by cyclization in their extensive studies of mobile ketoallyl systems.[96,114,119,227] The starting materials are the α-bromomethyl ketones (1), obtained by bromination with NBS. Reaction with amines occurs with rearrangement to give the amino-acrylophenones (2). Addition of HBr occurs stereoselectively to give one racemate of the aroyl γ-bromoamines (3), which is cyclized without isolation to give the *cis*-2-phenyl-3-aroylazetidine (5). The aminoacrylophenones (2) undergo quantitative rearrangement on heating to the aminomethylchalcones (4), which are cyclized by the same sequence to a mixture of the *cis*- and *trans*-azetidines. *Cis* → *trans* isomerization of the azetidines is readily effected in strong base. The synthesis has been extended to 3-acetylazetidines,[118] 2,4-diaryl compounds,[407] and 3-carboxylic esters.[282]



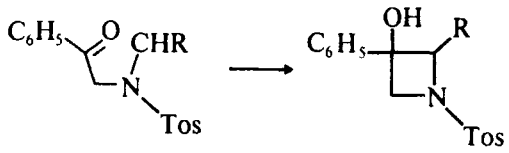
2. Formation of the C_2–C_3 Bond

A. *Photochemical Cyclization*

Practical syntheses of azetidines by closure of a C–C bond are limited essentially to one process, namely photocyclization of ketones containing a suitable N–CH group on the α-carbon to give 3-azetidinols.



The first well-documented examples of this method were reported by Gold,[169,170] who obtained several 1-tosyl-3-phenyl-3-azetidinols in 70–95% yields by irradiation of α-(*N*-alkyl-*N*-tosylamido)acetophenones in ether with a medium pressure mercury lamp. The *N*-ethyl compounds gave a 1:1 mixture of stereoisomers. A lower yield was experienced with the *N*-methyl-*N*-benzoyl ketone and, contrary to an earlier report,[92] no azetidinols were formed from *N,N*-dialkylaminoacetophenones, the only products isolated being acetophenone from a type II cleavage process. The factors governing cleavage vs. cyclization of aminoacetophenones have been discussed.[353]



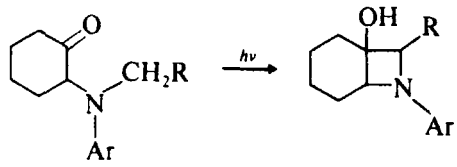
A series of α-*N*-methylanilinomethyl aryl or heteroaryl ketones gave 3-aryl-3-azetidinols in 20–50% yields on irradiation in ether or THF solution.[5a,203a]



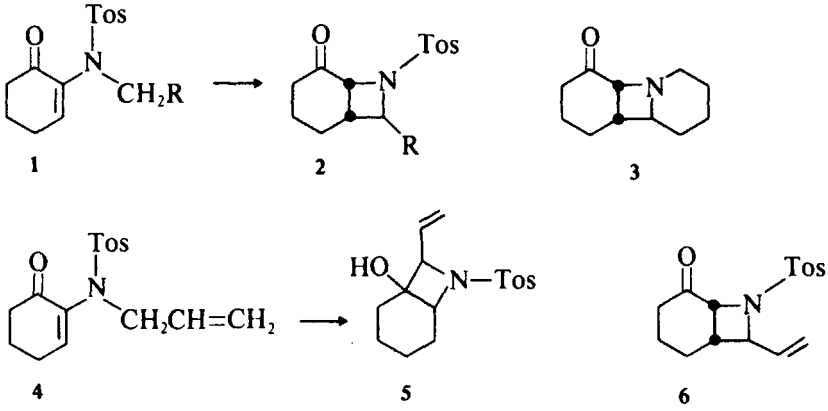
Ar = C_6H_5, *p*=X-C_6H_4, furyl, thienyl, pyrryl thiazolyl
Ar' = C_6H_5, *p*=X-C_6H_4

Hill and Townsend irradiated several *N*-alkylanilinoacetones and obtained in low yields mixtures containing indoles and other products, which were suggested to arise via formation and scission of an intermediate azetidinol.[213,214] In the case of 2-anilinocyclohexanones, bicylic 3-azetidinols were isolated in 40–60% yields.[212]

α-Tosylamidocyclohexenones (**1**) undergo cyclization at the β-position of the enone system to give the *cis*-fused azetidines (**2**) as major products (35–50%); a similar cyclization to (**3**) occurs with α-piperidinocyclohexenone, but not with

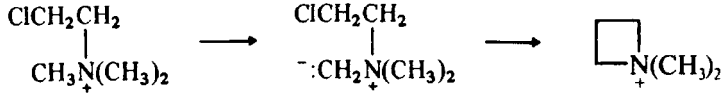


the pyrrolidine or acyclic amino derivatives. The *N*-allyltosylamido enones (**4**) give mixtures of azetidines (**6**) and azetidinols (**5**) arising from both possible cyclization pathways.[15]



B. *Other Methods*

One nonphotochemical example of C_2–C_3 ring closure is the reaction of β-chloroethyltrimethylammonium chloride with potassium *t*-butoxide.[271] The ylid produced by removal of a proton cyclizes to 1,1-dimethylazetidinium chloride in 60% yield.[271]



Formation of an azetidine by closure of a C–C bond has been proposed in the reaction of $CCl_3CH{=}NCO_2Et$ with a Grignard reagent,[242] but evidence for the azetidine structure is inadequate. Cyclization of iminodiacetic acid with acetic anhydride followed by hydrolysis of the enol acetate is claimed to give *N*-acetyl-3-azetidinone, but no structural evidence is available.[25]

3. Cycloaddition

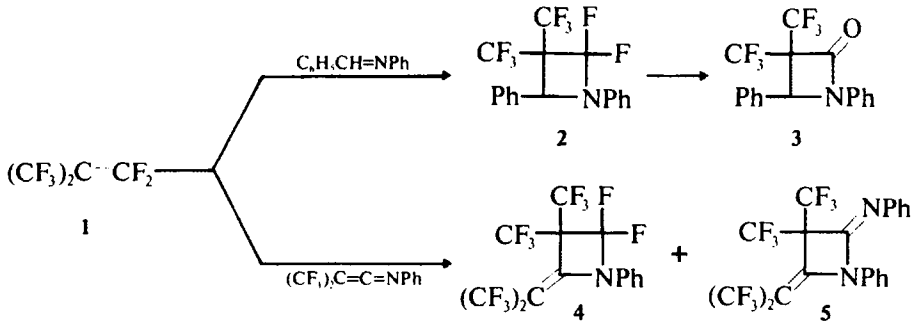
Cycloaddition leading to azetidines can be grouped into three general types: ground state or nonphotochemical [2+2] cycloaddition, photochemical [2+2]

additions, and [1+3] or [1+1+2] cycloaddition or insertion processes. These groupings are somewhat arbitrary, but they provide a convenient way to subdivide the material.

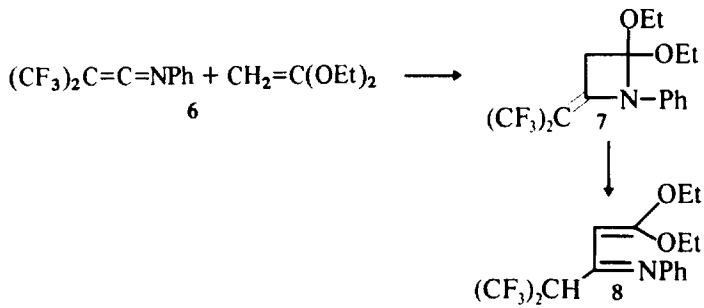
A. *Thermal [2+2] Cycloaddition*

Whereas cycloadditions of isocyanates and alkenes or imines with ketenes are general and important routes to azetidinones (thanks to the high reactivity of a heterocumulene in each case), the corresponding cycloaddition of alkenes with imines to form an azetidine occurs only in the presence of substituents that impart a high degree of polarization. For this reason, examples of azetidines prepared by ground state [2+2] additions are limited to a few rather special types.

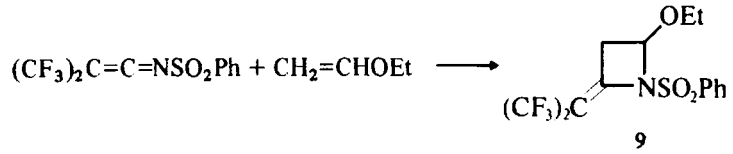
Russian workers have described several cycloadditions of perfluoroisobutylene (**1**) leading to 2,2-difluoro-3,3-bis(trifluoromethyl)azetidines. This perfluoroalkene, unlike tetrafluoroethylene, does not undergo diradical cycloadditions, but reaction with nucleophiles, including imines, are facilitated by the strongly electron-withdrawing CF_3 groups. With benzalaniline at 200°C, cycloaddition leads to the 2,2-difluoroazetidine (**2**), which can be hydrolyzed in acid to the azetidinone (**3**).[389] Cycloaddition with the *N*-methyl imine occurs by a [4+2] process to give a six-membered ring. With *N*-phenylbis(trifluoromethyl)ketenimine, azetidine **4** and the ketenimine dimer **5** are obtained.[106,487]



The ketenimine **6** adds to the C=N bond of ketene acetals.[104] The diethoxy azetidine **7** is thermally labile and undergoes ring opening via the 2-azetine to **8**.

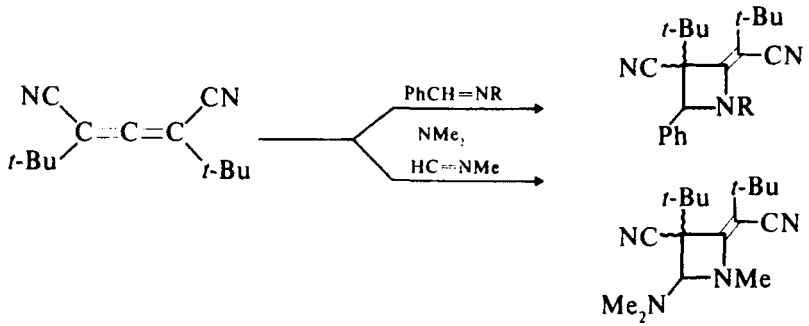


The more reactive *N*-sulfonylketenimine adds to ethyl vinyl ether to give the 2-ethoxyazetidine **9** in 60% yield.

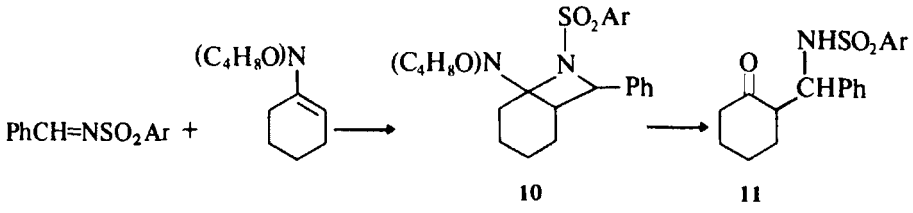


9

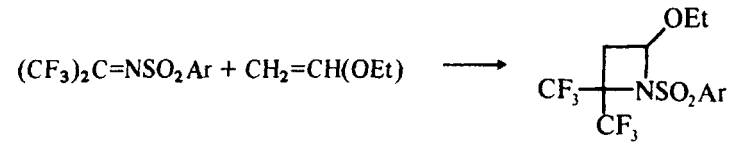
Several azetidines have been obtained by cycloaddition of an electrophilic allene to either imines or 1,1,3-trisubstituted formamidines.[394a]



N-Sulfonyl imines also undergo cycloaddition with nucleophilic alkenes to give 2-substituted azetidines. 1-Morpholinocyclohexene with *N*-sulfonylbenzaldimines gives the 2-aminoazetidines (**10**), which are easily hydrolyzed to the sulfonamido ketones (**11**).[123] Hexafluoroacetonesulfonylimine adds to ethyl vinyl ether to give the 2-ethoxyazetidine **12**.[486]



10 **11**



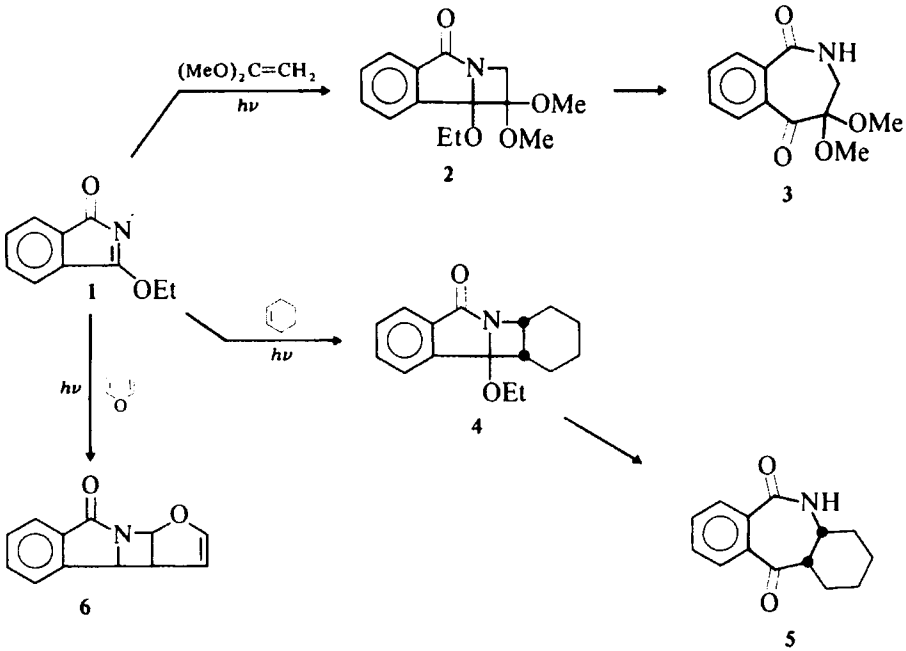
12

Another type of electrophilic imine capable of cycloadditions to produce azetidines is the *N*-(trifluoromethylthio)chlorotricyano vinyl system. Reactions with styrene or enol ethers at 25°C give adducts that can be cleaved to the secondary azetidines by treatment with pyridine or other nucleophiles.[194]

B. *Photochemical [2+2] Cycloaddition*

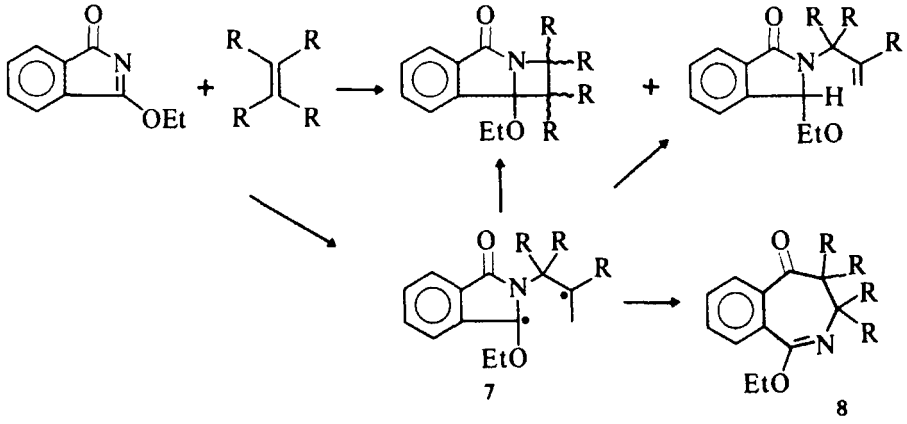
Although photochemical cycloadditions involving C=C and C=O bonds are general and useful processes leading to cyclobutanes and oxetanes, the corresponding cycloadditions of C=N bonds to give azetidines are much less common. The first well-documented examples of alkene additions with cyclic conjugated C=N bonds were reported in 1972 by Koch and co-workers[254,255] and Hyatt and Swenton.[223] Most of the subsequent work has been done by these two groups; the reaction has recently been reviewed.[251]

The most extensively studied system is 3-ethoxyisoindolone **1**, prepared by alkylation of phthalimide. Irradiation of **1** with ketene acetal or cyclohexene gave the fused azetidines **2** and **4**, respectively, in 50% yields. Hydrolysis of these adducts gave the benzazepinediones **3** and **5**. The reaction product with furan was assigned structure **6** on the basis of nmr chemical shifts only.

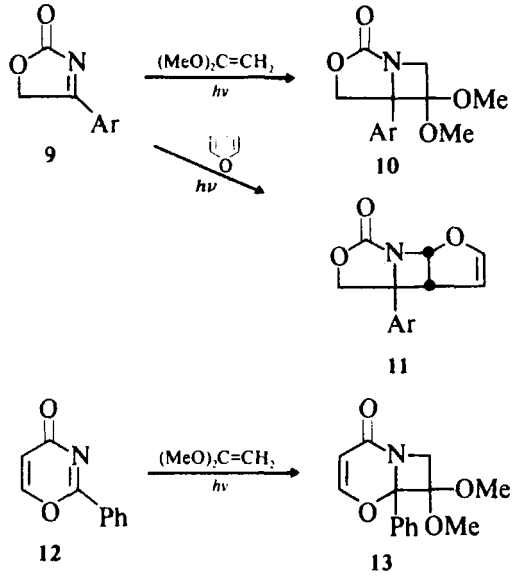


With isobutene and *cis*- and *trans*-butenes, the cycloadducts with **1** were accompanied by major amounts of ene products. The azetidines were formed as mixtures of stereoisomers. A minor product in the addition of tetramethylethylene was the benzazepinone **8**. Detailed photochemical kinetic studies[12] suggest the participation of two triplet exciplexes in these reactions, with the ene products and cycloadducts arising by different pathways. The diradical **7** is proposed as a late intermediate in the formation of the stereochemically random products.

Other systems that undergo photochemical cycloaddition are the 2-aryl-4-oxazolinone **9** and the oxazinone **12**. Fused azetidines **10** and **11** were obtained

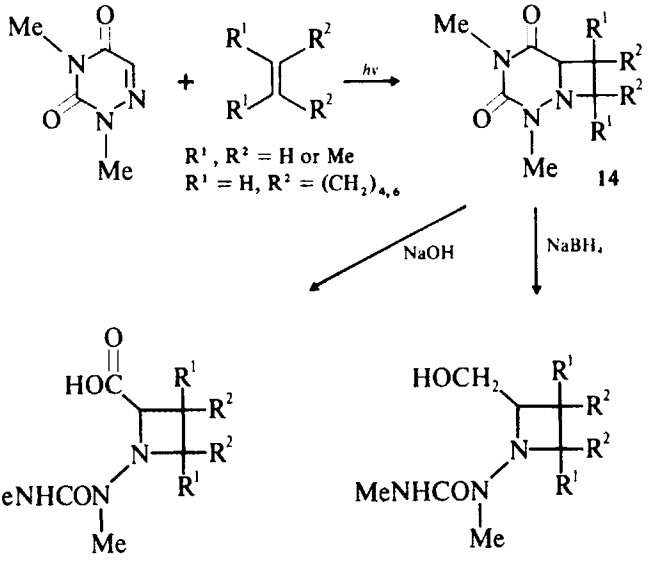


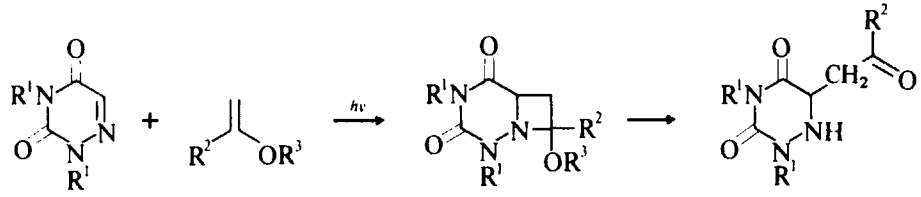
from **9** with dimethylketene acetal and furan, respectively. Other olefins that gave cycloaddition products with **1** did not give azetidines with **9**.[381] The oxazine, on irradiation with ketene acetal, gave the adduct **13**.[253]



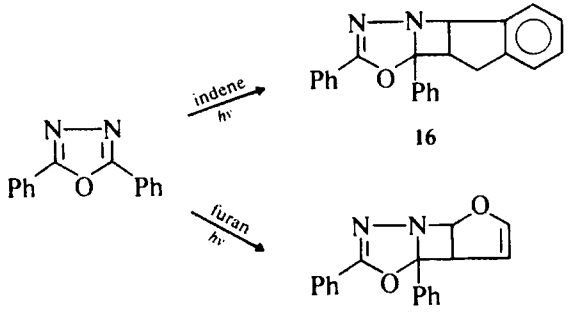
Swenton and Hyatt have obtained several bicyclic azetidines **14** in high yields by acetone-sensitized irradiation of 1,3-dimethyl-6-azauracil with alkenes or enol esters or ethers. Two of these adducts were converted by mild hydrolytic or reductive cleavage of the urea function to 1-aminoazetidines.[418]

Cycloaddition of 6-azauracil or the 1,3-dimethyl derivative with enol ethers and enol esters gives the epimeric bicyclic adducts **15** with only traces of regioisomers. Hyrolysis of these products with water provides a simple route to 5-substituted-6-aza-5,6-dihydrouracils, which can be oxidized with bromine to the azauracils.[417,418]

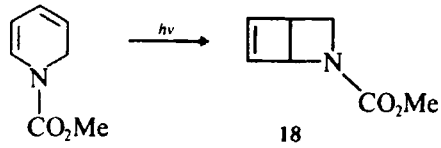




Tricyclic products **16** and **17**, containing an azetidine ring, have been isolated in low yield from the photochemical cycloaddition of 2,4-diphenyl-1,3,4-oxadiazole with indene[450] and with furan,[449] respectively.



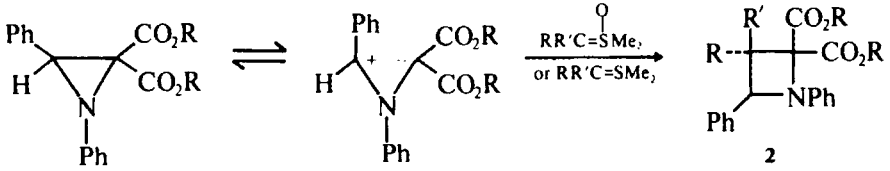
Internal cycloaddition (valence isomerization) of 1-methoxycarbonyl-1,2-dihydropyridine gave the bicyclic azetidine **18** in 95% yield.[143]



18

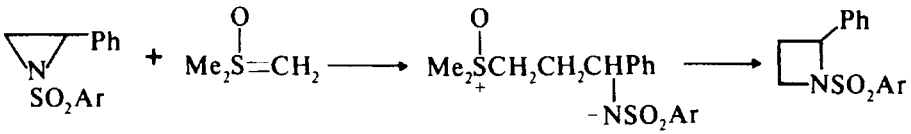
C. [3+1] *Cycloaddition*

A few examples of [3+1] cycloadditions that provide useful routes to certain types of highly substituted azetidines have been developed. Vaultier et al. have explored the reactions of sulfur ylids with azomethine ylids generated from aziridines or oxazolines.[457,458] With aziridines (**1**) these reactions, which take place at room temperature, lead to 1,4-diphenyl-2,2-bis(alkoxycarbonyl)azetidines (**2**) in which C_3 bears the substituents of the sulfur ylid. With the monosubstituted sulfur ylids (R^1 = H), the major product (95:5 — 80:20) is the azetidine with C_3 and C_4 substituents *trans*; this was shown to be the result of kinetic control. Cycloaddition of the azomethine ylid or the lithium enolate with bromomalonate anion also leads to azetidines.[456]

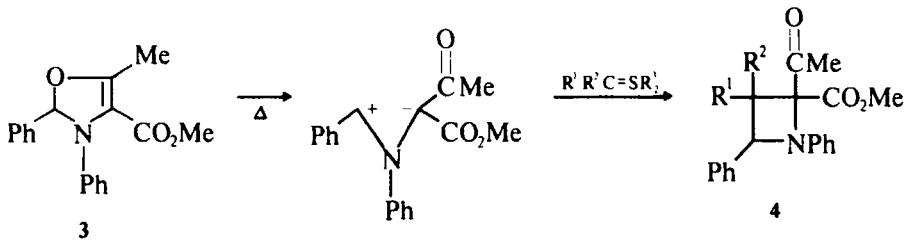


1 2

The reaction of dimethylsulfoxonium methylid with 1-benzenesulfonyl-2-phenylaziridines also gives the azetidines in 50–70% yields.[338a] The reaction in this case presumably involves nucleophilic attack on the aziridine rather than addition to the intermediate azomethine ylid.

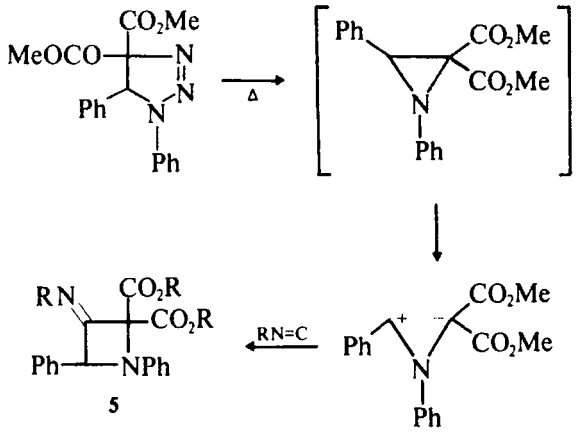


Reactions of the S-ylids with oxazoline **3** at 80° give the 2-acetylazetidines **4**.

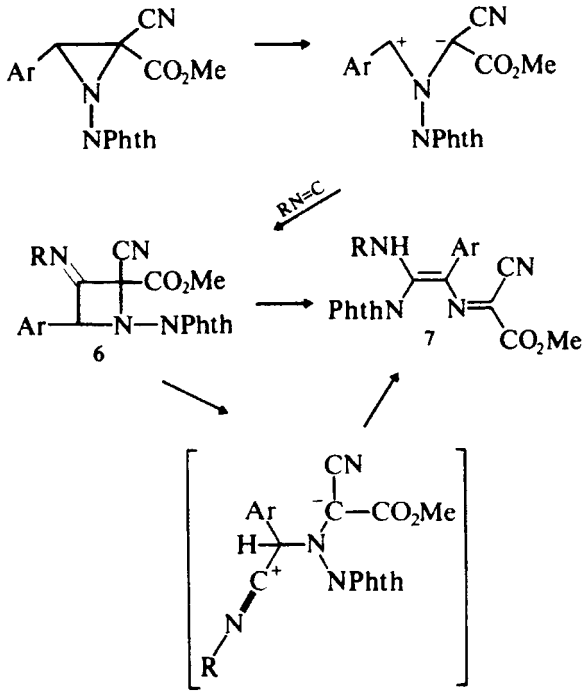


3 4

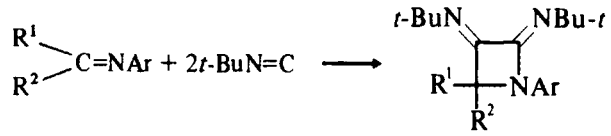
Another type of [3+1] cycloaddition leading to the azetidine ring is observed in the reaction of azomethine ylids with isocyanides. The ylid in this case was generated by thermolysis of a triazoline in boiling toluene in the presence of isocyanides. The 3-iminoazetidines **5** were isolated in 70–90% yields.[57]



Azomethine ylids arising from thermal ring opening of 1-phthalimidoaziridines also undergo cycloaddition with isocyanides to give 3-iminoazetidines (**6**) in 40–50% yields.[81] The imines derived from *t*-butyl or *t*-octyl isocyanides underwent ring opening and rearrangement to the azabutadienes **7**.

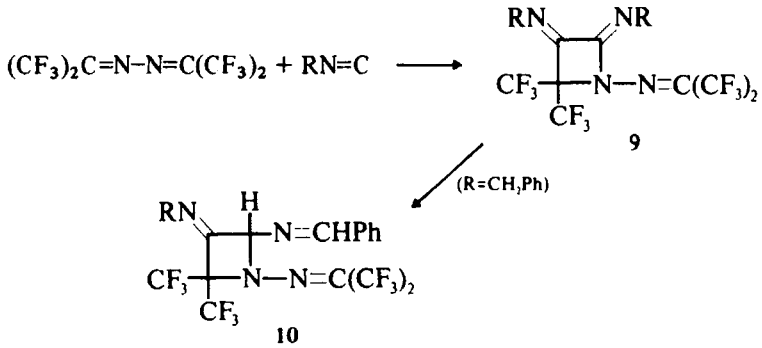


The insertion of two moles of *t*-butyl isocyanide into an azomethine bond leads to 2,3-bis(*t*-butylimino)azetidines (**8**). These reactions are acid catalyzed; indoles resulting from condensation with one mole of isocyanide are by-products in some cases.[113]



R^1, R^2 = Ar, H or CH_3, CH_3 **8**

A similar [2+1+1] cycloaddition occurs with isocyanides and hexafluoroacetone azine at −30°C to give the 1-amino-2,3-bis(alkyl or arylimino)-4,4-bis(trifluoromethyl)azetidines (**9**).[60] With benzyl isocyanide, the initial adduct tautomerized to the amidine **10**.



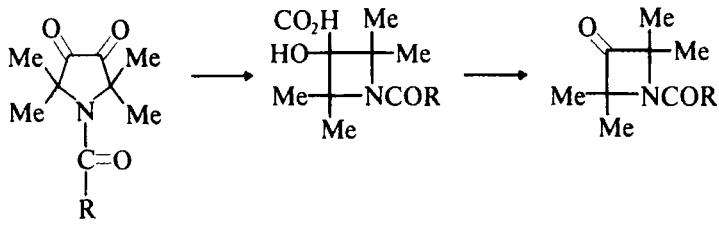
9

10

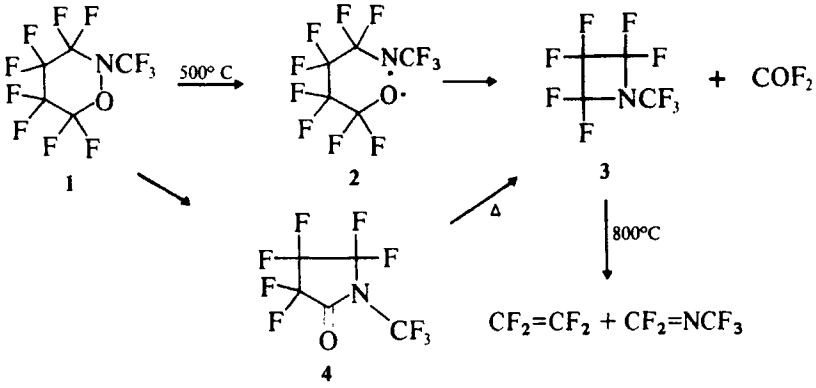
4. Formation of Azetidines from Other Ring Systems

Azetidines have been obtained from a variety of reactions starting with five- or six-membered rings; these ring contractions provide the most useful or the only practical route for a few azetidines.

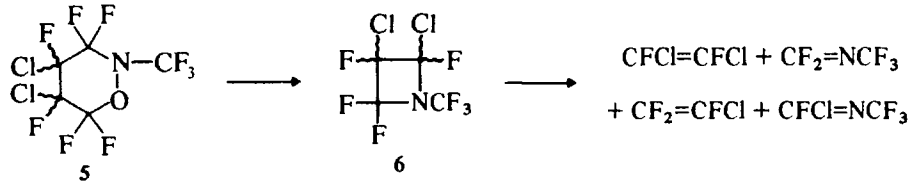
2,2,4,4-Tetramethylazetidines, which are not accessible by ring-closure methods or from β-lactams, have been obtained via Wolff rearrangement of the 1-acetyl-4-diazopyrrolidin-3-one[88,390] or by rearrangement of the 1-benzoylpyrrolidinedione in 20% KOH.[100] The hydroxy acids are cleaved with lead tetraacetate to the 3-azetidinone. Wolff–Kishner reduction gave the 1-benzoylazetidine.



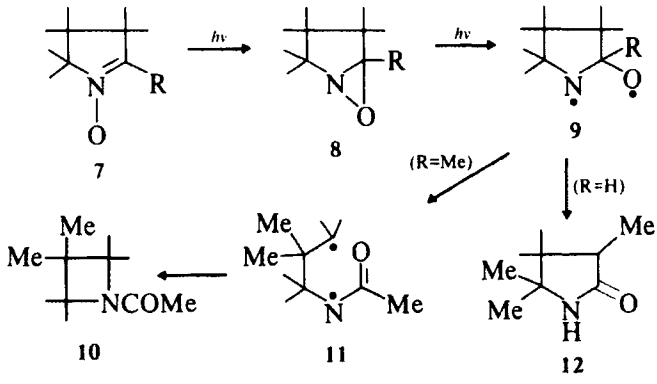
Perfluoro-1-methylazetidine (3) can be prepared in 70% yield by thermolysis of the oxazine 1 at 480–500°C.[27] Carbonyl difluoride, but not CO, is a by-product, indicating that 3 arises from 1 by fragmentation of the diradical 2 and not via the pyrrolidinone 4, although the pyrrolidinone can be obtained from 1 under other conditions and also gives 3 at 500°C. The azetidine 3 is remarkably stable but breaks down at 800°C to perfluoroethylene and the perfluoroazomethine.



Similar chemistry has been described for the 4,5-dichloroperfluoro-1,2-oxazine 5, which can be pyrolyzed to a mixture of *cis*- and *trans*-2,3-dichloroperfluoro-1-methylazetidine (6). Fragmentation of the azetidine gives equal amounts of products from both modes of cleavage.[26]

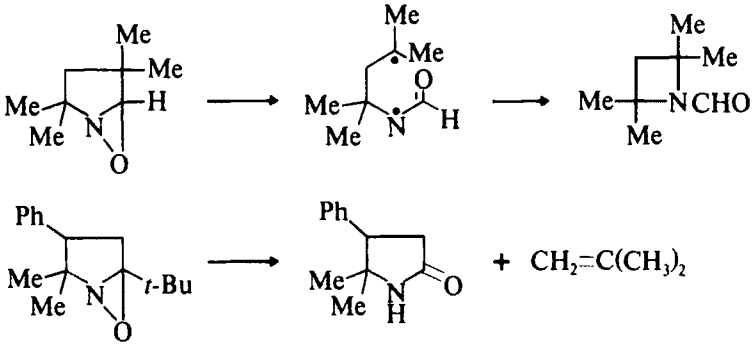


Photochemical rearrangement of cyclic nitrones (7) or oxaziridines (8) leads to acyl azetidines, pyrrolidinones, or other products, depending on the substitution at C_2 and C_3 in 7. The diradicals 9 and 11 are presumably intermediates. Kaminsky

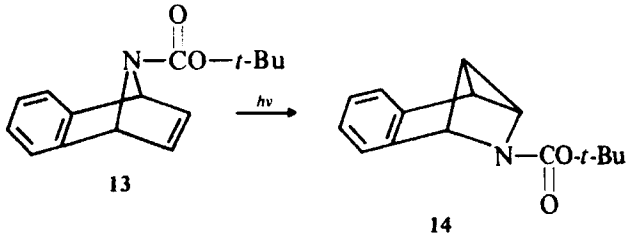


and Lamchen obtained 1-acetyl-3,3-dimethylazetidine (**10**) in 70% yield from the 2,4,4-trimethylpyrroline-1-oxide. With the 3,5,5-trimethyl system, hydrogen shift from C_2 leads to the pyrrolidinone (**12**).[240] Several other acetylazetidines have been reported without yield data.[405]

With two CH_3 groups at C_3, the tertiary radical is formed in preference to a hydrogen shift, and the 1-formyltetramethylazetidine is obtained.[40] However, with a 2-*t*-butyl group, a *t*-butyl radical is lost, and pyrrolidinone is again observed. 2-Cyanopyrrolin-1-oxides rearrange on photolysis to cyanoformylazetidines.[38]



Azetidine products have been found in two other photochemical reactions. Vapor phase photolysis of *N*-methylpyrrolidinone gives 1-methylazetidine (6% yield) with extensive polymer formation.[302,303] The acetone-sensitized irradiation of the 7-azabenzonorcaradiene carboxylate (**13**) leads, by way of several diradicals, to the extremely acid-sensitive caged azetidine **14**.[384]



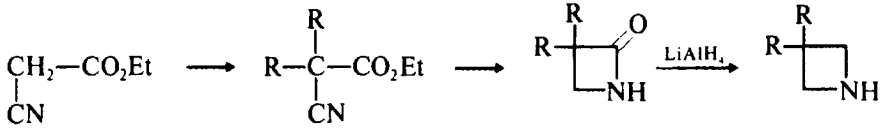
13 14

IV. INTRODUCTION AND TRANSFORMATION OF SUBSTITUENTS

Azetidines with a variety of functional groups can be obtained by cyclization methods, as described in Section III, but many others are best prepared by introduction or transformation of groups on the ring, including the ring nitrogen. These syntheses, as well as other reactions in which the ring remains intact, are discussed in this section.

1. Reduction of 2-Azetidinones and Malonimides

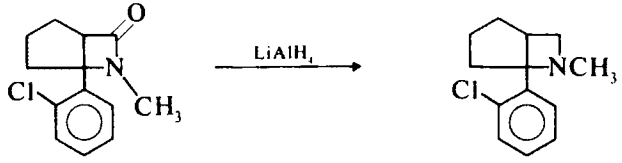
One of the most useful methods for preparing secondary azetidines with alkyl or aryl groups at C_2 and/or C_3 is reduction of *N*-unsubstituted azetidinones or malonimides with $LiAlH_4$ or diborane. The $LiAlH_4$ reaction was first described in 1959 by Testa and co-workers[434] and was frequently used in the extensive work on azetidines by the Lepetit group in the early 1960s.[41,65,429,430,433,437,438] The 3-mono- and disubstituted azetidinones used in most of these and other cases[37] were obtained by alkylation and reduction of α-cyano esters, followed by cyclization with Grignard reagent. Yields in the reduction are usually in the range of 50–60% for 3-monosubstituted azetidines and 70–80% for 3,3-disubstituted derivatives.



4-Substituted and 4,4-disubstituted azetidinones are also converted to azetidines in useful yield, but ring opening to the amino alcohol occurs to a small extent.[430] The $LiAlH_4$ reduction step has been applied to the preparation of bicyclic azetidines, the azetidinones being available from chlorosulfonyl isocyanate addition to a cycloalkene.[357,358]



With a single exception, the reduction of azetidinones to azetidines is strictly limited to compounds with an unsubstituted nitrogen; *N*-alkyl or *N*-aryl groups generally direct the course of the reduction to the ring-opened alcohol. A good yield of the tertiary azetidine was obtained, however, on reduction of an aryl bicyclic azetidinone.[359a]



Diborane has been used as an alternative to $LiAlH_4$;[473] again, ring opening occurs with *N*-substituted azetidinones.

2. Substituents at N_1

Azetidine and ring-substituted azetidines with a free NH position undergo all of the usual reactions of secondary amines, and a wide variety of resulting 1-substituted

azetidines have been reported. Most cyclization methods for preparing azetidines lead to products containing a fairly bulky *sec-* or *tert*-alkyl group or a sulfonyl group at N_1. Removal of the latter is a common step, and several methods for accomplishing this have been developed. On the other hand, only *N*-unsubstituted azetidines are obtained by the reduction of β-lactams, and *N*-substituents must be introduced in a subsequent step.

A. *N-Alkylation*

Introduction of a simple alkyl group at N_1 can be accomplished by direct alkylation with a halide or sulfonate or by one of several types of reductive alkylation. Some inferences on the relative merits of various methods can be obtained from the extensive work of Testa and collaborators on the preparation of *N*-substituted azetidines with alkyl and aryl groups at C_2 and/or C_3.[442]

Alkylation of 3-phenylazetidine with benzyl and cinnamyl chlorides gives 60–65% yields of the tertiary amines; yields are very poor with secondary or branched halides.[441] The reaction of 3-azetidinol with ethyl iodide and α-phenylethyl tosylate gives the *N*-alkyl compounds in 6 and 60% yields, respectively.[347] Alkylation with 1-bromoadamantane at 250°C was reported in unspecified yield.[171]

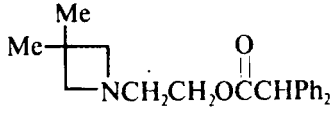
The most frequently used method for *N*-methylation of azetidines is the Clarke–Eschweiler reaction with formaldehyde–formic acid.[37,170,336,397,433,440] Reductive alkylation with other aldehydes by catalytic hydrogenation has been used to introduce higher alkyl groups.[34]

Another type of reductive alkylation is effected by adding a solution of the secondary azetidine and an ester to a refluxing solution of $LiAlH_4$.[400] *N*-Ethylazetidines are obtained with ethyl acetate in 70–90% yields,[426,429,440] and this appears to be a convenient and satisfactory method, although polymeric products were obtained in the case of 3-phenylazetidine-3-methanol.[433] *N*-Butyl, -benzyl, and -cinnamyl derivatives have been obtained with the corresponding esters in somewhat lower yields.[440,441]

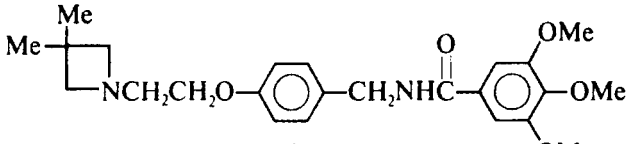
The most general and widely used approach for introducing *N*-alkyl groups is hydride reduction of the *N*-acylazetidine. This method has been used by Testa et al. to alkylate a variety of 2- and 3-substituted azetidines.[426,430,433,440,441,442] The yields in the reduction step are generally somewhat higher than in the direct alkylation procedures.

Azetidines containing functionally substituted *N*-alkyl groups have been obtained by reactions with epoxides; Mannich condensation; alkylation with haloketones, -esters, -nitriles, etc.; and electrophilic olefins.[442] The reaction of 3,3-disubstituted azetidines with ethylene oxide gives 1-(β-hydroxyethyl) derivatives in 50–60% yields.[430,440] 2,2,4,4-Tetramethylazetidine has been converted to 1-(3-aralkoxy-2-hydroxy)propyl derivatives by heating and 3-aralkoxy-1,2-epoxypropanes.[360] β-Chloroethylazetidines can be prepared by reaction of the alcohols with thionyl chloride.[435] Several 1-azetidinylethyl ethers and esters

(illustrated by **1** and **2**), which are analogous to analgesic, spasmolytic, and antiemetic drugs containing the corresponding dialkylaminoethyl structure, have been obtained from the alcohols or chlorides for pharmacological comparison.[435,439]

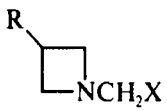


1

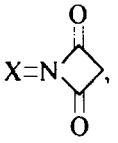


2

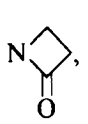
Mannich condensation of azetidines has been carried out with formaldehyde and several types of nucleophiles to give derivatives of the general structure **3**.



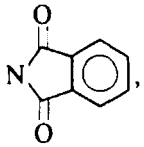
3



(Ref. 427)



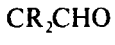
(Ref. 427)



(Ref. 430)

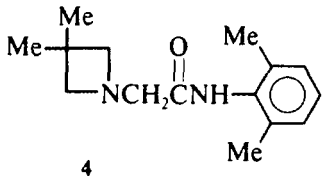


(Refs. 429, 430)

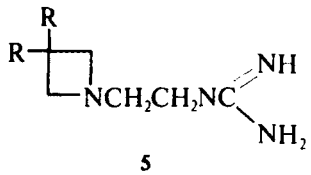


(Ref. 439)

Azetidines have been alkylated with phenacyl chlorides[34,439] and with α-chloroacetamides and chloroacetanilides.[34,130,435] The lidocaine analog **4** has a higher analgesic potency than the diethylaminoacetoxylidide (lidocaine).[442] Alkylation of 3,3-disubstituted azetidines with chloroacetonitrile followed by reduction and reaction with *S*-methylisothiourea leads to the guanidines **5**, which are devoid of the hypotensive activity reported for analogous pyrrolidines.[33,479] Azetidinoethyl and -propyl derivatives of chlorophenothiazine have been prepared.[236,435]

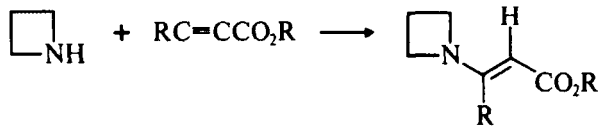


4

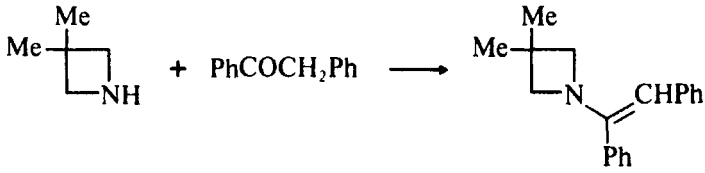


5

The addition of azetidine to acrylic esters and acrylonitrile provides a route to β-(1-azetidino)propionates and propionitriles.[84,86,315,463] The yields of the latter are somewhat better with 3,3-diethylazetidines.[84] The reaction of azetidine with methyl propiolate or dimethyl acetylenedicarboxylate in aprotic solvents gives only the *cis* addition products, with some *trans* addition occurring in methanol, as observed with acyclic *sec*-amines (but not aziridines).

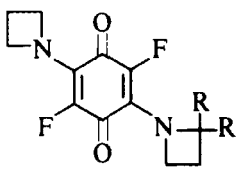


Azetidine condenses with acetoacetic ester and acetyl acetone to give the enaminocarbonyl derivatives. Enamines are obtained in very low yields with cyclopentanone and cyclohexanone.[86] The reaction of 3,3-dimethylazetidine with deoxybenzoin gave the enamine in 95% yield after 16 days' refluxing; with 3,3,4,4-tetramethyl pyrrolidine, the addition required only 22 hours.[203]

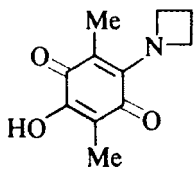


B. *N-Arylation*

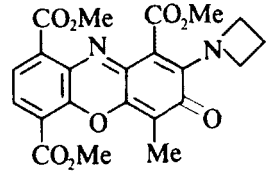
Nucleophilic substitution with azetidine has been accomplished with several halonitrobenzenes.[102] Reactions were carried out at 50°C in a sealed tube in a large excess of azetidine, and yields ranged from 40 to 95%. An *ortho-* or *para*-nitro group is required for activation. In the reactions of a series of cyclic imines with *p*-fluoronitrobenzene, the order of nucleophilicity parallels the basicity; the rate with azetidine is about twice that of pyrrolidine and 300-fold faster than with aziridine.[133] A few *N*-arylazetidines have also been obtained by addition of azetidines to haloquinones.



(Ref. 465)



(Ref. 32)

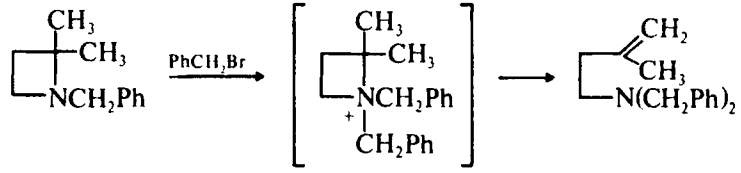


(Ref. 466)

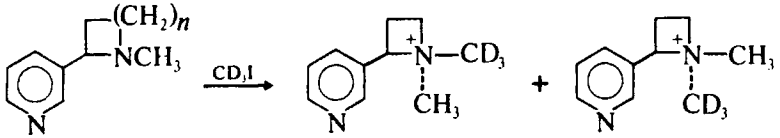
C. *Quaternization*

Alkylation of a tertiary azetidine with methyl iodide or benzyl bromide has been carried out on numerous occasions, and the quaternary halides are generally isolated in high yields. Attempted quaternization of 1-(2-carbethoxyethyl)azetidine with *n*-butyl tosylate without solvent gave only polymeric products.[461] A series of methiodides of 1,3-dialkylazetidines were obtained in 40–70% yields as hygroscopic

solids;[435,441] these products were probably stereoisomeric mixtures. 1,2,2-Trimethyl- and 1-benzyl-3,3-dimethylazetidine can be alkylated with benzyl bromide, but a quaternary halide could not be obtained from 1-benzyl-2,2-dimethylazetidine because of the rapid Hofmann elimination brought about by unreacted tertiary amine.[281]

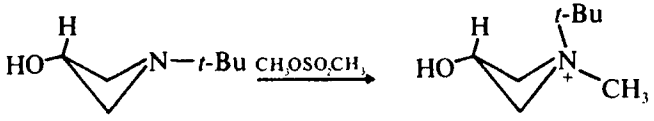


Seeman et al. have studied the quaternization of 1-methyl-2-(3-pyridyl)azetidine (**1**, $n = 1$) and the five-, six-, and seven-membered ring homologs with CH_3I, CD_3I, and $^{13}CH_3I$. The relative rates for the series decreased in order of ring size ($4 > 5 > 6 > 7$); the azetidine ($n = 1$) reacted about six times faster than nicotine ($n = 2$), as indicated by the selectivity for attack at the imine nitrogen. The *cis*-CD_3 isomer predominated in the mixture of azetidine methiodides, suggesting a larger steric requirement for the CH_3 group in the starting imine than for CD_3I in the transition state.[399]



1 *cis* *trans*

Methylation of 1-*t*-butyl-3-azetidinol with methyl methanesulfonate results in stereospecific formation of the quaternary mesylate with hydroxyl and methyl groups cis (established by crystallography). This isomer presumably arises by reaction of the azetidine in the preferred conformation **2**.[304]



2

D. *Removal of Groups at N_1*

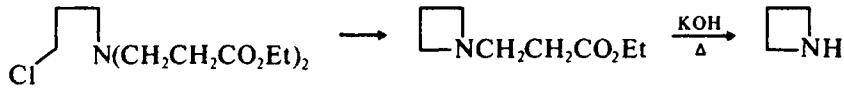
In several synthetic sequences for ring-substituted secondary azetidines, benzyl or benzhydryl groups have been employed to control the cyclization of a γ-aminopropyl halide or sulfate (Section III.1), with catalytic hydrogenolysis of the *N*-blocking group as the final step. Benzyl and α-methylbenzyl groups can be removed by hydrogenation with palladium on charcoal.[34,170,455] Removal of a benzoyl group has been accomplished by reduction with $LiAlH_4$ followed by hydrogenolysis.[100,416] Benzhydryl groups have been used in syntheses of azetidin-3-ol and azetidine-2- and azetidine-3-carboxylic acids; the preferred catalyst in this

case is 20% $Pd(OH)_2$ on charcoal.[7,83,361,376] Methylation of a 1-benzhydrylazetidine followed by hydrogenolysis of the quaternary iodide has been used to prepare an *N*-methylazetidine unavailable by direct cyclization.[380]

A standard route to secondary azetidines is cyclization to an *N*-sulfonyl derivative followed by removal of the sulfonyl group. The oldest and one of the most widely used methods is reduction with sodium in boiling alcohol, usually pentanol.[145,336,455] Sodium in liquid ammonia was used in the preparation of azetidine-2-carboxylic acid from the sulfonamide,[313] but this reagent cleaves the azetidine ring in the presence of a 2-aryl substituent.[397] In more recent work, the radical anion sodium naphthalenide has been found to be a superior reagent for cleavage of the tosyl group. The parent azetidine is conveniently obtained as a 1 *M* solution in diglyme in 70% yield.[475] Secor and Edwards have used sodium naphthalenide in glyme at $-60°C$ in the presence of *t*-butyl alcohol as a proton source to avoid decomposition of the amide anion formed in the reduction.[397]

Detosylation has been effected in rather low yields by $LiAlH_4$,[310,455] and this reagent has also been used for the simultaneous cleavage of the *N*-chlorosulfonyl group and lactam reduction to obtain the secondary azetidine directly from the adduct of chlorosulfonyl isocyanate and 1,2-dihydronaphthalene.[336] Sodium bis(2-methoxyethoxy)aluminum hydride cleaved the tosyl group in a 3-methoxymethyl-3-phenylazetidine in 70% yield.[174] Although electrochemical reduction of a tosyl group has not been reported for azetidines, this would most likely provide a suitable method.[293]

One of the most efficient methods for obtaining secondary azetidines involves removal of the *N*-(β-ethoxycarbonylethyl) group. The tertiary azetidines, obtained by cyclization of γ-chloroalkyliminodipropionates (Section III.1), are heated under carefully controlled conditions with KOH at 200–250°C.[461] The parent azetidine is obtained in 80–87% yields.[462]



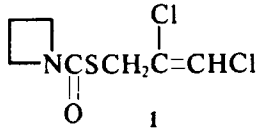
Removal of an *N*-allyl group has been accomplished by heating the *N*-allylazetidine with potassium *tert*-butoxide in DMSO.[34]

E. *N-Acylation and Carbamylation*

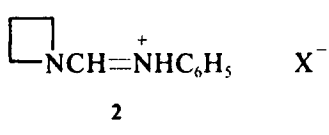
1-Acylazetidines have been obtained from a number of 2- and 3-substituted azetidines by Testa et al. by treatment with the acid chlorides and triethylamine (60–80% yield) or by refluxing with anhydrides (40–70%).[440,441] Better yields could probably be obtained under milder reaction conditions. Bisazetidines are obtained with adipoyl chloride.[440] A series of 1-aroyl derivatives was prepared in 50–70% yields by reaction of a 1 *M* solution of azetidine in diglyme with the acid chloride and triethylamine.[475] Trifluoroacetyl, methoxalyl, formyl, and ethoxycarbonyl derivatives of azetidine have been described.[404] Several 1-chloroacetylazetidines have been prepared and converted to the thiocyanates

with KCNS.[373] Thiobenzoylazetidine is obtained in 84% yield with *S*-(thiobenzoyl)-thioglycolic acid.[234]

Alkoxycarbonyl derivatives have been prepared from several azetidines by Testa et al.[440,441] with ethyl chloroformate. 1-Phenoxycarbonylazetidine was obtained with phenyl chloroformate by interfacial acylation.[233] Reaction of 2,3,3-trimethylazetidine with carbon oxysulfide, followed by *S*-alkylation, gave the thiolcarbamate **1**, which is effective as an herbicide.[132] The formamidine **2** was prepared by conversion of *N*-formylazetidine with $POCl_3$ to the imido chloride and treatment with aniline.[93]



1



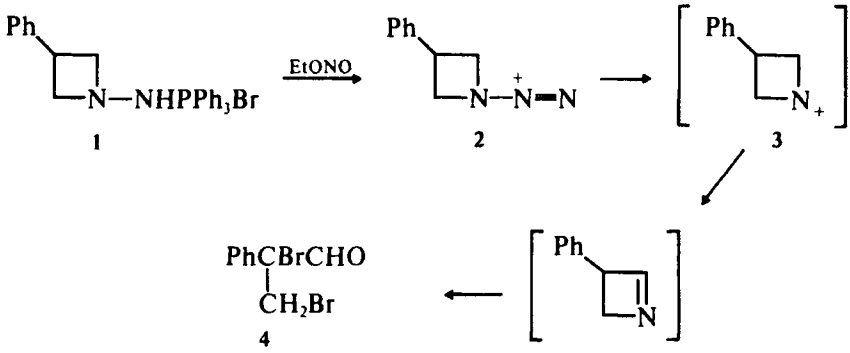
2

1-Carbamylazetidines have been obtained by treatment of azetidine, 2- or 3-monosubstituted, and 3,3-disubstituted azetidines with sodium cyanate and hydrochloric acid, but these derivatives could not be prepared from 2,2-disubstituted azetidines.[430] Reaction with phenyl isocyanate is general for all substituted azetidines studied. *N*-Arenesulfonyl derivatives of 2,2-dimethylazetidine, prepared with sulfonyl isocyanates, are effective hypoglycemic agents.[24]

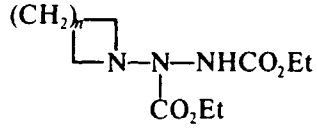
F. *Nitrogen Substituents at N_1*

N-Aminoazetidines are obtained by reduction of the nitroso compounds with $LiAlH_4$[145,374,435,441] or by direct amination of the azetidine with hydroxylamine-*O*-sulfonic acid.[245] These hydrazines have been converted to *N*-*p*-nitrobenzylidene derivatives[441] and to arylsulfonyl semicarbazides with sulfonyl isocyanates.[145]

1-Amino-3-phenylazetidine and several related 1-amino cyclic imines react with triphenylphosphine dibromide to give crystalline phosphonium bromides (**1**), which are converted by nitrous acid to azidonium intermediates (**2**). In the case of three- and five-membered rings, subsequent reactions lead to azide products. The less stable azetidine derivative, however, loses nitrogen to give polymeric products and a low yield of the aldehyde **4**, presumably via the nitrenium species **3**.[243]

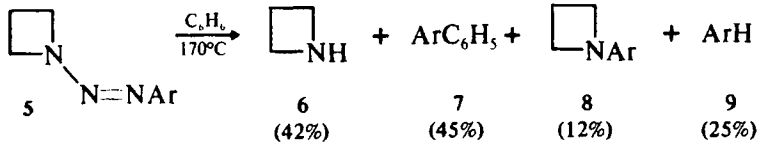


Stable triazane derivatives have been obtained by addition of azetidine and other cyclic imines to diethyl azodicarboxylate.[288]



$n = 2, 3, 4, 5$

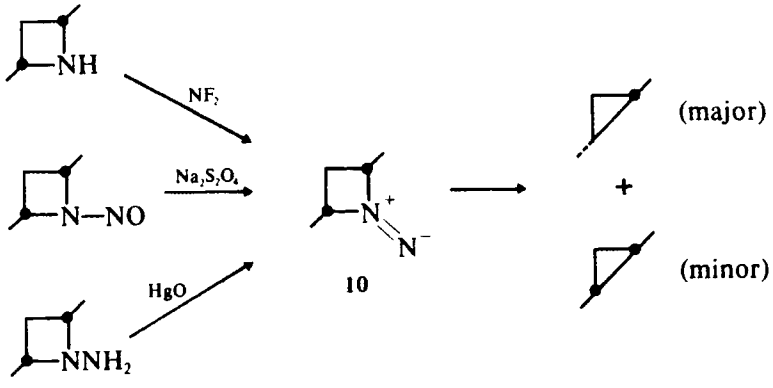
N-Arylazoazetidines (**5**), prepared by azo coupling of azetidine at pH 6, decompose on heating in benzene in a sealed tube to give products **6–9** (characteristic of homolytic dissociation), and no cyclopropane or azide, which may result from a concerted pericyclic reaction. The latter process is observed with *N*-arylazoaziridines. The contrasting behavior was attributed to the smaller amount of *p* character in the sigma bonds of the azetidine.[5]



5	6	7	8	9
	(42%)	(45%)	(12%)	(25%)

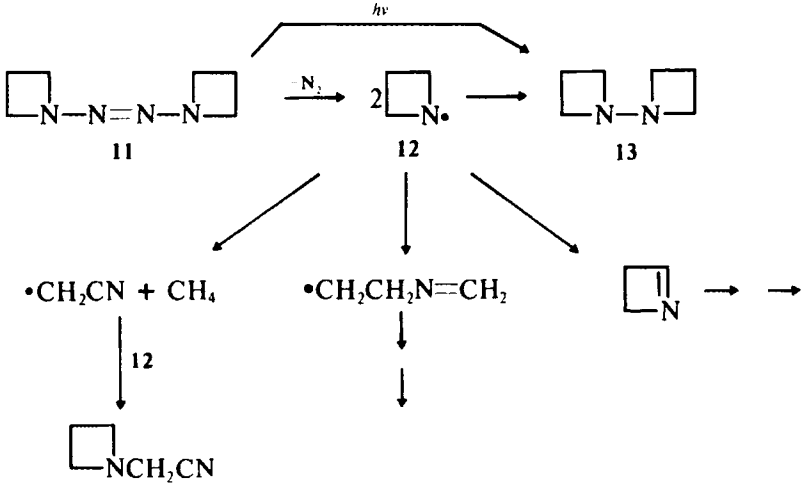
N-Nitroso derivatives have been obtained from azetidine and a number of its C-substituted analogs. The nitrosamine of 2-phenylazetidine could not be isolated.[429] *N*-nitrosoazetidine is a potent carcinogen;[285] unlike other *N*-nitrosamines, administration of *N*-nitrosoazetidine to rats leads to alkylation of DNA and RNA bases in the liver.[286] Oxidation of *N*-nitrosoazetidine with trifluoroperacetic acid gives *N*-nitroazetidine in 47% yield.[54] Treatment of *N*-nitrosoazetidine with lithium diethylamide followed by electrophiles permits introduction of functional substituents at C_2.[398]

Trimethylenediazene intermediates (**10**) can be generated from azetidines in several ways, and lead to cyclopropanes without formation of olefinic products. Reaction of azetidine with difluoroamine gives cyclopropane in 40% yield.[53] Deamination of *cis*-2,4-dimethylazetidine with NF_2, reduction of the nitroso derivative with alkaline dithionite, and oxidation of the hydrazine with mercuric



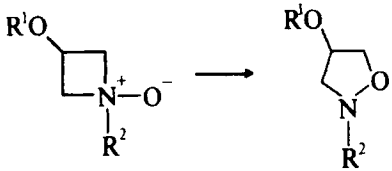
oxide – all give mixtures of *trans*- and *cis*-dimethylcyclopropane in a 5:1 ratio. The *trans*-dimethylazetidines gave *cis*- and *trans*-dimethylcyclopropanes in about a 2:1 ratio. The stereochemical results are similar to those observed in pyrolysis of the dimethyl-Δ^1-pyrazolines, and are explained in terms of a disrotatory linear expulsion of nitrogen to give a trimethylene diradical.[145]

Mild oxidation of 1-aminoazetidine with iodine gives a 21% yield of bis(trimethylene)tetrazene (**11**).[245] Photolysis converts the tetrazene to 1,1′-biazetidinyl (**13**) in low yield. Pyrolysis of the tetrazene in the gas phase at 300°C leads to a complex mixture of products which arise by formation and decomposition of the 1-azetidyl radical **12**.[244] The major compound isolated was 1-azetidineacetonitrile (39%); other products included the homologous cyanoethyl- and cyanopropylazetidines, *N*-ethylazetidine, and hydrocarbons. The formation of these products presumably involves several competing fragmentation pathways of 1-azetidyl; methane was observed by mass spectrometry.[244]

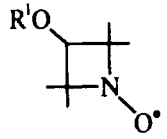


G. *Oxygen Substituents at N_1*

The preparation of 1-hydroxy- and 1-alkoxyazetidine-2-carboxylates by cyclization of the 2,4-dibromobutyrate esters with hydroxylamine or alkoxyamines has been reported by Kostyanovskii and Prosyanik.[261] Tertiary azetidine-*N*-oxides have been obtained from the 1-substituted azetidine and *m*-chloroperbenzoic acid[305] or hydrogen peroxide.[424] 3-Hydroxy-, 3-halo-, and 3- or 4-alkoxy-*N*-oxides have been converted to 2,4- and 2,5-disubstituted isoxazolidines by the thermal Polonovsky rearrangement.[416,424]

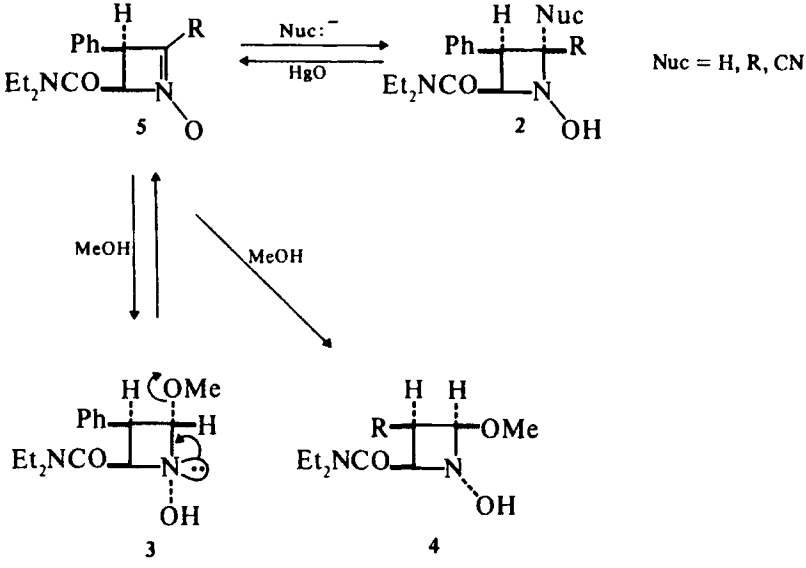


3-Hydroxy-2,2,4,4-tetramethylazetidine and the 3-benzoate ester can be oxidized in the presence of phosphotungstic acid to the stable nitroxyls **1**.[416] These derivatives are superior to five- and six-membered nitroxyls for spin labeling because of the small, rigid ring and shorter distance between the free electron and the labeled substrate. Nitroxyls can also be obtained by chloroperbenzoic acid oxidation of the 2,2,4,4-tetrasubstituted azetidine, even with terminal double bonds in the 2-alkyl chains.[126]



1

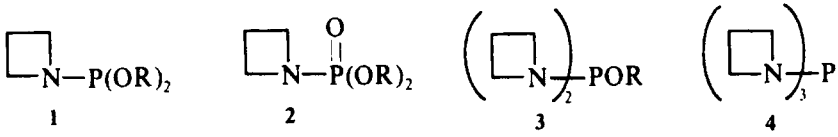
2-Substituted-1-hydroxyazetidines (**2**) are readily obtained by addition of hydride, cyanide, Grignard reagents or methoxide to the highly substituted azetine-1-oxides (**5**) (Section VII.1).[360c] The addition of hydroxide to **5** leads to ring-opened products (Section VII.1). In methanol the 2-methoxyazetidine (**3**), derived by methanol addition from the less hindered side of the ring, is obtained by brief reaction in alkaline methanol, but the more congested epimer (**4**) is obtained on longer reaction time. The lability of the presumably more stable isomer (**3**) is suggested to be due to *anti*-elimination with the unshared electron pair on nitrogen, while the stability of **4** arises because of the high energy barrier to inversion of the electron pair, estimated as 16 kcal/mole in the 1-hydroxyazetidine. Oxidation of the hydroxyazetidines (**2**) with HgO yields the nitrones.



3 **4**

H. *Substitution at N_1 with Other Elements*

Grechkin has prepared a number of azetidine phosphonamides and phosphoramides (**1–4**) by standard reactions with the corresponding phosphonyl halides or esters.[180,181,182]



1 **2** **3** **4**

1-Silyl derivatives of azetidine have been obtained by transamination with $(CH_3)_3SiNH_2$[419] or reaction with SiH_3Br.[164] The trimethylsilyl group is removed in the usual way by reaction with water, alcohols, or amines; acetic anhydride gives 1-acetylazetidines.[341]

Titanium derivatives of azetidine (**5** and **6**) have been prepared by reactions with $(Et_2N)_3TiBr$ and $(Me_2N)_4Ti$.[51,52] The thermal stability in each case was lower than that of the corresponding derivatives of aziridine or pyrrolidine.

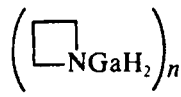


5 **6**

Dimethylaluminum, -gallium, and -indium compounds of cyclic imines have been synthesized and their properties compared by Storr, Thomas, and Penland.[409] The aziridine derivatives exist as trimers, whereas the compounds from five- and six-membered imines are dimeric because of the greater steric requirement. The degree of association of the azetidine dimethylaluminum derivative indicated a temperature-dependent equilibrium composition of the dimer **7** and trimer **8** that shifts toward the entropically favored dimer at higher temperatures. Similar studies have been reported also on the gallium hydride **9**.[410]



7 **8**



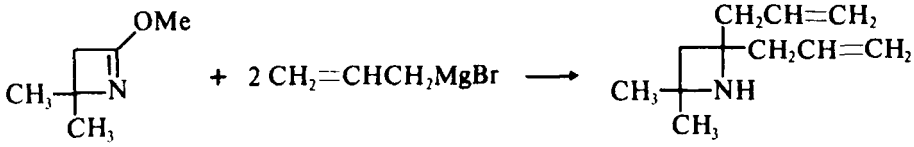
9

3. Substituents at C_2

Azetidines with substituents at C_2 have been obtained by cyclization methods (Section III) and also by introduction and interconversion of groups at the azetidine C_2-position. The primary products of ring-closure methods include 2-carboxylic acids, esters, nitriles, and ketones. In this section the interconversions and reactions of these compounds and methods for introduction of various groups at the 2-position are summarized.

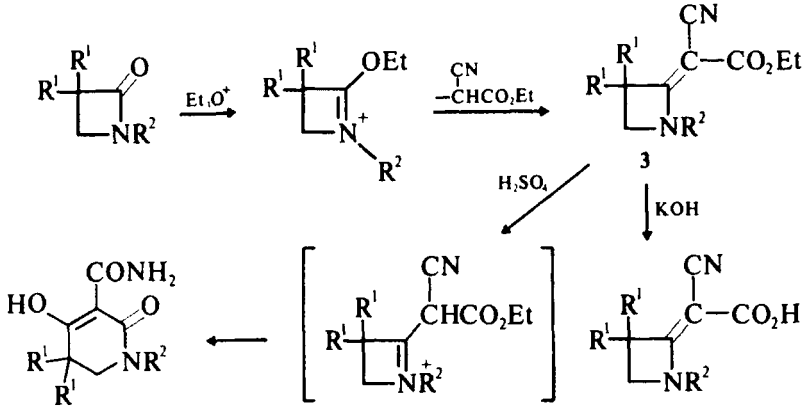
A. *2-Alkyl- and 2-Alkylideneazetidines*

The introduction of alkyl and alkylidene groups at C_2 can be accomplished by utilizing the electrophilic properties of 2-methoxyazetines (Section VII.2). Addition of allylmagnesium bromide to the imino ether **1** gives a 40% yield of the 2,2,4,4-tetrasubstituted azetidine **2**, which is inaccessible by ring-closure methods.[126]



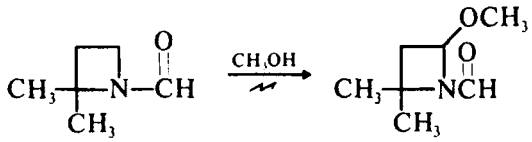
1 **2**

1-Alkyl-2-alkylideneazetidines (**3**) are available by condensation of 2-ethoxyazetinium salts (obtained by alkylation of β-lactams; Section VII) with the sodium salts of ethyl cyanoacetate or malononitriles.[364] These enamines are stable, neutral compounds ($pK_a < 1.5$), the esters undergoing hydrolysis in alkali to the cyano acids. A *cis* orientation of the CN and C_3 was inferred from the facts that the nitrile resists acid-catalyzed alcoholysis and that condensation of the azetinium salts fails with diethyl sodiomalonate. In sulfuric acid at 100°C, the alkylidene azetidines undergo ring expansion and hydrolysis to give the enolized 3-carbamoylpiperidinediones **4** in high yield.[365]

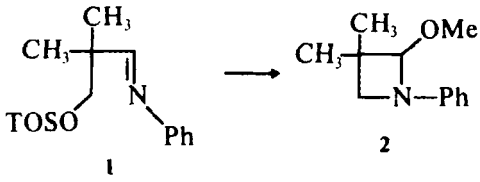


B. *2-Alkoxyazetidines*

The direct introduction of a functional group at the 2-position can be accomplished by electrolytic alkoxylation of 1-acylazetidines. Thus 1-formyl-2-methoxy-4,4-dimethylazetidine is obtained in 50% yield by electrolysis of the azetidine in methanol solution with tetramethylammonium fluoborate as the conducting salt.[311,312] Presumably, the method is generally applicable for 2-alkoxyazetidines; yields and current efficiencies are much higher in the α-alkoxylation of 1-acylpyrrolidines and piperidines.

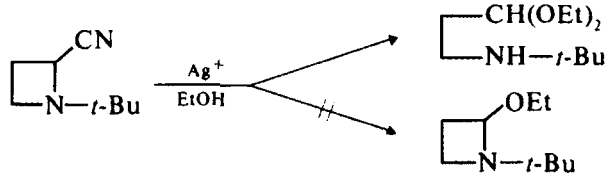


Formation of the 2-methoxyazetidine **2** in trace amounts by cyclization of the anil **1** with potassium methoxide has been reported.[343] Attempts to detect a



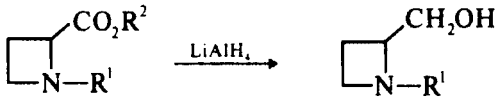
1 **2**

2-alkoxyazetidine in the reaction of a 2-cyanoazetidine with silver ion in ethanol were unsuccessful and led only to the β-amino acetal.[299]



C. *Azetidine-2-alkanols and -amines*

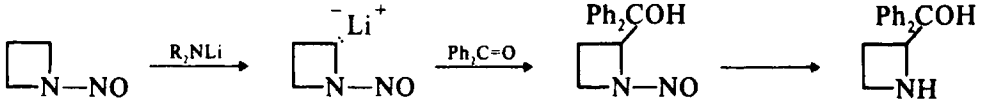
Azetidine-2-methanols are obtained in good yields by reduction of 2-carboxylates with $LiAlH_4$.[85,88,300,379]



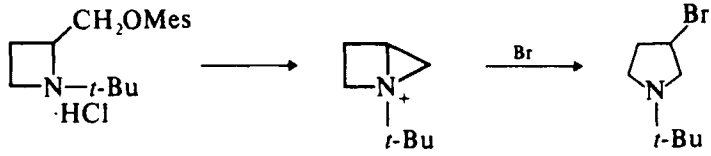
Reduction of 2-acylazetidines to secondary alcohols leads to diastereoisomeric mixtures. 2-Benzoyl-1-*t*-butylazetidine was reduced with $LiAlH_4$ in 86% yield to

a 7:3 mixture of carbinols; the configurations were not specified.[377] Treatment of 1-benzhydryl-2-benzoylazetidine with $NaBH_4$ is stated to give predominantly the *threo* alcohol, while the *erythro* isomer was isolated from a reduction with $LiBH_4$. Few experimental details are provided, and the basis for the assignment of configuration was not discussed.[175] The alcohols are claimed to decrease carbohydrate utilization and to be useful as anorexigenic agents.

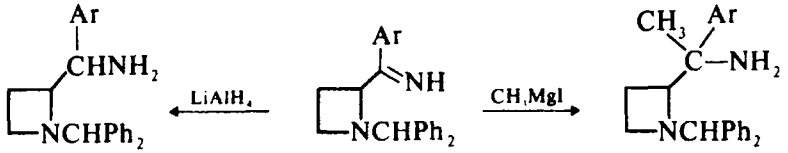
A different approach to azetidine-2-carbinols, and potentially other types of 2-substituted azetidines as well, is provided by the reactions of α-lithio-*N*-nitrosoazetidine, obtained from the nitrosamine and lithium diisopropylamide.[398] Treatment of the anion with benzophenone gave a 65% yield of the tertiary alcohol, which was quantitatively denitrosated to the *N*-unsubstituted azetidine.



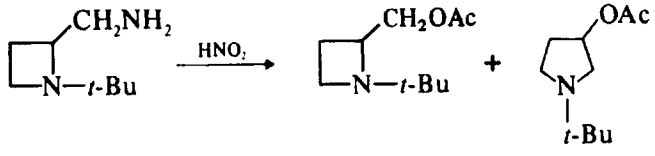
1-*t*-Butylazetidine-2-methanol is converted cleanly to the acetate[85] or methanesulfonate hydrochloride. The latter compound, on neutralization or reaction with Ph_3PBr_2, undergoes rearrangement, presumably via the 1-azoniabicyclo[2.1.0]-pentanonium ion, to 3-substituted pyrrolidines.[300]



Paralleling the chemistry of the alcohols, 2-azetidinyl alkylamines are obtained by reduction of nitriles, amides, or imines. 1-*t*-Butylazetidine-2-methanamine has been prepared by $LiAlH_4$ reduction of the amide (61%)[379] or the nitrile (84%, not distilled).[85] Imines, prepared by the addition of Grignard reagents to nitriles, have been reduced to diastereoisomeric amines with hydride, and have also been converted to tertiary carbinamines by reaction with methyllithium.[175]

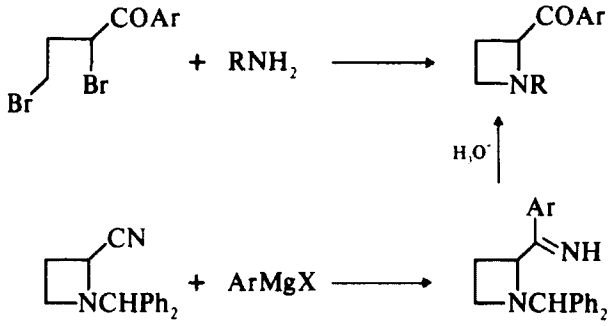


Deamination of 1-*t*-butyl-2-azetidinemethanamine with nitrous acid in aqueous acetic acid leads to about equal amounts of the acetoxymethylazetidine and ring-expansion product (the 3-acetoxypyrrolidine).[85]

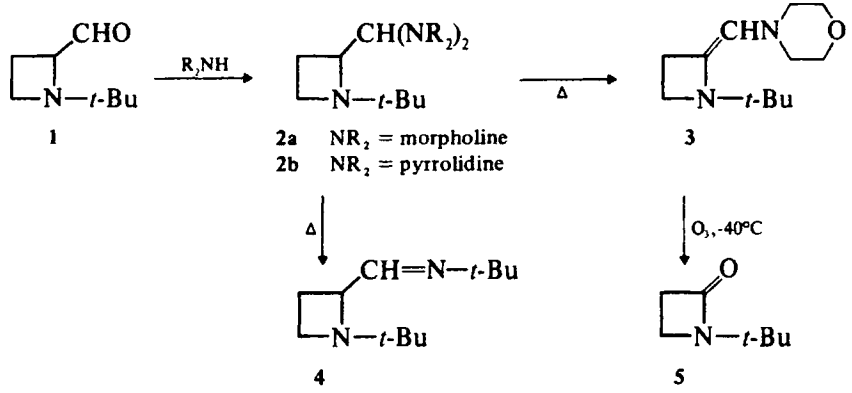


D. *2-Acyl- and 2-Alkylideneazetidines*

Cromwell and co-workers have prepared a number of 2-aroylazetidines by cyclization of 2,4-dibromoketones.[377,380] Other examples have been obtained from the reaction of Grignard reagents with nitriles followed by hydrolysis of the imines.[175] The infrared spectra of these 2-aroylazetidines show two carbonyl stretching frequencies, which are attributed to contributions from two conformers.[380]



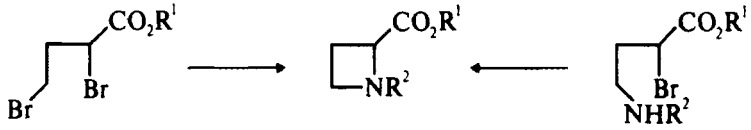
1-*t*-Butyl-2-formylazetidine (**1**) has been reported in 89% yield from the reduction of the methyl ester with diisobutyl aluminum hydride at $-72°C$.[115] This aldehyde is more stable than the corresponding 2-formylpyrrolidine and shows no tendency for rearrangement. Reactions of **1** with morpholine or pyrrolidine lead to the aminals **2a** and **2b**. The former, on heating, loses a mole of amine to produce the enamine **3**, but the pyrrolidine derivative gives a complex mixture from which the *t*-butyl imine **4** was isolated in 28% yield. Ozonolysis of enamine **3** gives the azetidinone **5**.[116]



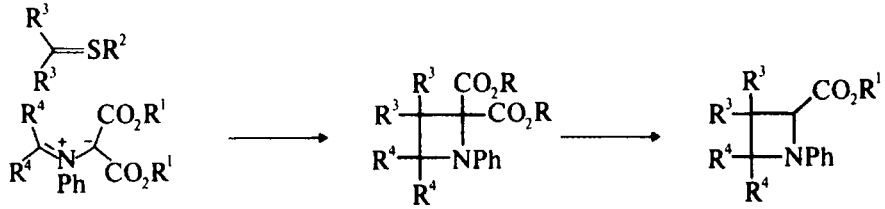
E. *Azetidine-2-carboxylates*

1-Alkylazetidine-2-carboxylic esters are available by cyclization of α,γ-dibromobutyrates with bulky primary amines[173,260,339,361,375,380] or by ring closure

of α-bromo-γ-alkylamino esters.[379] The 4-methyl-2-carboxylic ester was obtained as a mixture of geometric isomers in approximately equal amounts.[380] Equilibration in base increased the yield of the more stable *cis* isomer to 75%. In the 4-phenyl series, only the *cis* isomer was observed.



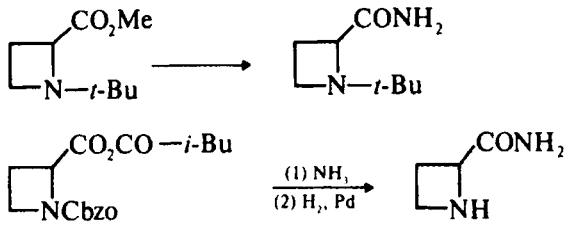
Methyl 1-tosylazetidine-2-carboxylate has been prepared by cyclization of the γ-chloro (or bromo)-α-tosylaminobutyrate.[88,313] *N*-Arylazetidine-2-carboxylates are obtained from the cycloaddition of azomethine ylids and sulfur ylids[457] (see Section III.3.C).



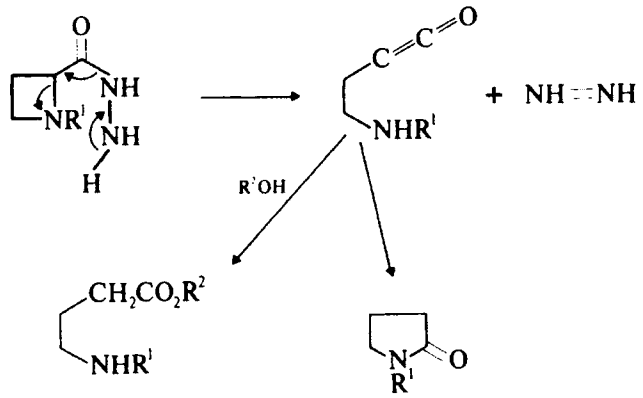
The parent unsubstituted compound, methyl azetidine-2-carboxylate, obtained by esterification of the amino acid in the presence of thionyl chloride, is an unstable oil which, on standing or distillation, is converted to the diketopiperazine in 67% yield.[361] Activated esters of *t*-BOC-L-azetidinecarboxylic acid have been prepared for peptide synthesis by carbodiimide coupling with pentachlorophenol and *N*-hydroxysuccinimide.[44]

F. *Azetidine-2-carboxamides, Hydrazides, and Nitriles*

1-*t*-Butylazetidine-2-carboxamide has been prepared in 94% yield by reaction of the methyl ester with ammonia at 25°C[299] or from the acid via the mixed anhydride with $ClCO_2Et$ (77%).[379] The latter method was unsuccessful with other 1-alkyl-2-carboxylic acids. The unsubstituted azetidine-2-carboxamide was obtained by ammonolysis of a 1-benzyloxycarbonyl-2-carboxylic mixed anhydride followed by hydrogenolysis;[361] attempted ammonolysis of the 1-unsubstituted methyl ester led to the diketopiperazine.



Treatment of methyl 1-alkylazetidine-2-carboxylates with 90% hydrazine at room temperature gives the 2-carbohydrazides in good yields.[361] These derivatives are converted to stable hydrazones with acetone, but on warming in protic solvents they undergo a rearrangement with loss of diimide and ring opening to give transient aminoketene intermediates.[283,379] A similar process occurs with aziridine 2-carbohydrazides. When the alkyl group is *t*-butyl, the ketene is trapped by solvent to give γ-*t*-butylaminobutyric acid or a derivative, but with benzyl or cyclohexyl substituents the 1-alkyl-2-pyrrolidinone is obtained by intramolecular attack.

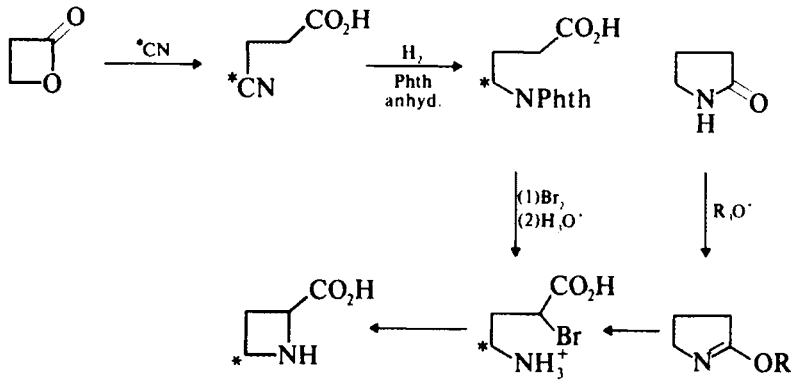


1-Alkylazetidine-2-carbonitriles have been obtained by cyclization of α,γ-dibromobutyronitriles with bulky amines[175] or by dehydration of the 1-*t*-butyl-2-carboxamide with triphenylphosphine dibromide in acetonitrile.[85,299] The cyano group can be reduced with $LiAlH_4$ to the primary amine, which undergoes addition of Grignard reagents to furnish 2-imidoylazetidine.[175]

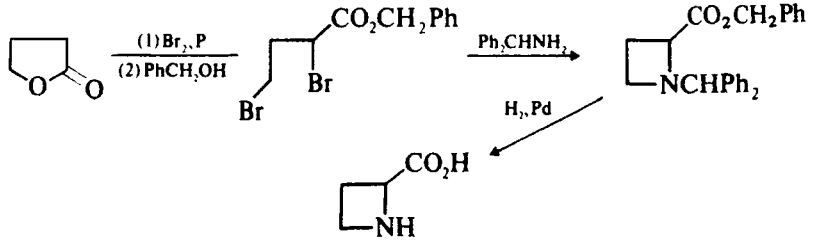
G. *Azetidine-2-carboxylic Acid*

Several 1-alkylazetidine-2-carboxylic acids have been prepared by saponification of the methyl esters with $Ba(OH)_2$ followed by acidification with CO_2 or by hydrogenolysis of the benzyl esters.[339,375,379] A number of methods have been developed for synthesis of the biologically interesting parent azetidine-2-carboxylic acid. The original preparation by Fowden[139] involved cyclization of γ-amino-α-bromobutyric acid. This route was later adapted to the preparation of the 4-^{14}C-labeled acid via the 3-^{14}C-cyano acid.[362] Another preparation of the amino bromoacid involves bromination of a 1-alkoxypyrroline, available from pyrrolidinone.[481]

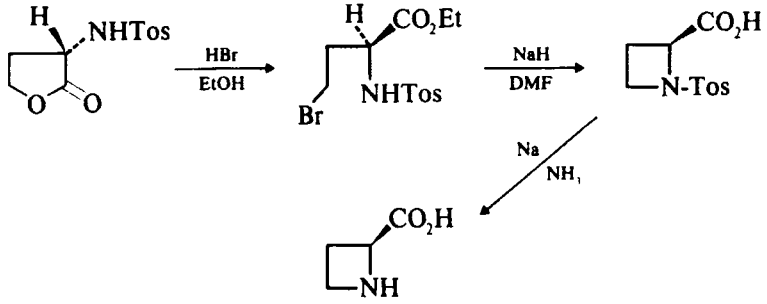
An important route to azetidine-2-carboxylic acids involves the readily available γ-butyrolactone; a key step is the very efficient cyclization of the benzyl dibromoester with benzhydrylamines.[361,376,470] Resolution of the DL-acid was carried out by separation of the diastereoisomeric salts of the *N*-carbobenzoxy acid with L-tyrosine hydrazide.[378]



A convenient synthesis of the L-amino acid proceeds from *N*-tosylmethionine via homoserine lactone and the γ-bromo-*N*-tosyl ester. The overall yield from the

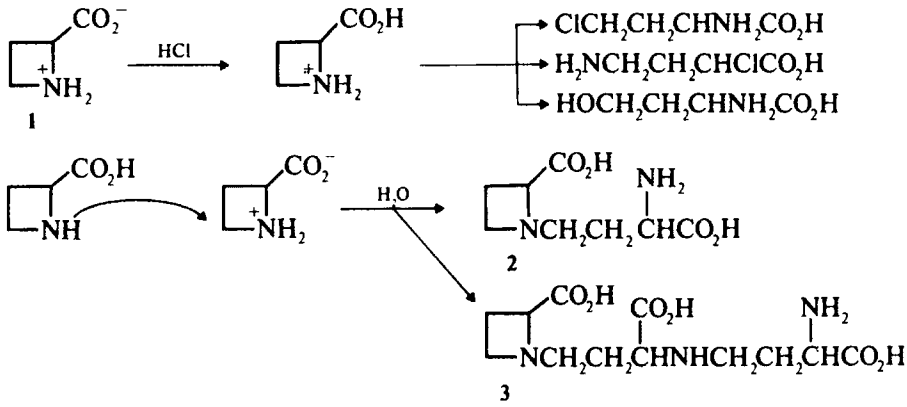


lactone is about 60%. Since no steps involve bonds to the asymmetric center, the optical purity of the starting material is retained.[313]

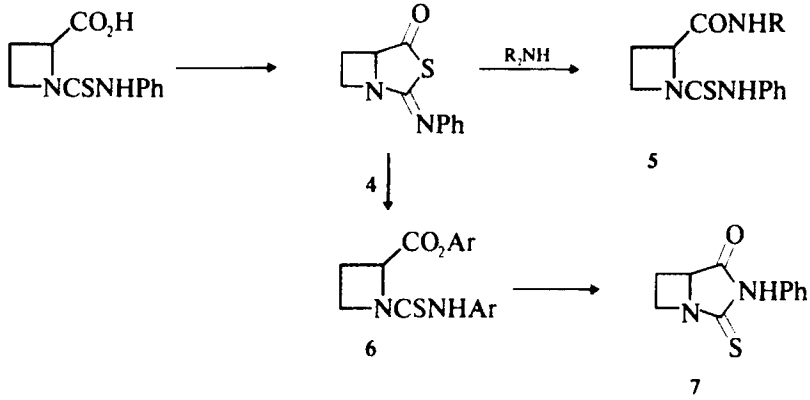


Azetidine-2-carboxylic acid undergoes ring opening on heating in acid; in HCl the products, identified by paper chromatography, include α-amino-γ-chlorobutyric acid, γ-amino-α-chlorobutyric acid, and homoserine.[139] The acid is stable in aqueous solution on prolonged storage, but extensive ring opening occurs in water at 100°C for 24 hours to give homoserine and the dimeric and trimeric amino acids **2** and **3**.[262] These products must result from nucleophilic attack of the zwitterion **1** at C_4 by the NH group of an uncharged amino acid molecule. Since the concen-

tration of the latter is small, addition of one-half equivalent of NaOH causes increased formation of **2** and **3**, with less homoserine. In the presence of ammonia, pyridine, or methanethiolate ion, the respective γ-substituted-α-amino acids were observed by paper chromatography.

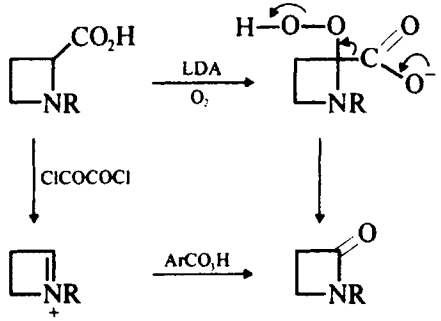


Azetidine-2-carboxylic acid undergoes the usual transformations of NH and CO_2H groups to simple derivatives,[361] but several reactions characteristic of α-amino acids, including proline, are abnormal. The *N*-chloroformyl compound cannot be cyclized to the oxazolidinedione (Leuch's anhydride),[44] and formation of the phenylthiohydantoin does not occur under the usual Edman conditions. The *N*-phenylthiourea can be cyclized with a carbodiimide to the bicyclic iminothiazolidinone (**4**), which is an active acylating agent. Thermal conversion of **4** to the thiohydantoin **7** is accompanied by extensive racemization, but optically active **7** was obtained by conversion to the *p*-nitrophenyl ester **6** and recyclization.[339] The same sequence was also carried out with the oxygen counterpart, leading to the hydantoin.



The *N*-nitroso derivative of azetidine-2-carboxylic acid, conveniently prepared in aprotic solvents with nitrosyl tetrafluoroborate,[340] undergoes decarboxylation in aqueous alkaline solution to give *N*-nitrosoazetidine.[284]

Wasserman and co-workers have developed several methods for oxidative decarboxylation of *N*-alkylazetidinecarboxylic acids as a route to β-lactams. Oxygenation of the dianion, formed with excess lithium diisopropylamide, followed by acidification of the α-hydroperoxide gave lactams in 50–61% yields.[468,470] Alternatively, the *t*-butyl esters were converted to α-silyl derivatives and then to the lactams by sensitized photooxygenation.[469,470] A different approach, applicable also to *N*-benzyl derivatives, involves conversion of the azetidinecarboxylic acid to the iminium salts with oxalyl chloride and then treatment with *m*-chloroperbenzoic acid to give the lactam.[470]



β-Lactams have also been obtained in low yields by oxidation of azetidines with ruthenium tetroxide.[404]

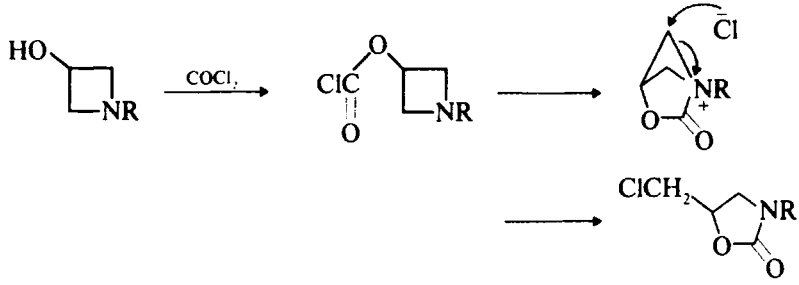
4. Substituents at C_3

The main sources of azetidines with functional substituents at C_3 are the 3-azetidinols obtained by cyclization of amine with epichlorohydrin (Section III.1). Also readily accessible by cyclization are 3-aroylazetidines. The availability of 3-azetidinols has led to a number of studies and applications of displacement reactions at C_3 via the derived sulfonate esters.

A. *3-Azetidinols and Derivatives*

In addition to the preparation of 1-substituted 3-azetidinols from epichlorohydrin via the aminochloropropanols, a few secondary azetidinols have been obtained by reduction of 3-azetidinones. Tertiary azetidinols have been prepared by Grignard addition to the ketones[337] and by photocyclization of acylaminoketones (Section III.2).

1-Alkyl-3-azetidinols are typical secondary alcohols. Nmr data indicate that N_1 and 3-OH substituents have a cis diequatorial relationship.[209] Esterification proceeds normally with the usual reagents, and mild oxidation leads to 3-ketones.[82,170,337] The acylation of 1-alkyl-3-azetidinols with phosgene is accompanied by a further reaction at nitrogen, with the formation of an oxazolidinone by opening of the four-membered ring.[237]

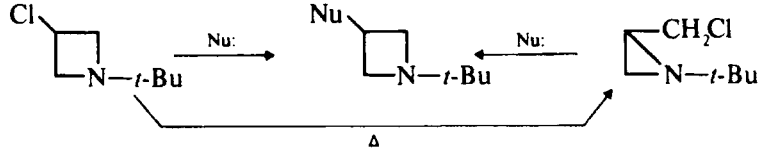


3-Chloro 1-substituted azetidines are obtained in 50–70% yield by treatment of the azetidinol with Ph_3P–CCl_4;[154] the reaction is very slow (72 hours at 76°C) compared to that of acyclic secondary alcohols. The reaction of 1-*t*-butylazetidinol with thionyl chloride–pyridine led to the bisazetidinyl sulfite;[152] with the 1-*t*-butyl-2,2-dimethyl compound and $SOCl_2$, the 3-chloride was reported in unspecified yield.[189] A 3-bromoazetidine has been prepared in good yield by displacement of the 3-mesyloxy group with NaBr in diethylene glycol.[7]

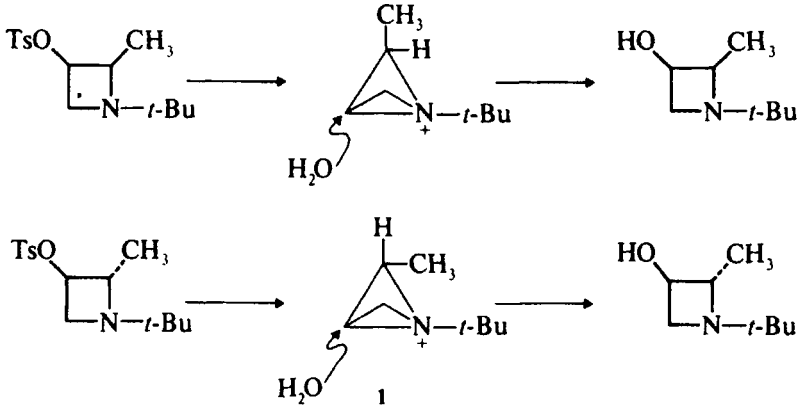
For preparative purposes, nucleophilic substitutions at C_3 have usually been carried out with tosylates and mesylates. With tosyl chloride in pyridine, 1-*t*-butyl-3-azetidinol was converted to the tosylate in 70% yield, but 1-cyclohexyl-3-azetidinol was reported to undergo ring opening to give *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol.[89] Reaction of tosyl chloride with the azetidinol alkoxide, obtained with NaH, has also been used.[207,210] Mesylates appear to be generally superior to tosylates. Anderson and Lok obtained 90–100% yields of 1-benzhydryl-3-azetidinol mesylate with mesyl chloride, compared to 40% for the tosylate.[7] Okutani et al. prepared a series of azetidinol-3-alkylsulfonates with the sulfonyl chloride and triethylamine; a sulfene intermediate was assumed. The mesylates are stable in the form of salts, but resinify when stored as free bases.[347]

B. *Mechanistic Considerations in Nucleophilic Substitution*

Several studies of azetidines with leaving groups at C_3 have dealt with the question of rearrangements and ring opening in reactions with nucleophiles, analogous to those observed in cyclobutyl–cyclopropylcarbinyl systems. 3-Chloro-1-*t*-butylazetidine rearranges thermally in acetonitrile to an equilibrium mixture containing predominately 1-*t*-butyl-2-chloromethylaziridine.[154,158] In reactions of the chloroazetidine with nucleophiles, however, when HCl is efficiently neutralized, rearrangements are not observed.[154] Rearrangement does occur in reactions of 2-chloromethylaziridine with nucleophiles, and 3-substituted azetidines are the major products.[154,158]

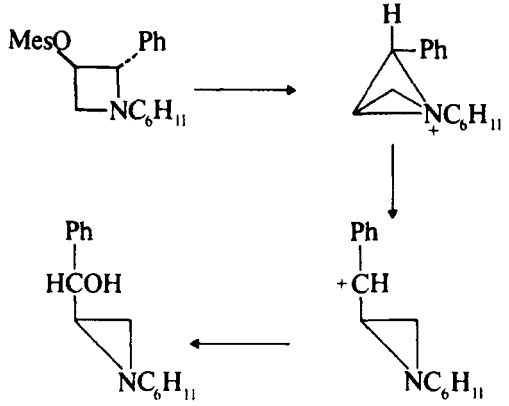


Kinetic and stereochemical studies with azetidine 3-tosylates have shown conclusively that reactions with nucleophiles proceed via 1-azoniabicyclo[1.1.0]butane intermediates. Solvolysis rates in aqueous ethanol or acetone indicate a small rate enhancement (because of nitrogen participation) compared to cyclobutyl tosylate.[158,206] From activation data, the rate acceleration is due mainly to a higher $\Delta S^{\ddagger}$ in the azetidine solvolyses, indicative of charge development in the transition state. The reaction with cyanide ion at 0°C is first order in tosylate and independent of the concentration of nucleophile.[206] Higgins and Cromwell also found that solvolysis of 1-*t*-butyl-*cis*-2-methylazetidine-3-tosylate and the trans isomer in 60% acetone led stereospecifically to the respective alcohols with retention of configuration.[207] The hydrolysis was ~300-fold more rapid with the cis isomer. The relatively sluggish reaction of the trans isomer is attributed to the eclipsing of 1-*t*-Bu and 2-CH_3 groups in the bicyclic intermediate **1**.

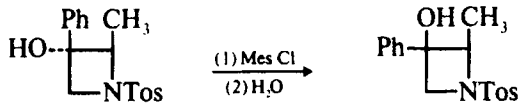


1

In a similar study, Okutani and Masuda observed retention of configuration in reactions of 1-cyclohexyl-*cis*- and *trans*-2-phenylazetidine-3-methanesulfonates with methoxide, cyanide, acetate, and thiolates.[348] In the hydrolysis of the *trans*-mesylate, but not the *cis* isomer, the 2-α-hydroxybenzylaziridines were also formed by collapse of the bicyclic intermediate.



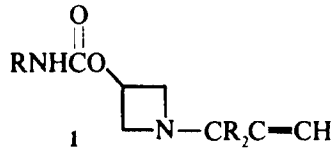
Note that participation of nitrogen and retention of configuration at C_3 are not observed when the azetidine nitrogen carries a tosyl group. Thus Miller et al. effected inversion of configuration in 49% yield by mesylation and hydrolysis of *cis*-2-methyl-3-phenyl-1-tosyl-3-azetidinol.[310]



C. *3-Amino-, Alkoxy- and Alkylthioazetidines*

3-Aminoazetidines have been obtained by nucleophilic substitutions of 1-substituted 3-halides or 3-sulfonates with ammonia or primary and secondary amines.[85,87,154,305,347,414] Primary aminoazetidines are formed in 40–80% yields by treatment of the mesylate with methanolic ammonia at room temperature.[347] A series of 41 secondary and tertiary amino azetidines were prepared from 1-isopropyl-, ethyl-, or *t*-butylaminoazetidine-3-mesylate with *N*-aryl- and *N*-alkyl-*N*-amines at room temperature; the compounds had analgesic and anti-inflammatory activity.[414] Primary amines have been converted to amides and ureas, and a series of 3-guanidino azetidines was obtained in relatively low yields by reaction of the 1-substituted 3-mesylates with guanidine.[347] 1-Cyclohexyl-3-guanidinoazetidine shows antihypertensive activity.

1-Alkyl-3-alkoxyazetidines have been prepared from the 3-chlorides and alkoxides[154] or from the reaction of alcohols with 3-mesyloxy derivatives.[7,343] 3-Acyloxyazetidines are obtained from the azetidinol by acylation in the presence of triethylamine or pyridine. Some 1-(1,1-dialkyl-2-propynyl)-3-azetidinyl carbamates **1** have been prepared from the azetidinols and isocyanates;[146] the diethyl *N*-*n*-propyl compound, at dose levels below those causing muscle relaxation, showed significant CNS activity. Insecticidal 1-*t*-butyl-3-azetidinyl phosphates and thiophosphates have been obtained from 3-*t*-butylazetidinol tosylate.[454]



1

Azetidines with sulfur substituents at C_3 have been obtained by treatment of 1-substituted 3-mesylates or 3-tosylates with thiols[87] or thiolates.[348] The reaction with KSH gave mainly a polymeric product resulting from ring opening; a low yield of 1-*t*-butyl-3-acetylthioazetidine was isolated after acetylation of the reaction mixture. Ring opening occurred also with thiobenzoic acid. Oxidation of the 1-*t*-butyl-3-methylthioazetidine with permanganate gave the sulfone (30%).[87]

D. *3-Cyano- and 3-Carboxyazetidines*

A number of 1-alkyl-3-cyanoazetidines have been prepared in generally good yields by reactions of 3-mesylates and 3-tosylates with cyanide ion in alcohol or dimethylformamide.[85,89,146,154,211,305,347,348] These nitriles have provided entry to several other groups of 3-substituted azetidines. Alkaline hydrolysis gives the carboxylic acids.[7,89,347] Okutani et al. reported low yields of the acids on $Ba(OH)_2$ hydrolysis of 1-adamantyl- and 1-diphenylmethylazetidine nitriles and prepared these acids via the methyl esters, which were obtained from the nitrile with methanolic HCl; however, Anderson and Lok describe the hydrolysis of the diphenylmethyl compound with KOH in 86% yield. Reactions of the nitriles with Grignard reagents have been used to prepare ketones.[211,348,376] Reduction with $LiAlH_4$ gives 3-aminomethylazetidines,[7,85,305] and a reduction with diisobutylaluminum hydride gives the 3-azetidinecarboxaldehyde.[305] An amidoxime has been prepared from the 3-azetidine nitrile by addition of hydroxylamine.[146]

Higgins and Cromwell studied the reactions of several carbanions with 1-*t*-butyl-3-azetidinyl tosylate.[210] Fair yields of C_3-substituted azetidines were obtained with the sodio derivatives of acetoacetic and malonic esters, but not with indanedione. Reaction of 1-alkyl-3-azetidine mesylates with sodio diphenylacetonitrile gave the 3-diphenylcyanomethylazetidines.[66,67]

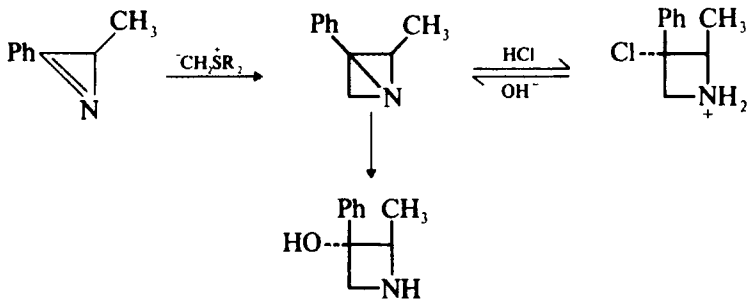
E. *3-Substituted Azetidines from 1-Azabicyclo[1.1.0]butanes*

Complementing the substitution reactions at C_3 in tertiary azetidines, which occur via 1-azoniabicyclic intermediates, are processes involving formation and ring opening of 1-azabicyclo[1.1.0]butanes to give secondary azetidines. Several of these bicyclic amines have been prepared, and they provide a rather versatile route to azetidines, particularly *N*-unsubstituted compounds.

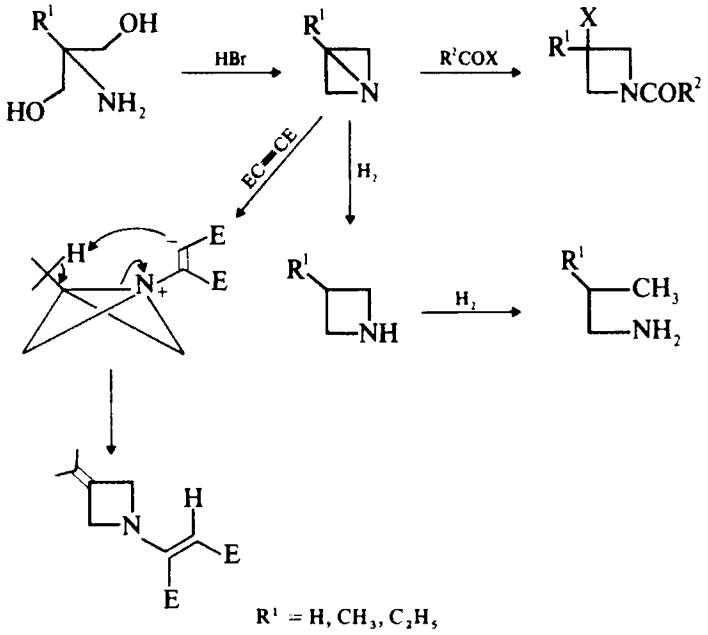
Hortmann et al. prepared 3-phenyl-1-azabicyclobutanes by the reaction of dimethylsulfonium ylid with 2-phenylazirines.[220,221] 3-Alkyl derivatives are obtained by the traditional Gabriel synthesis of 2-amino-1,3-propanediols with HBr followed by base.[149] 3-*t*-Butoxycarbonyl-1-azabicyclobutane was prepared by treatment of 3-*t*-butoxycarbonyl-1-chloroazetidine with NaH.[6]

Acid-catalyzed solvolysis of the 3-phenyl-1-azabicyclobutanes occurs cleanly to give 3-hydroxy- or 3-methoxyazetidines in high yield. With the 2-methyl compound, the process is quite stereoselective and leads to *cis*-2-methyl-3-phenylazetidinol. Ring opening with anhydrous HCl produces the 3-chloroazetidine hydrochlorides,[221] which recyclize spontaneously to the azabicyclobutane. Slow hydrolysis of the hydrochloride leads to an epimeric mixture of alcohols.

Funke obtained a number of 1,3-disubstituted azetidines by ring opening of the bicyclic amines with acid chlorides, anhydrides, thiols, and amines.[149] No ring opening at the 1,2-bond to give aziridine products was observed. Hydrogenation also opens the 1,3-bond, and subsequently the azetidine ring, to give isobutyl or 2-methylbutyl amine, respectively. With dimethyl acetylenedicarboxylate, electro-



philic attack at N_1 is followed by proton transfer from the 3-alkyl group, leading to the 1-vinyl-3-alkylideneazetidines.

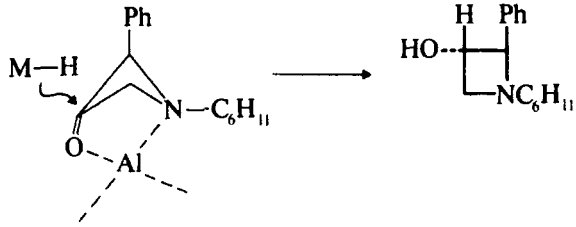


F. *3-Azetidinones*

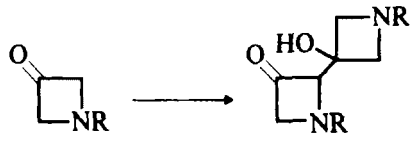
A few monocyclic 3-azetidinones have been obtained by cyclization of 1-halo-3-alkyl-3-alkylaminobutanones (Section III.1.F), or by oxidation of 1-substituted azetidinols. Chromic acid,[82] DMSO with pyridine·SO_3 complex,[170,337] and *N*-chlorosuccinimide–Me_2S have been used for the oxidation of azetidin-3-ols, and a 3-hydroxy-3-carboxylic acid has been cleaved to the 3-one with $Pb(OAc)_4$.[88]

The azetidinones have properties characteristic of highly strained and reactive carbonyl groups. The infrared stretching frequency is reported as 1805–1820 cm^{-1}.[82,337] Stable hydrates and hemiketals are formed,[189,326,338] and a variety of typical carbonyl addition reactions with hydride and organometallic reagents,

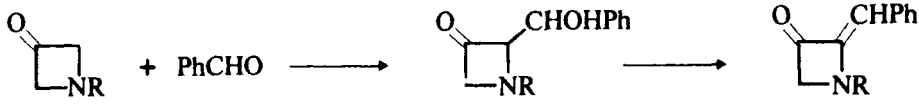
ylids, cyanide, and amines have been carried out.[82,170,189,337] Several tertiary alcohols have been prepared by Grignard addition to 3-azetidinones; these compounds are mild analgesics.[337] Hydride reduction of 1-cyclohexyl-2-phenyl-3-azetidinone gives predominantly the *trans*-alcohol, because the reagent attacks from the less hindered face of the complexed ketone.[337]



A major side reaction in the DMSO–pyridine–SO_3 oxidation of the alcohol is aldol condensation to dimeric products. Condensation with benzaldehyde gives

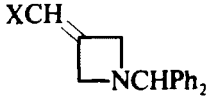


the 2-α-hydroxybenzyl derivative, which can be dehydrated to the 2-benzylidene-3-azetidinone.[337]



G. *3-Alkylideneazetidines*

Reactions of 3-azetidinones with phosphorus ylids provide a preparative method for 3-alkylidene derivatives. 1-Benzhydryl-3-methyleneazetidine (**1a**) is obtained in 75% yield with triphenylphosphinemethylene,[337] and the substituted compounds **1b–d** have been prepared with the dimethylphosphonate.[402]

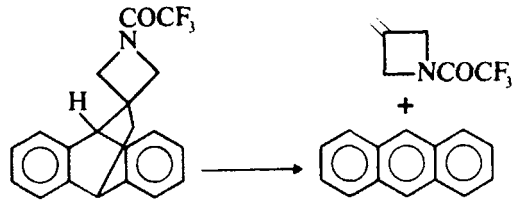


1

a. X = H
b. X = Cl
c. X = CN
d. X = CO_2CH_3

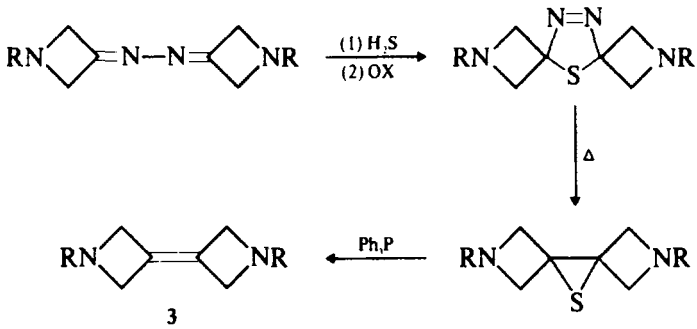
Another route to a 3-methyleneazetidine is the reverse Diels–Alder condensation of the spiro compound **2**. Pyrolysis of **2** at 250°C leads to 1-trifluoroacetyl-3-

methylene azetidine, which reacts further with 9,10-dimethyl anthracene to give the dimethyl derivative of **2**.[34]



2

The diazabicyclobutylidene **3** has been prepared from 1-benzhydryl-3-azetidinone via the azine, thiadiazoline, and thiirane.[401]

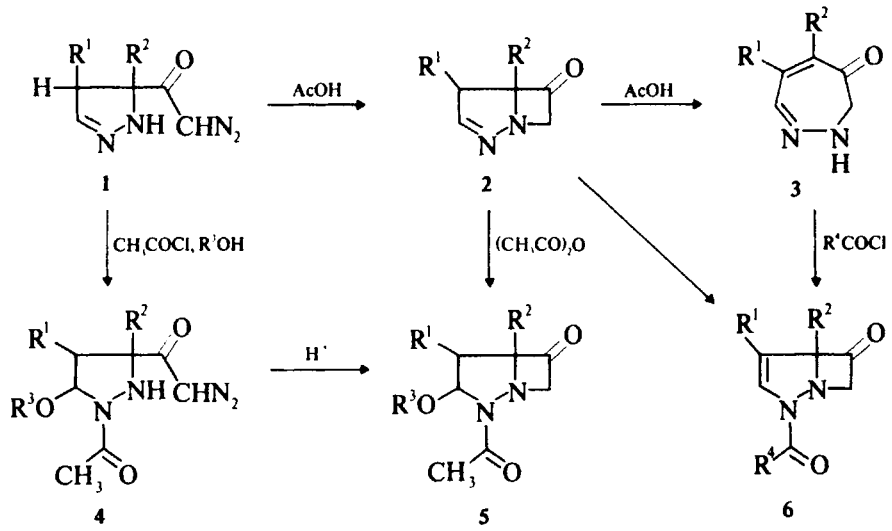


H. *1,2-Diazabicyclo[3.2.0]heptanones*

A number of 3-azetidinones have been prepared in the 1,2-diazabicyclo[3.2.0] heptane series. The ketones **2** and **5** are formed in 60–90% yields by cyclization of the 3-diazoacetylpyrazolines (**1**) or pyrazolidines (**4**).[99,326,327,328,333,338] The 3-substituted bicycloheptanones (**5**) are quite stable under acid conditions permitting interchange of the OR′ groups.[327,333] Δ^3-Bicyclic ketones (**6**) are obtained in 90% yield by transannular acylation of the diazepinones (**3**).

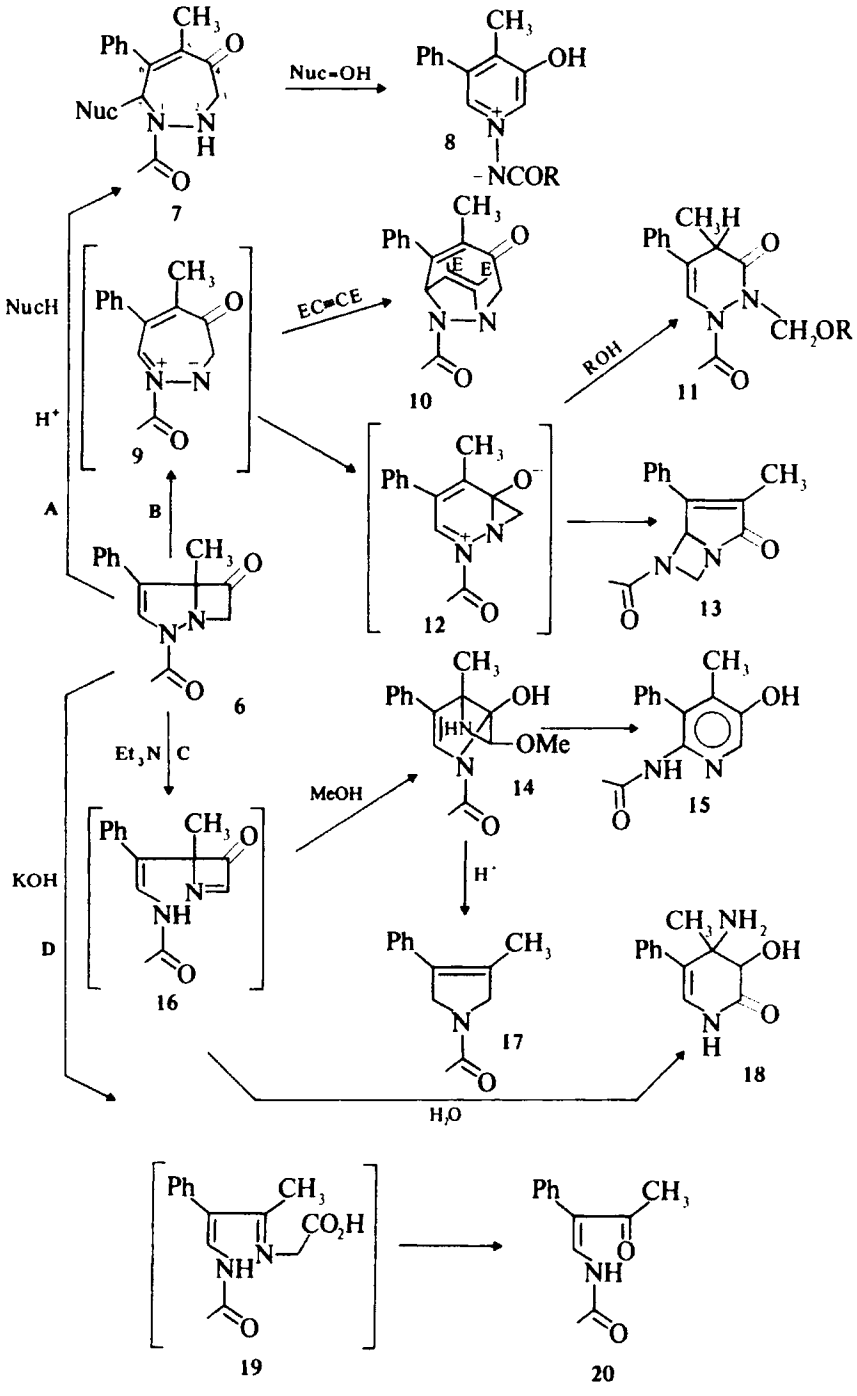
The unsaturated ketones **6** are highly labile compounds and are converted to a variety of products under remarkably mild conditions. Most of the reactions are unique to this bicyclic system and have no counterpart in the chemistry of simple 3-azetidinones, since they depend upon the interplay of functional groups in the entire molecule. The reactions of **6** have been interpreted in terms of four primary processes, designated **A–D** in Scheme 5, involving different bond-breaking steps in the four-membered ring, with subsequent steps leading to the products **7–15**.[329]

In two of the paths **A** and **B**, the bridging bond opens to give a diazepine intermediate. In **A**, which occurs in acidic media, protonation of N_1 and nucleophilic attack at C_3 lead to 7-substituted tetrahydrodiazepinones (**7**) or subsequent transformation products such as the 1-aminopyridinium cation **8**.[327] Path **B** involves thermal ring opening (which occurs rapidly at 70–80°C) to the diazepinium imine



Compound	Substituent	Ref.
	R^1 = Ph, R^2 = CH_3	327
1	R^1 = R^2 = Ph	99, 338
	R^1 + R^2 = steroid D ring	326, 328, 333
2	R^1 = Ph, R^2 = CH_3	327
	R^1 + R^2 = steroid	326, 338
3	R^1 = Ph, R^2 = CH_3	327
	R^1 = R^2 = Ph	99, 338
	R^1 = R^2 = steroid	328
	R^1 = CO_2Me, R^2 = CH_3	338
4	R^1 = Ph, R^2 = CH_3	327
	R^1 = R^2 = Ph	99
	R^3 = H, CH_3, Ac	
5	R^1 = Ph, R^2 = CH_3	327
	R^1 = R^2 = Ph	99
	R^1 + R^2 = steroid	328, 333
	R^3 = H, CH_3, Ac	
6	R^1 = CH_3, R^2 = Ph	
	R^4 = CH_3, Ph	325, 327
	R^1 = R^2 = Ph	
	R^4 = CH_3, Ph	325
	R^1 = CH_3, R^2 = Ph	
	R^4CO = Tos	331

9, which can be trapped by cycloaddition to give **10** or related products.[385] In the absence of a dipolarophile, **9** undergoes valence isomerization to **12**, which can be trapped by alcohols and converted to the pyridazinones **11**.[330] In the absence of alcohol, further isomerization leads eventually (in 80% overall yield) to the 1,6-



Scheme 5

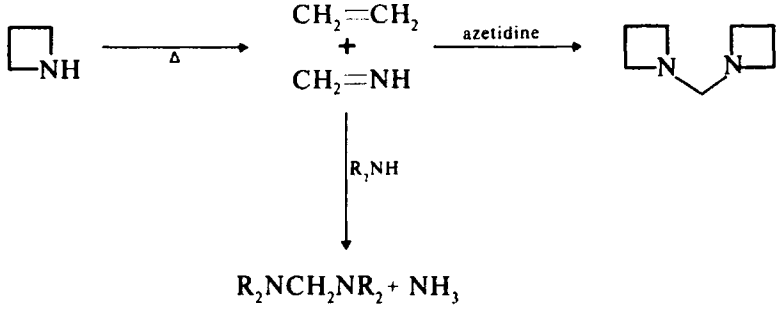
diazabicycloheptenone **13**.[122] In the third path (**C**), which takes place at 30°C in chloroform–methanol containing a trace of triethylamine, β-elimination produces the azetinone **16**, which can be trapped as the bicyclic carbinol amine **14**. This methoxyazetidinol, on standing, decomposes to the pyridine **15** or, in acid, to the pyrrolinone **17**.[332] The final path (**D**), observed in hydroxide solution, involves attack at the carbonyl of **6** and elimination to the imine **19**, which is hydrolyzed to the enaminoketone **20** and glycine.[329,332]

V. RING-OPENING AND REARRANGEMENT REACTIONS OF AZETIDINES

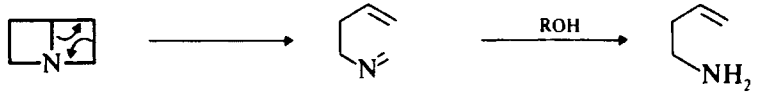
Azetidine and simple tertiary azetidines are stable compounds, with no pronounced tendency to deteriorate spontaneously, but they do undergo ring opening or rearrangement to a larger ring under a variety of conditions, including thermal cleavage, attack of nucleophiles, and photolysis. These reactions are discussed in this section.

1. Thermal Ring Cleavage

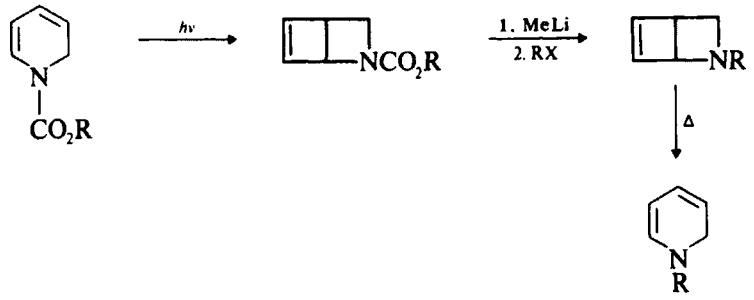
Azetidine undergoes decomposition in a flow reactor at 420–450°C to give bis(azetidinyl)methane, ethylene, and ammonia in 50–60% conversion.[127] These products clearly result from cycloreversion of the four-membered ring to ethylene and methylene imine, followed by addition of unreacted azetidine to the latter fragment. By freezing out the pyrolysis products, the methylene imine was observed by infrared spectroscopy and trapped by addition of amines.[459]



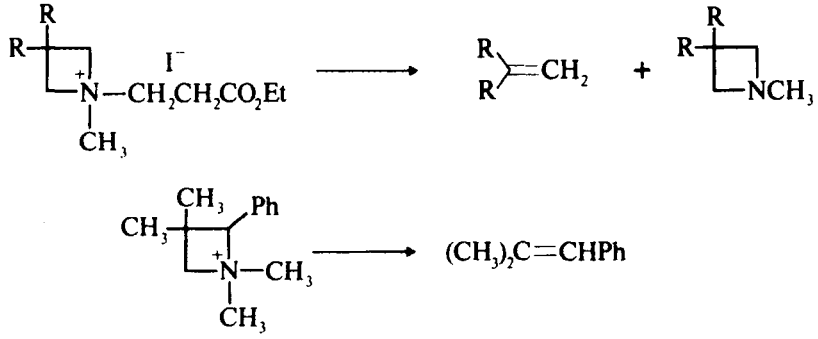
As mentioned in Section III.3.A, a temperature of 800°C is required for cycloreversion of 1-trifluoromethylperfluoroazetidine.[26,27] At the other extreme, the highly strained 1-azabicyclo[2.2.0]hexane undergoes ring opening on codistillation with ethanol to give 4-amino-1-butene.[183]



Thermal ring opening of the azetidine ring in the 2-azabicyclo[2.2.0]-5-hexene system is the final step in a general synthesis of 1-alkyl-1,2-dihydropyridines. The cycle of photochemical valence isomerization, functional group change, and thermal cycloreversion is a more practical process than manipulation of the sensitive dihydropyridine.[42]

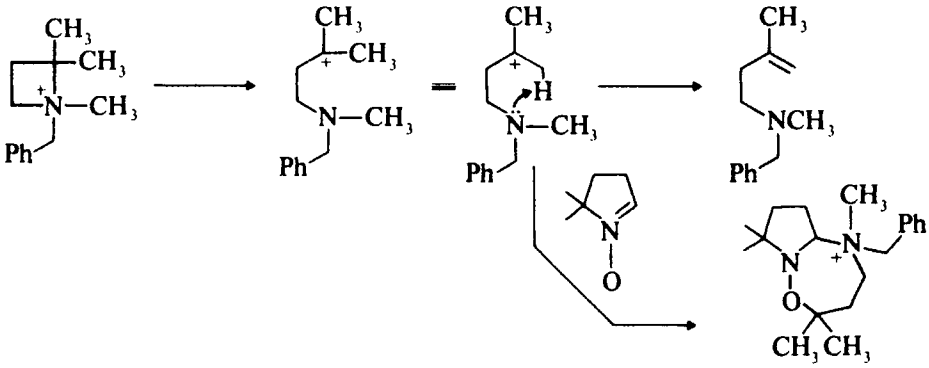


Quaternary azetidinium salts can undergo fragmentation in competition with loss of one of the N_1 substituents. In a gas chromatographic inlet port at 300°C 1-methyl-1-(carbethoxyethyl)-3,3-dipentylazetidine is converted to the alkene in 50–60% yields. In a mass spectrometer or in the presence of base, the 1-methylazetidine is the major product.[463] Thermal decomposition of 2-phenyl-1,1,3,3-tetramethylazetidinium iodide at 200°C gives dimethylstyrene.[9]

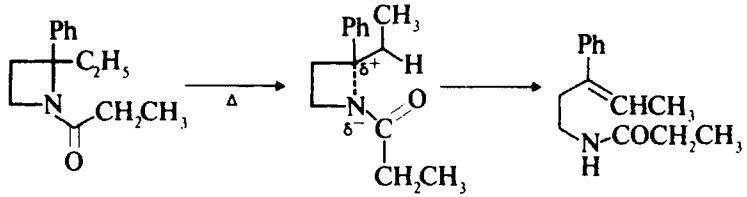


1-Benzyl-1,2,2-trimethylazetidinium perchlorate undergoes thermal ring opening in nonnucleophilic solvents at 50–60°C to the terminal alkene, which is suggested to arise by intramolecular proton abstraction in the carbonium ion. In the presence of a nitrone, the carbonium ion is trapped by cycloaddition.[281] 1,1,2,2-Tetramethylazetidinium perchlorate did not undergo similar ring opening under these conditions.

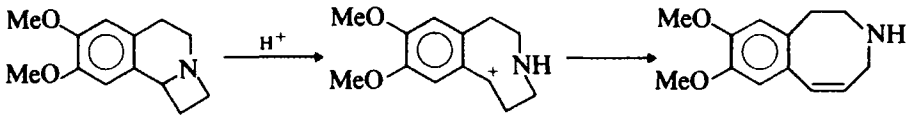
1-Acylazetidines are usually quite stable thermally, but ring opening has been observed on heating 1-propionyl-2-ethyl-2-phenylazetidine at 150°C; the 2,2-diethyl or 2-monoalkyl derivatives did not react.[430] The reaction presumably occurs by cyclic elimination, requiring development of positive charge at C_2, which is stabilized by the phenyl group.



Ring opening occurs on heating 6,7-dimethoxytetrahydroazeto[2,1-*a*]isoquinoline in hydrochloric acid. The resulting highly stabilized carbocation loses a proton



to give the benzo[4,5-d]azocine.[248] Ring opening can also be brought about by heating in acetic anhydride.



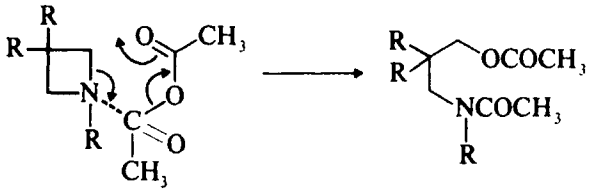
2. Ring Opening with Nucleophiles

Cleavage of the azetidine ring with substitution of a nucleophile at the $C_{2(4)}$ position can occur under a wide range of conditions. Although alkylation, acylation, and other types of substitution have been reported many times with secondary azetidines (cf. Section IV.2), yields of 1-substituted azetidines are rather variable, and Testa suggests that competing ring opening is usually the cause.[442] The susceptibility of the ring depends very strongly on the number and position of substituents. In general, substitution, especially at C_3, stabilizes the azetidine significantly.

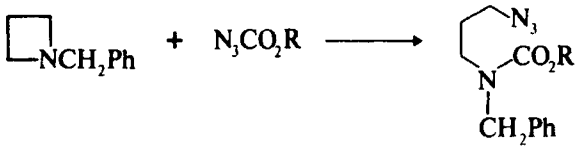
The profound effect of substituents on the reactivity of the azetidine ring is illustrated by the contrasting behavior of azetidine-2-carboxylic acid, which undergoes ring opening in hot water or dilute acid (Section IV.3), and 3-aryl- or 3-alkyl-3-arylazetidines, which can be isolated as the hydrochlorides in 70–80% yields after hydrolysis of the 1-acetyl derivatives with boiling 3–6 *M* hydrochloric acid.[432,438] 2-Arylazetidines are relatively sensitive to acid and undergo ring opening with

elimination to give cinnamyl amines.[431] The ring is also destroyed on attempted nitrosation or carbamylation of 2-phenylazetidine.[429]

Ring opening of 1-alkyl-3,3-disubstituted azetidines occurs on heating with acetic anhydride.[431,433] This reaction, which is probably a general one for tertiary azetidines, is reminiscent of the addition of acetic anhydride to C=N bonds and can be represented as a cyclic process.

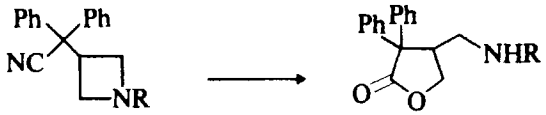


Similar ring cleavage has been observed in the reaction of 1-benzylazetidine with alkyl azidoformates to give *N*-benzyl-*N*-(3-azidopropyl)carbamates. The reaction is much slower than the analogous ring opening of aziridine despite the greater nucleophilicity of the azetidine.[200]



A dependence of the 1-alkyl group on ring opening was observed in the reaction of 1-alkyl-3-azetidinols with tosyl chloride in pyridine or *p*-nitrobenzoyl chloride in acetone. In both reactions 1-cyclohexylazetidinol gave mainly ring-opened products, while the *t*-butyl compound gave 3-substituted azetidines.[89]

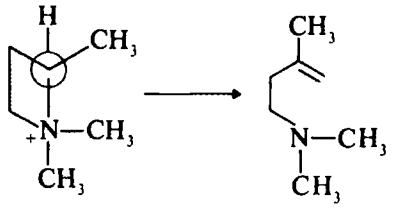
1-Alkyl-3-azetidine(α,α-diphenyl)acetonitriles undergo ring opening in hot 70% sulfuric acid and recyclization to give aminoalkyl furanones.[66]



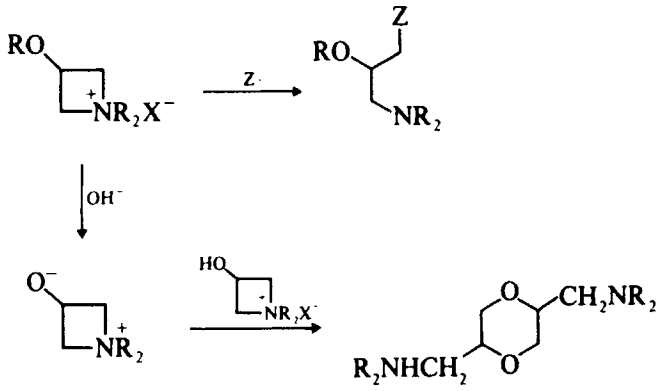
Ring opening by nucleophiles has been studied with several azetidines and azetidinols. 1-*t*-Butyl-3-azetidinol or the acetate are opened to the 3-aminopropyl acetates in high yield with potassium acetate in acetic acid. Ring opening of *t*-butylazetidinol or *t*-butylazetidine with amines or methanol requires acid catalysis.[151] Frehel et al. encountered ring opening by chloride on heating 1-*t*-alkylazetidinol hydrochlorides.[146] A number of papers and patents describe the reaction of 1-alkyl-3-azetidinols with phenoxides and the preparation of 1-aryloxy-3-alkylamino-2-propanols for use as adrenolytic agents.[98,256,451,452] Nucleophilic ring openings have been reported with 3,3-dimethylazetidine and isopropylamine at 130°C[186] and with *N*-tosylazetidine and an *N*-nitrotoluenesulfonamide.[350]

1-Azabicyclo[2.2.0]hexane is extremely reactive toward nucleophiles; the bridging bond opens to give 4-substituted piperidines under very mild conditions.[183]

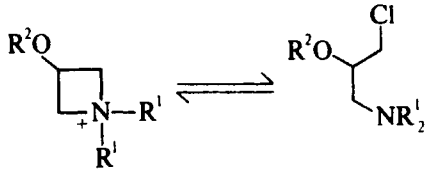
Quaternary azetidinium compounds undergo facile ring opening with good nucleophiles, but they are much less reactive alkylating agents than aziridinium salts. Thus Leonard and Durand found 1,1,2,2-tetramethylazetidinium perchlorate unreactive to refluxing methanol, a reaction condition which destroys the three-membered quaternary ring. With sodium methoxide, Hofmann elimination occurred exclusively because of the favorable antiperiplanar geometry.[281]



Gaertner has studied ring opening of several 1,1-dialkyl-3-hydroxyazetidinium salts.[157] Alkoxides, amines, phenoxides, or cyanide as nucleophiles (Z) are alkylated in high yields. With hydroxide, the zwitterion that is formed acts as a nucleophile to give bis(dialkylamino)methyldioxane.

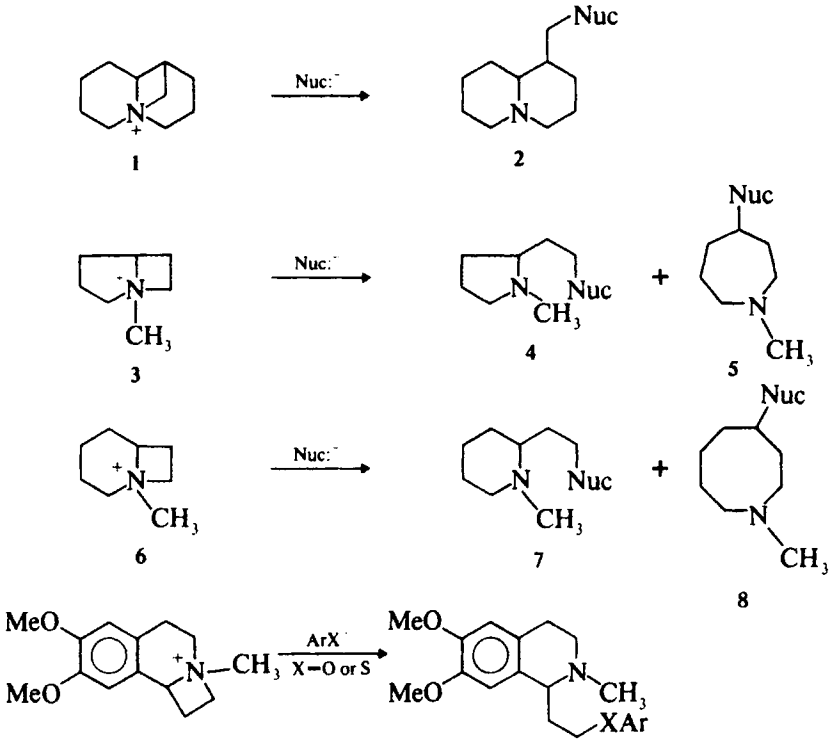


Chloride ion is a relatively ineffective nucleophile; however, the azetidinium chlorides and the ring-opened products are in equilibrium, and the 1-dialkylamino-3-chloro-2-propanol can be obtained by distillation into a cold trap. The position of the equilibrium has been studied for a series of 3-hydroxyazetidinium chlorides and the acetate esters in acetonitrile.[153] The fraction of azetidinium salt ranged from 70 to 90% with the hydroxy compounds, and only from 3 to 12% with the acetates. Thermodynamic parameters showed that the cyclization process is entropy controlled; the "ring opening" effect which results from increasing the steric bulk at either the N_1 or the C_3 group is attributed to 1,3-interactions of these substituents that destabilize the cyclic structure.



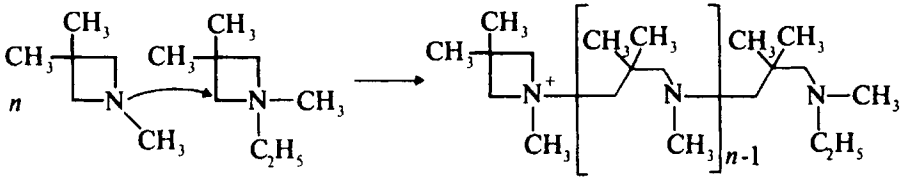
	% Cyclic at 30°C	
	$R^2 = H$	$R^2 = Ac$
$R^1_2 = (CH_2)_5$	89.3	11.9
$R^1_2 = (Et)_2$	86.7	8.3
$R^2_1 = (n\text{-}Bu)_2$	68.6	3.5

Ring opening by nucleophiles has been reported with several bi- and tricyclic azetidinium salts. The 1,5-methanoquinolizidinium system **1** gives exclusively the 4-substituted-methylquinolizidines **2**; the less strained ethano-bridged compound is unreactive with the same nucleophiles.[136] The 1-methyl-1-azoniabicyclo[3.2.0]heptane salt **3** gives approximately equal amounts of products **4** and **5**, resulting from attack at the 5- and 7-positions; the homologous azonia[4.2.0] system **6** gives predominately the 2-substituted piperidine **7** and a small amount of the azocine **8**. Formation and ring opening of tricyclic azetidino[2,1-a]isoquinolinium salts with phenoxides was found to be the most expeditious synthetic method to obtain 1-phenoxyethyltetrahydroisoquinolines.[324]



3. Polymerization

The propensity of azetidines to give polymeric products is mentioned at various points in the literature, but only recently have several cationic polymerizations of azetidines been carefully studied, mainly by Schacht, Goethals, and co-workers. The simplest case is 1,3,3-trimethylazetidine.[392] Polymerization can be initiated by a variety of electrophiles at temperatures over 60°C. At 80°C with triethyloxonium fluoroborate, the azetidine is converted to a tacky polymer, with 90% conversion after 80 hours. Initiation is very rapid, and the polymerization proceeds by successive alkylation of monomer units by a quaternary site in the chain.

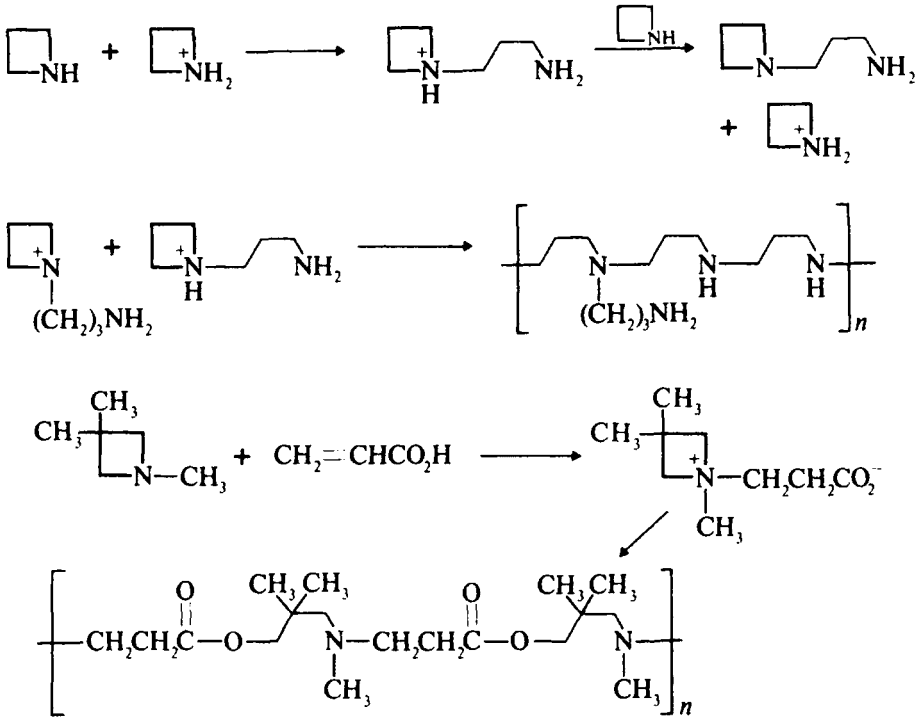


The concentration of growing chains remains constant and equal to the initiator concentration.[165] After a second monomer addition, the polymerization resumes at the same rate, indicating a living polymer with no termination steps. The absence of chain branching or termination is attributed to the fact that the basicity and reactivity of the cyclic monomer ($pK_a = 11.3$) is greater than that of the acyclic tertiary amino groups in the polymer chain.

In the cationic polymerization of 1-methylazetidine ($pK_a = 10.4$), propagation is much faster than that of the trimethyl compound because of the greater reactivity of the ring without *gem*-substituents at C_3. Some chain termination occurs in the 1-methylazetidine polymerization by reaction of growing chains with tertiary amino groups of other chains instead of monomer units. These termination steps, which lead to branching, reflect the lower basicity of the monomer compared to trimethylazetidine.[391] 1-β-Cyanoethylazetidine gives a crystalline polymer on initiation with alkylating agents.[482] 1-Alkyl-3-azetidinols give low molecular weight regular polymers on cationic initiation at 70°C.[28]

The parent azetidine undergoes polymerization by a different process. In the initially formed dimer, the cyclic imino group is less basic ($pK_a \cong 10.3$) than that of the azetidine monomer ($pK_a = 11.3$), and proton transfer occurs, initiating another dimerization. Thus the first stage of the process is conversion of over 70% of the monomer to dimer, which then leads to polymer. Further reaction can occur with either the cyclic tertiary amino group or the primary amine as the nucleophile, and the polymer has a branched structure containing about 20% primary, 20% tertiary, and 60% secondary amino groups.[393]

An alternating polymer of 1,3,3-trimethylazetidine and acrylic acid has been prepared from an equimolar mixture of the comonomers (without added initiator) via the betaine.[387,388]

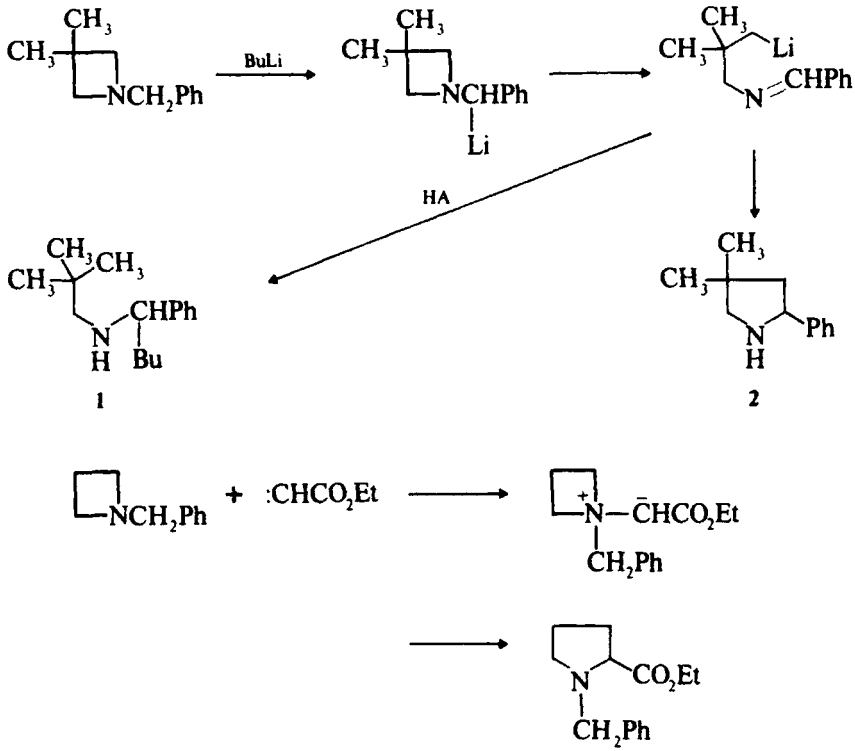


4. Rearrangements

A number of rearrangements have been observed in which the azetidine ring undergoes expansion or contraction. Certain of these reactions have been mentioned in Section IV in connection with functional group transformations at C_2 and elsewhere; others are discussed here.

Reactions of azetidines and azetidinium salts with strong bases lead to carbanion and ylid intermediates, which usually undergo rearrangement, when possible, to open-chain or five-membered cyclic products. *N*-Benzyl-3,3-dimethylazetidine is converted by butyllithium to a mixture of the pyrrolidine **2** and amine **1**, both arising by ring opening of the α-lithio compound.[8] 1-Benzylazetidine undergoes Stevens rearrangement on treatment with carbethoxycarbene to give the 1-benzylproline ester.[201]

Anderson and Wills have investigated the behavior of several azetidinium salts with strong bases and found a number of interesting and complex rearrangements. The reaction of the tetramethyl azetidinium salt **3** with butyllithium in ether gives (in 80% total yield) the products **4**, **5**, **6**, **7**, and **8**, shown at the right in Scheme 6, in respectively decreasing amounts.[476] The pathways indicated were demonstrated by carrying out the reaction with 2,2-d_2-, CD_3-, and 2,2-d_2-CD_3-labeled **3**, and interpretation of isotope distribution and kinetic isotope effects. The Stevens rearrangement product **4**, for which the secondary isotope effect indicates a

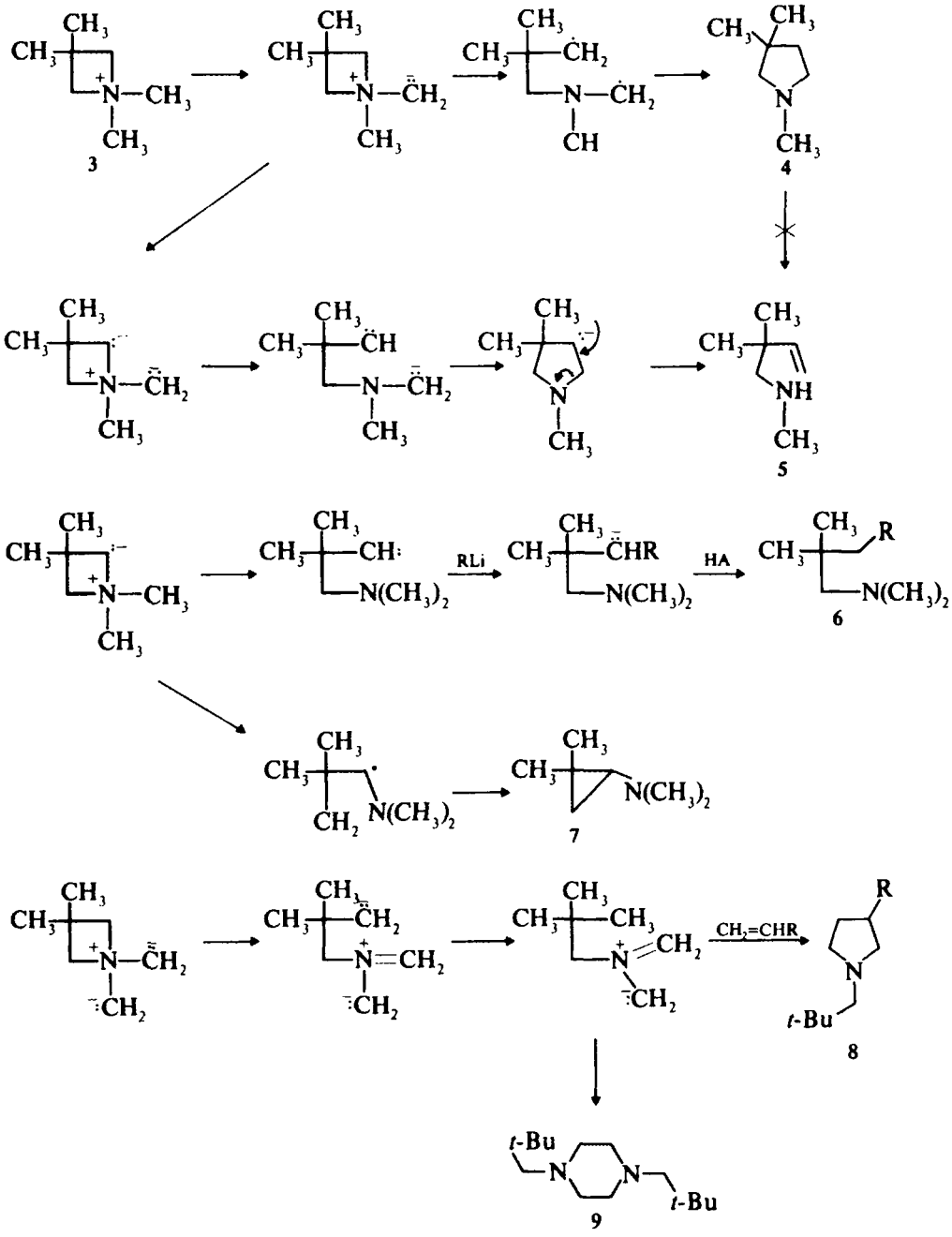


diradical mechanism, was shown not to be a precursor of the unsaturated amine **5**. The latter product, which was not formed in the reaction of **3** with the less basic phenyllithium, can be accounted for by a mechanism involving an ylid carbanion. Interestingly, the amine **6** – and presumably also analogous products from similar reactions of other quaternary azetidines[9] – is formed not by S_N2 substitution, but rather via a carbene. The minor product **8** is suggested to arise by dipolar cycloaddition of an alkene formed from cleavage of the solvent ether by the lithium reagent. In liquid ammonia, the piperazine **9** can be isolated.

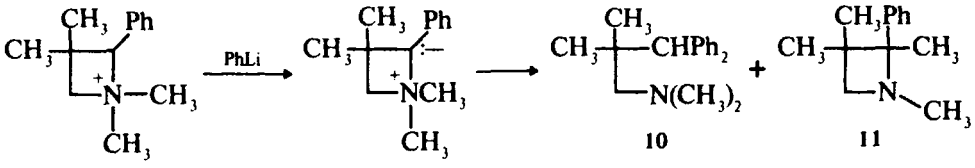
The reaction of 2-phenyl-1,1,3,3-tetramethylazetidinium ion with phenyllithium leads to **11** and **13**, which are Stevens rearrangement products of two different ylids, plus the Sommelet rearrangement product **12** and the amine **10**, presumably again from a carbene pathway.[9]

In the reactions of the 1,1-dimethyl- and 1-benzyl-1-methylazetidinium iodides with potassium amide in ammonia, only a single Stevens rearrangement product was obtained in each case. The 1,1-dibenzylazetidinium salt gave the Sommelet product **14** in 98% yield and only a trace of the Stevens product **15**.[11]

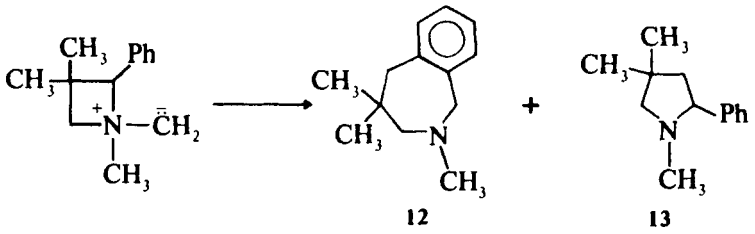
Isomerizations of 1-acyl-, thioacyl-, and carbamylazetidines have been systematically investigated by Iwakura, Nabeya, and co-workers. 1,3-Oxazines and 1,3-thiazines are obtained from acyl and thioacyl azetidines, respectively, by heating with catalysts such as toluenesulfonic acid, picric acid, or boron trifluoride.[232,234] With acids having a nucleophilic counterion such as chloride, ring opening is a



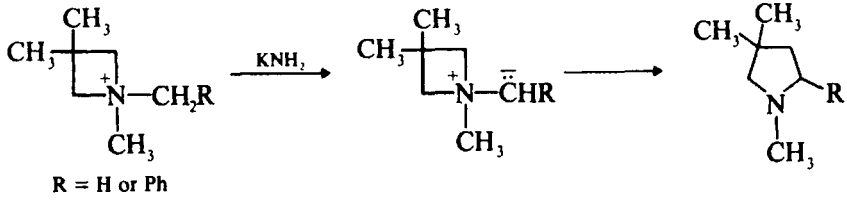
Scheme 6



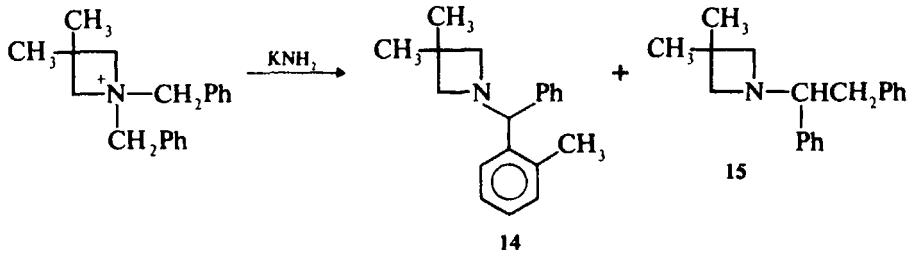
10 11



12 13

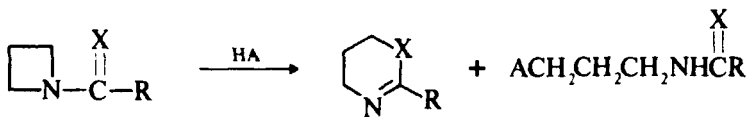


R = H or Ph



14 15

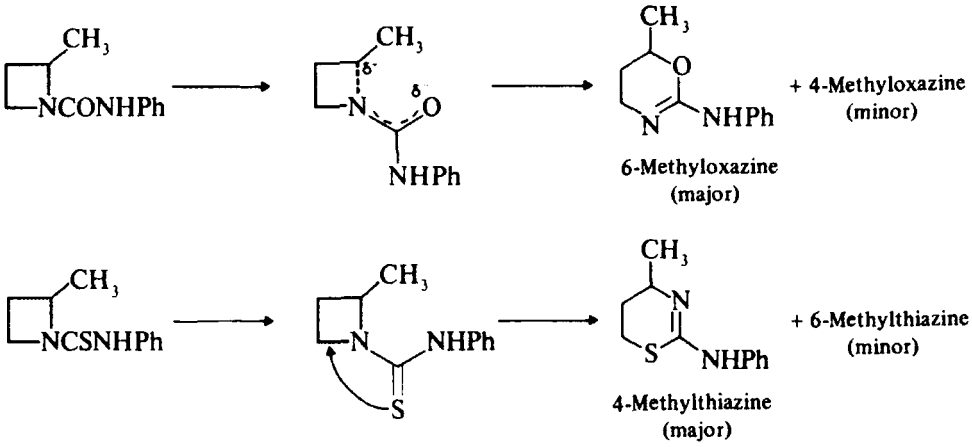
competing process. The tendency for attack of external nucleophile on the ring is more pronounced with amides than with the more nucleophilic thioacyl derivatives. Formation of an oxazine is particularly facile with a 2,2-disubstituted 1-acylazetidine.[40]



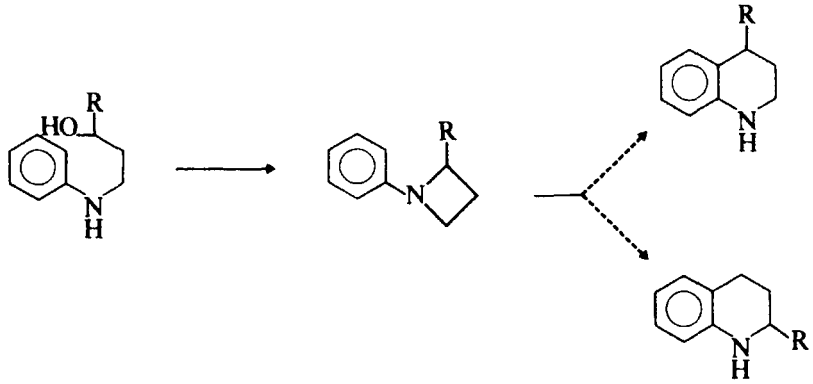
X = O or S

1-*N'*-Arylcarbamyl- and thiocarbamylazetidines rearrange under similar conditions to 2-aryliminooxazines and -thiazines; no pyrimidines were observed. In all cases, higher temperatures are required than for isomerization of the analogous aziridines to oxazolines.[232] The relative importance of S_N1-like and S_N2-like mechanisms in these reactions was explored by comparing the products obtained from the

1-phenylcarbamyl and 1-phenylthiocarbamyl derivatives of 2-methylazetidine.[234] With the urea, the major product with sulfonic or picric acid (and the only product with BF_3) was the 6-methyloxazine, resulting from attack at the 2-position of the ring, with developing charge stabilized by the methyl group. Conversely, the major or exclusive product from the thiourea was the 4-methylthiazine, resulting from attack at the less hindered 4-position of the azetidine.[234]

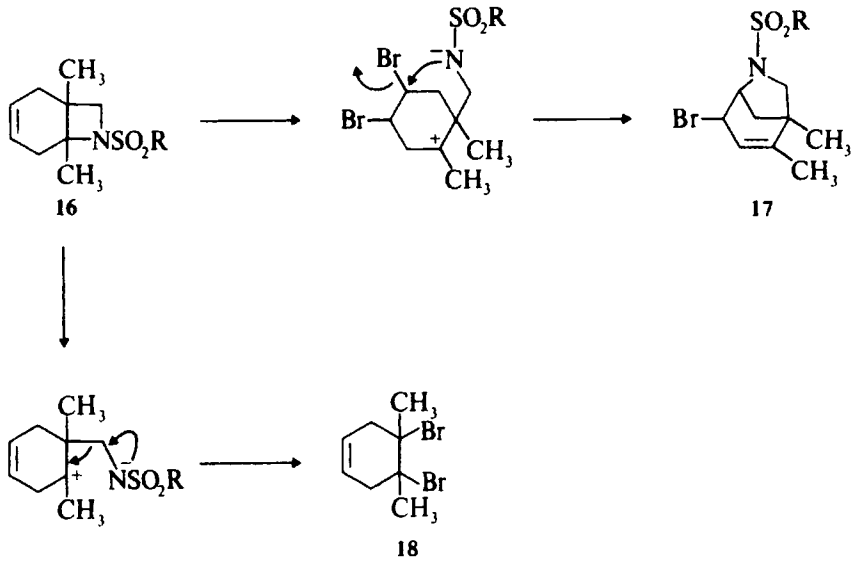


The isomerization of 1-arylazetidines in acid to tetrahydroquinolines has been assumed to be responsible for the scrambling of 2- and 4-substituents that is observed in the cyclodehydration of 1-arylamino-3-propanols in acid solution.[166,168,444] Azetidines have been isolated in small amounts in these reactions, but it has not been demonstrated that both tetrahydroquinolines can be obtained from an isolated azetidine by ring opening in different directions.

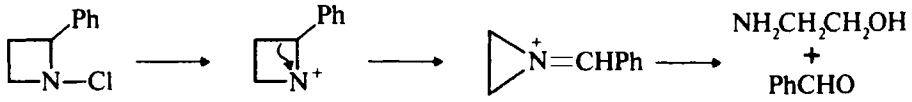


An unusual skeletal rearrangement occurs on addition of bromine to the unsaturated [4.2.0]bicyclic azetidine **16**.[358] The major product isolated is the 6-azabicyclo[3.2.1]heptene **17**, arising by migration of the sulfonamido group. Smaller amounts of the cyclohexadiene dibromide **18** and sulfonamide were also

isolated. Without the two methyl groups in **16**, the rearrangement does not occur, indicating a requirement for stabilization of the positive charge as the C–N bond breaks.

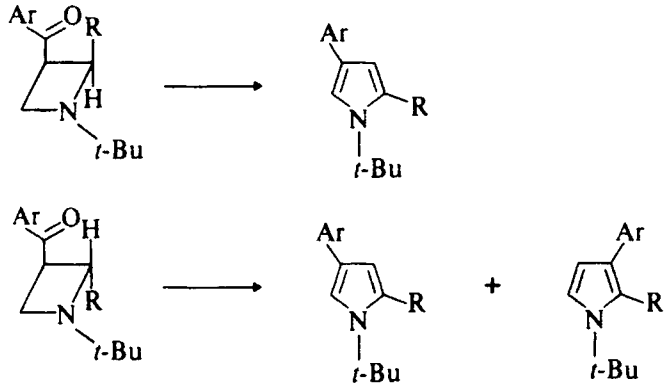


A rare case of ring contraction is observed in the reaction of 1-chloro-2-phenylazetidine with methanolic silver trifluoroacetate. The nitrenium ion formed by removal of chloride rearranges to the aziridinium cation; hydrolysis leads to benzaldehyde and 2-aminoethanol.[161]

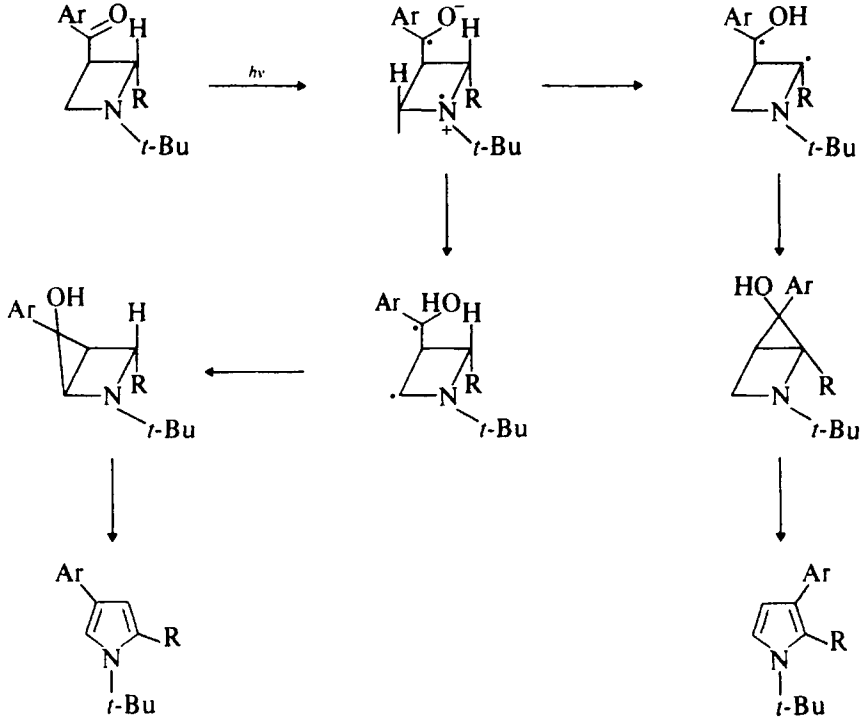


5. Photochemistry

Simple azetidines without chromophoric groups are transparent in the near ultraviolet and are photochemically inert.[302] As noted in Section III.2, a number of azetidines have been prepared in high yields by photochemical cyclization. The 2- and 3-acylazetidines are quite sensitive to photolysis, and Padwa and co-workers have encountered several interesting rearrangements and fragmentations. 1-*t*-Butyl- or cyclohexyl-3-aroyl- and *cis*-3-aroyl-2-phenyl azetidines are converted to 3-aryl- and 2-phenyl-3-arylpyrroles in high yield on direct irradiation or triplet sensitization.[352,354] The *trans*-3-aroyl-2-phenyl isomers give 2:1 mixtures of 2,4- and 2,3-disubstituted pyrroles.

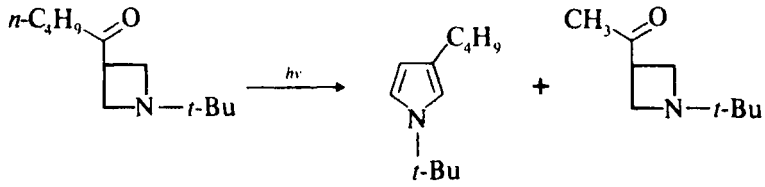


A mechanism that accounts for the products (and the fact that no rearrangement occurs in acid solution or with the hydrochlorides) is electron transfer from nitrogen to the π-π^* triplet followed by hydrogen abstraction from either C_2 or C_4 or both, depending on the availability of a *cis* hydrogen at C_2. Formation of an azabicyclopentanol is followed by ring opening and loss of water. This pathway is consistent with the distribution of deuterium labels in the pyrrole.[352,355]

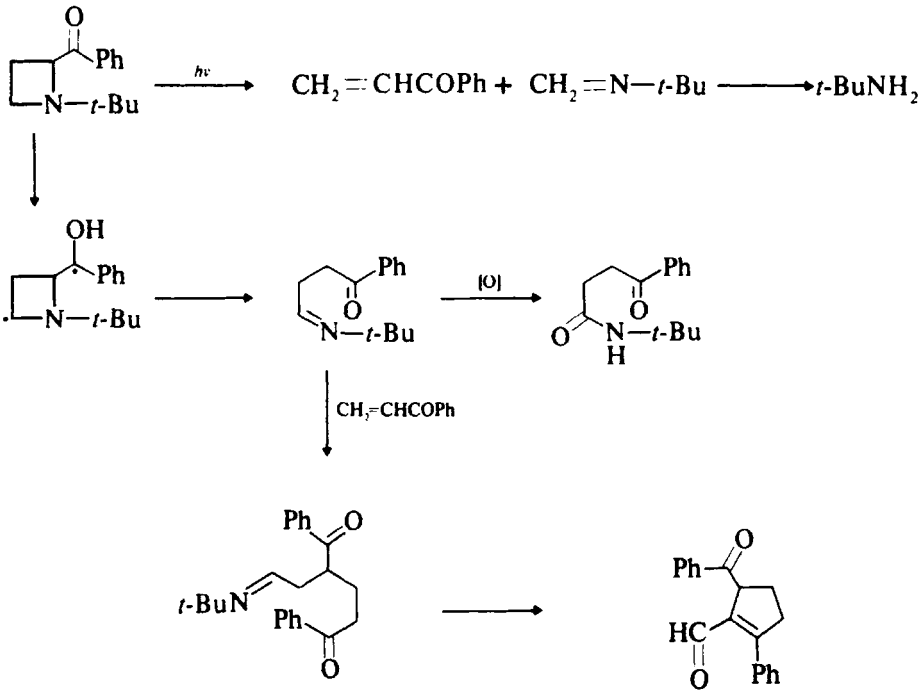


The 3-azetidinyl butyl ketone, on irradiation in ethanol, gives the 3-butyl pyrrole together with a small amount of the methyl ketone, arising via the enol

by type II ketonic cleavage of the alkyl chain. Fragmentation to the methyl ketone also occurs, as the only pathway, in acid solution. The latter finding, together with sensitization experiments, confirms that the pyrrole arises from the excited triplet, and the methyl ketone from the singlet.[352]

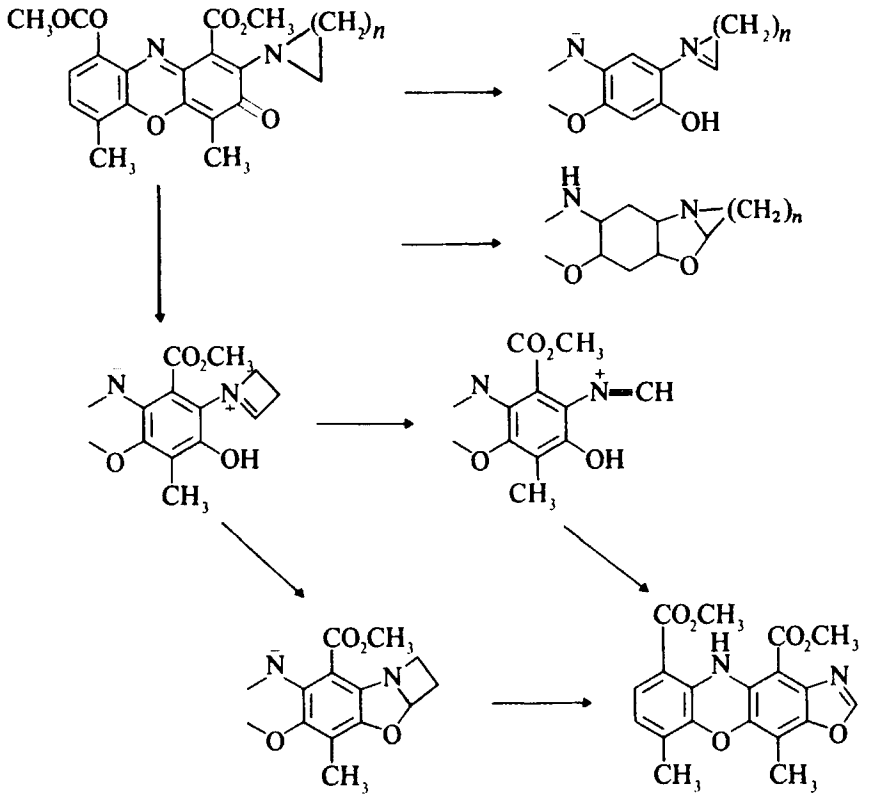


In contrast to the 3-acylazetidines, 1-*t*-butyl-2-benzoylazetidine undergoes fragmentation on photolysis to give a complex mixture of products. The compounds isolated in largest amount are phenyl vinyl ketone and *t*-butylamine, which arise by cycloreversion of the ring. Several products obtained in very small amounts can be rationalized by a diradical and open-chain imine. 1-Benzyl-2-*p*-phenylbenzoylazetidine, on irradiation, gives none of the analogous products, but rather a trace of the 1-benzyl-2-arylpyrrole.[352]



In a study of the photochemistry of 2-polymethyleneiminophenoxazones, pentacyclic oxazolidines were produced on irradiation of the pyrrolidine and higher members.[466] From the azetidine, however, the unsubstituted oxazoline was obtained by fragmentation of either the iminium intermediate or the penta-

cyclic oxazolidine. In the photolysis of the aziridine counterpart, the three-membered ring of the intermediate was opened by solvolysis.



2,5-Di(1-azetidino)-1,4-benzoquinones were found to be photostable compounds and did not give oxazolidines analogous to those obtained with the dialkylamino-quinones.[68]

VI. NATURALLY OCCURRING AZETIDINES

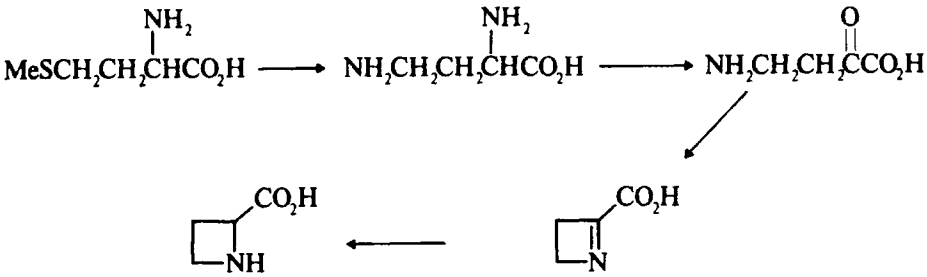
The presence of L-azetidine-2-carboxylic acid in *Convallaria majalis* (lily of the valley) was established in 1955.[140] Since then this amino acid and a few closely related compounds have been found in a number of plant sources, and their biological significance has been explored.

1. L-Azetidine-2-carboxylic Acid

L-Azetidine-2-carboxylic acid accumulates to the extent of 3–6% of the dry weight of a few plants, but it has not been detected in the proteins of these species.

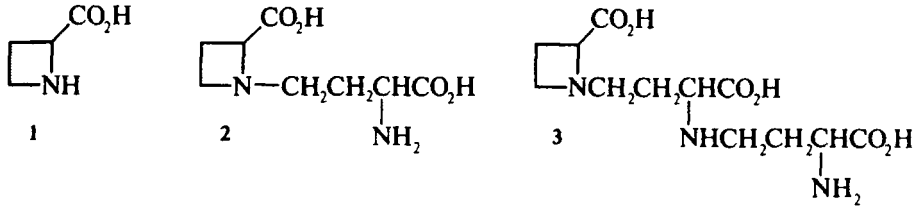
In addition to a number of members of the family Liliaceae, it has also been found in certain species of Agavaceae, Amaryllidaceae, Fagaceae,[262] Leguminosae[412] and Caesalpinacaeae,[413] and also in *Nicotinana* (Solanaceae),[277] the sugar beet *Beta vulgaris* (Chenopodiaceae),[141] and red marine algae.[228]

The biosynthetic origin of azetidinecarboxylic acid has been investigated in several plants. In feeding experiments with *C. majalis* using variously labeled L-methionine and *S*-adenosylmethionine, the incorporation and distribution of radioactivity in isolated azetidine-2-carboxylic acid were consistent with incorporation of the intact four-carbon chain of these precursors.[276,411] However, when methionine labeled with tritium at C_2 was fed, the azetidinecarboxylic acid was devoid of label, demonstrating that methionine is not a direct precursor.[278] Moreover, Sung and Fowden found that both α,γ-diaminobutyric acid and homoserine are more efficiently incorporated into azetidinecarboxylic acid than methionine in seedlings of *Delonix regia*,[413] leaving open the possibility that the final steps may involve the formation of γ-amino-α-ketobutyric acid, cyclization to the azetine, and reduction.[278]



L-Azetidine-2-carboxylic acid is an analog of L-proline, and its toxic inhibitory effects and incorporation into protein have been the subject of numerous studies. Some of the earlier work has been reviewed by Fowden.[138] A few examples are the inhibition of growth in *E. coli*,[179] plant tissue cultures,[142] and somatic mammalian cells.[367] The amino acid competes with proline and is incorporated into collagen in embryonic cartilage[95,270,422] and into hemoglobin in rabbit reticulocytes.[31]

Two other naturally occurring amino acids very closely related to azetidine-2-carboxylic acid **1** are the dimer **2** and the trimer **3**. These compounds, which can be synthesized *in vitro* by heating the parent azetidine acid **1** in water (Section IV.3), have been isolated from *Fagus sylvaticus* under conditions in which the oligomerization does not occur.[262,263] The trimer, called nicotinianamine, was originally isolated from tobacco leaves (*N. tabacum*) and assigned a different structure.[345] Nicotinianamine has also been isolated in significant amount from several other plants of the families Solanaceae and Graminae.[344] The variations in the concentration of the monomer **1** and the trimer **3** and the fact that the dimer **2** is not mentioned among the amino acids of tobacco indicate that the formation of these oligomers is enzymatically controlled and suggest that their formation may be a detoxication mechanism for protection of certain plants from excessive concentrations of **1**.

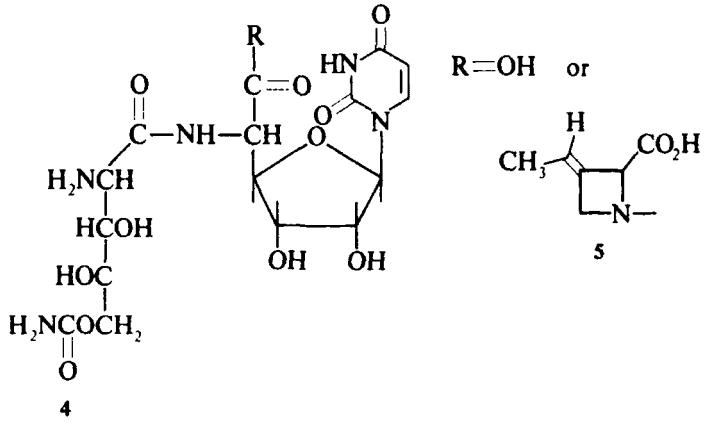


1 2 3

Other azetidine-2-carboxylic acids in combined form are found in the azetomycins, which are metabolites of *Streptomyces* antibiotics in which azetidinecarboxylic acid (added to the culture medium) is incorporated into one or both side chains of actinomycin-like structures.[13]

2. Polyoximic Acid

The polyoxins are a group of nucleoside-containing peptide antibiotics isolated from *S. cacaoi* that are useful antifungal agents against sheath blight in rice. These substances have the general structure shown in **4**. The R group, E-3-ethylidene-L-azetidinecarboxylic acid (**5**) in several structures is attached as the C-terminal unit of the tripeptide chain.[229]

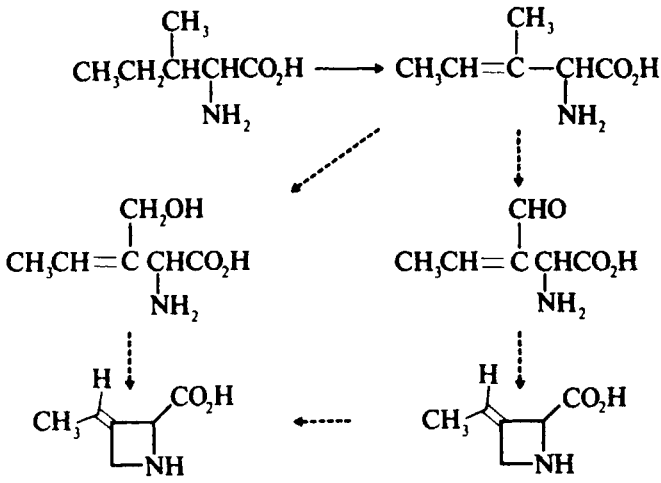


4 R=OH or 5

The racemic unsaturated azetidine acid is released by alkaline hydrolysis of the antibiotic. Racemization is avoided by reduction of the double bond prior to hydrolysis, and an optically active dihydro polyoximic acid (3-ethylazetidinecarboxylic acid) is obtained from the hydrogenated antibiotic. The L-configuration was assigned by comparison of the positive Cotton effect in the ORD spectrum of the *N*-(ethyldithiocarbamate) with that of L-azetidinecarboxylic acid. The E-configuration was based on the 22% NOE enhancement of the intensity of the 4-CH_2 signal on irradiation at the CH_3 frequency. Ozonolysis of the unsaturated acid takes an abnormal course to give monomethyl iminodiacetate.

The biogenetic precursor of polyoximic acid has been shown to be isoleucine, whose carbon chain is converted intact to the azetidine.[230] Incorporation of iso-

leucine requires functionalization of the methyl group to a primary alcohol or aldehyde, both of which have been isolated from plants.



VII. AZETINES (DIHYDROAZETES)

The name azetine for a four-membered ring containing one nitrogen atom and one double bond is prescribed by the Hantzsch–Widman system for naming heterocyclic compounds.[231] The position of the double bond is specified by a locant. Names based on azetine are in general use in the literature, and were used for indexing in *Chemical Abstracts* until 1971.



1-Azetine
(3,4-dihydroazete)



2-Azetine
(1,4-dihydroazete)

At the beginning of the *9th Collective Index* period, *Chemical Abstracts* discontinued *azetine* as an index term and now uses *dihydroazete.*

In the earlier edition of this volume, prepared in 1963, the chemistry of azetines was summed up in the statement that no adequately characterized compounds of this structure were known. In 1967, 2-ethoxy-1-azetines were obtained from azetidinones, and since this time a few dozen examples of these and other types of 1-azetines and a much smaller number of 2-azetines have been described. The most useful preparative routes to azetines in general are rearrangement or cycloaddition processes, which for the most part are not broadly applicable methods. Azetines, as a rule, are rather thermally labile and reactive compounds. The chemical properties depend very much on the substituents that are inherent in the

synthetic method, and reactions are therefore discussed together with the preparations.

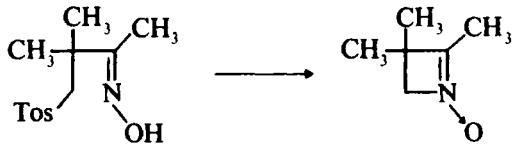
1. 1-Azetines

The largest single group of 1-azetines are 2-alkoxy compounds; these are functionally imino ethers and are discussed in a separate section. Other 1-azetines have been obtained by a variety of methods, most of which have been applied to only a few compounds with specific substituent patterns. The stability and properties of 1-azetines depend greatly on the presence of substituents; most examples contain a stabilizing group such as aryl at C_2, and often additional electronegative substituents.

A. *Cyclization Methods*

Conceptually, the most direct approach to a 1-azetine is cyclization of a β-amino aldehyde or ketone. Unsuccessful attempts to obtain azetines by this route have been mentioned,[324a] but no evidence for these products was demonstrated.

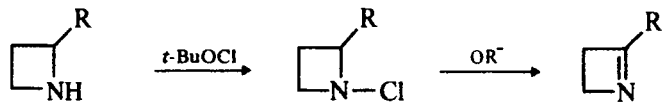
One example of an azetine by direct cyclization has been described.[39] This is the internal alkylation of the oxime 1 with 1,8-bis(dimethylamino)naphthalene to give the cyclic nitrone 2. The spectral properties of the rather unstable product were consistent with the azetine-1-oxide structure, and not with the isomeric oxazolines.



1 2

B. *Elimination Methods*

Dehydrohalogenation of 1-chloroazetidines has been used in two examples of 1-azetine synthesis, including the parent unsubstituted compound.

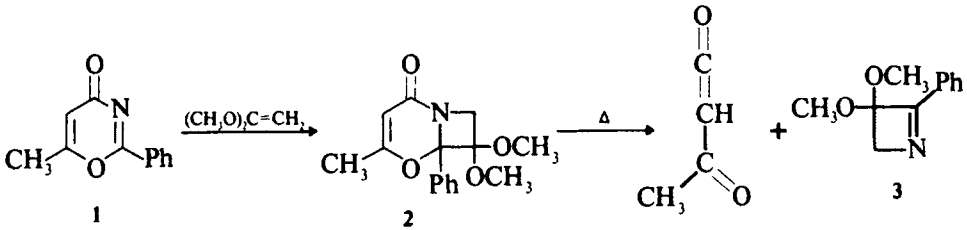


[R = H, Ph]

The first use of this method was in the preparation of 2-phenyl-1-azetine, which was obtained in 60% yield as a rapidly polymerizing oil by reaction of 1-chloro-2-phenylazetidine with sodium methoxide.[258]

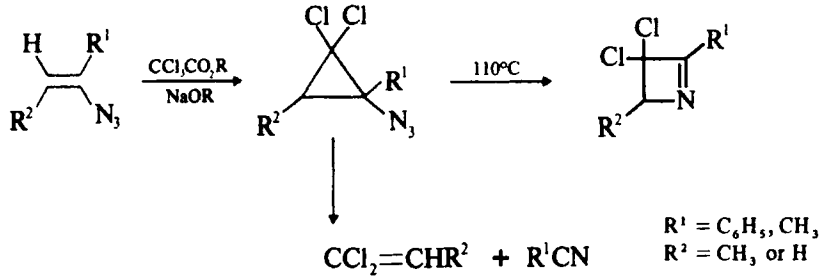
To obtain the parent compound, 1-chloroazetidine was passed in the gas phase at 94°C over potassium *t*-butoxide supported on silica gel to give 1-azetine in 98% yield and 95% purity.[184a] The compound was trapped in liquid nitrogen; it polymerizes rapidly at 20°C. Characteristic spectral data include a strong infrared band at 1570 cm^{-1}; ^1H nmr; δ 3.09 (t,2,8 Hz), 4.00(t), 8.22 (s); ^{13}C nmr: δ 36.1(C_3), 58.8(C_4), 187.0(C_2, $J^{13}C$–H 182). 1-Azetine is converted to the readily polymerized 2-azabutadiene by flash vacuum pyrolysis at 450°C.

Another case of azetine formation by elimination was observed on thermal decomposition of the bicyclic oxazine 2. 3,3-Dimethoxy-2-phenylazetine (3) was obtained in 57% yield by pyrolysis of 2 at 255°C. Mild acid hydrolysis of the azetine gave the α,α-dimethoxy-β-amino ketone.[253]



C. *Rearrangement of Cyclopropyl Azides*

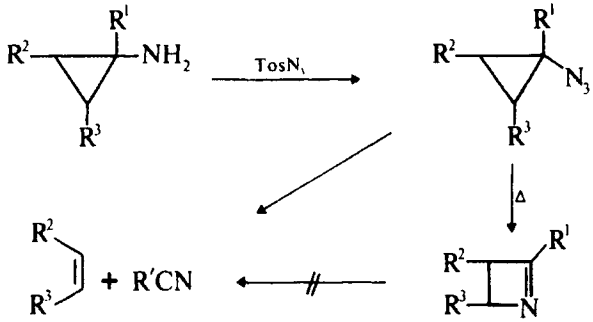
The first examples of 1-azetines (other than 2-alkoxy derivatives) were obtained by Levy and Hassner via thermal rearrangement of cyclopropyl azides, prepared in 40–60% yield by dichlorocarbene addition to vinyl azides.[197] Three 3,3-dichloroazetines were obtained in 55–75% yields by this reaction; the nitrile and alkene were minor side products.



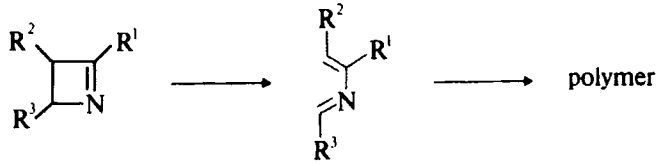
Szeimies and co-workers have studied the thermolysis of azides obtained by the diazo transfer reaction of sulfonyl azides and cyclopropylamines.[191,421] 2-Phenyl and 2-*p*-chlorophenyl-1-azetine were obtained in 60–70% yields; azetines were not observed in several other cases. Cyclopropyl azides without a substituent at C_1 (which would lead to a 2-unsubstituted azetine) give exclusively HCN and an alkene. The latter process occurs with complete stereospecificity, and is the only reaction observed with any cyclopropyl azides, including the dihalo compounds, on photolysis.[198,480] It has been shown conclusively that the alkene and nitrile

fragments observed in the thermal reactions do not arise by fragmentation of the initially formed azetine, but are primary products formed directly from the azide.

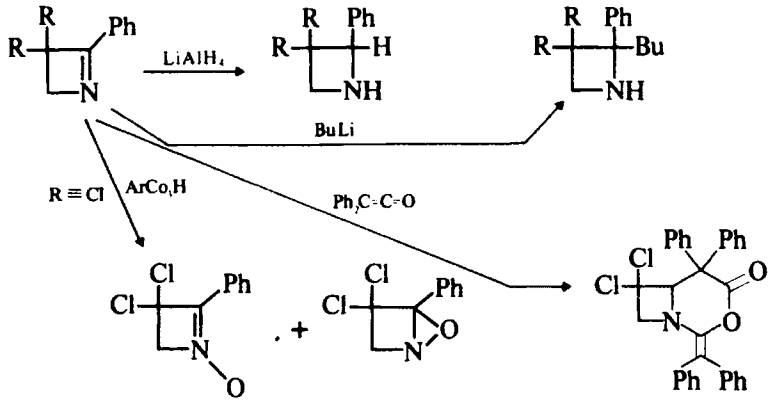
Thermal decomposition of cyclopropyl azides is very much faster (ca. 10^3-fold) than that of other azidocycloalkanes, suggesting participation of the three-membered ring in a concerted or partially concerted process. The possibility of vertical stabilization of an intermediate nitrene has been mentioned.[421] Hassner et al. suggest that the nitrene is involved in the photochemical cleavage to nitriles,[198] but not in the thermal reaction. The rate of azide decomposition depends to only a small extent on the substituents in the cyclopropyl ring, but the ratio of 1-azetine vs. alkene and nitrile products depend strongly on the nature and position of substituents.[198,420]



The principal limitation in the preparation of 1-azetines by this approach appears to be the instability of the products in many cases, in which only polymeric material is obtained. The major decomposition pathway is a pericyclic reaction leading to a 2-azabutadiene, which then rapidly polymerizes.[191] The dienes have been characterized by hydrolysis and *in situ* reduction. The ring opening is facilitated by aryl groups in the 3- or 4-position of the azetine, and these derivatives represent an exception to the usual situation in which small-ring heterocycles are stabilized by substitution.

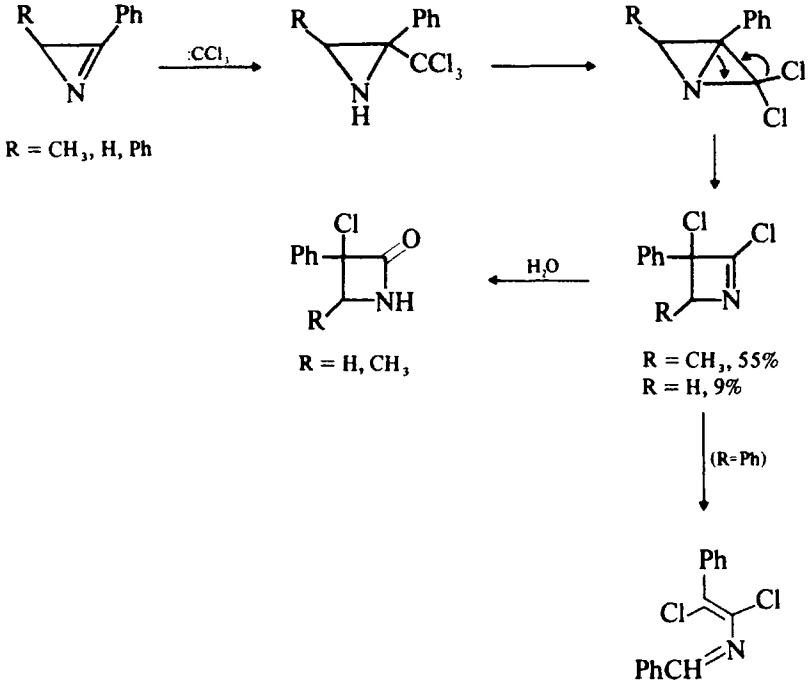


The chemical investigation of the 1-azetines prepared by this and other routes has been limited. Mild acid hydrolysis opens the ring to the amino ketone; this reaction and a characteristic IR absorption for the strained C=N bond at ν 1570–1580 have been used as structural evidence for the 1-azetine system. Lithium aluminum hydride reduction leads to azetidine in poor to moderate yields; addition of butyllithium to 2-phenyl-1-azetine gives 2-butyl-2-phenylazetidine.[197,421] Oxidation of 3,3-dichloro-2-phenylazetine with peracid leads to a mixture of the 1-oxide and a trace of the bicyclic oxaziridine.[191] 3,3-Dichloro-2-phenyl-1-azetine undergoes cycloaddition with two equivalents of diphenylketene to form the C–C ring-closure product, analogous to the reaction of simple imines, rather than the O–C closure product corresponding to that obtained with an azirine.[196]



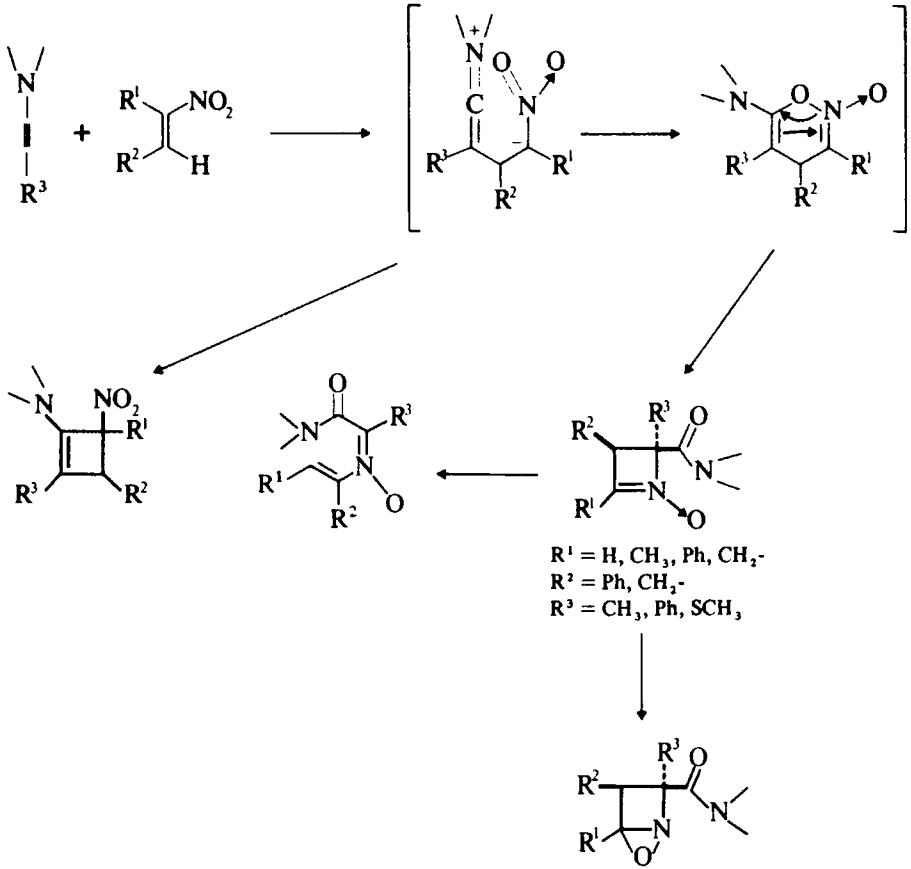
D. *Ring Expansion of Trichloromethylaziridines*

Hassner and co-workers have obtained 2,3-dichloro-1-azetines by the action of strong base on trichloromethylaziridines, produced in turn from azirines.[195] The azetines presumably arise by rearrangement of an intermediate 1-azabicyclo[1.1.0]-butane. Azetine structures for the 3-phenyl and 3-phenyl-4-methyl compounds were confirmed by acid hydrolysis to 3-chloroazetidinones. The 3,4-diphenylazetine (R = Ph) was not isolated; as observed in other series, the additional phenyl substituent facilitates ring opening to the azabutadiene.

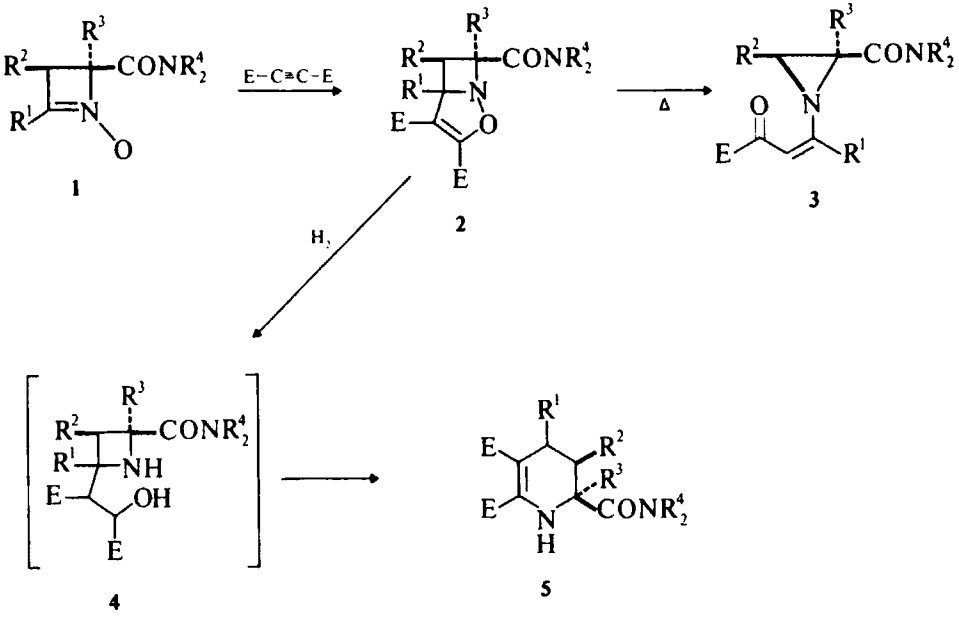


E. *Azetine-1-oxides from Nitroalkenes and Ynamines*

Several 1-azetine-1-oxides have been obtained as crystalline solids in 20–30% yields from the reaction of ynamines and nitroalkenes.[111,360b] Cyclobutenes are also formed. The pathway leading to the azetine oxides is suggested to be ring closure of the initially formed 1,4-dipole to a cyclic nitronate ester, followed by ring contraction. The stereochemistry of the products, with R_2 and carbamoyl groups *cis*, indicates that the rearrangement is a concerted, symmetry-forbidden $[{}_{\sigma}2_s + {}_{\pi}2_s]$ 1,3-sigmatropic process. The 1-azetine-1-oxides are thermally labile and undergo, on standing, conrotatory ring opening to the *E,E*-vinyl nitrones.[360b] Irradiation leads to the bicyclic oxaziridine.[360a]



Cycloaddition of acetylene dicarboxylate to the strained cyclic nitrones (**1**) leads to the azeto[1,2-*b*]isoxazoles (**2**) which rearrange thermally to aziridines (**3**). Analogous addition occurs also with methyl propiolate to give isomeric mixtures of the azetoisoxazoles. Hydrogenation of the adducts (**2**) leads to breaking of the N–O bond and ultimately rearrangement to the pyridines (**5**).[360a]

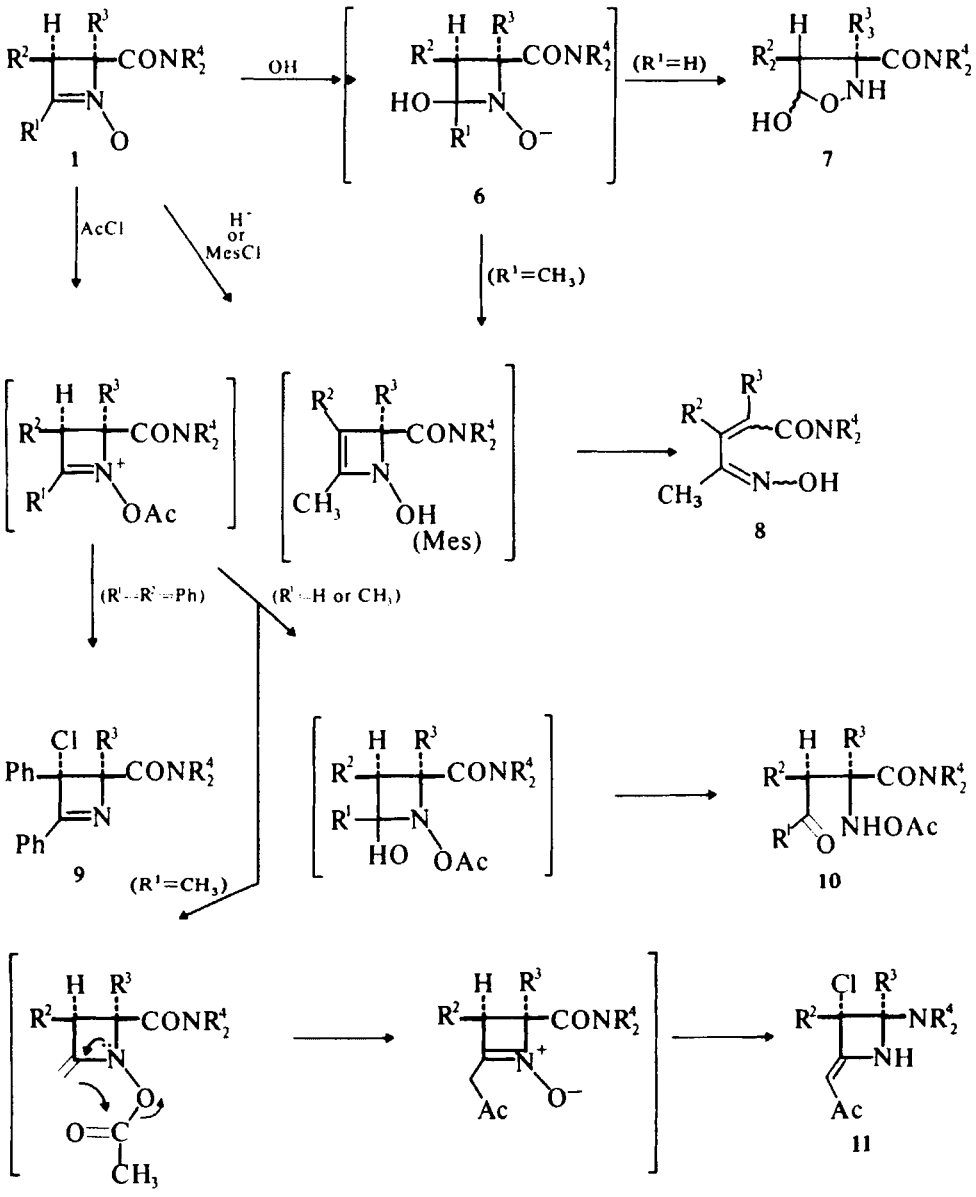


The azetine oxides undergo addition of hydroxide at the C=N bond; subsequent reactions depend on the substitution pattern. When $R_1 = H$, ring opening of the addition product (**6**) to an aldehyde followed by reclosure gives the 5-hydroxyisoxazolidines (**7**). With $R_1 = CH_3$, the products are oximes (**8**), presumably formed by elimination of water from **6** followed by electrocyclic ring opening of the 2-azetine.[360c] The latter process also occurs via iminium intermediates on protonation of the nitrones (**1**) in acetic acid or treatment with mesyl chloride.[360d] With acid chlorides, the final product depends on substituents and conditions. When $R_1 = H$ or CH_3, rapid quenching in water leads to the open-chain carbonyl derivatives (**10**). With $R_1 = CH_3$, enamine equilibria and acetyl transfer followed by hydride shift and chloride ion capture gives the chloro azetidine (**11**). The latter steps occur also in the original iminium salt when $R^1 = R^2 = Ph$, and provide the chloroazetine (**9**).

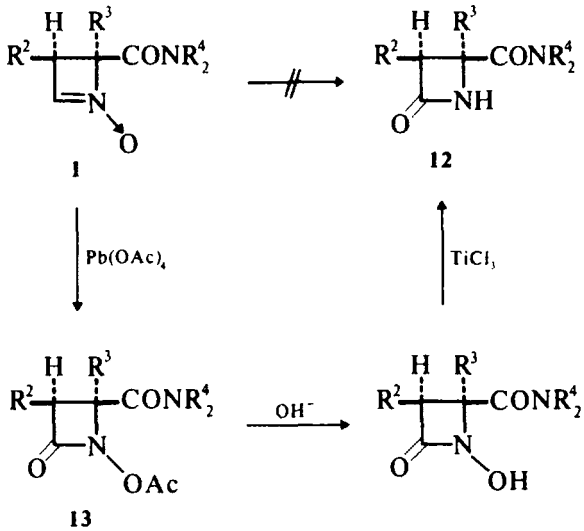
Azetidinones (**12**) were not observed among the products of any reactions of **1** with electrophilic reagents; apparently the elimination step required for a nitrone–amide conversion is of higher energy than that for the alternative pathways that are actually followed. Transformation to the azetidinone was accomplished by treatment of the nitrone (**1**) with $Pb(OAc)_4$, which led to the *N*-acetoxylactam (**13**) in 51% yield. Hydrolysis of the acetate and $TiCl_3$ reduction gave the azetidinone (**12**).

F. [2+2] *Cycloaddition*

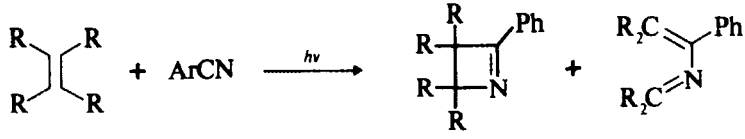
Several 1-azetines have been prepared by photochemical cycloaddition of benzo- or naphthonitriles with tetramethylethylene and a few other highly substituted



alkenes. Yang and co-workers isolated the 2-aryl-3,3,4,4-tetramethylazetines as crystalline sublimable solids in 30–40% yield after irradiation in hexane.[483] Cantrell studied the reactions of benzonitrile with a series of alkenes and obtained 1-azetines in low yields with tri- and tetramethylethylene and dimethylcyclohexene.[70] Azadienes are major by-products in these reactions; in the case of the 2-phenyltetramethylazetine, the diene was shown to be a secondary photoproduct formed from the azetine. In the irradiation of several alkenes and enol ethers, the azabutadiene



was the only product.[70] The presence of three or four methyl groups in these azetines has a significant stabilizing effect. Thus the compounds can be isolated by gas chromatography and purified by extraction into aqueous acid and rebasification.[70]

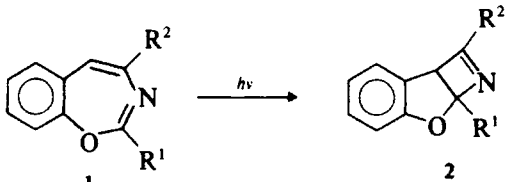


A major limitation in this photocyclization route is the fact that many alkenes add to the aromatic ring of the nitrile to give 1-cyanobicyclo[4.1.0]octadienes. It has been suggested that both azetines and bicyclic nitriles arise from exciplexes of different structures, with the complex required for azetine formation arising only from highly electron-rich alkenes.[70]

G. *Intramolecular Cycloaddition*

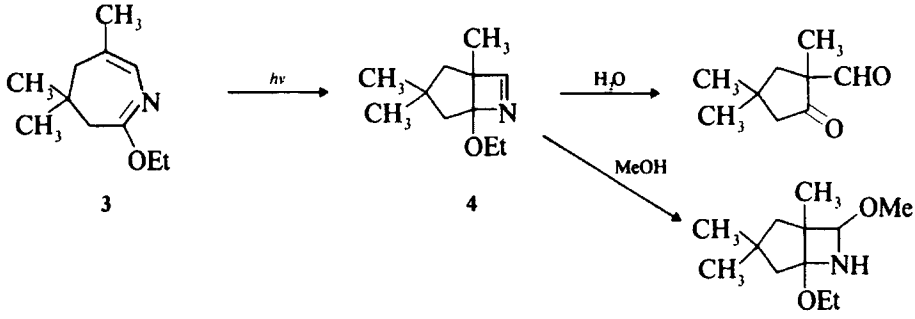
Another type of [2+2] cycloaddition leading to the 1-azetine system involves valence isomerization (cyclization) of the 2-azadiene system, i.e., the reverse of the ring opening discussed above. This process has been observed in a few cyclic systems, which on irradiation lead to bicyclic 1-azetines or products derived therefrom.

Lohse found that the benzoxazepines **1**, obtained by photochemical isomerization of isoquinoline oxides, are converted on further irradiation to benzofuroazetines (**2**).[292] Koch and Brown irradiated the ethoxydihydroazepine **3** with acetophenone sensitization. The bicyclic valence tautomer **4** was converted by acid hydrolysis to a ketoaldehyde, or, by addition of methoxide, to the 2-methoxyazetidine **5**.[252]



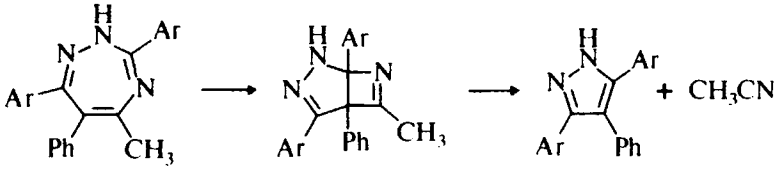
1 2

$R^1 = CN$; $R^2 = CH_3$, (m.p. = 70–71°C)
$R^1 = CH_3$; $R^2 = H$ (oil)

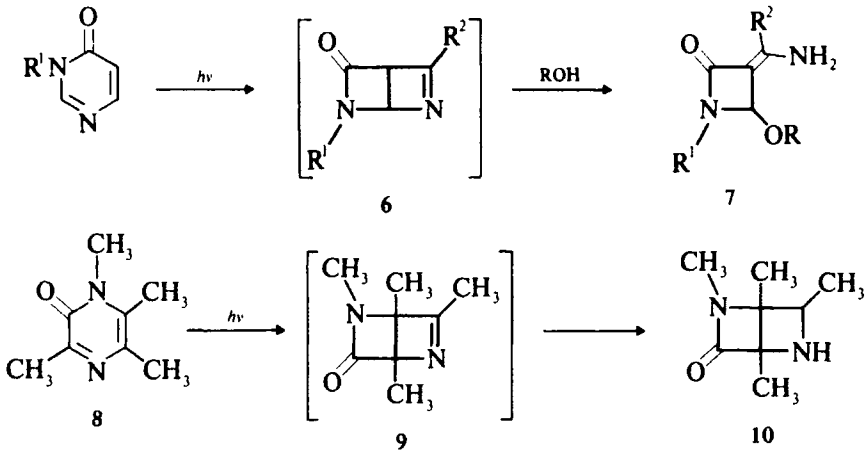


3 4 5

In some cases the postulated bicyclic azetine intermediate loses nitrile.[11a]



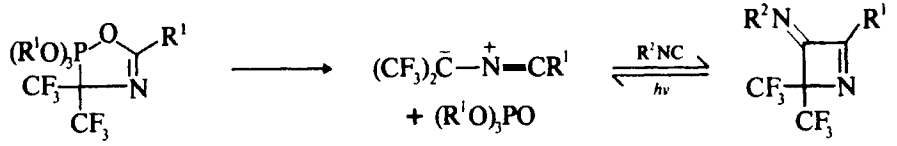
Irradiation of 3H-4-pyrimidinones in alcohol solution gives 4-alkoxy-3-alkylideneazetidinones (7), which arise by addition of alcohol to the bicyclic azetines **6**.[216] Similarly, the pyrazinone **8** is converted photochemically to the unstable 2,5-diazabicyclo[2.2.0]hexenone **9**, which was trapped by reduction to give the bicyclic azetidine **10**.[150]



6 7 8 9 10

H. [1+3] *Cycloaddition*

The cycloaddition of a nitrile ylid and isocyanide has been used by Burger et al. to obtain a series of 3-imino-1-azetines.[56] The ylids were generated by thermal decomposition of bistrifluoromethyl oxazaphospholines in the presence of the isocyanide. Decomposition of the thiazaphospholines occurs at lower temperature, but the nitrile ylid is accompanied by the *N*-(hexafluoroisopropylidene)thioamide, which in the presence of isocyanide leads to an iminothiazoline as an impurity in the azetidine.[58] The iminoazetines are distillable oils, formed in 60–80% yield. These products appear to be among the most stable and least reactive azetines that have been obtained. Hydrolysis in refluxing HCl cleaves the ring to the α-ketoacid; $LiAlH_4$ reduction gives the iminoazetidines.

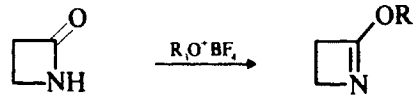


$R^1 = (CH_3)_3C$, Ar
$R^2 = C_6H_{11}$, Ar

Photolysis of the 2-aryl-3-cyclohexyliminoazetines leads to a cheletropic elimination of isocyanide, regenerating the nitrile ylid, which can be trapped by the usual reagents.[55,59]

2. 2-Alkoxy-, Alkylthio-, and Amino-1-azetines

2-Alkoxy-1-azetines are obtained in good yield by *O*-alkylation of 2-azetidinones with trialkyloxonium salts. Since azetidinones are accessible by a number of efficient methods, this simple and general alkylation process makes 2-methoxy or ethoxy compounds by far the most readily available 1-azetines.

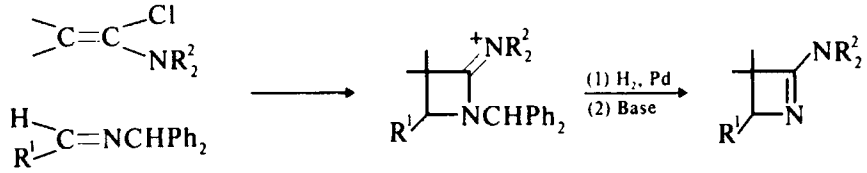


The first alkoxy azetines were reported by Testa et al., who treated 3,3-disubstituted azetidinones with triethyloxonium fluoborate in methylene chloride.[363] The procedure was extended by Borman to a series of 2-ethoxyazetines with 3- and 4-substituents,[46] and by Paquette and co-workers to a number of bicyclic and tricyclic 2-methoxy derivatives.[356] The methoxy compounds are usually prepared with trimethyloxonium fluoborate, but dimethyl sulfate can also be used, and is more convenient for larger scale preparations.[46] 2-Ethylthioazetines are obtained in high yields by alkylation of 2-azetidinethiones.[363]

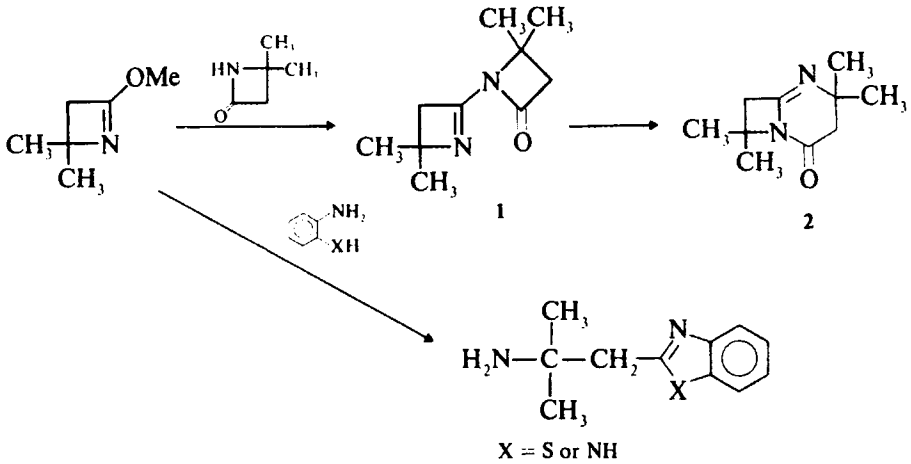
2-Alkoxyazetines are mobile liquids with a characteristic IR peak for C=N at 1610–1630 cm^{-1}; they form stable picrates and fluoborates. As strained imino

ethers, these azetines are extremely sensitive to moisture and acids, and must be dried over KOH before distillation.[46] Hydrolysis with aqueous acid gives azetidinones. 2-Alkylthio-1-azetines ($\nu_{C=N}$ = 1535) are more stable than the alkoxy counterparts and less prone to hydrolysis. They can be distilled without difficulty and converted to salts in aqueous solution.[363]

2-Dialkylamino-1-azetines have been obtained from the iminium salts, which are available by hydrogenolytic removal of the *N*-benzhydryl group from the cycloadducts of α-chloroenamines and Schiff bases.[295a]

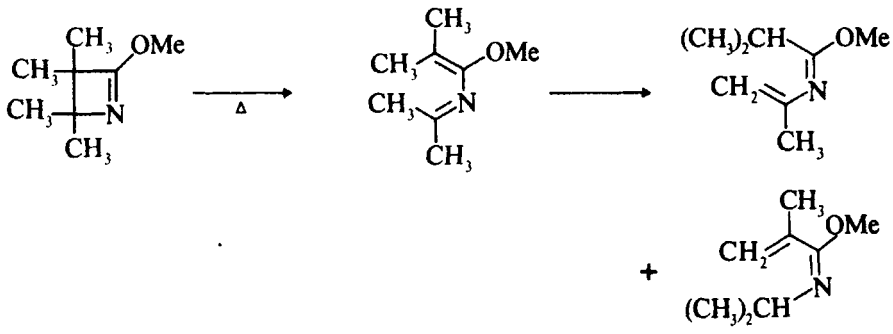


The imino ether system in 2-alkoxy-1-azetines is susceptible to attack by nucleophiles. Although this type of reaction should be capable of general exploitation for the preparation of a variety of azetines or azetidines, only a few reactions have been described (cf. Section IV.3). Lithium aluminum hydride reduction brings about reduction to the azetidine. 4,4-Dimethyl-2-methoxy-1-azetine reacts with 4,4-dimethylazetidinone to give the amidine **1**, which can be transformed by base to pyrimidine **2**.[45] With bifunctional amines, the azetine is converted to a 2-aminoalkylbenzimidazole or thiazole.[47]



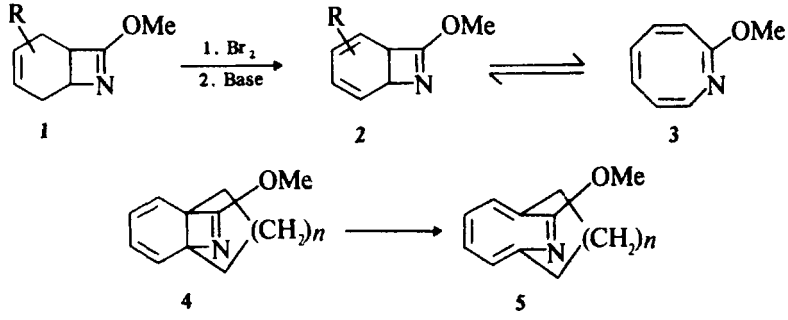
A. *Thermal Stability and Valence Isomerization*

2-Alkoxyazetines, when pure and dry, are quite stable and can be distilled at temperatures above 100°C. At higher temperatures, thermal gas phase decomposition occurs by pericyclic ring opening to alkoxyazadienes, which undergo hydrogen migration to unsaturated imino ethers.[19,359]



Aue and Thomas found that the relative rates of ring opening of three azetines were 3,4,4-trimethyl > 4,4-dimethyl > 3,3,4,4-tetramethyl.[19] The faster rate of the trimethyl compound was ascribed to the relief of CH_3–CH_3 interaction on ring opening, and the slower rate of the tetramethyl derivative was attributed to increased CH_3 repulsions in the azadiene. The rates were of the same magnitude as those of cyclobutene ring openings. In the liquid phase at 130°C with acrylonitrile as a diluent, 4,4-dimethyl-2-ethoxy-1-azetine undergoes Chapman rearrangement to the 1-ethyl azetidinone. Conversion of the 2-alkoxy-1-azetine to 1-methylazetidinone also occurs on treatment with methyl iodide.[357]

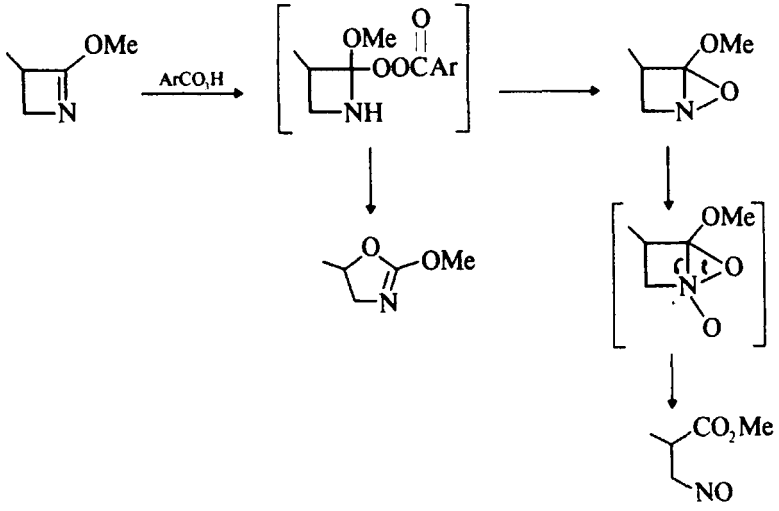
The bicyclic methoxyazabicyclo[4.2.0]dienes (**1**), on bromination and dehydrohalogenation, give 1-methoxyazocines (**3**), the bicyclic azetines **2** undergoing rapid valence isomerization.[145] Paquette et al. found the equilibrium between **2** and **3** to lie so far to the right that the bicyclic structures could not be detected spectrally, although [4+2] cycloaddition products of **2** were obtainable. In the azapropellane structures (**4**), the tricyclic azetine structure is maintained with a chain of four methylene groups ($n = 2$) because of "pinching" of the azocine ring in the bicyclic structures. With a five-carbon bridge ($n = 3$), the nmr spectrum indicates ring opening to **5** at elevated temperature; with $n = 4$, the bicyclic azocine **5** is the dominant structure.



B. *Oxidation*

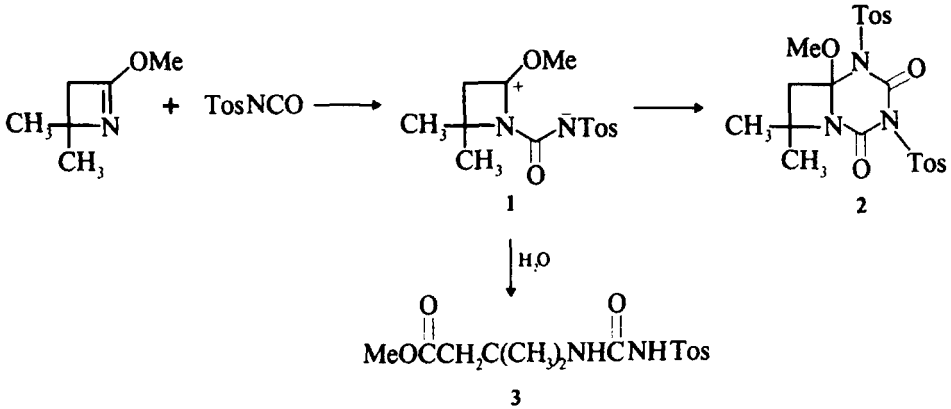
The reaction of 2-methoxy-1-azetines with peracid has been studied by Aue and Thomas.[18] The first step is presumed to be addition of peracid to the C=N bond.

Subsequent product distribution depends on the extent of methyl substitution at C_3. With no methyl groups, the intermediate peroxide decomposes to the transient 1-aza-5-oxabicyclopentane, observable by nmr. Further oxidation leads to the nitroso ester, analogous to the products obtained from several other cyclic imidates. With a methyl group at C_3, a competing process is Baeyer–Villiger type decomposition leading to the oxazoline. This pathway requires both the relief of ring strain and a suitable migratory group, and is most favored and indeed the only reaction observed with the 3,3-dimethyl compound.

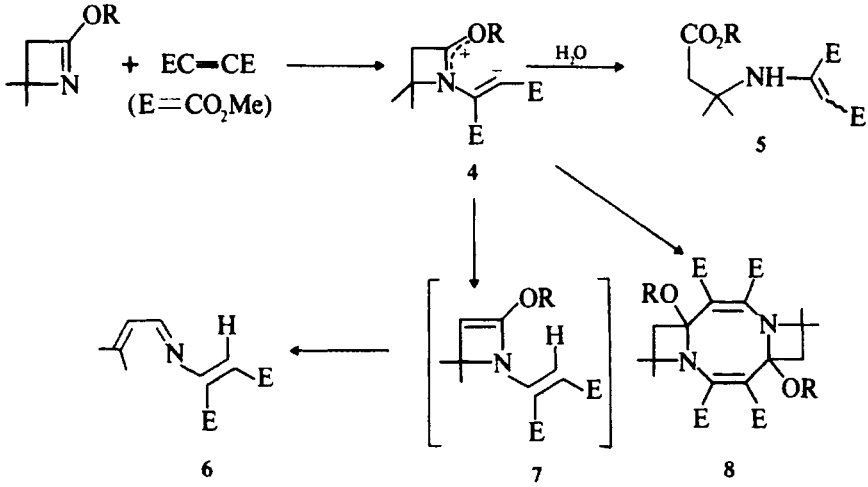


C. *Cycloaddition*

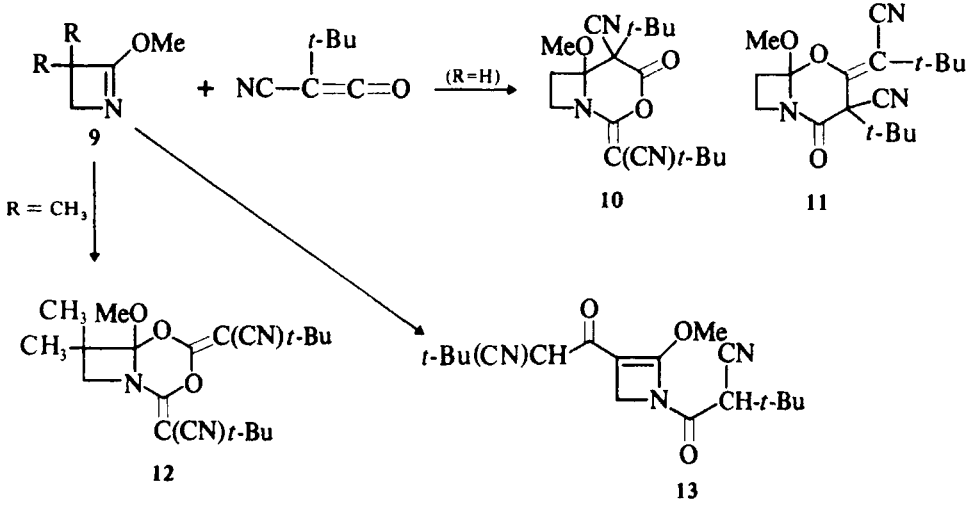
2-Alkoxyazetines react with isocyanates, ketenes, and activated acetylenes to give a variety of addition and cycloaddition products. With two moles of tosyl isocyanate, the normal 2:1 cycloaddition product **2** is formed. With excess azetine, the intermediate dipolar adduct **1** can be isolated; this adduct undergoes further addition of isocyanate to **2** or hydrolysis to the urea **3**.[20]



With dimethyl acetylenedicarboxylate in dichloromethane, 2-methoxyazetines (with hydrogen at C_3) give ring-opened addition product **6**, which apparently arises via the 2-azetine **7**. In the presence of water, the dipolar intermediate **4** is hydrolyzed to the open-chain ester **5**. In the less polar solvent CCl_4, dimeric 2:2 addition products, which are assigned the diazocine structure **8**, are formed.[21]



The reaction of alkoxyazetines with *t*-butylcyanoketene have been investigated by two groups with somewhat different results. From the 4,4-dimethylazetine **9**(R = H) plus cyanoketene in benzene, Aue and Thomas isolated in low yield a 1:2 adduct that was assigned the oxazinone structure **10** on the basis of spectral data.[22] Schaumann and Mrotzek obtained from the addition of **9** to either the ketene or ketene dimer a different product, to which they assigned the structure **11**. When monomeric ketene was added to a solution of the azetine, another 2:1 adduct, which was considered to be the 2-azetine derivative **13**, was obtained.[394] Cyclo-



addition of the ketene and 3,3-dimethylazetine **9**($R = CH_3$) gave a product which was formulated as the dioxazine **12**;[22] an alternative structure analogous to **11** has been proposed.[394] Additional information on these structures from crystallographic data is needed.

3. 2-Azetines

Only a few well-authenticated 2-azetines have been described. The 2-azetine structure readily undergoes valence isomerization to a 1-azabutadiene structure, and several compounds reported as 2-azetines have been shown to be or may be the open-chain isomers instead; available spectral data frequently do not distinguish between these possibilities.

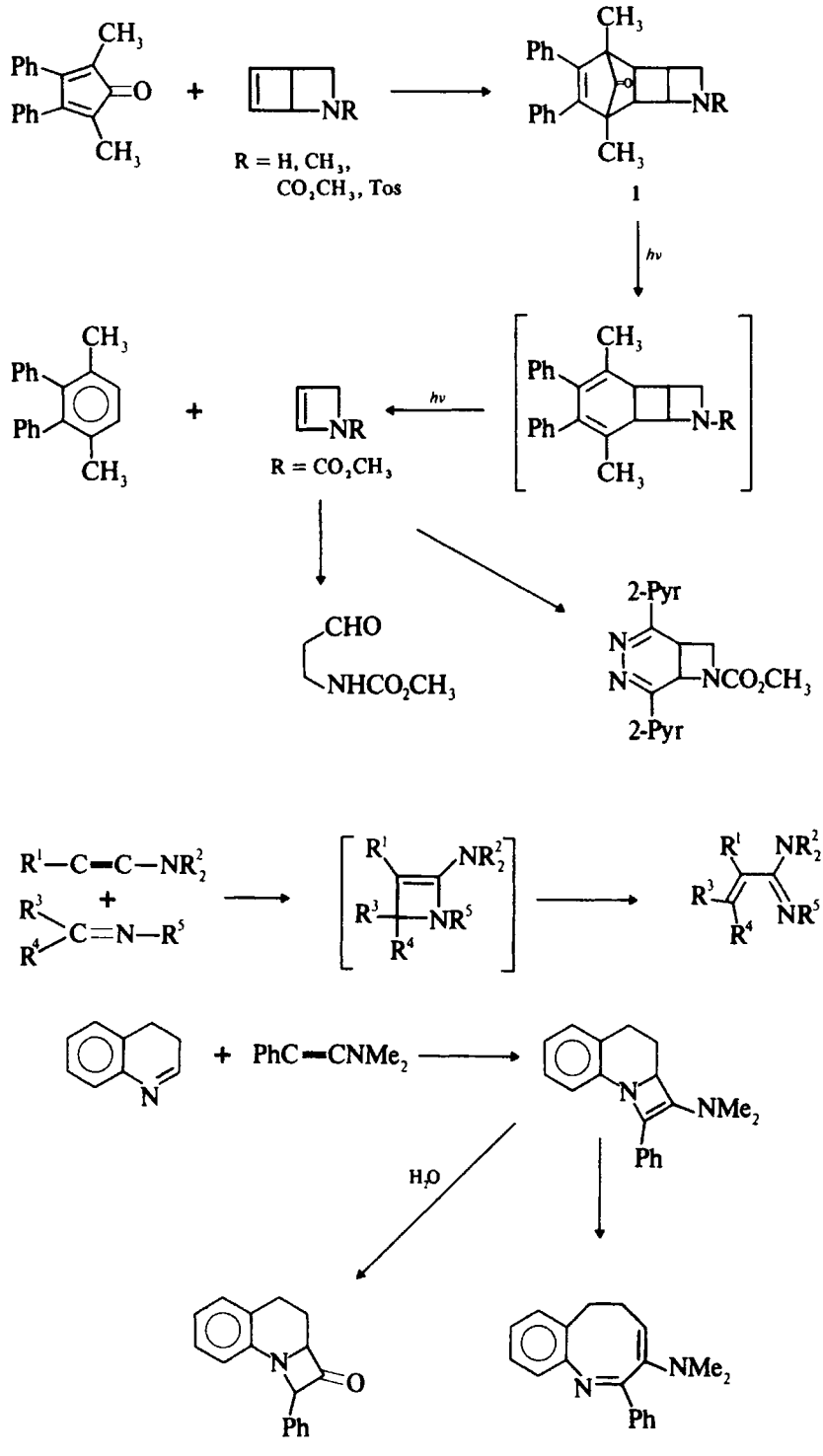
A. *Elimination*

The only simple 2-azetines have been obtained by an ingenious reverse cycloaddition process starting with the Diels–Alder adduct of dimethyldiphenylcyclopentadienone and the bicyclic azetidines obtained via dihydropyridines (Section III.3). Irradiation of the adduct **1** with an electronegative *N*-substituent gave the 2-azetine; the parent compound or the 1-methyl derivative were not obtained.[467] The methoxycarbonyl azetine was thermally stable below 50°C. It hydrolyzed slowly in aqueous acid (and more rapidly with irradiation) to the aldehyde; it underwent cycloaddition with dipyridyltetrazine, but not with typical enamine-trapping reagents.

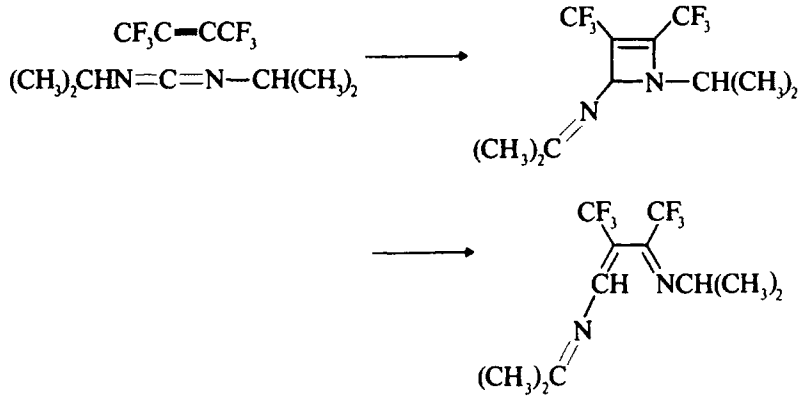
B. *Cycloaddition*

Formation of a monocyclic 2-azetine by cycloaddition requires the [2+2] addition of an acetylene and a C=N bond. The reactions of highly nucleophilic aminoalkynes and azomethines have been investigated by Fuks and Viehe.[147] 2-Azetines were not isolated; the products obtained were the unsaturated amidines formed by pericyclic ring opening of the azetines, analogous to the amides obtained via oxetenes in the reactions of ynamines and carbonyl compounds. Addition of 1-dimethylamino-2-phenylacetylene to 3,4-dihydroisoquinoline in the presence of BF_3 gave a mixture of the aminobenzazocine and the fused ring azetidinone. When the reaction mixture was quenched with water, only the azetidinone was produced, clearly indicating the presence of the tricyclic azetine.

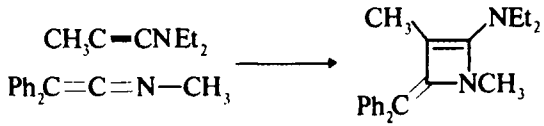
2-Azetine structures proposed for other cycloaddition products of ynamines and azomethines[453] and of ketene-*N*,*N*-acetals with sulfonyl imines (followed by loss of amine)[123] have been suggested[147] to be in fact the valence isomeric amidines, and the evidence available seems to bear this out. An azetine structure was also suggested for the cycloaddition product of hexafluoro-2-butyne and diisopropyl-


CH3
Ph
Ph
O
CH3
+
NR
R = H, CH3,
CO2CH3, Tos
CH3
Ph
Ph
O
NR
CH3
1
hν
CH3
Ph
Ph
CH3
+
NR
hν
R = CO2CH3
CH3
Ph
Ph
N-R
CH3
CHO
NHCO2CH3
2-Pyr
N
N
NCO2CH3
2-Pyr
R1—C≡C—NR2
2
+
R3
R4
C=N—R5
R1
NR2
R3
NR5
R4
R1
NR2
R3
NR5
R4
+ PhC≡CNMe2
N
N
NMe2
Ph
H2O
N
O
Ph
N
NMe2
Ph

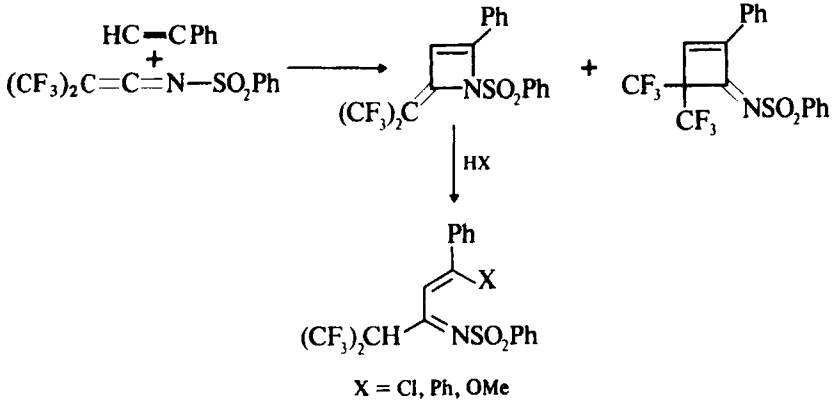
carbodiimide,[192] but nmr data are more consistent for the ring-opened valence isomer.[193]



Stable 2-azetines appear to have been obtained in two alkyne–ketenimine cycloadditions. The reaction of 1-diethylamino-1-propyne with *N*-methyldiphenylketenimine gives an equimolar mixture of 1:1 and 1:2 cycloaddition products. The 1:1 product is assigned the 2-azetine structure;[163] the energy barrier for isomerization to the open-chain allene is expected to be higher than for 2-azetines lacking the exocyclic double bond at C_4. The corresponding reaction with *N*-aryl ketenimines leads to quinoline products.

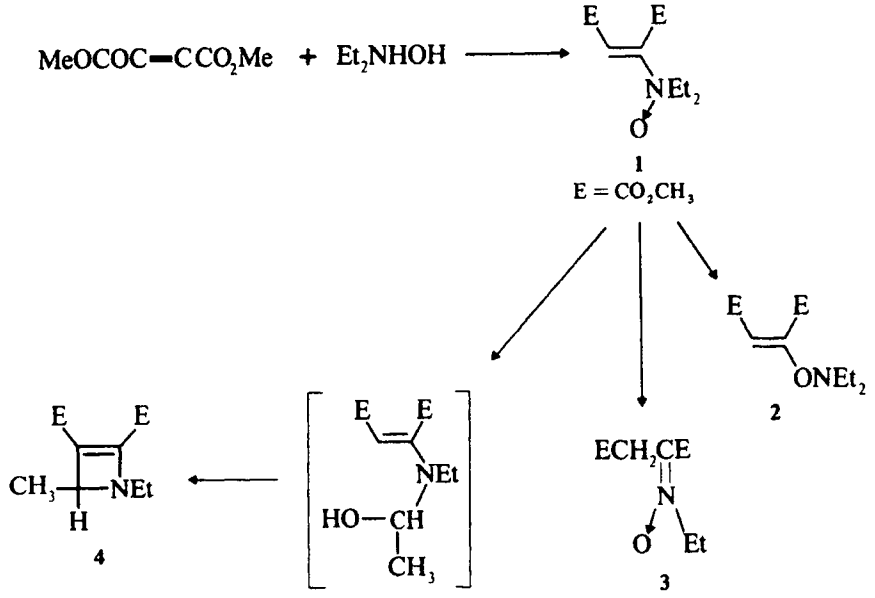


The second case is the reaction of the *N*-sulfonylhexafluoro ketenimine with phenylacetylene, which leads to a separable 2:1 mixture of 2-azetine and cyclobutene.[105] The azetine is stable on prolonged heating at 100°C. With HCl or aniline, the ring opens to give addition products formulated as sulfonylimino enol derivatives.



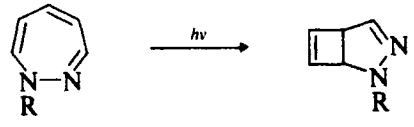
X = Cl, Ph, OMe

Reactions of acetylenedicarboxylic ester with C=N bonds generally lead to 2:1 cycloaddition products, but one compound considered to be a 2-azetine has been obtained indirectly by addition of diethylhydroxylamine to dimethyl acetylenedicarboxylate.[478] The initial adduct is the vinylamine oxide **1**, which decomposes by rearrangement to the O-adduct **2** or by alkene elimination to the nitrone **3**. Under slightly different conditions, a third product, stable to distillation and to mild acid hydrolysis, was isolated in 9% yield and described as the azetine **4**, but this structure cannot be accepted without reservations on the basis of the limited data available.



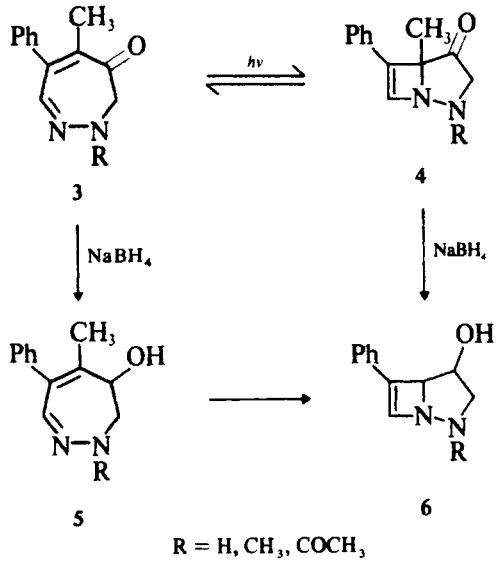
C. *Intramolecular Cycloaddition*

A potential route to bicyclic structures encompassing a 2-azetine unit is intramolecular [2+2] cycloaddition of a cyclic 1-azadiene system. A number of azepines and diazepines contain this system, and their cyclization reactions have been reviewed.[372] In most cases these compounds have available also an alternative cycloaddition path leading to a valence isomer with a carbocyclic four-membered ring, and this is the reaction observed, as in the 1,2-diazepines **1**.



1 **2**

Bicyclic 2-azetines are obtained in high yield from the dihydrodiazepine derivatives **3** and **5**.[443] Irradiation of the yellow ketone **3** with sunlight leads to the bicyclic isomer **4**; the photochemical conversion is more rapid with R = H or CH_3 than $COCH_3$. The colorless alcohol **5**, on irradiation at 254 nm, gives epimeric mixtures of bicyclic azetines, with the NH or NCH_3 compounds in this case cyclizing at much lower rates. The bicyclic ketone **4** (with R = H or CH_3) reverts rapidly back to the diazepinone in the dark, presumably by way of a highly polar transition state, but the other bicyclic azetines are thermally stable, since conrotatory ring opening is sterically impossible.



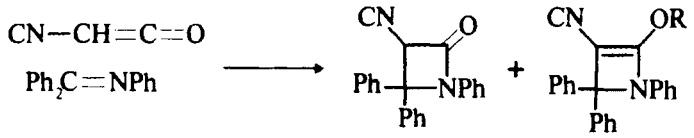
3 **4**

5 **6**

R = H, CH_3, $COCH_3$

D. *Enolic Azetidinones and Imines*

Enolic structures of 2-azetidinones or the imines are formally 2-azetines. Two examples have been described. The azetidinone derived from isocyanoketene and benzophenone anil had spectral characteristics consistent with a 1:1 mixture of azetidinone **1** and enol **2a**; reaction of the anion with $(CH_3)_3SiCl$ gave the trimethylsilyl derivative **2b**.[217]

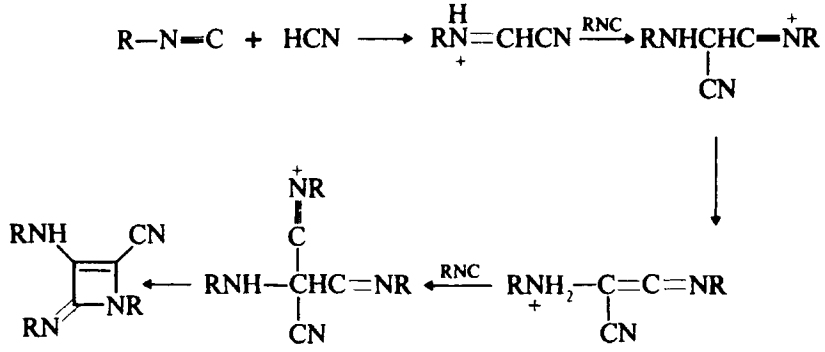


1 **2**

2a R = H

2b R = $SiMe_3$

The second case is a product obtained by HF-catalyzed condensation of diisobutylene and HCN. Among other products, de Vries described a compound assigned structure 3, derived from three moles of alkene and four of HCN. The principal intermediate is *t*-octyl isocyanide, which condenses with HCN followed by addition of two further moles of isocyanide in the equivalent of a [1+1+2] cycloaddition process.[108] This azetine was relatively inert toward hydrolytic or reductive conditions. In refluxing toluene, a mole of alkene is lost (with ring expansion) to give an imidazole.



3

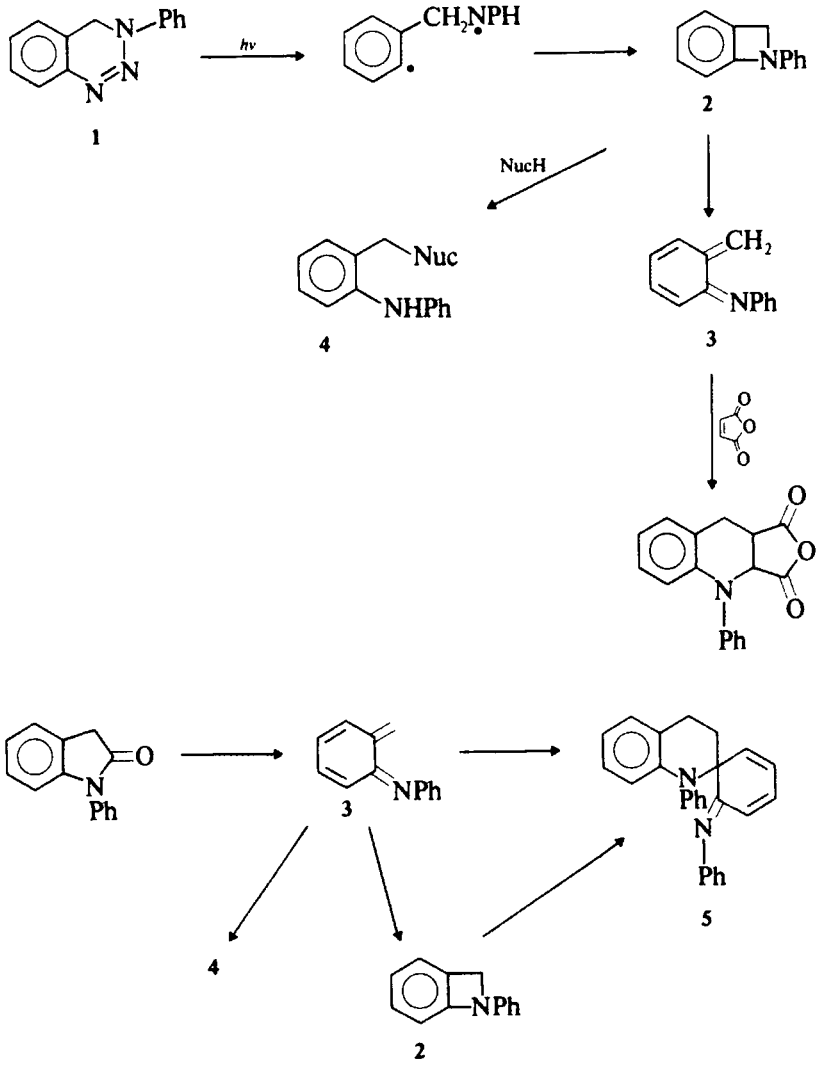
R = $(CH_3)_3CCH_2C(CH_3)_2$

4. Benzazetines

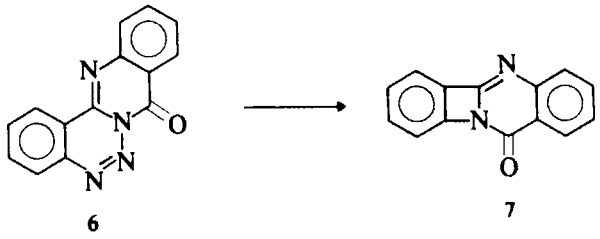
2-Azetines in which the double bond is fused with an aromatic ring are commonly named benzazetines. These compounds are more stable than monocyclic 2-azetines, although extended MO calculations with partial geometry optimization indicate a lower S_0 energy for the quinone methide imine isomer.[257]

The first benzazetine described was the 1-phenyl derivative 2, obtained in 50% yield by irradiation of the benzotriazine 1, together with benzalaniline and 9,10-dihydrophenanthridine.[61] These products are suggested to arise from the diradical generated by loss of nitrogen. The benzazetine 2 undergoes ring opening to the quinonemethide anil 3 on heating or photolysis; it is also readily attacked by nucleophiles to give ring-opened products (4).

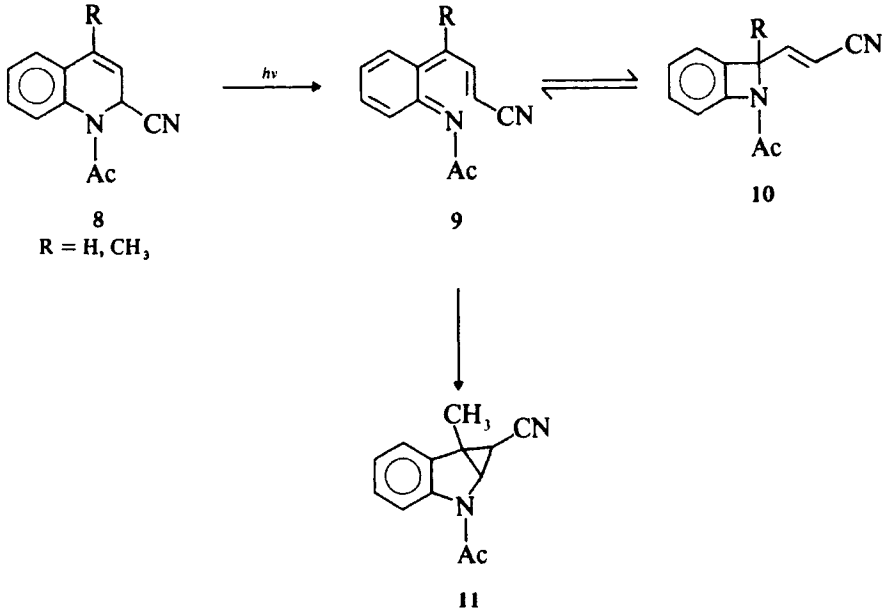
An attempt to generate 1-phenylbenzazetine by photolytic decarbonylation of 1-phenyloxindole gave in high yield the spiro dimer (5) of the quinonemethide anil 3. Quantum yield measurements indicated the formation of a low concentration of benzazetine 2, derived from 3; separate irradiation of the benzazetine also led to dimer 5, probably by condensation of a mole of 2 and 3.[135] Irradiation of the oxindole in the presence of nucleophiles gave addition products (4) of the quinonemethide anil.[134]



An analogous photochemical ring contraction of a triazine has been reported with the polycyclic triazine **6**, which led to the azetine **7** in 35% yield.[124]



Another type of precursor reported to give benzazetines is the 2-cyano-1,2-dihydroquinoline **8**. Irradiation in this case is presumed to involve the intermediate triene **9**, which isomerizes rapidly and reversibly to an unstable oil, considered to be the benzazetine **10**, and irreversibly to **11**.[225]



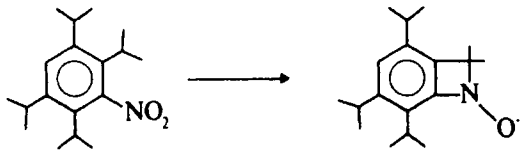
8
R = H, CH_3

9

10

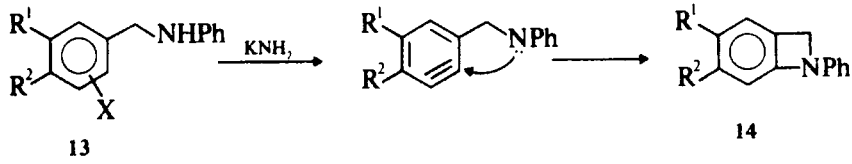
11

Irradiation of 2,3,5,6-tetraisopropylnitrobenzene leads quantitatively (by C–H abstraction) to the stable nitroxide **12**.[246]



12

1-Phenylbenzazetines have been obtained in low yields by cyclization of the benzynes generated from several *N*-phenyl-2- or 3-halobenzylamines.[264] The benzazetines were accompanied by dihydrophenanthridines and products arising from attack of benzyne by amide anion. 1-Alkylbenzazetines were not formed from *N*-alkyl-2- or 3-halobenzylamines; the only products were derived from amide insertion or hydride transfer.



13

	R^1	R^2	Yield (%)
a	OCH_2O	OCH_2O	30
b	OCH_3	OCH_3	6
c	H	OCH_3	1

5. Dewar Pyridines, Azaprismanes, and Benzvalenes

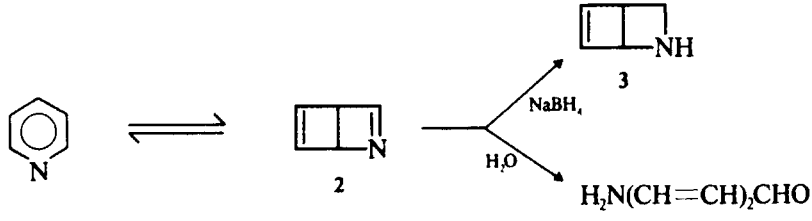
A special group of compounds with bicyclic azetine structures are the Dewar pyridines and related valence isomers of pyridine and diazines which are obtained by irradiation of the heteroaromatic compounds. Photochemical cyclization of pyridines can lead to two possible *para*-bridged or Dewar structures, 1-azabicyclo-[2.2.0]hexa-2,5-diene (**1**) and the 2-aza isomer (**2**), both of which have been observed.



1 2

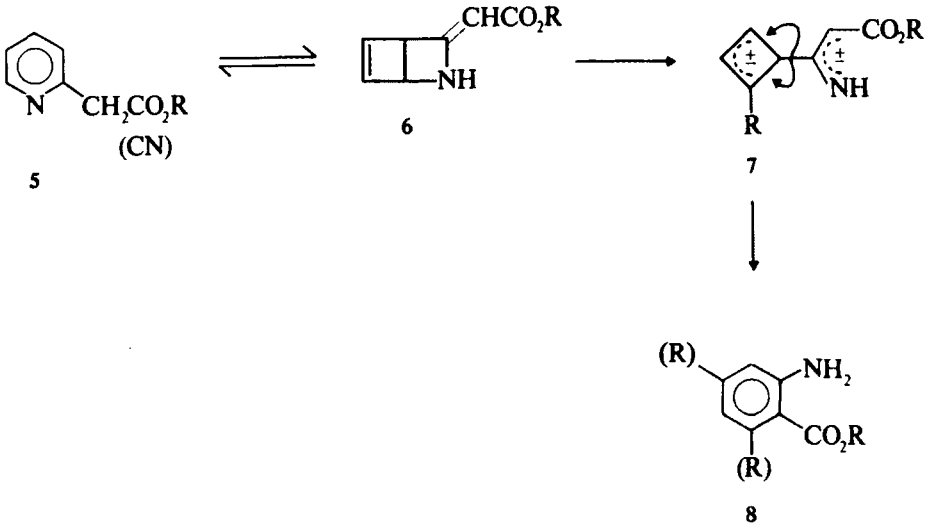
MO calculations have been carried out for both of these structures. By CNDO/2 methods, the values calculated for the energy differences between 1 and 2 and pyridine are 40.5 and 23.1 kcal/mole, respectively.[272] Thus the 2-aza isomer is the more stable by 17.4 kcal/mole. A value of 16 kcal/mole for the difference between 1 and 2 was obtained by MNDO calculations, with activation energies of 29.8 and 30.6 kcal for the isomerization of 1 and 2 to pyridine.[109]

Wilzbach and Rausch obtained the first Dewar pyridine in 1970 by irradiation of pyridine at $-30°C$ in butane solution.[477] Spectral data and chemical behavior established the 2-aza bicyclic structure 2. At 25°C, the bicyclic azetine reverts to pyridine, with a half-time of 2.5 min; at 0°C, $t_{1/2}$ is 36 min. Treatment of 2 with borohydride or irradiation of pyridine in the presence of $NaBH_4$ gives the bicyclic azetidine 3. It was also shown that reaction of 2 with water leads to 5-aminopentadienal (**4**), isolated previously as the photohydration product of pyridine.



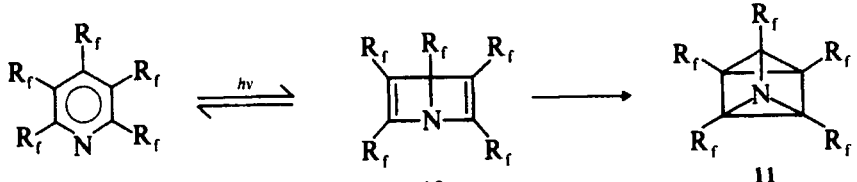
4

Irradiation of 3,5-dimethylpyridine gives an unstable 2-aza photoisomer analogous to **2**.[477] 2-Pyridylacetate esters or nitrile (**5**) are converted to labile photoisomers, which were shown to have structure **6**.[346] These products revert to **5** and undergo hydrolysis to the aminodienals; on further irradiation, they are converted to anthranilic acid derivatives (**8**). Studies with substituted analogs of **5** indicate scrambling, perhaps via a monocyclic intermediate such as **7**.



5 6 7 8

The most extensive work on Dewar pyridines has been done by British groups with perfluoroalkyl derivatives. In this series, paralleling the chemistry of benzene valence isomerization, perfluoroalkyl groups significantly stabilize the high energy photoisomers. Irradiation of pentakis(pentafluoroethyl)pyridine (**9**) with a pyrex filter ($\lambda > 270$ nm) gives in high yield the stable 1-azabicyclohexadiene **10**. With short wavelength light, **10** is further isomerized to the azaprismane **11**. These valence isomers are quite stable thermally; **10** reverts to **9** at 170°C, with a $t_{1/2}$ of 104 hours; **11** rearranges more rapidly to a mixture of **9** and **10**.[30,199]

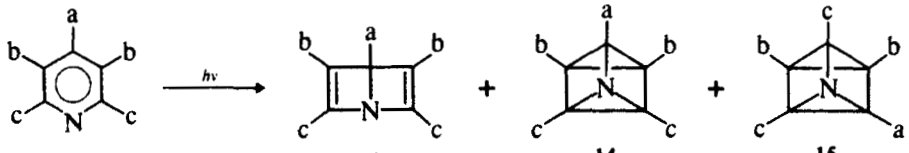


9 10 11

$R_f = C_2F_5$

The symmetrical pyridine **12**, with three different R_f groups, is converted on irradiation to the Dewar pyridine **13** and two azaprismanes (**14** and **15**).[80] The latter products, on heating at 175°C, were converted to pyridines with substituent patterns different from that in **12**. The formation of the rearranged prismane **15**

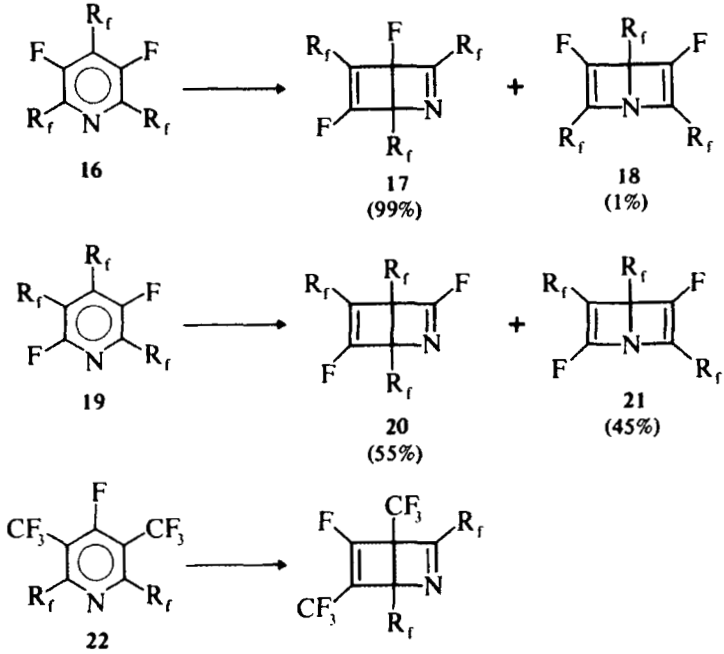
was suggested to involve initial formation of the 2-azabicyclohexadiene, followed by bond reorganization. The structural assignments for the pyridines and valence isomers in these and related perfluoro compounds were based on detailed analysis of ^{19}F-*nmr* coupling constants.



12 13 14 15

a = C_2F_5
b = CF_3
c = *i*-C_3F_7

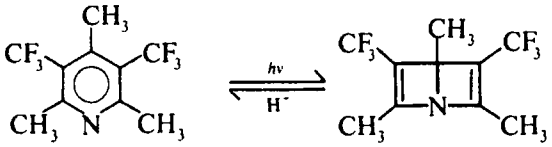
Valence isomers of tri- and tetraperfluoroalkylpyridines cannot be obtained by photolysis in solution,[30,79] but by transfer of the photolysis products to a cold trap. Dewar pyridines were isolated from the pyridines **16**, **19**, and **22** and found to be largely or exclusively the 2-azabicyclo[2.2.0]hexadiene isomers.[79] The 2-aza compound **23** reverted slowly to **22** at 25°C; the other Dewar pyridines were stable at room temperature and were rearomatized at 160°C.



R_f = *i*-C_3F_7

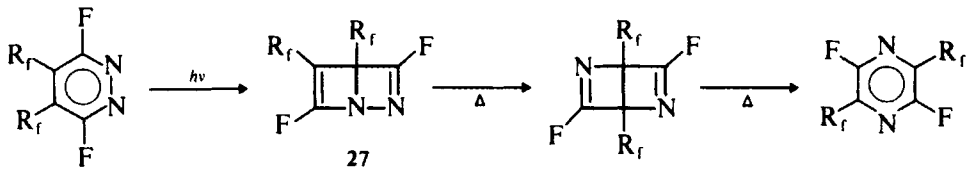
The results of the photoisomerization studies of variously substituted pyridines reveal that the 2-aza structures (i.e., **2**, **17**, **20**, and **23**) are preferred in the absence of overriding steric factors. When the substitution pattern in the pyridine places three or four bulky groups on one ring of the 2-aza isomer, as in the case of **19** or the pentasubstituted pyridine **9**, the 1-aza isomer then becomes significant or dominant.

The 1-aza valence isomer **25** was isolated from irradiation of 3,4,6-trimethyl-3,5-bis(trifluoromethyl)pyridine, but no photoproducts were obtained when the CF_3 groups were replaced by CH_3 or when the 4-CH_3 was absent. The formation of **25** is attributed to a "push-pull" interaction, stabilizing the Dewar pyridine, together with steric repulsion of substituents at the 3-, 4-, and 5-positions of the pyridine. The bicyclic isomer **25** was stable at room temperature but was rapidly converted to the pyridine by a trace of acid. The CH_3 protons at the 2- and 6-positions of **25** were exchanged for deuterium in alkaline CD_3OD.[247]



24 **25**

An interesting series of bicyclic azetines was obtained by isomerization of the fluorinated pyridazines **26**. The initial photoproducts were the 1,2-diaza valence isomers **27**. These Dewar pyridazines, on passage over firebrick, were isomerized to the 2,5-diazabicyclo[2.2.0]hexadienes **28**, which were rearranged thermally to the pyrazines **29**.[78]



26 **27** **28** **29**

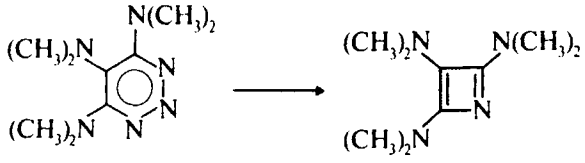
VIII. AZETES AND BENZAZETES

1. Azetes

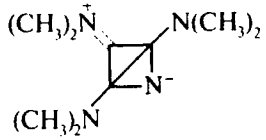
Azete is the heterocyclic counterpart of cyclobutadiene. Considered as azacyclobutadiene, azete can be expected to be anti-aromatic, and molecular orbital calculations by several methods confirm a large negative resonance energy for azete. SCF calculations give a value of − 15.5 kcal/mole,[110] compared to − 18 kcal/mole for

cyclobutadiene, indicating some stabilization because of the nitrogen atom. The resonance energy per electron calculated by parametric methods is $-0.16\,\beta$[205] and that obtained by a topological approach is $-0.193\,\beta$,[185] both indicating a highly anti-aromatic system. From these considerations, it is clear that azetes in general should be highly unstable and elusive substances, requiring carefully designed experiments to permit isolation or detection.

As in the case of butadiene, in which "push–pull" substitution markedly decreases the anti-aromatic character,[177] the presence of substituents (particularly electron donor groups such as NR_2 or F) at the 2- and 4-positions is predicted to stabilize the azete ring.[204,403,464] Following this principle, Seybold, Jersak, and Gompper obtained tris(dimethylamino)azete (**2**), the first and thus far (1980) the only fully characterized monocyclic azete. The synthesis was effected by flash-vacuum pyrolysis (at 527°C) of the 1,2,3-triazine **1**, obtained from the cyclopropenium salt and azide.[403] The azete is a dark red substance, stable at −80°C; it decomposes to dimethylcyanamide. The presence of the 3-dimethylamino group in **2** was calculated to increase the bond order between C_2 and C_4 and to distort the ring,[464] but the azete formula **2** is more consistent with spectral data than the bicyclic structure **3**.



1 **2**

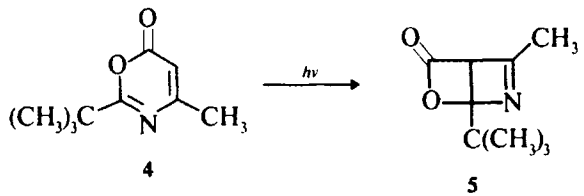


3

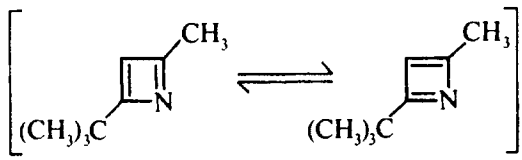
Two other approaches to azetes have led to products that indicate quite clearly the presence of an azete intermediate. Prolonged photolysis of the oxazinone **4** at 7°K in a rare gas matrix produced CO_2 and the alkyne and nitrile fragments **8–11**. The fact that fragments **10** and **11** are obtained in slightly larger amounts than **8** and **9** suggests that decomposition of the bicyclic lactone **5** occurs at least in part via the azetes **6** and **7**.[294] Similar conclusions have been drawn from a flash vacuum pyrolysis study of several 2,4,5-trisubstituted oxazinones.[163a]

Photolysis of the perfluoropyridazine **12** gives, in addition to the rearrangement products mentioned in Section VII.3, nitrile **15** and products **16–18**, which appear to arise from the perfluoroazete **14** by dimerization.[77]

More slender circumstantial evidence exists for the formation of triphenylazete in the products of irradiation of the triazafulvenes **19** and **20**; the azete is one of



4 5

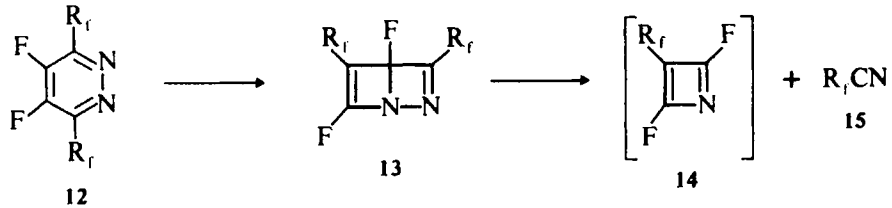


6 7



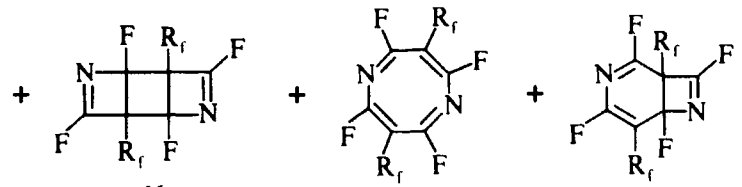
8 10

9 11



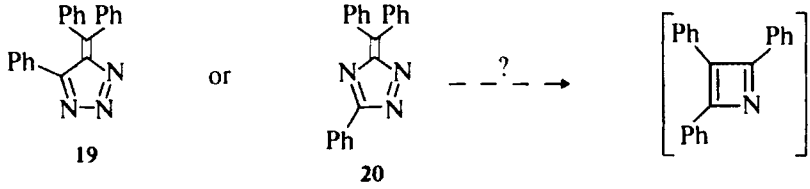
12
$R_f = CF(CF_3)_2$

13 14 15



16 17 18

several possible intermediates.[62] An earlier attempt to generate an azete by high temperature reverse Diels–Alder reaction was unsuccessful;[357] in view of later experience, it is not expected that an azete could be detected from this reaction.

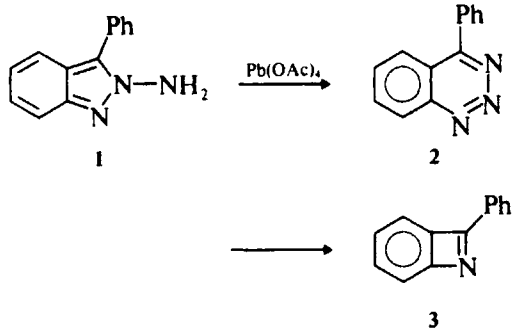


19 20

2. Benzazetes

Benzazetes are azalogs of the well-known benzocyclobutadiene and, by analogy, are expected to be more accessible and stable than monocyclic azetes. This is born out by the work of Rees and co-workers, who have generated several benzazetes and examined their chemistry. This work (till 1979) has been covered in a comprehensive review.[368]

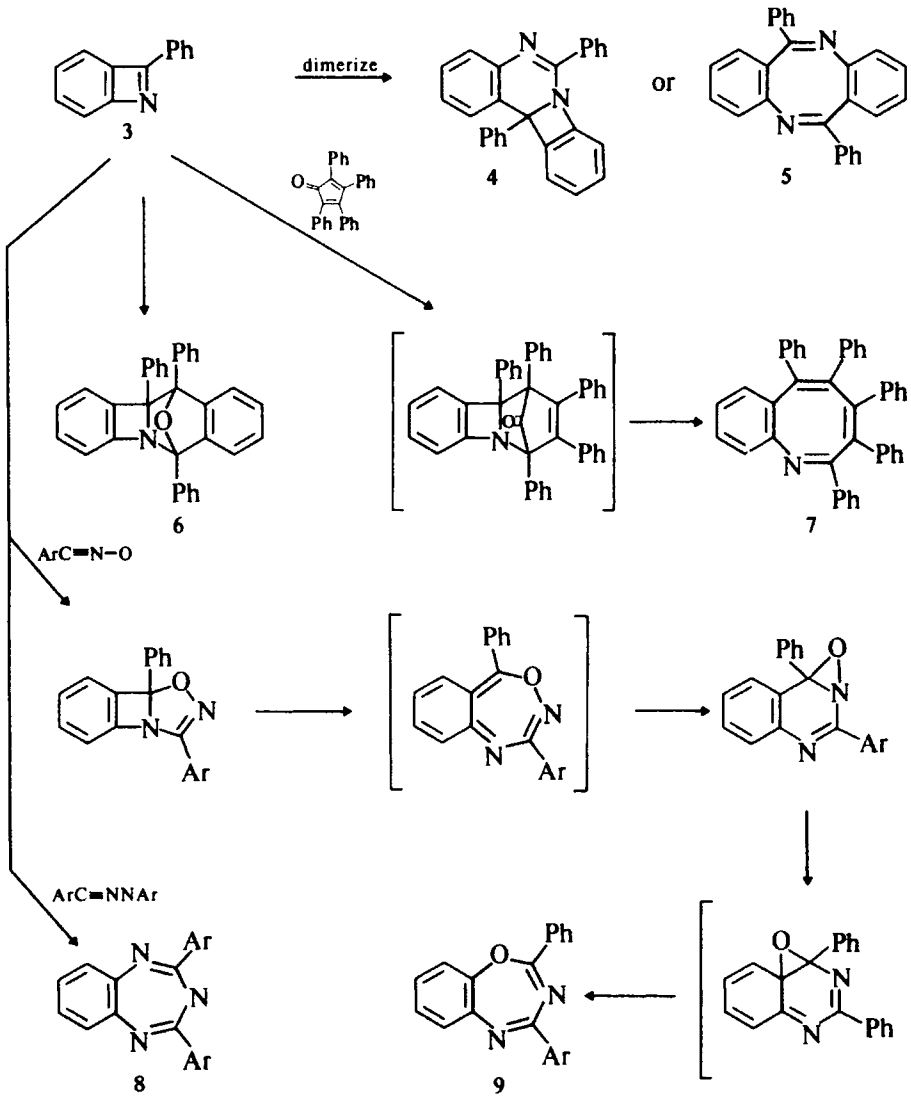
Various methods to obtain benzazetes via *o*-carbenonitrenes were attempted,[3] and a successful precursor was found in benzo-1,2,3-triazines (**2**), which are obtained by oxidation of *o*-aminohydrazones or, more conveniently, of 2-aminoindazoles (**1**).[1] 2-Phenylbenzazete (**3**) was obtained in about 60% yield from the 4-phenyltriazine **2** by flash-vacuum pyrolysis at 450°C[2,4,69] or by photolysis at −80°C.[370]



1 2 3

2-Phenylbenzazete is a red oil that can be stored below −20°C. The introduction of electron-releasing groups on the phenyl ring stabilizes the compound significantly.[368] 2-Phenylnaphthazete is an orange solid that is stable at room temperature. Indirect evidence for the formation of 2-*t*-butylbenzazete as a transient intermediate was obtained from the structures of the final products.[371] 2-Phenylbenzazete gives rise to a dimer which has been shown to have the angular structure **4**, and is not the diazocine **5**.[67a]

2-Phenylbenzazete is a highly reactive dienophile and undergoes Diels–Alder additions to give, *inter alia*, products **6** and **7**. It also reacts as a dipolarophile with nitrile oxides[369] and nitrile imines[368] to form adducts that undergo rearrangement to the 1,3,5-benzoxadiazepines **9** and benzotriazepines **8**, respectively (Scheme 7).



IX. TABLES

In the following tables are listed azetidines recorded in the literature through 1979. With a few exceptions, coverage includes all papers and patents listed in the references. In the case of patents, all azetidines included in examples and claims

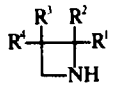
are listed; compounds mentioned in the body of the patent with no data or preparative details are not included.

The tables are arranged according to the methods of preparation in Sections III and IV. Within each table the compounds are listed according to carbon content. Yields refer to those stated for the method of preparation covered in the table. Salts are indicated by an entry giving the anion; these are abbreviated as follows:

Abbreviations for Anions in Tables

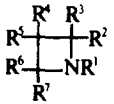
Pic	Picrate
Br	Bromide
Cl	Chloride
I	Iodide
MeI	Methiodide
Ts	*p*-Toluenesulfonate
Ac	Acetate
Bz	Benzoate
ClO_4	Perchlorate
Mes	Methanesulfonate
Bzs	Benzenesulfonate
Bzl	Benzilate
HSO_4	Hydrogen sulfate or sulfate
BF_4	Tetrafluoroborate

TABLE 1. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION. FORMATION OF THE N_1–C_2 BOND. SECONDARY AZETIDINES



	R^1	R^2	R^3	R^4	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_3	H	H	H	H	–	(62–63/–)	8.9	374, 232
C_4	COOH	H	H	H	–	–	58	481
C_5	CH_2CH_2Br	H	H	H	Pic	107–108	–	183
	H	H	CH_3	CH_3	–	(88–91/–)	37	203
	H	H	CH_2OH	CH_2OH	Pic	118–120	67	308
					Cl	–	56	308
C_6	CH_3	CH_3	OH	CN	–	–	–	287, 188, 189, 190
C_8	H	H	1-Pyrrolidyl	CH_3	–	–	50	149
C_9	H	H	SC_6H_5	H	–	(90/0.3)	64	149
	H	H	1-Piperidyl	CH_3	–	–	36	149
C_{10}	H	H	CH_3	SC_6H_5	–	–	79	149

TABLE 2. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1–C_2 BOND. *N*-ALKYLAZETIDINES



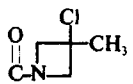
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_3	NO	H	H	H	H	H	H	–	104–106 (dec)	91	340
C_6	C_2H_5	CH_3	H	H	H	H	H	–	(39/200)	60	386
	CH_3	H	H	CH_3	CH_3	H	H	–	(77–79/–)	57	10
								Pic	222–224	–	10
	$COCH_3$	H	H	CH_3	Cl	H	H	–	–	70	149
C_7	$C(CH_3)_3$	H	H	H	H	H	H	–	–	92	361, 144
	COCN	CH_3	CH_3	H	H	H	H	–	(65–70/0.1)	36	38
	CH_3	CH_3	H	CH_3	CH_3	H	H	–	(105–108/–)	76	476
								MeI	210–211	–	476
	CH_2CH_2OH	H	H			H	H	–	(66–68/–)	31	308
C_8	$CH_2CH_2COOC_2H_4$	H	H	H	H	H	H	–	(56/0.4)	70	461, 462
	$CH_2CHCOOCH_3$ (CH_3)	H	H	H	H	H	H	–	(77/14)	57	203
	$C(CH_3)_3$	CH_3	H	H	H	H	H	–	–	44	144
	COCN	CH_3	CH_3	CH_3	H	H	H	–	(80–83/0.9)	33	38
	CHO	CH_3	CH_3	H	H	CH_3	CH_3	–	–	22	40
C_9	C_6H_{11}	H	H	H	H	H	H	–	(66–73/22)	26	361
	$CH_2CH_2OCH_2CHO$	H	H	CH_3	CH_3	H	H	–	–	28	209
	$CH_2CH_2CH_2CH_3$	H	H	CH_2OH	CH_2OH	H	H	Ts	78.5	62	308
	CH_3	CH_3	CH_3	$N(CH_3)_2$	CN	H	H	–	42–43	–	287, 188, 189 190
		H	H	CH_3	Cl	H	H	–	96.5	88	149

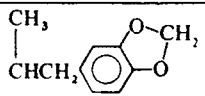
TABLE 2 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2CH_2NHCOCH_3$	H	H			H	H	–	(120–122/–)	24	308
	COCN	CH_3	CH_3	H	H	CH_3	CH_3	–	53–54	24	38
	$CH_2C_6H_5$	H	H	H	H	H	H	–	(87/0.1)	73	461, 455
								Pic	84–89	26	455
	CH_3	C_6H_5	H	H	H	H	H	–	(46–47/1)	41	408
	$CH_2CH_2COOC_2H_4$	H	H	C_2H_5	H	H	H	–	(59–60/0.5)	62	461
	$C(COOCH_3)$=$CHCOOCH_3$	H	H	=CH_2		H	H	–	104	83	194
	$COCH_3$	CH_3	CH_3	COOH	H	CH_3	CH_3	–	229–230	–	89
C_{11}	$CH_2C_6H_5$	CH_3	H	H	H	H	H	–	(86–87/9)	67	448, 461
	$CMe_2CH_2CMe_3$	H	H	H	H	H	H	–	–	56	144
	$C(COOCH_3)$=$CHCOOCH_3$	H	H	=$CHCH_3$		H	H	–	56.5	84	149
	COC_6H_5	H	H	CH_3	Cl	H	H	–	48	48	149
C_{12}	$CH_2C_6H_5$	CH_3	CH_3	H	H	H	H	–	147–149	42	281
	$CH_2C_6H_5$	H	H	CH_3	CH_3	H	H	–	(40–41/0.1)	87.5	10
	$CH_2C_6H_5$	H	H	CH_2OH	CH_2OH	H	H	–	90	54	308
	$CH_2C_6H_5$	H	H			H	H	Ts	169	26	308
	CH_3	C_6H_5	H	CH_3	CH_3	H	H	–	(85–89/9)	65	9
	$CH_2C_6H_5$	CH_3	H	H	H	CH_3	H	–	–	65	144
C_{13}	$C(CH_2CH_2CH_3)_3$	H	H	H	H	H	H	–	(112–115/14)	57	366
								Cl	93	15	238
	$CH_2CH_2OC_6H_3$-$(CH_3)_2$-2,6	H	H	H	H	H	H	–	132–133.5	15	238

TABLE 2 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH(CH_3)_2$	COC_6H_5	H	H	H	H	H	–	(100–102/0.6)	13	380
								Pic	177–178	–	380
	COCN	CH_3	CH_3	C_6H_5	H	H	H	–	(145–150/0.6)	53	38
C_{14}	$C(CH_3)_3$	COC_6H_5	H	H	H	H	H	–	53–55	40.8	377
	$CHCH_2C_6H_5$ (CH3)	H	H	CH_3	CH_3	H	H	–	(88–115/1.5)	–	218, 219
	$CHCH_2C_6H_4Cl$-*m* (CH3)	H	H	CH_3	CH_3	H	H	–	(116–120/1.9)	–	218, 219
	$CHCH_2C_6H_4Cl$-*p* (CH3)	H	H	CH_3	CH_3	H	H	–	(110–124/1.1)	–	218, 219
	$CHCH_2C_6H_3$-3,4-Cl_2 (CH3)	H	H	CH_3	CH_3	H	H	–	(138–141/1.5)	–	218, 219
	$CHCH_2C_6H_4$-*m*-F (CH3)	H	H	CH_3	CH_3	H	H	–	(87–89/1.4)	–	218, 219
	$CHCH_2C_6H_4$–*p*-F (CH3)	H	H	CH_3	CH_3	H	H	–	(87–91/1.5)	–	218, 219
C_{15}	Benzocycloheptyl (CH3)	H	H	$NHCH_3$	H	H	H	–	–	–	306
	$CHCH_2C_6H_4$-CF_3 (CH3)	H	H	CH_3	CH_3	H	H	–	(93–103/2)	–	218, 219
	$CHCH_2C_6H_4$–*p*-CF_3 (CH3)	H	H	CH_3	CH_3	H	H	–	(97–103/1.3)	–	218, 219

TABLE 2 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		H	H	CH_3	CH_3	H	H	–	(136–142/1.3)	–	218, 219
C_{16}	CH_3	C_6H_5	H	C_6H_5	H	H	H	*cis*	(120–122/1)	60	408
								trans	(118–119/0.5)	60	408
	COC_6H_5	C_6H_5	H	OH	H	H	H	–	165–167	–	353
C_{17}	CH_3	$COC_6H_4C_6H_5$-*p*	H	H	H	H	H	–	–	20	380
	$CH(C_6H_5)_2$	CN	H	H	H	H	H	–	103.5–105	–	175
	$CH(C_6H_5)_2$	H	H	$NHCH_3$	H	H	H	–	–	–	306
	$CCH_2C_6H_3(CH_2)_3$	H	H	CH_3	CH_3	H	H	–	(133–137/1.3)	–	218, 219
C_{18}	$CH_2CH_2COOC_2H_5$	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	H	–	(89–92)/0.003)	48	461
C_{19}	$CHCH_2C_6H_5$	H	H	CH_3	CH_3	H	H	–	(121–122/–)	90	10
								Pic	209–211	–	10
	$CH_2C_5H_5$	H	H	CH_2OH	$CH_2NHCH_2C_5H_5$	H	H	Ts	197–198	50	308
C_{20}	$C(CH_3)_3$	$COC_6H_4C_6H_5$-*p*	H	H	H	H	H	–	–	40	380
	$C(CH_3)_3$	COC_6H_5	H	C_6H_5	H	H	H	*cis*	165	84	96
								trans	128		96
C_{23}	$CH(C_6H_5)_2$	CHC_6H_5 (OH)	H	H	H	H	H	*erythro*	131–131.5	–	175
								threo	87.5–88.5	–	175
	$CH_2C_6H_5$	$COC_6H_4C_6H_5$-*p*	H	H	H	H	H	–	106–108	–	352

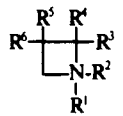
[a] Stereochemical configuration also denoted.

TABLE 3. SPIROAZETIDINE-9,10-ETHANOANTHRACENES[34]



R	Salt	m.p. (°C)
CH_3	–	125–127
CH_3	Ac	119–120
CH_3	Bz	115–117
CH_3	Cl	296–297
CH_3	I	247–248
C_2H_5	Cl	279–280
$HOCH_2CH_2$	Cl	244–245
$CH_2CH{=}CH_2$	–	61–63
$CH_2CH_2CH_2OH$	Cl	250–251
$CH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_3$	Cl	278–288
$CH_2CH_2CH_2OCH_3$	–	210–211
$\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2OCH_3$	Cl	218–219
$CH_2CH_2OC_2H_5$	Cl	206–208
$CH_2CH_2OCH_2CH_2OH$	Cl	226–227
$CH_2CH_2OCH_2CH_2OH$	–	202–204
$CH_2CH_2OCH_2CH_2OH$	Cl	224–225
$CH_2C_6H_5$	–	141.5–142
$CH_2C_6H_5$	Cl	256–257
$CH_2C_6H_4F$-*p*	Cl	203 (dec)
$SO_2C_6H_4CH_3$-*p*	–	187.5–188
$CH_2CH_2C_6H_5$	Cl	266–267
$CH_2CH_2C_6H_4Cl$-*p*	Cl	256–256.5
$\underset{\displaystyle CH_3}{\underset{\vert}{C}}HC_6H_5$	Cl	269–270
$CH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HC_6H_5$	Cl	266–268
$CH_2CH_2CH_2C_6H_5$	Cl	223–225
$CH_2CH_2C_6H_4OCH_3$-*p*	Cl	243.5–244.5
CH_2CN	Cl	217–218.5
$CH_2CH{=}CH_2$	Cl	221–222
CH_2CH_2COOH	Cl	230–231
$CH_2CH_2CH_2COC_6H_4$-F-*p*	Cl	211–213
H	Cl	285–286
H	–	291 (dec)
$COCH_2CH_3$	–	100–102
$NHCOCH_3$	Cl	218–219

TABLE 4. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1–C_2 BOND. QUATERNARY AZETIDINIUM COMPOUNDS



	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p. (°C)	Yield (%)	Ref.
C_3	H	H	H	H	Br	H	Cl	102–104	99	6
C_4	H	H	H	H	CH_3	Cl	Cl	120	85	149
C_5	CH_3	CH_3	H	H	H	H	Cl	180–182 (dec)	60	271
C_6	CH_3	H	CH_3	CH_3	H	H	ClO_4	165–166	100	281
C_7	$CH_2CH(OH)CH_2Cl$	CH_3	H	H	OH	H	Cl	–	–	94
	C_2H_5	C_2H_5	H	H	OH	H	Cl	154–155 (dec)	38	153, 382, 157
							ClO_4	181–183	–	153
							Picrylsulfonate	192–193	–	224
							Ts	193.5–194.5	–	224
	CH_3	CH_3	CH_3	CH_3	H	H	–	173–175	2	184
	CH_3	CH_3	H	H	CH_3	CH_3	I	188–189 (dec)	84	10
	$CH_2CH_2OCH_2CH_2$		H	H	OH	H	Cl	75–80	–	224
							Mes	162–163	–	224
	C_2H_5	$CH_2CH(OH)CH_2Cl$	H	H	OH	H	Cl	–	–	94
	$(CH_2)_5$		H	H	H	H	Cl	239–240	–	281
							ClO_4	172–173	48	281
	$(CH_2)_5$		H	H	OH	H	Cl	147–148.5	76	153
	$(CH_2)_5$		H	H	OH	H	Ts	110.5–111.5	–	224

TABLE 4 CONTINUED

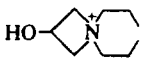
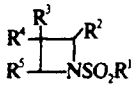
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p. (°C)	Yield (%)	Ref.
C_9	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	OH	H	Cl	154–155	–	224
		OH | CH_2CHCH_2Cl								
	$CH(CH_3)_2$	CH_2CHCH_2Cl	H	H	OH	H	Cl	–	–	94
	$(CH_2)_3CH_3$	H	H	H			Ts	125–126	28	308
			H	H	OH	H	Di-Bzs	255–256	–	224
							Di-Mes	247–248	–	224
							Di-Cl	97–100	–	224
C_{11}	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	H	H	OH	H	Ts	80–81	–	224
C_{12}	$CH_2C_6H_5$	H	CH_3	CH_3	H	H	ClO_4	151–151.5	85	281
C_{13}	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	H	H	H	I	64–66	–	461
	CH_3 | $CHCHC_5H_5$ | OH	CH_3	H	H	OH	H	Cl	148	62	265
	OH | CH_2CHCH_3	CH_3	H	H	OH	H	Bzs	98–99	–	224
	CH_3	CH_3	C_6H_5	H	CH_3	CH_3	I	122 (dec)	11	9
	OH | CH_2CHCH_2									
	$CO_2C_6H_4CH_3$-*p*	CH_3	H	H	OH	H	Ts	165–166	–	224
	$(CH_2)_5$		H	H	OH	C_6H_5	Cl	166–167	70	309
C_{19}	$CH_2C_6H_5$	$CH_2C_6H_5$	H	H	CH_3	CH_3	Br	152–152.5	82	10

TABLE 5. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF N_1–C_2 BOND. *N*-ARYLAZETIDINES



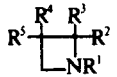
	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_9	C_6H_5	H	H	H	H	–	(104/11)	98	36, 103, 48
	C_6H_4Cl-*o*	H	H	H	H	–	(85/1)	20	103
	C_6H_4Cl-*m*	H	H	H	H	–	(85/1)	20	103
	C_6H_4Cl-*p*	H	H	H	H	–	40	22	103, 102
C_{10}	$C_6H_4CH_3$-*o*	H	H	H	H	–	(58/1)	22	103
	$C_6H_4CH_3$-*m*	H	H	H	H	–	(80/1)	29	103
	$C_6H_4CH_3$-*p*	H	H	H	H	–	38–39	25	103, 102
						Pic	122–123	–	102
C_{11}	$C_6H_3(CH_3)_2$-2,6	H	H	H	H	–	–	–	103
C_{12}	$C_6H_2(CH_3)_3$-2,4,6	H	H	H	H	–	(78/1)	6	103
	$C_6H_4OCH_3$-*m*	CH_3	H	H	CH_3	–	(100/0.02)	–	167
	C_6H_5	OCH_3	CH_3	CH_3	H	–	–	2.5	343
C_{16}	2-Fluorenyl	H	H	H	H	–	124	62	29
	$C_6H_4OCH_3$-*m*	C_6H_5	H	H	H	–	(140–145/0.0009)	18	166, 168, 167
C_{17}	$C_6H_4OCH_3$-*m*	C_6H_5	CH_3	H	H	–	94	–	167
	$C_6H_4OCH_3$-*m*	CH_3	H	H	C_6H_5	–	–	–	167, 444
C_{20}	Dibenzocycloheptyl	CH_2NHCH_3	H	H	H	Cl	125–150	30	306

TABLE 6. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1–C_2 BOND. *N*-SULFONYLAZETIDINES



	R^1	R^2	R^3	R^4	R^5	Configuration	m.p. (°C)	Yield (%)	Ref.
C_4	CH_3	H	H	H	H		81–82	66.6	455
C_{10}	$C_6H_4CH_3$-*p*	H	H	H	H		116–120	93	455, 36, 475, 149, 209
C_{11}	$C_6H_4CH_3$-*p*	CH_3	H	H	H		97–99	67.7	455
	$C_6H_4CH_3$-*p*	COOH	H	H	H		145.5–147	95	313
	$C_6H_4NO_2$-*p*	CH_2CH_2Br	H	H	H		122	–	423
	$C_6H_4CH_3$-*p*	H	CH_3	H	H		50–51	–	209
	$C_6H_4CH_3$-*p*	H	CH_3	Cl	H		70.5	62	149
	C_6H_5	H	CH_3	OCH_3	H		–	–	297
	C_6H_4Cl-*p*	H	CH_3	OCH_3	H		37–40	14.5	297
C_{12}	$C_6H_4CH_3$-*p*	$COOCH_3$	H	H	H		102–103	60	89
	$C_6H_4CH_3$-*p*	CH_2CH_2Br	H	H	H		167	–	423
	$C_6H_4CH_3$-*p*	CH_3	H	H	CH_3	*cis*	141.5–142	75	145
						cis + *trans*	126–134	17	209
	$C_6H_4CH_3$-*p*	H	C_2H_5	Cl	H		66	85	149
C_{15}	$C_6H_4CH_3$-*p*	H	3-Pyridyl	H	H		95–96.5	38	397
	$C_6H_4CH_3$-*p*	3-Pyridyl	H	H	H		141–142	92	397
C_{16}	$C_6H_4CH_3$-*p*	H	C_6H_5	H	H		133–134	91	397

TABLE 7. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1–C_2 BOND. *N*-ALKYL-2-AZETIDINOLS AND 3-AZETIDINONES



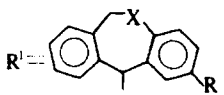
	R^1	R^2	R^3	R^4	R^5	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_6	$CH(CH_3)_2$	H	H	OH	H	Cl	140–141	66	347
						–	56–57	–	347, 152, 156
	CH_3	H	H	OCH_2OCH_3	H	–	(69/73/40)	–	159
	CH_3	CH_3	CH_3	=O		–	–	–	287, 189, 188, 190
C_7	$C(CH_3)_3$	H	H	OH	H	–	44–46	78	152, 83, 156
						Cl	161–163	55	347, 304
	C_2H_5	CH_3	CH_3	=O		Cl	–	–	287, 189, 188, 190
C_8	$CH_2C(CH_3)_3$	H	H	OH	H	–	(56/0.3)	32	152, 156
	$CMe_2C{\equiv}CH$	H	H	OH	H	Cl	152	30	146, 73
	$C(CH_3)_3$	CH_3	H	OH	H	–	(65–68/0.7)	28	152, 156
	$C(CH_3)_3$	H	H	OH	CH_3	–	(63–64/2)	32	209, 149
						Pic	170–172	–	209
C_9	C_6H_{11}	H	H	OH	H	–	79–80	55	156, 347, 361 454, 152
	$CH_2CH_2CH_2CH_3$	H	H	OCH_2OCH_3	H	–	(71–73/2.5)	23	159
	$C(CH_3)_3$	H	H	$OCOCH_3$	H	–	–	30	156
	$C(CH_3)_3$	CH_3	CH_3	=O		–	(96/51)	–	287, 189, 190
	$(CH_2)_5\overset{CH_3}{\underset{\vert}{C}}$-	H	H	OH	H	–	(92–98/0.4)	55	347
	$CEt_2C{\equiv}CH$	H	H	OH	H	–	(93/–)	30	146, 73
						Cl	141	52	146, 73

TABLE 7 CONTINUED

	R^1	R^2	R^3	R^4	R^5	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	C_6H_{11}	H	H	OSO_2CH_3	H	–	100–101	81	347
	C_6H_{11}	H	H	OH	CH_3	–	(75–76/0.01)	28	209
C_{11}	$CMe_2CH_2CMe_3$	H	H	OH	H	–	52–53	68	156, 152
	C_6H_5 | $CHCH_3$	H	H	OH	H	–	44–49	45	347, 172
	$(CH_2)_5C(CH_3)C{\equiv}CH$	H	H	OH	H	Cl	165	61	146, 73
	CH_3 | $CHCH_2C_6H_5$	H	H	OH	H	–	83–45.5	9	347
	3,3,5-Trimethyl-cyclohexyl	H	H	OH	H	–	(96–98/0.3–0.6)	36	347
	$CH_2C_6H_5$	H	H	OCH_2OCH_3	H	–	(103–105/0.4)	13	159
	CH_3	H	H	$OCH_2OCH_2C_6H_5$	H	–	(90–100/0.1)	30	237
	$CH(CH_3)_2$	H	H	OH	C_6H_5	–	86–87	–	172
						Cl	222–223	20	309
	Cyclopropyl	H	H	OH	C_6H_5	–	57–58	–	172
C_{13}	2-Adamantyl	H	H	OH	H	–	171–172	49	347, 171
	$CH_2CH_2C_6H_5$	H	H	OCH_2OCH_3	H	–	(128–130/1)	4	159
	$CMe_2CH_2CMe_3$	H	H	$OOCCH_3$	H	–	–	14	156
	$C(CH_3)_3$	H	H	OH	C_6H_5	Cl	202–204	35.4	309
C_{15}	C_6H_{11}	C_6H_5	H	OH	H	*trans*	138–140	52	347
						cis	101–102.5	4	347
	C_6H_{11}	H	H	OH	C_6H_5	Cl	216–217	14.3	309
C_{16}	$CH(C_6H_5)_2$	H	H	OH	H	–	113	61	7, 209, 83
	$CH_2C_6H_5$	H	H	OH	C_6H_5	–	188–189	35.5	309

TABLE 7 CONTINUED

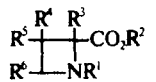
C_{17}–C_{19}



X	R	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	Yield (%)	Ref.
O	H	H	H	OH	H	Cl	153–157	47	306
O	Cl	H	H	OH	H	Cl	152–157	37	306
S	H	H	H	OH	H	Cl	157–159	27	306
CH_2	H	H	H	OH	H	Cl	160–163	57	306
=CH	H	H	H	OH	H	–	105–109	38	306
O	OMe	H	H	OH	H	Cl	135–145	33	306
S	OMe	H	H	OH	H	–	–	40	306
CH=CH	H	H	H	OH	H	Cl	195–197	57	306
CH_2	H	CH_3	H	OH	H	Cl	195–197	41	306
C_{22}	$CH(C_6H_5)_2$	H	H	OH	C_6H_5	Cl	194–195	15	309

[a] Stereochemical configurations also denoted.

TABLE 8. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1-C_2 BOND. *N*-ALKYLAZETIDINE-2-CARBOXYLATES AND RELATED COMPOUNDS



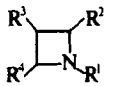
	R^1	R^2	R^3	R^4	R^5	R^6	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_4	NO	H	H	H	H	H	–	115–116	83	340
C_5	OH	CH_3	H	H	H	H	–	(50–51/01)	10	261
C_6	CH_3	CH_3	H	H	H	H	–	(55/13)	29	260
C_7	C_2H_5	CH_3	H	H	H	H	–	(68.5–69/12.5)	73	260
	CH_3	C_2H_5	H	H	H	H	–	(58–59/9)	30	260
	OC_2H_5	CH_3	H	H	H	H	–	(34/1.5)	10	261
C_8	$CH(CH_3)_2$	CH_3	H	H	H	H	–	(40–42/0.6)	61.5	380, 260
	CH_3	$CH(CH_3)_2$	H	H	H	H	–	(62/8)	59	260
	C_2H_5	C_2H_5	H	H	H	H	–	(70.5/8)	64	260
	$OCH(CH_3)_2$	CH_3	H	H	H	H	–	(38/2.5)	25	261
C_9	C_2H_5	$CH(CH_3)_2$	H	H	H	H	–	(69–70/10)	58	260
	$CH(CH_3)_2$	C_2H_5	H	H	H	H	–	(53–54/3)	60	260
	$C(CH_3)_3$	CH_3	H	H	H	H	–	(38.5/1.5)	46	260, 379
							Cl	117–118	48.2	375
C_{10}	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	H	H	–	(56.5/3)	54	260
	$C(CH_3)_3$	C_2H_5	H	H	H	H	–	(51.5–52.5/1.5)	42	260
	$C(CH_3)_3$	CH_3	H	H	H	CH_3	–	(49–55/1.4)	–	380
C_{11}	$C(CH_3)_3$	$CH(CH_3)_2$	H	H	H	H	–	(41–42/1)	48.3	260
	C_6H_{11}	CH_3	H	H	H	H	Cl	–	65	375
							–	(95–97/2)	58.2	375
C_{12}	$CH_2C_6H_5$	CH_3	H	H	H	H	–	(96–97/0.5)	15.6	260
							Cl	–	79.2	375
	CH_3	$CH_2C_6H_5$	H	H	H	H	–	(57/0.5)	69	260
	$OCH_2C_6H_5$	CH_3	H	H	H	H	–	(91/0.1)	10	261

TABLE 8 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{13}	C_2H_5	$CH_2C_6H_5$	H	H	H	H	–	(99.5–100.5/0.5)	32	260
	$CH_2C_6H_5$	C_2H_5	H	H	H	H	–	(91–92/0.2)	21	260
	$C(CH_3)_2CH_2C(CH_3)_3$	CH_3	H	H	H	H	–	(83–85/0.7)	61.8	380
	$OCH_2C_6H_5$	C_2H_5	H	H	H	H	–	(98/0.1)	11	261
C_{14}	$CH(CH_3)_2$	$CH_2C_6H_5$	H	H	H	H	–	(109.5–110.5/0.5)	64	260, 380
	$CH_2C_6H_5$	$CH(CH_3)_2$	H	H	H	H	–	(99–100/0.5)	26.5	260
	$OCH_2C_6H_5$	$CH(CH_3)_2$	H	H	H	H	–	(95.5/0.1)	8	261
C_{15}	$C(CH_3)_3$	$CH_2C_6H_5$	H	H	H	H	–	(118–119/0.65)	72.8	380
	1-Adamantyl	CH_3	H	H	H	H	–	(131–135/0.2)	–	173
							Cl	147–147.5	–	173
	$C(CH_3)_3$	CH_3	H	H	H	C_6H_5	*cis*	–	28	266
							Pic	162.5–164	–	266
C_{17}	C_6H_{11}	$CH_2C_6H_5$	H	H	H	H	–	(141–142/0.5)	56.4	380
	C_6H_5	CH_3	H	H	H	C_6H_5	–	(150–155/–)	100	457
C_{18}	$CH(C_6H_5)_2$	CH_3	H	H	H	H	–	(142–144/0.25)	72.2	380
C_{21}	C_6H_5	CH_3	$COOCH_3$	CN	CN	C_6H_5	–	160–161	71	456
C_{23}	C_6H_5	CH_3	$COOCH_3$	$COOCH_3$	$COOCH_3$	C_6H_5	–	182	73	456
	Phthalimido	CH_3	CN	$=NCH(CH_3)_2$		C_6H_5	–	148	46	81
	Phthalimido	CH_3	CN	$=NCH(CH_3)_2$		C_6H_4Cl-*p*	–	–	40	81
C_{24}	$CH(C_6H_5)_2$	$CH_2C_6H_5$	H	H	H	H	–	61–63	82	361, 376
							Br	–	87.5	361
	Phthalimido	CH_3	CN	$=NC(CH_3)_3$		C_6H_5	–	144	49	81
	Phthalimido	CH_3	CN	$=NC(CH_3)_3$		C_6H_4Cl-*p*	–	150	47	81
	Phthalimido	CH_3	CN	$=NCH(CH_3)_2$		$C_6H_4CH_3$-*p*	–	157	47	81
	Phthalimido	CH_3	CN	$=NC_6H_{11}$		C_6H_5	–	134	48	81

[a] Stereochemical configuration also indicated.

TABLE 9. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE N_1–C_2 BOND. *N*-ALKYL-2-ARYL-3-ACYLAZETIDINES



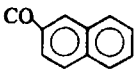
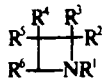
	R^1	R^2	R^3	R^4	Salt[a]	m.p. (°C)	Yield (%)	Ref.
C_{14}	$C(CH_3)_3$	C_6H_5	$CONH_2$	H	–	–	20	282
	$C(CH_3)_3$	C_6H_5	CN	H	–	–	0.9	282
C_{15}	C_6H_{11}	C_6H_5	OH	H	*cis*	–	10	347
					trans	–	13	347
	$C(CH_3)_3$	C_6H_5	$COCH_3$	H	Pic	165.5–166.5	70	118
	$C(CH_3)_3$	C_6H_5	$COOCH_3$	H	Pic	160.5–162	100	282
	$C(CH_3)_3$	C_6H_4Cl-*p*	$COOCH_3$	H	Pic	181–182.5	100	282
C_{16}	C_6H_{11}	C_6H_5	OSO_2CH_3	H	–	84–85	93	347
C_{19}	$CH(CH_3)_2$	C_6H_5	COC_6H_5	H	*cis*	84–85	76	114
					trans	42–43	80	114
C_{20}	$C(CH_3)_3$	C_6H_5	COC_6H_5	H	*cis*	116–118	80	227, 354
					trans	61–63	75	227, 354
	$C(CH_3)_3$	$C_6H_4NO_2$-*p*	COC_6H_5	H	*cis*	116–168	78	119
					trans	98–99.5	100	119
C_{22}	C_6H_{11}	C_6H_5	COC_6H_5	H	*cis*	102–103	61	114
					trans	96–97	80	114
C_{23}	CH_3	C_6H_5	$COC_6H_4C_6H_5$-*p*	H	*cis*	142–143	32	114
					trans	63–64	40	114
C_{24}	C_3H_5	C_6H_5	$COC_6H_4C_6H_5$-*p*	H	*cis*	137–138	58	114
					trans	70–71	65	114
	$C(CH_3)_3$	C_6H_5	CO 	H	*trans*	109–110	–	355
C_{25}	$CH(CH_3)_2$	C_6H_5	$COC_6H_4C_6H_5$-*p*	H	*cis*	141–142	79	114
					trans	109–110	92	114

TABLE 9 CONTINUED

	R^1	R^2	R^3	R^4	Salt[a]	m.p. (°C)	Yield (%)	Ref.
C_{26}	$C(CH_3)_3$	C_6H_5	$COC_6H_4C_6H_5$-*p*	H	*cis*	165–166	92	114, 96
					trans	127–128	54	114
	$C(CH_3)_3$	C_6H_5	COC_6H_5	C_6H_5	–	104.5–107	22.9	407
C_{28}	C_6H_{11}	C_6H_5	$COC_6H_4C_6H_5$	H	*cis*	172–173	74	114
					trans	142–143	87	114
	C_6H_{11}	C_6H_5	COC_6H_5	C_6H_5	*cis, trans*	157–160	–	407, 226
					trans, trans	114.5–119	–	407, 226
C_{29}	$C(C_2H_5)_3$	C_6H_5	$COC_6H_4C_6H_5$-*p*	H	*cis*	109–110	74	114
					trans	75–76	80	114

[a] Stereochemical configuration also denoted.

TABLE 10. SYNTHESIS OF THE AZETIDINE RING BY CYCLIZATION: FORMATION OF THE C_2–C_3 BOND

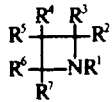


	R^1	R^2	R^3	R^4	R^5	R^6	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{10}	CH_3	H	H	OH	C_6H_5	H	(56–57/0.05)	9	92
	SO_2CH_3	H	H	OH	C_6H_5	H	–	–	172
	SO_2CF_3	H	H	OH	C_6H_5	H	–	–	172
	$COOC_2H_5$	$NHCOOC_2H_5$	H	Cl	Cl	CCl_3	96–97.5	30	242
C_{11}	$COCF_3$	H	H	OH	C_6H_5	H	–	–	172
	$COOCH_3$	H	H	OH	C_6H_5	H	–	–	172
	CH_3	CH_3	H	OH	C_6H_5	H	–	–	169
C_{12}	$COCH_2CH_3$	H	H	OH	C_6H_5	H	–	–	172
	$COCH_2CHF_2$	H	H	OH	C_6H_5	H	–	–	172
	C_2H_5	CH_3	H	OH	C_6H_5	H	(72–73/0.05)	26	92
	C_2H_5	CH_3	H	$OCOCH_3$	C_6H_5	H	(65–67/2)	–	92
C_{13}		H	H	OH	C_6H_5	H	–	–	172
	$COCH_2CF_2CF_3$	H	H	OH	C_6H_5	H	–	–	172
C_{14}	$CH(CH_3)_2$	CH_3	CH_3	OH	C_6H_5	H	(88–89/0.05)	22	92
C_{16}	COC_6H_5	H	H	OH	C_6H_5	H	101.5–103.5	50	169, 170, 172
	$SO_2C_6H_4CH_3$-*p*	H	H	OH	C_6H_5	H	142.5–143	> 95	169, 172
	$SO_2CH_2C_6H_5$	H	H	OH	C_6H_5	H	–	–	172
C_{17}	CH_3	H	H	$OCH(C_6H_5)_2$	H	H	45–48	52	237
	CH_3 | CHC_6H_5	H	H	OH	C_6H_5	H	89.5–90.5	–	170
	$SO_2C_6H_4CH_3$-*p*	CH_3	H	OH	C_6H_5	H	–	78	169, 172

TABLE 10 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{18}	C_2H_5	H	H	$OCH(C_6H_5)_2$	H	H	(135–142/0.1)	47.5	237
	$COCH_2CH_2C_6H_5$	H	H	OH	C_6H_5	H	–	–	172
	$COOCH_2C_6H_5$	CH_3	H	OH	C_6H_5	H	–	–	172
	$SO_2C_6H_4CH_3$-*p*	C_2H_5	H	OH	C_6H_5	H	–	–	172
	$SO_2C_6H_4CH_3$-*p*	CH_3	CH_3	OH	C_6H_5	H	118–118.5	74	169
	$SO_2C_6H_4CH_3$-*p*	CH_3	H	OH	C_6H_5	CH_3	–	–	172
C_{19}	$SO_2C_6H_4CH_3$-*p*	$CH(CH_3)_2$	H	OH	C_6H_5	H	–	–	172

TABLE 11. SYNTHESIS OF THE AZETIDINE RING BY CYCLOADDITION

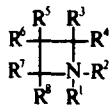


	R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{10}	H	$C(CN)=C(CN)_2$	Cl	OC_2H_5	H	H	H	–	–	194
	SCF_3	$C(CN)=C(CN)_2$	Cl	OCH_3	H	H	H	139–140	–	194
	C_2H_5	F	F	CF_3	CF_3	$=C(CF_3)_2$		(82–85/80)	72	487
C_{11}	SCF_3	$C(CN)=C(CN)_2$	Cl	OC_2H_5	H	H	H	98–104	–	194
	SCF_3	$C(CN)=C(CN)_2$	Cl	$OCH=CH_2$	H	H	H	132.8–134	74	194
	$COOC_2H_5$	F	F	CF_3	CF_3	$=C(CF_3)_2$		(63–65/12)	81	487
C_{12}	H	$C(CN)=C(CN)_2$	Cl	1-(2-Oxopyrrolidinyl)	H	H	H	222–223 (dec)	–	194
	$CH_2CH_2CH_2CH_3$	F	F	CF_3	CF_3	$=C(CF_3)_2$		(82–84/25)	80	487
C_{13}	SCF_3	$C(CN)=C(CN)_2$	Cl	$OCH_2CH_2CH_2CH_3$	H	H	H	106–106.6	–	194
C_{14}	$SO_2C_6H_4CH_3$-*p*	OC_2H_5	H	H	H	CF_3	CF_3	57–58	45	486
	C_6H_5	F	F	CF_3	CF_3	$=C(CF_3)_2$		(74–75/6)	77	487, 106
	$C_6H_4NO_2$-*p*	F	F	CF_3	CF_3	$=C(CF_3)_2$		68–71	62	487
C_{15}	H	$C(CN)=C(CN)_2$	Cl	$C_6H_4OCH_3$-*p*	H	H	H	262–263.5 (dec)	–	194
	SCF_3	$C(CN)=C(CN)_2$	Cl	C_6H_5	H	H	H	115–117	–	194

TABLE 11 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{16}	SCF_3	$C=C(CN)_2$ (CN)	Cl	$C_6H_4OCH_3$-*p*	H	H	H	132.8–133.6	–	194
	C_6H_5	OC_2H_5	OC_2H_5	H	H	$=C(CF_3)_2$		(89–91/0.011)	89	104
	$N=C(CF_3)_2$	$=NC(CH_3)_3$		$=NC(CH_3)_3$		CF_3	CF_3	48–49	73	60
C_{17}	C_6H_5	F	F	CF_3	CF_3	C_6H_5	H	83–85	70	389
	$C_6H_4OOCC_2H_5$	=NH		CF_3	CF_3	$=C(CF_3)_2$		–	21	487
	$C_6H_4OOCC_2H_5$	F	F	CF_3	CF_3	$=C(CF_3)_2$		(151–152/10)	60	487
C_{19}	$C_6H_4NO_2$-*p*	$=NC(CH_3)_3$		$=NC(CH_3)_3$		CH_3	CH_3	138–139	52	113
C_{20}	C_6H_5	$=NC_6H_5$		CF_3	CF_3	$=C(CF_3)_2$		–	19	487
	$C_6H_4NO_2$-*p*	$=NC_6H_4NO_2$-*p*		CF_3	CF_3	$=C(CF_3)_2$		165–167	6	487
	$N=C(CF_3)_2$	$=NC_6H_{11}$		$=NC_6H_{11}$		CF_3	CF_3	40	71	60
C_{22}	$NC(CF_3)_2$	$=NC_6H_4CH_3$-*o*		$=NC_6H_4CH_3$-*o*		CF_3	CF_3	89	68	60
	$N=C(CF_3)$	$=NCH_2C_6H_5$		$=NCH_2C_6H_5$		CF_3	CF_3	–	–	60
C_{23}	C_6H_5	$COOCH_3$	$COOCH_3$	$=NC(CH_3)_3$		C_6H_5	H	(138–139/–)	82	57
	C_6H_5	$=NC(CH_3)_3$		$=NC(CH_3)_3$		$C_6H_4NO_2$-*p*	H	147–152	–	113
	$C_6H_4NO_2$-*p*	$=NC(CH_3)_3$		$=NC(CH_3)_3$		C_6H_5	H	141.5–143	51	113
	$C_6H_4NO_2$-*p*	$=NC(CH_3)_3$		$=NC(CH_3)_3$		$C_6H_4NO_2$-*p*	H	175–177	76	113
C_{25}	C_6H_5	$COOCH_3$	$COOCH_3$	$=NC_6H_{11}$		C_6H_5	H	(128–129/–)	86	57
	C_6H_5	$COOCH_3$	$COOCH_3$	$=NC_5H_5$		C_6H_5	H	(125/–)	75	57
C_{26}	C_6H_5	$COOCH_3$	$COOCH_3$	$=NCH_2C_6H_5$		C_6H_5	H	(126/–)	72	57
	C_6H_5	$COOCH_3$	$COOCH_3$	$=NC_6H_4CH_3$-*o*		C_6H_5	H	(121–122/–)	89	57
	C_6H_5	$COOCH_3$	$COOCH_3$	$=NC_6H_4CH_3$-*p*		C_6H_5	H	(152–153/–)	74	57
	C_6H_5	$COOCH_3$	$COOCH_3$	$=NCH_2CH_2CH_2$-N⟨O⟩		C_6H_5	H	(116/–)	78	57

TABLE 12. SYNTHESIS OF THE AZETIDINE RING FROM OTHER RING SYSTEMS



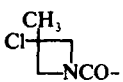
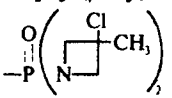
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_4	CH_3	–	H	H	H	H	H	H	–	–	6	302
	H	H	H	H	CH_3	Cl	H	H	Cl	120	85	149
	CF_3	–	F	F	Cl	F	Cl	F	–	(67.5/1)	32	26
	CF_3	–	F	F	F	F	F	F	–	(9.6/–)	73	27
C_6	$COCH_3$	–	CH_3	H	H	H	H	H	–	–	–	405
	$COCH_3$	–	H	H	CH_3	H	H	H	–	–	–	405
	$COCH_3$	–	H	H	CH_3	Cl	H	H	–	(65/0.2)	70	149
C_7	$COCH_3$	–	CH_3	CH_3	H	H	H	H	–	–	–	405
	$COCH_3$	–	H	H	CH_3	CH_3	H	H	–	–	–	405
C_8	$COCH_3$	–	H	H	$OOCCH_3$	CH_3	H	H	–	(82/0.05)	56	149
	H	–	H	H	1-Pyrrolidinyl	CH_3	H	H	–	(38/0.04)	50	149
C_9	H	–	H	H	1-Piperidyl	CH_3	H	H	–	(58/2)	36	149
		–	H	H	CH_3	Cl	H	H	–	96.5	88	149
C_{10}	$SO_2C_6H_4CH_3$-*p*	–	H	H	Cl	H	H	H	–	106	72	149
	$C(COOCH_3)=CHCOOCH_3$	–	H	H	$=CH_2$		H	H	–	104	83	149
	H	–	H	H	SC_6H_5	CH_3	H	H	–	(63/0.01)	79	149
	$COCH_3$	–	CH_3	CH_3	COOH	H	CH_3	CH_3	–	229–230	–	88
	$COCH_3$	–	CH_3	CH_3	COOH	OH	CH_3	CH_3	–	205–210 (dec)	64	390

TABLE 12 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{11}	$COOCH_3$ | $C{=}CHCOOCH_3$	–	H	H	$=CH_2CH_3$		H	H	–	56.5	84	149
	COC_6H_5	–	H	H	CH_3	Cl	H	H	–	48	48	149
	$SO_2C_6H_4CH_3$-*p*	–	H	H	Cl	CH_3	H	H	–	70.5	62	149
C_{12}	$SO_2C_6H_4CH_3$-*p*	–	H	H	C_2H_5	Cl	H	H	–	66	85	149
		–	H	H	CH_3	Cl	H	H	–	110–120	52	149
C_{15}	COC_6H_5	–	CH_3	CH_3	COOH	OH	CH_3	CH_3	–	253–255 (dec)	91	100
C_{16}	$COC(CH_3)_3$	–	CH_3	CH_3	C_6H_5	H	H	H	–	–	30	40
C_{19}	C_6H_5	–	$COOCH_3$	$COOCH_3$	H	H	C_6H_5	H	–	108	~100	458
C_{21}	C_6H_5	–	$COCH_3$	$COOCH_3$	$COOCH_3$	H	C_6H_5	H	–	154	–	458
	C_6H_5	–	$COOCH_3$	$COOCH_3$	$COOCH_3$	H	C_6H_5	H	*trans*	114	95	458
C_{22}	C_6H_5	–	$COOCH_3$	$COOCH_3$	COC_6H_5	H	$COOCH_3$	H	*cis*	164	38	457
	C_6H_5	–	$COOCH_3$	$COOCH_3$	$COOC_2H_5$	H	C_6H_5	H	*trans*	104	95	458
	C_6H_5	–	$COOCH_3$	$COOCH_3$	Br	$COOC_2H_5$	C_6H_5	H	*trans*	150	52	457
	C_6H_5	–	$COCH_3$	$COOCH_3$	Cl	$COOC_2H_5$	C_6H_5	H	–	126	28	457
	C_6H_5	–	$COOCH_3$	$COOCH_3$	Cl	$COOC_2H_5$	C_6H_5	H	–	154	72	457
C_{26}	C_6H_5	–	$COCH_3$	$COOCH_3$	COC_6H_5	H	C_6H_5	H	–	160	–	458
	C_6H_5	–	$COOCH_3$	$COOCH_3$	COC_6H_5	H	C_6H_5	H	*cis*	200	21	458, 457
									trans	152	79	458, 457

[a] Stereochemical configuration denoted.

TABLE 13. SYNTHESIS OF FUSED AZETIDINE RINGS BY CYCLIZATION OR CYCLOADDITION

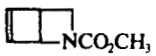
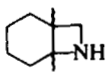
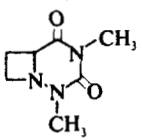
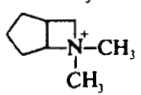
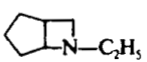
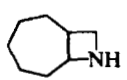
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_6		Pic	166–167	92	178
C_7		–	–	–	30
		Pic			
		cis	131	83	178, 336
		trans	146–147	86	178
		Cl	205	–	121
		Pic	256	–	121
		–	(73–5/–)	91	418
C_8		Ts	–	–	183
		–	(88–89/105)	19	183, 162
		Pic	163–164	–	183, 162
		MeI	186–187	–	183, 162
		Pic			
		cis	135–136	88	178
		trans	160–162	92	178
		Cl	180	–	121

TABLE 13 CONTINUED

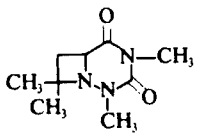
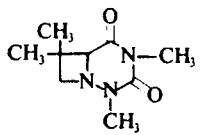
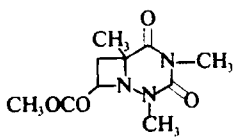
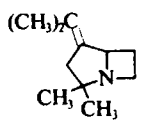
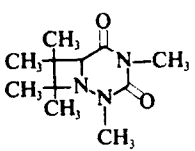
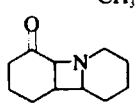
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_9		–	–	78	418
		–	–	–	418
C_{10}		–	–	–	418
C_{11}		–	(110/40)	–	307
		–	61–63	88	418
		–	–	30	15

TABLE 13 CONTINUED

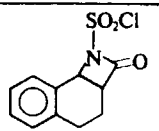
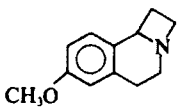
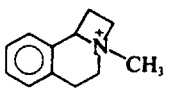
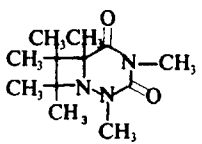
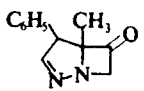
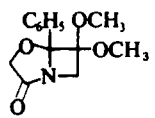
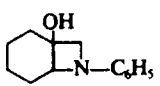
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		–	76–78 (dec)	76	336
C_{12}		– Pic	(88–90/0.02) 133.5–134.5	– –	342 342
		Br	182–185	79	324, 319
		–	–	70	418
		–	51–53	34	327
C_{13}		–	50–51	65	255, 381, 251
		–	–	38	212

TABLE 13 CONTINUED

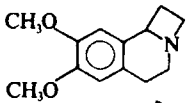
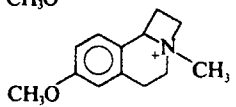
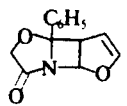
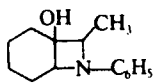
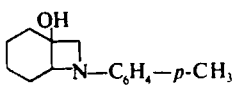
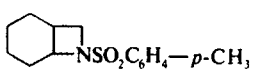
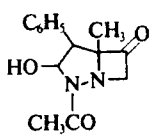
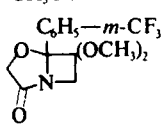
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		–	75–76	–	248, 250
		Cl	169–170	–	248
		*p*-BrBzs	78	144–146	324, 319
		–	144–147	45	381, 251
C_{14}		–	–	40	212
		–	–	58	212
		*trans*	104.5–106	55	336
		cis	89–90	22	336
		–	156–158	–	99
		–	–	59	381, 251

TABLE 13 CONTINUED

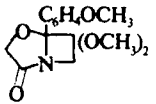
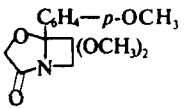
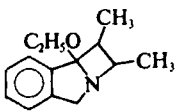
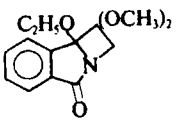
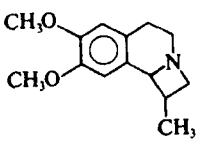
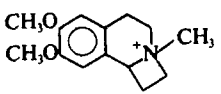
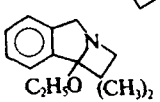
Compound	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	–	–	75	381, 251
	–	117–118	69	381, 251
	*cis* *trans*	– –	8 18	222, 251 222, 251
	–	62–65	50	222, 251, 378
	CH_3I	194–195 (dec)	–	250, 249
	*p*-BrBzs	182–184.5	72	324, 319, 318, 317, 50, 321, 320, 323, 324
	–	–	–	222, 251

TABLE 13 CONTINUED

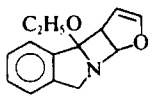
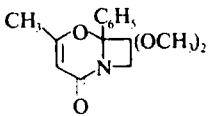
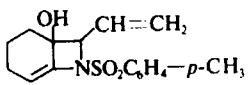
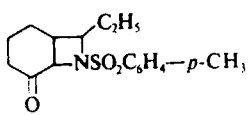
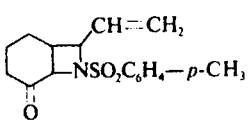
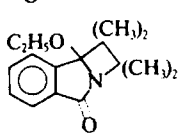
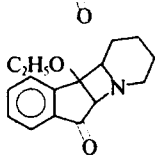
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		–	35–37	54	222, 251
C_{15}		–	103–104	78	253, 251
C_{16}		–	–	35	15
		–	–	30	15
		–	–	40	15
		–	–	20	222, 251
		–	84–85	51	222

TABLE 13 CONTINUED

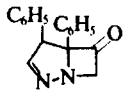
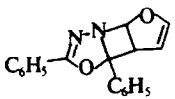
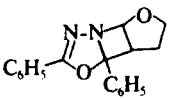
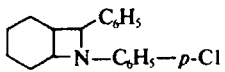
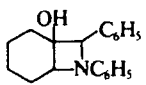
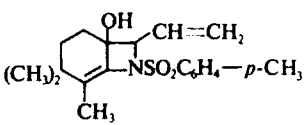
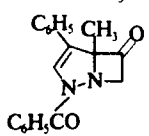
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{17}		*cis* *trans*	108–110 80–81	65 –	338 338
C_{18}		–	179–181	26	449, 251
		–	–	–	449
C_{19}		–	–	–	125
		–	–	58	212
		–	–	25	150
		–	112–114; 122–124	65	327

TABLE 13 CONTINUED

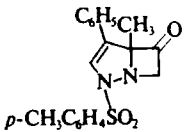
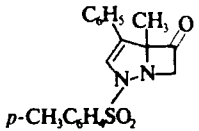
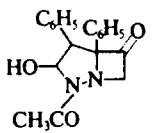
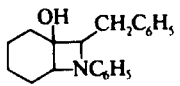
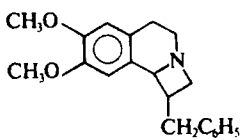
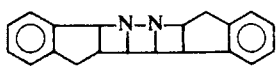
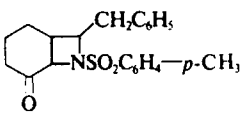
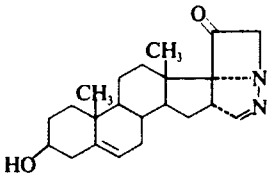
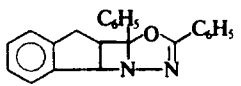
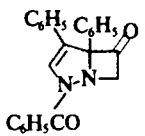
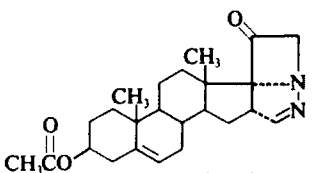
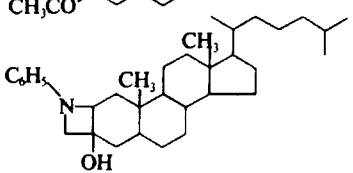
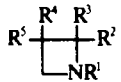
Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		–	148–150	–	331
		–	158–160	50	325
		*cis* *trans*	165–167 185–187 (dec)	– –	99 99
C_{20}		–	–	39	181
		HI	194	93	86
		–	–		251
C_{21}		–	–	50	15

TABLE 13 CONTINUED

Compound		Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{22}		–	234–236	78	326
C_{23}		–	196.5–197	–	450
C_{24}		–	133 (dec)	–	325
		–	186–192	82	326
C_{34}		–	–	43	212

[a] Stereochemical configuration denoted.

TABLE 14. SYNTHESIS OF AZETIDINES BY REDUCTION OF 2-AZETIDINONES



	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_5	H	H	H	CH_3	CH_3		(90–92/–)	44.5	437
						Cl	96–98	–	437
						Ts	119.5–120.5	56.9	186
C_6	H	$CH_2CH_2CH_3$	H	H	H		(123–125/–)	36	430
						Pic	105–106	–	430
C_7	H	H	H	$CH_2CH(CH_3)_2$	H		(80–83/0.51)	68	41, 426
						Pic	127–128	–	41, 426
	H	C_2H_5	C_2H_5	H	H		(140/760)	65	430
						Cl	119–121	–	430
						Pic	183–141	–	430
	H	H	H	C_2H_5	C_2H_5	–	(84–86/120–140)	70.6	437
C_9	H	H	H	C_6H_{11}	H		(90–92/0.15)	50	41, 426
						Cl	91–93	–	41, 426
	H	C_6H_5	H	H	H	Pic	122–123	81	473
	H	H	H	C_6H_5	H		(87–89/3.5)	57.5	441, 437
						Cl	78–80	–	441, 437
						HSO_4	110–112	–	441
	H	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	–	(87/20)	72.4	437, 427
	H	H	H	OH	C_6H_5	Hemioxalate	190–192	31	428
							160–162	–	428
	H	C_6H_5	H	NH_2	H	Di-Cl	154–156	84	473
	H	C_6H_4Cl-*p*	H	NH_2	H	Di-Cl	130–133	73	473
C_{10}	H	H	H	$CH_2C_6H_5$	H		(98/0.8)	49	41, 426
						Oxalate	148–149	–	41, 426
	H	H	H	$C_6H_4CH_3$-*p*	H		(83/0.4)	41	41
						Cl	120	–	41
						Pic	151–152	–	41

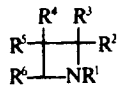
TABLE 14 CONTINUED

	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	H	CH_3	C_6H_4Cl-*p*	H	H		(132/12)	–	65
	H	H	H	C_6H_5	CH_3		(73/0.3)	64.2	437
						Cl	155	–	437
	H	H	H	C_6H_5	CH_2OH		135–137	51	433
						Cl	211–212	–	433
C_{11}	$CONH_2$	CH_3	C_6H_5	H	H		121–122	–	65
	H	C_2H_5	C_6H_5	H	H		(85–86/2.5)	84	430, 65
						Pic	110–112	–	430
	CH_3	CH_3	C_6H_4Cl-*p*	H	H		(72–79/0.5)	–	65
	H	H	H	C_6H_5	C_2H_5		*(85–87/1.2)	77.5†	437,* 425†
						Cl	219–220 (dec)		437
	H	H	H	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$		(110/11)	87	437
						Cl	96–99	–	437
	H	H	H	$C_6H_4OCH_3$-*m*	CH_3	Cl	152–153	74	37
C_{12}	H	$CH_2CH{=}CH_2$	C_6H_5	H	H		(118/12)	–	65
	H	H	H	$CH_2CH_2CH_3$	C_6H_5		(88–90/0.4)	73.5	437
	H	H	H	$CH(CH_3)_2$	C_6H_5		36–38	75.3	437
						Cl	244–246	–	437
	H	H	H	$C_6H_4CH_3$-*p*	C_2H_5		(89–91/0.5)	79	438
						Pic	208–210		438
	H	H	H	$C_6H_4OCH_3$-*m*	C_2H_5		(114/1.0)	84	37
	H	H	H	$CH_2C_6H_5$	C_2H_5		(120–130/0.4)	29	437
						Cl	120–124	–	437
	CH_2CH_2OH	CH_3	C_6H_4Cl-*p*	H	H		(134–135/1.4)	–	65
C_{13}	H	H	H	2-Naphthyl	H		(151–154/1.0)	45	426, 41
						Cl	182–183	–	426, 41
	C_2H_5	C_2H_5	C_6H_5	H	H		(128–130/10)	–	65
	$COCH_3$	C_2H_5	C_6H_5	*H*	*H*		(165/1.5)	–	65
	H	H	H	$CH_2CH_2CH_2CH_3$	C_6H_5		(85–90/0.2–0.4)	73.5	437
						Cl	128–130	–	437

TABLE 14 CONTINUED

	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	H	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	–	(115/0.9)	60	37
						Cl	184–185	74	37
	H	H	H	$CH_2CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_2CH_3$	–	(97/0.38)	86	463
C_{14}	H	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_2CH_3$	–	(134/1.5)	69	37
	$COOC_2H_5$	C_2H_5	C_6H_5	H	H	–	(113–118/0.7)	–	65
C_{15}	H	H	H	$C_6H_4C_6H_5$-*p*	H	Cl	155–157	43	426, 41
	H	C_6H_5	C_6H_5	H	H	–	131	–	65
	H	H	H	C_6H_{11}	C_6H_5	–	85–87	74.5	437
						Cl	210–211	–	437
	H	H	H	C_6H_5	C_6H_5	–	95–96	43	437
						Cl	245–247	–	437
	H	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_2CH_2CH_2$	–	104–105	55	37
	H	H	H	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	–	(125–130/0.4)	30	438
	H	H	H	$CH_2C_6H_5$	C_6H_5	–	62–64	85.5	437
						Cl	171–172	–	437
	$CH_2C_6H_5$	CH_3	C_6H_5	H	H	–	126–127	–	65
	$CH_2C_6H_5$	C_2H_5	C_6H_5	H	H	–	(152–157/1.4)	–	65
	$COCH_3$	$CH_2C_6H_5$	C_6H_5	H	H	–	(182–185/0.4)	–	65

TABLE 15. SYNTHESIS OF AZETIDINES BY *N*-ALKYLATION



	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_5	CH_2CH_2OH	H	H	H	H	H	–	–	–	117
C_6	CH_2CH_2CN	H	H	H	H	H	–	(85–90/20)	60	482, 86
	CH_3	$COOCH_3$	H	H	H	H	–	(70–72/40)	8	380
	CH_3	H	H	CH_3	CH_3	H	–	(68/–)	–	392
C_7	$CH_2CH{=}CHCH_3$	H	H	H	H	H	–	(70/90)	–	275
	$CH{=}CHCOOCH_3$	H	H	H	H	H	–	46.5–47	5.2	250
	$CH_2N(CH_2)_3$	H	H	H	H	H	–	–	90	460
	C_2H_5	H	H	H	H	H	–	(185–190/0.5)	–	439
							Cl	132–134	–	439
	CH_2CH_2Cl	H	H	CH_3	CH_3	H	–	(47–51/24)	–	435
	CH_2CH_2OH	H	H	CH_3	CH_3	H	–	(80–83/24)	57	435
	$C(NH)NHC(NH)NH_2$	H	H	CH_3	CH_3	H	Cl	240–242	–	439
	$CH_2CH_2NH_2$	H	H			H	–	–	–	308
	CH_2CH_2OH	H	H			H	Bzl	108–108.5	63	308
							Bzl-Cl	176–177	89	308
							MeI	139–140	–	308
C_8	CH_3 | $C{=}CHCOCH_3$	H	H	H	H	H	–	52–57	–	86
	$CH_2CH_2NHCNH_2$ ‖ NH	H	H	CH_3	CH_3	H	–	200–203	–	479
	$CH_2CHCOOCH_3$ | CH_3	H	H	H	H	H	–	(56–58/1)	–	275

TABLE 15 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2CH_2Si(CH_3)_3$	H	H	H	H	H	–	(65/25)	–	275
	1-Cyclopentenyl	H	H	H	H	H	–	(60–66/15)	15	86
	CH_2SO_3Na	H	H	$CH_2CH(CH_3)_3$	H	H	–	219–221	57	41, 426
	$CH_2CH_2CH_2Cl$	H	H	CH_3	CH_3	H	Cl	–	–	435
C_9	3-Cyclohexenyl	H	H	H	H	H	–	(48/1)	–	275
	1-Cyclohexenyl	H	H	H	H	H	–	(51–53/4)	22	86
	$CH_2CH{=}CHNH\text{-}CH_2CH_2CH_3$	H	H	H	H	H	–	(86/3)	–	275
	$CH(CH_3)CHCOOCH_3$ CH_2COOCH_3	H	H	H	H	H	–	(89–90/3)	57	86
	$C(COOCH_3){=}CHCOOCH_3$	H	H	H	H	H	–	65.5–67	57	86
	CH_3	3-Pyridyl	H	H	H	H	–	(49–50/0.025)	40	397
	C_6H_{11}	H	H	Cl	H	H	–	(62–63/1)	49	154
	CH_2CH_2OH	H	H	$CH_2CH(CH_3)_2$	H	H	–	(99–100/6)	37	426, 41
	CH_3	H	H	3-Pyridyl	H	H	–	(63–65/–)	59	397
							Di-Pic	191–192	–	397
	C_2H_5	C_2H_5	C_2H_5	H	H	H	–	(160–162/> 60)	–	430
							Pic	167	–	430
	CH_2CH_2OH	C_2H_5	C_2H_5	H	H	H	–	(100/0.10)	–	430
	CH_2CH_2Cl	H	H	C_2H_5	C_2H_5	H	–	(85–95/5)	–	435
							Cl	197–198	–	435
	CH_2CH_2OH	H	H	C_2H_5	C_2H_5	H	–	(73–75/0.6–0.8)	64.5	435
C_{10}	$CH_2CH_2COOC_4H_9$-*n*	H	H	H	H	H	–	(78–79/1)	–	275
	CH_2SO_3Na	C_6H_5	H	H	H	H	–	160–165	68.5	429
	$CH(CH_2COOCH_3)COOCH_3$	H	H	CH_3	H	H	–	(62–65/0.02)	83	149

TABLE 15 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	CH_3	H	H	C_6H_5	H	H	–	(62–64/2)	87	441
							Cl	107–110	–	441
	$CH_2CH_2CH_2OH$	H	H	C_2H_5	H	H	–	(65–69/1.5)	88	84
	$CH_2CH_2CH_2NH_2$	H	H	C_2H_5	C_2H_5	H	–	(55–57/1.5)	75	84
							Pic	199.5–201.5 (dec)	–	84
	CH_2CH_2CN	H	H	C_2H_5	C_2H_5	H	–	(65–67/1.5)	~ 100	84
	CH_3	H	H	OH	C_6H_5	H	–	54–56	~ 100	169, 172
C_{11}	$CH_2CH_2C_6H_5$	H	H	H	H	H	–	(125/26)	–	275
	$CH_2CH_2Si(C_2H_5)_3$	H	H	H	H	H	–	(114/20)	–	275
	C_2H_5	C_6H_5	H	H	H	H	–	(90–95/0.10)	84	429
							Pic	152–156	–	429
	CH_2CH_2Cl	C_6H_5	H	H	H	H	–	(97–103/0.5)	–	429
							Cl	99–102	–	429
	CH_2CH_2OH	C_6H_5	H	H	H	H	–	(90–92/0.45)	39	429
	C_2H_5	H	H	C_6H_{11}	H	H	–	(96–98/0.10)	60	41
							Cl	137–140	–	41, 426
							Pic	139–141	–	41, 426
	C_2H_5	H	H	C_6H_5	H	H	–	(110–115/8)	77	441
							Cl	142–143	–	441
							Pic	161–162	–	441
	CH_2CH_2Cl	H	H	C_6H_5	H	H	–	(90–93/0.3)	79	441
							Cl	136–138	–	441
	CH_2CH_2OH	H	H	C_6H_5	H	H	–	(110–115/0.8)	42	441
	$CHCH_2COOCH_3$ $COOCH_3$	H	H	C_2H_5	H	H	–	(95/0.1)	84	149
	C_2H_5	H	H	C_6H_5	OH	H	–	182–182.5	–	435
	CH_3	H	H	C_6H_5	CH_2OH	H	–	96–97	–	433
							Cl	151–153	–	433
							MeI	182–183	–	433
							Pic	157–159	–	433

TABLE 15 CONTINUED

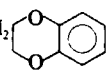
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2CH_2COOCH_3$	H	H	C_2H_5	C_2H_5	H	–	(64.5–67.5/1.5)	91	84
	$CHCH_2CN$ $\vert$ CH_3	H	H	C_2H_5	C_2H_5	H	–	(68–75.5/1.5)	68	84
							Pic	157–158	–	84
	$CHCH_2CH_2OH$ $\vert$ CH_3	H	H	C_2H_5	C_2H_5	H	–	(85–90/1.5)	70	84
	$CH_2CH_2NH_2$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	–	(95/5)	55	33
	$CHCH_2CH_2NH_2$ $\vert$ CH_3	H	H	C_2H_5	C_2H_5	H	–	(62–63/1.5)	88	84
							Pic	238–241	–	84
	CH_2CN	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	–	(109/7)	64	33
	$C(NH)NHC(NH)NH_2$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	Cl	210–214	–	439
C_{12}		H	H	H	H	H	–	–	–	314
	$CH(CH_3)_2$	H	H	C_6H_5	H	H	–	(72–74/0.8)	35	441
	$CH_2CH{=}CH_2$	H	H	C_6H_5	H	H	–	(65/0.3)	51	441
	C_2H_5	H	H	$CH_2C_6H_5$	H	H	–	(83–85/1)	77	426, 41
							Pic	131–133	–	426, 41
				CN $\vert$						
	$C(CH_3)_3$	H	H	$CHCOOC_2H_5$	H	H	–	(108–114/0.8)	11	210
	CH_2SO_3Na	C_2H_5	C_6H_5	H	H	H	–	56–58	–	430
	$CH_2C_6H_4Br$-*o*	H	H	CH_3	CH_3	H	–	(95–97/–)	–	439
							MeI	137–140	–	439
	$CHCH_2COOCH_3$ $\vert$ CH_3	H	H	C_2H_5	C_2H_5	H	–	(67–68/1.5)	84	84
	COC_6H_4Br-*o*	H	H	CH_3	CH_3	H	–	(136–140/0.9)	–	439
	CH_2CH_2OH	H	H	C_6H_5	CH_3	H	–	(107–110/0.1)	58.4	435

TABLE 15 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	CH_3	H	H	$C_6H_4OCH_3$-*m*	CH_3	H	–	(78–80/0.2)	55	37
	CH_2CH_3	H	H	C_6H_5	CH_2OH	H	–	90–91	–	433
							Cl	158	–	433
							MeI	113–115	–	433
							Pic	125–127	–	433
	$CH_2CH_2NH_2$	H	H	CH_3	C_6H_5	H	–	(87/0.2)	50	33
	CH_2CN	H	H	CH_3	C_6H_5	H	–	(100/0.2)	73	33
	$CH_2CH_2NH(NH)NH_2$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	–	187–189	91	33
	$C(NH)NH_2$	H	H	C_2H_5	C_6H_5	H	–	278–281	79	33
	CH_3	C_6H_5	H	CH_3	CH_3	H	–	(85–89/9)	3	9
	CH_3	CH_3	CH_3	OH	C_6H_5	H	–	–	–	439
C_{13}	$(CH_2)_2SiMe_2$-C_6H_5	H	H	H	H	H	–	(102/5)	–	275
	$CH_2CH_2CH_2CH_3$	H	H	C_6H_5	H	H	–	(83–85/0.5)	93	441
	$CH_2CH(CH_3)_2$	H	H	C_6H_5	H	H	–	(74–75/0.4)	29	441
	$CH_2COOC_2H_5$	H	H	C_6H_5	H	H	–	(123–124/0.5)	29	441
				$CHCOCH_3$						
	$C(CH_3)_3$	H	H	$COOC_2H_5$	H	H	–	(90–95/0.5)	67	210
	C_2H_5	C_2H_5	C_6H_5	H	H	H	–	(87–88/2.5)	–	430
	CH_2CH_2OH	C_2H_5	C_6H_5	H	H	H	–	(107–110/0.5)	–	430
	CH_2CH_2Cl	H	H	C_6H_5	C_2H_5	H	–	(101–103/0.5)	–	435
							Cl	182–183	–	435
	CH_2CH_2OH	H	H	C_6H_5	C_2H_5	H	–	(100–105/0.4)	31.4	435
	$CH_2CH_2NH_2$	H	H	C_6H_5	C_2H_5	H	–	(97/0.2)	61	33
	CH_2CN	H	H	C_2H_5	C_6H_5	H	–	65–66	70	33
	CH_3	H	H	$C_6H_5OCH_3$-*m*	C_2H_5	H	–	(88/0.5)	74	37
	$COOCH_2C(CH_3)(CH_2OH)CH_2CH_3$	H	H	CH_3	CH_3	H	–	(127–130/0.2)	–	439

TABLE 15 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2CH_2NHC(NH)NH_2$	H	H	CH_3	C_6H_5	H	–	239–240	56	33
	CH_3	C_6H_5	CH_3	CH_3	CH_3	H	–	–	1.9	9
C_{14}	$CH_2CH_2Si(CH_3)[N(C_2H_5)_2]_2$	H	H	H	H	H	–	(125/5)	–	275
	$C(CH_3)_3$	H	H	$CH(COOC_2H_5)_2$	H	H	–	(100–104/0.6)	39	210
	$CH_2CH_2CH_3$	C_2H_5	C_6H_5	H	H	H	–	(110/2.5)	–	430
	$CH_2C_6H_5$	C_2H_5	C_2H_5	H	H	H	–	(93–95/0.6)	–	430
	CH_3	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	–	–	91	463
							Cl	96.5–98	–	463
	C_2H_5	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_3$	H	–	121–123	72	37
	CH_3	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	Cl	117–118	85	37
	CH_2CH_2OH	H	H	C_6H_5	$CH_2CH_2CH_3$	H	–	(110–120/0.2)	57.3	435
	CH_2CH_2OH	H	H	C_6H_5	$CH(CH_3)_2$	H	–	58–60	58	435
	$CH_2CH_2OC_6H_4CH_2NH_2$-*p*	H	H	CH_3	CH_3	H	–	(120–123/2)	–	439
	$COOCH_2C(CH_3)(CH_2CH_2CH_3)CH_2OCNH_2$	H	H	CH_3	CH_3	H	–	84–86	–	439
	$CH(CH_3)COC_6H_5$	H	H	CH_3	CH_3	H	Cl	170–172	–	439
	$CH_2CH_2OC_6H_4CHO$-*p*	H	H	CH_3	CH_3	H	–	(131–134/0.2)	–	439
							Cl	140–142	–	439
							Oxime	132–133	–	439
	$C(NH)NH_2$	H	H	$(CH_2)_3CH_3$	C_6H_5	H	HSO_4	240–241	68	33
	$CH_2CH_2NHC(NH)NH_2$	H	H	C_2H_5	C_6H_5	H	–	214–215	87	33
C_{15}	$CH_2CH{=}CHC_6H_5$	$CH_2CH_2CH_3$	H	H	H	H	–	(118–120/0.1)	–	430
	C_2H_5	H	H	2-Naphthyl	H	H	Cl	160–161	–	41

TABLE 15 CONTINUED

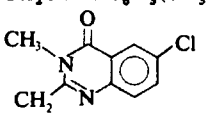
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$C(C_2H_5)_2C{\equiv}CCH_2N(C_2H_5)_2$	H	H	OH	H	H	Fumarate	141	62	146, 73
	$C(C_2H_5)_2C{\equiv}CCH_2N(CH_2)_4$	H	H	OH	H	H	Difumarate hydrate	125	27	146, 73
	CH_2CH_2OH	H	H	C_6H_5	$(CH_2)_3CH_3$	H	–	(125–130/0.3–0.5)	51	435
	$CH_2CH_2NH_2$	H	H	$(CH_2)_3CH_3$	C_6H_5	H	–	(112/0.4)	60	33
	CH_2CN	H	H	$(CH_2)_3CH_3$	C_6H_5	H	–	(128/0.4)	66	33
	CH_3	H	H	$C_6H_4OCH_3$-*m*	$(CH_2)_3CH_3$	H	–	(113–114/0.8)	82	37
	$CH_2CONHC_6H_3(CH_3)_2$-2,6	H	H	CH_3	CH_3	H	–	(175–185/0.5)	93–95	435
		CH_3	CH_3	H	H	H	Cl	199–203 (dec)	–	130
	"	CH_3	CH_3	H	H	H	–	113–114	–	130
							HSO_4	166 (dec)	–	130
	$CH_2C_6H_5$	CH_3	CH_3	CH_2OH	OH	$(CH_3)_2$	–	75	–	416
C_{14}	$CH_2C_6H_5$	C_6H_5	H	H	H	H	–	(120–122/–)	63	429
	$CH_2C_6H_5$	H	H	C_6H_5	H	H	–	(122–127/0.4)	64	441
	$-C(CH_2)_5C{\equiv}CCH_2N(C_2H_5)_2$	H	H	OH	H	H	–	80	39	146, 73
	$C(C_2H_5)_2C{\equiv}CCH_2N(CH_2)_5$	H	H	OH	H	H	Cl	137	18	146, 73
	$C(CH_2)_5{-}C{\equiv}CCH_2N(CH_2)_4$	H	H	OH	H	H	–	75	56	146, 73
	$CH_2CH{=}CHC_6H_5$	C_2H_5	C_2H_5	H	H	H	–	(128–130/0.8)	–	430
	Phthalimidomethyl	C_2H_5	C_2H_5	H	H	H	–	96–98	–	430

TABLE 15 CONTINUED

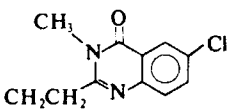
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2C_6H_5$	H	H	C_6H_5	OH	H	–	187.5–188.5	–	170
	$CH_2C(CHO)CH_2CH_3$ C_6H_5	H	H	CH_3	CH_3	H	–	(135–140/0.6)	–	439
	$CH_2C(C_6H_5)CH_2CH_3$ CH_2OH	H	H	CH_3	CH_3	H	–	(118–120/0.4)	–	439
							Cl	98–101	–	439
	CH_3	H	H	$C_6H_4OCH_3$-*m*	$(CH_2)_4CH_3$	H	–	(109–111/0.45)	55	37
	$CH_2CH_2NHC(NH)NH_2$	H	H	$(CH_2)_3CH_3$	C_6H_5	H	–	151–154	73	33
		CH_3	CH_3	H	H	H	–	96–98	–	130
							HSO_4	147–148.5	–	130
C_{17}	$C(CH_2)_5C{\equiv}CCH_2N(CH_2)_5$	H	H	OH	H	H	–	103	36	146, 73
	$CH_2C_6H_5$	H	H	C_6H_5	CH_2OH	H	–	89–91	–	433
							Cl	148–150		
							MeI	143	–	433
	$CH_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	C_2H_5	H	–	(110–115/0.4)	–	435
	$CH_2CON(C_2H_5)_2$	H	H	C_6H_5	C_2H_5	H	–	(155/0.5)	–	435
C_{18}	$CH_2CH{=}CHC_6H_5$	C_6H_5	H	H	H	H	–	(140–150/0.5)	52	429
	Phthalimidomethyl	C_6H_5	H	H	H	H	–	85–88	46.5	429
	$CH_2CH{=}CHC_6H_5$	H	H	C_6H_5	H	H	–	(155–160/0.6)	30	441
	CH_3	H	H	$C(C_6H_5)_2CN$	H	H	–	112–115	64	474

TABLE 15 CONTINUED

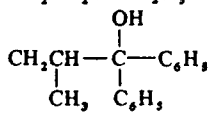
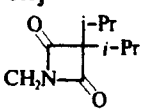
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH_2C_6H_5$	C_2H_5	C_6H_5	H	H	H	–	(138–140/0.6)	–	430
	$CH_2CH_2COOC_2H_5$	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	–	(94–100/0.01)	86	463
C_{19}		H	H	H	H	H	Cl	167–170	32	315
	$CH_2CONHC_6H_3$-$(CH_3)_2$-2,6	H	H	C_6H_5	H	H	–	113–116	53	441
	$CHCH_2C_6H_5$ | C_6H_5	H	H	CH_3	CH_3	H	–	–	2	11
	$CHC_6H_4CH_3$-*o* | C_6H_5	H	H	CH_3	CH_3	H	–	48–51	98	11
	Adamantyl	H	H	C_6H_5	OH	H	–	133.5–134	–	171
							Cl	219–219.5	–	171
	$CH_2CH_2C_6H_5$	H	H	$C_6H_4OCH_3$-*m*	CH_3	H	–	149–150	50	37
	$CH_2CH_2C_6H_5$	H	H	$C_6H_4OCH_3$-*m*	CH_3	H	–	(140–142/0.09)	50	37
	$CH_2CH_2OC_6H_5$	H	H	C_6H_5	C_2H_5	H	–	(160–170/0.3)	–	435
	$CH_2CH_2NHC_6H_5$	H	H	C_6H_5	C_2H_5	H	–	(160–165/0.6)	–	435
	$CH_2CONHC_6H_5$	H	H	C_6H_5	C_2H_5	H	–	(195–200/0.4)	–	435
	Phthalimidomethyl	H	H	C_6H_5	CH_2OH	H	–	165–167	–	433
	$C(C_2H_5)_2$-$C{\equiv}CCH_2$-$N(CH_2)_5$	H	H	$COONHC_3H_7$-*n*	H	H	–	139	42	146, 73
	$CH_2CH{=}CHC_6H_5$	C_2H_5	C_6H_5	H	H	H	–	(160–170/0.6)	–	430
	Phthalimidomethyl	C_2H_5	C_6H_5	H	H	H	–	96–98	–	430
	CH_3	H	H	C_6H_4-$OCH_2C_6H_5$-*m*	$CH_2CH_2CH_3$	H	–	52–53	53	37
		H	H	C_6H_5	CH_2OH	H	–	90–92	–	433

TABLE 15 CONTINUED

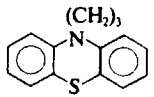
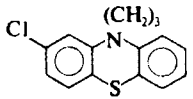
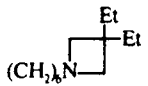
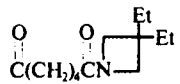
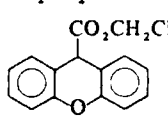
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
		H	H	CH_3	CH_3	H	–	(210–225/0.4)	–	435
		H	H	CH_3	CH_3	H	–	(205–210/0.4)	–	435
		H	H	C_2H_5	C_2H_5	H	–	(135–145/0.2–0.4)	–	208
							MeI	180–181 (dec)	–	208
		H	H	C_2H_5	C_2H_5	H	–	(40–45)	–	208
C_{20}	$CH_2CHCH_2C_6H_4$-$C(CH_3)_3$-*p* (CH₃ on CH)	CH_3	CH_3	H	H	CH_3	–	(134/0.3)	–	215
C_{21}	$(CH_2)_{17}CH_3$	H	H	OH	H	H	–	75.5–78	–	176
	$CH(C_6H_5)_2$	H	H	$COOC(CH_3)_3$	H	H	–	110–111	–	6
	$CH_2CH_2C_6H_5$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	–	(174–178/0.5)	50	37
	$CH_2CH_2C_6H_4NH_2$-*p*	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	Di-Cl	245–246	89	37
	$CH_2CH_2C_6H_4NO_2$-*p*	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	–	53–56	85	37
	$CH_2CH_2OOCCH(C_6H_5)_2$	H	H	CH_3	CH_3	H	–	(175–180/0.2)	–	435
							Cl	104–108	–	435
		H	H	CH_3	CH_3	H	–	–	70.5	435

TABLE 15 CONTINUED

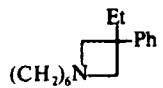
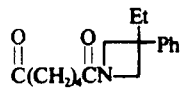
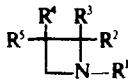
	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{23}	$CH(C_6H_5)_2$	$CH(OH)C_6H_5$	H	H	H	H	–	175–176 (dec)	–	175
	$CH_2\overset{\overset{C_6H_5}{\vert}}{C}CH_2OOCC_6H_5$ $\underset{\underset{CH_2CH_3}{\vert}}{}$	H	H	CH_3	CH_3	H	–	140–142	–	439
C_{24}	$CH_2CH(C_6H_5)_2$	$CH(OH)C_6H_5$	H	H	H	H	Cl	159.5–160.5 (dec)	–	175
	$CH_2CH_2OC_6H_4CH_2$-$NHCOC_6H_2(OCH_3)_3$-3,4,5	H	H	CH_3	CH_3	H	–	97–98	–	439
							Cl	177–179	–	439
C_{27}	$CH_2CH_2C_6H_4NO_2$-*p*	H	H	$C_6H_4OCH_2C_6H_5$-*m*	$CH_2CH_2CH_3$	H	–	114–115	91	37
C_{28}		H	H	C_6H_5	C_2H_5	H	–	60–62	–	208
							MeI	100 (dec)	–	208
		H	H	C_6H_5	C_2H_5	H	–	149–150	–	208

TABLE 16. SYNTHESIS OF AZETIDINES BY *N*-ARYLATION



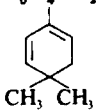
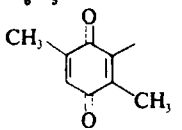
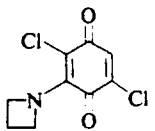
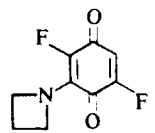
	R^1	R^2	R^3	R^4	R^5	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_9	$C_6H_4NO_2$-*o*	H	H	H	H	53.5	–	102
	$C_6H_4NO_2$-*p*	H	H	H	H	119	–	102
		H	H	H	H	(106–114/0.1)	35	296
C_{10}	C_6H_3-2-NO_2-4-Me	H	H	H	H	65–68	–	102
	$C_6H_3(NO_2)_2$-2,4	COOH	H	H	H	119–120	80	339
C_{11}	C_6H_5	H	H	CH_3	CH_3	–	1	343
		H	H	H	H	73–74	48	68
	C_6H_3-2-NO_2-4-(1-Azetidinyl)	H	H	H	H	123	–	102
C_{12}		H	H	H	H	243–245	–	465
		H	H	H	H	249	82	465

TABLE 16 CONTINUED

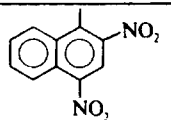
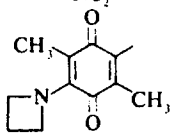
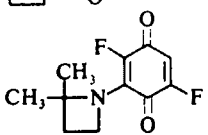
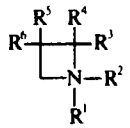
	R^1	R^2	R^3	R^4	R^5	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{13}		H	H	H	H	209–210	–	102
C_{14}		H	H	H	H	238–239	4.3	68
C_{16}		CH_3	CH_3	H	H	197	64	465

TABLE 17. SYNTHESIS OF AZETIDINIUM SALTS BY QUATERNIZATION

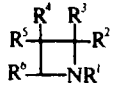


	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p. (°C)	Yield (%)	Ref.
C_3	H	H	H	H	Br	H	Cl	102–104	99	6
C_4	H	H	H	H	SO_2CH_3	H	Cl	104–105	104	7
C_6	H	CH_3	H	H	CH_3	CH_3	Br	174	–	392
							Cl	160	–	392
							ClO_4	124	–	392
C_7	CH_3	CH_3	CH_3	CH_3	H	H	ClO_4	172.5–173	89	281
	CH_3	CH_3	H	H	CH_3	CH_3	I	–	–	392
							Mes	90	–	392
	CD_3	CH_3	H	H	CH_3	CH_3	I	188–189	–	476
C_8	CH_3	$C(CH_3)_3$	H	H	OH	H	Mes	188–191	–	304
	H	H	H	H	$COOC(CH_3)_3$	H	Cl	120–123	88	6
	C_2H_5	CH_3	H	H	CH_3	CH_3	BF_4	238	–	165
C_9	CH_3	CH_2CH_2COOH	H	H	CH_3	CH_3	Acrylate	92	70	387
C_{10}	H	H	CH_3	H	OH	C_6H_5	Cl	–	–	310
C_{11}	CH_3	CH_3	H	H	C_6H_5	H	I	137–139	69	441
C_{12}	C_2H_5	CH_3	H	H	C_6H_{11}	H	I	158–160	–	426, 41
	CH_3	C_2H_5	H	H	C_6H_5	H	I	114–116	53	441
C_{13}	CH_3	$CH(CH_3)_2$	H	H	C_6H_5	H	I	148–150	65	441
	CH_3	$CH_2CH=CH_2$	H	H	C_6H_5	H	I	115–118	75	441
	CH_3	C_2H_5	H	H	$CH_2C_6H_5$	H	I	99–100	–	41, 426
	CH_3	$CH_2C_6H_5$	CH_3	CH_3	H	H	ClO_4	142.5–143	93	281
							Br	114–144 (dec)	–	281
	CH_3	$CH_2C_6H_5$	H	H	CH_3	CH_3	I	163–164 (dec)	91.5	10
							Cl	194	–	392
							Br	210	–	392

TABLE 17 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p. (°C)	Yield (%)	Ref.
	CH_3	CH_3	C_6H_5	H	CH_3	CH_3	I	122 (dec)	80	9
C_{14}	CH_3	$(CH_2)_3CH_3$	H	H	C_6H_5	H	I	121–123	40	441
	CH_3	$CH_2CH(CH_3)_2$	H	H	C_6H_5	H	I	110–112	70	441
	CH_3	$CH_2COOC_2H_5$	H	H	C_6H_5	H	I	111–113	46	441
C_{16}	C_2H_5	CH_3	H	H		H	–	150–151	–	426, 41
C_{17}	CH_3	$CH_2C_6H_5$	H	H	C_6H_5	H	I	140–142	44	441
C_{19}	CH_3	$CH_2CH_2COOC_2H_5$	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	I	171.5	96	463

TABLE 18. SYNTHESIS OF AZETIDINES BY REMOVAL OF GROUPS AT N_1



	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_3	H	H	H	H	H	H	–	(62/–)	98	461, 462, 455 475, 209, 102
							Pic	166–169	–	445, 423
	H	H	H	OH	H	H	–	113–116	–	170
							Cl	91–92	–	83
C_4	H	CH_3	H	H	H	H	–	(72–76/755)	78.2	455
							p-Nitrobenzamide	42–43	–	455
	H	H	H	CH_3	H	H	–	(74–75/–)	58	209
	H	$CONH_2$	H	H	H	H	–	109–111	97.2	361
	H	COOH	H	H	H	H	–	210	73	313, 361 254, 376
	H	H	H	COOH	H	H	–	230–275 (dec)	99	7
C_5	H	$CH_2CH_2NH_2$	H	H	H	H	Pic	199	–	423
	H	H	H	C_2H_5	H	H	–	(106–108/–)	87	461
							Pic	128–129	–	461
	H	H	H	CH_3	CH_3	H	–	(91–92/–)	76	209
	H	CH_3	H	CH_3	H	H	–	(84–86/750)	89	145
	H	CH_3	H	H	H	CH_3	–	(78–81/750)	78	209
C_6	H	3-Pyridyl	H	H	H	H	–	(70–74/0.04)	35	397
							Di-Pic	196–198	–	397
	H	H	H		H	H	–	(93–97/0.15)	27	397
							Di-Pic	200–201	–	397
	Cl	H	H	$COOC(CH_3)_3$	H	H	–	–	–	6
C_9	H	C_6H_5	H	H	H	H	–	(76–78/2.5)	61	429
							Pic	128–129	–	429

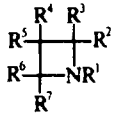
TABLE 18 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	H	H	H	C_6H_5	H	H	–	–	48	397
	H	H	H	C_6H_5Br-*p*	H	H	Cl	173–175	73	41
							–	(85–90/0.5)	–	41
	H	H	H	C_6H_4Cl-*p*	H	H	–	(90–100/1)	–	41
							Cl	151–152	–	41
							Pic	174	–	41
	H	H	H	$C_6H_3(Cl)_2$-3,4	H	H	Cl	139–143	68	432
	H	H	H	C_6H_3Cl-4-NH_2-3	H	H	–	190–193	78	432
	H	H	H	$C_6H_3NO_3$-3-Cl-4	H	H	–	175–177	62	432
	H	H	H	C_6H_4OH-*p*	H	H	–	185–186	–	41
							Pic	214–215	–	41
	H	H	H	$C_6H_3NH_2$-3-OH-4	H	H	–	270–273	82	432
	H	H	H	C_6H_3-3-NO_2-4-OH	H	H	Cl	183–185	81	432
	H	H	H	C_6H_5	OH	H	–	157–158.5	–	172
	H	C_6H_5	H	NH_2	H	H	–	–	–	472
	H	C=C(CNH)$_2$ | CN	Cl	OCH_3	H	H	–	166–167.4	64	194
C_{10}	H	H	H	$C_6H_4OCH_3$-*p*	H	H	–	(92/0.3)	45	41
							Cl	125–127	–	41
							Pic	152–154	–	41
	H	H	H	C_6H_3Cl-3-OCH_3-4	H	H	Cl	197–199	65	432
	H	H	H	$C_6H_3NH_2$-3-OCH_3-4	H	H	Cl	233–235	58	432
	H	H	H	$C_6H_3NO_2$-3-OCH_3-4	H	H	Cl	194–196	74	432
	H	H	H	C_6H_4CN-*p*	H	H	Cl	169–170	78	41
							–	(110–120/0.4)	–	41
							Pic	185	–	41
	H	CH_3	H	OH	C_6H_5	H	–	133	45	310
C_{11}	H	H	H	$C_6H_4NH_2$-*p*	C_2H_5	H	–	(135–140/0.4)	–	438
	H	H	H	$C_6H_4NO_2$-*p*	C_2H_5	H	–	229–231	–	438
	H	H	H	OCH_2OCH_3	C_6H_5	H	–	153.5–154	69	174

TABLE 18 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{13}	H	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	–	(72–78/0.03)	50	461
C_{14}	CH_3	H	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	–	–	–	463
C_{15}	H	$\begin{matrix}CN\\\vert\\C{=}C(CN)_2\end{matrix}$	Cl	$C_6H_4OCH_3$-*p*	H	H	–	255–257 (dec)	–	194
C_{17}	H	H	H	$\begin{matrix}C_6H_5\\\vert\\CCONH_2\\\vert\\C_6H_5\end{matrix}$	H	H	–	171–173	13	

TABLE 19. SYNTHESIS OF AZETIDINES BY *N*-ACYLATION, *N*-CARBAMYLATION, *N*-THIOCARBONYLATION, AND *N*-THIOCARBAMYLATION



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_4	CHO	H	H	H	H	H	H	(43/0.65)	87	404
C_5	$COCH_3$	H	H	H	H	H	H	(46/1)	74	404, 341
	$COCH_2Cl$	H	H	H	H	H	H	–	–	373
	$COCF_3$	H	H	H	H	H	H	(38/0.9)	61	404
C_6	$COCH_2SCN$	H	H	H	H	H	H	–	–	373
	$COOC_2H_5$	H	H	H	H	H	H	(78/15)	63	404
	$COCOOCH_3$	H	H	H	H	H	H	(97.5-98.5/–)	68	404
	$COCH_3$	COOH	H	H	H	H	H	90	77	43
	COCl	Cl	Cl	H	H	CH_3	CH_3	34	–	129
C_7	$CONH_2$	$CH_2CH_2CH_3$	H	H	H	H	H	185–187	–	430
	$COCONH_2$	CH_3	CH_3	H	H	H	H	148–150	65	38
	2-Furoyl	H	H	H	H	H	H	120–120.5	65	475
	$CONH_2$	H	H	$CH_2CH(CH_3)_2$	H	H	H	199–201	66	41, 426
	$COCH_2SCN$	C_2H_5	H	H	H	H	H	–	–	373
	$COCONH_2$	CH_3	CH_3	CH_3	H	H	H	132–133	74	38
	COCl	Cl	Cl	CH_3	CH_3	CH_3	CH_3	96	–	129
	$COCH_2CH_2$	$CH_2CH_2CH_3$	H	H	H	H	H	(84–87/0.2)	–	430
	$COOC(CH_3)_3$	COOH	H	H	H	H	H	104–106	89	44
	$COCH_3$	C_2H_5	C_2H_5	H	H	H	H	(85–86/0.3)	–	430
	$COCH_2CH_2SCN$	CH_3	H	H	H	CH_3	H	–	–	373
C_9	$COCONH_2$	CH_3	CH_3	H	H	CH_3	CH_3	164–166	56	38
	$CH{=}NC_6H_5$	H	H	H	H	H	H	188–190	–	93
	COC_6H_5	H	H	H	H	H	H	61–62	54	475, 232
	COC_6H_4Cl-*p*	H	H	H	H	H	H	107	45	475
	$COC_6H_4NO_2$-*p*	H	H	H	H	H	H	122–123	56	475

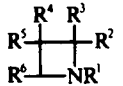
TABLE 19 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$COC_6H_3(NO_2)_2$-3,5	H	H	H	H	H	H	155–156	48	475
	CSC_6H_5	H	H	H	H	H	H	102–103.5	84	234
	$COOC_6H_4Cl$-*p*	H	H	H	H	H	H	59–60.5	81	233
	$CONHC_6H_5$	H	H	H	H	H	H	189–191	–	232
	$CSOC_6H_4Cl$-*p*	H	H	H	H	H	H	(95/1)	85	234
	$CSOC_6H_4NO_2$-*p*	H	H	H	H	H	H	138–139	60	234
	$CSNHC_6H_5$	H	H	H	H	H	H	105–107	–	232
	$CSSC_6H_4Cl$-*p*	H	H	H	H	H	H	96–98	–	234
	$CONH_2$	C_6H_5	H	H	H	H	H	195–197	89	429
	$CONH_2$	H	H	C_6H_5	H	H	H	231–233	–	441
	$COCH_2CH_3$	C_2H_5	C_2H_5	H	H	H	H	(85/0.2)	–	430
	COCl	Cl	Cl	H	H	C_6H_5	H	103 (dec)	–	129
	$COSCH_2\underset{\displaystyle Cl}{\overset{\displaystyle |}{C}}=CHCl$	CH_3	CH_3	H	H	CH_3	H	–	–	132
C_{11}	$COC_6H_4CH_3$-*p*	H	H	H	H	H	H	86–86.5	68	475
	$CSOC_6H_4CH_3$-*p*	H	H	H	H	H	H	70–72	85	234
	$COCH_3$	C_6H_5	H	H	H	H	H	(120–125/0.5)	83.5	429
	$CONHC_6H_5$	CH_3	H	H	H	H	H	115–116	–	234
	$CSNHC_6H_5$	CH_3	H	H	H	H	H	–	–	234
	$CONHC_6H_5$	COOH	H	H	H	H	H	147–151	84	339
	$COCH_3$	H	H	C_6H_5	H	H	H	(135–137/1.0)	88	41, 441
	3-Niatiryl	H	H	CH_3	CH_3	H	H	(130–135/0.6)	–	435
	$CONH_2$	H	H	C_6H_5	CH_2OH	H	H	180–182	–	433
C_{12}	COC_2H_5	C_6H_5	H	H	H	H	H	(110–115/0.4)	70 -	429
	$COOCH_2C_6H_5$	COOH	H	H	H	H	H	–	98	361, 306
	$COC_6H_3(NO_2)_2$-3,5	$COOCH_3$	H	H	H	H	H	93–95	21	361
	$COCH_3$	H	H	$CH_2C_6H_5$	H	H	H	(137–139/0.5)	72	426, 41
	COC_2H_5	H	H	C_6H_5	H	H	H	(125/0.6)	54	441
	$COOC_2H_5$	H	H	C_6H_5	H	H	H	(105–107/0.3)	50	441
	$CONHSO_2C_6H_5$	CH_3	CH_3	H	H	H	H	102–103	76	24
	$COCH_2SCN$	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	–	–	373
	$CONH_2$	H	H	C_6H_5	CH_2OOCNH_2	H	H	221–223	–	433

TABLE 19 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{13}	$COCH_2CH_2CH_3$	H	H	C_6H_5	H	H	H	(131–133/0.4)	75	441
	$CONHSO_2C_6H_4CH_3$-*p*	CH_3	CH_3	H	H	H	H	108–110	60	24
	$COCONH_2$	CH_3	CH_3	C_6H_5	H	H	H	–	62	38
C_{14}	$COOCOC_6H_4$-OOCCH$_2$NH$_2$	COOH	H	H	H	H	H	–	78.8	43
	$CON(C_2H_5)_2$	H	H	C_6H_5	H	H	H	(130–133/0.6)	78	441
	$COCH_2CH_3$	C_2H_5	C_6H_5	H	H	H	H	–	–	430
	$CONHC_6H_5$	C_2H_5	C_2H_5	H	H	H	H	98–110	–	430
	$COCHOHCH_3$	H	H	C_6H_5	C_2H_5	H	H	79–81	49	438
	$CONH_2$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	H	159–160	80	76
	$COCH_3$	H	H	C_5H_5	CH_2OOCCH_3	H	H	104–105	–	433
C_{15}	COC_2H_5	H	H	$C_6H_4CH_3$-*p*	C_2H_5	H	H	(140–145/0.5)	80	438
	$COCH_3$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	H	(162–163/0.5)	65	76
	COC_2H_5	H	H	$CH(CH_3)_2$	C_6H_5	H	H	(140/0.4)	90	438
C_{16}	$CON(C_6H_5)_2$	H	H	H	H	H	H	92–94	–	232
	$CONHC_6H_5$	C_6H_5	H	H	H	H	H	(124–126/–)	69	429
	$CONHC_6H_5$	H	H	C_6H_5	H	H	H	202–204	87	441
	COC_2H_5	H	H	$(CH_2)_3CH_3$	C_6H_5	H	H	(150/0.6)	89	438
	$COCH_2CH_3$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	H	(160–163/0.5)	42	76
	COC_2H_5	H	H	C_6H_5	$CH_2OOCC_2H_5$	H	H	(175–185/0.4)	–	433
	$COOC_2H_5$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_3$	H	H	(128–130/0.1)	84	76
C_{17}	COC_6H_5	H	H	C_6H_5COO	H	H	H	71.5–73	–	172
	$CONHC_6H_5$	H	H	C_6H_5	CH_2OH	H	H	211–212	–	433
C_{18}	$CONHC_6H_5$	C_2H_5	C_6H_5	H	H	H	H	160–162	–	430
	$COCH_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	C_2H_5	H	H	142	41	438
	$COCH_2CH_2N(CH_2CH_2)_2O$	H	H	C_6H_5	C_2H_5	H	H	165–168	35.5	438
	COC_2H_5	H	H	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	H	(160–165/0.4)	20	438
C_{19}	$COC_6H_2(OCH_3)_3$-3,4,5	H	H	C_6H_5	H	H	H	109–111	69	441
C_{21}	$CO(CH_2)_{16}CH_3$	H	H	OH	H	H	H	87–87.5	–	176
C_{24}	COC_6H_5	H	H	C_6H_5	$CH_2OOCC_6H_5$	H	H	98–100	–	433

TABLE 20. AZETIDINES WITH NITROGEN SUBSTITUENTS AT N_1

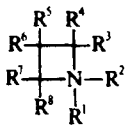


	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_3	NH_2	H	H	H	H	H	–	–	45	374, 245
	NO	H	H	H	H	H	–	(60/3.5)	–	54, 284
	NO_2	H	H	H	H	H	–	(59/1.5)	47	54
C_4	NO	COOH	H	H	H	H	–	106–107 (dec)	–	284
C_5	NH_2	CH_3	H	H	H	CH_3	–	–	92	145
	NO	CH_3	H	H	H	CH_3	–	(55/2.5)	85	145
C_6	$(CH_2)_3N$-	H	H	H	H	H	–	–	21	245
	N–N=N-	H	H	H	H	H	–	–	31	245
C_9	C_6H_4Br-*p*	H	H	H	H	H	–	42–43.5	–	5
	$NNHCOOC_2H_5$ | $COOC_2H_5$	H	H	H	H	H	–	49–51	60	288
	$N{=}NC_6H_4Br$-*p*	H	H	H	H	H	–	71–74	69	5
	$N{=}NC_6H_4NO_2$-*p*	H	H	H	H	H	–	148–149	83	5
	NH_2	H	H	C_6H_5	H	H	–	(78–82/0.5)	–	441
	NO	H	H	C_6H_4	H	H	–	33–35	69	441
C_{10}	$NHCONHC_6H_5$	H	H	H	H	H	–	189–191	30	5
	$NHSO_2C_6H_4CH_3$-*p*	H	H	H	H	H	Toluene-sulfonamide	121	–	461
							Pic	166–167	–	461
C_{10}	NH_2	H	H	C_6H_5	CH_2OH	H	–	109–112	–	433
	NO	H	H	C_6H_5	CH_2OH	H	–	72–75	–	433
C_{11}	NH_2	H	H	C_6H_5	C_2H_5	H	Cl	132–135	–	435
	NO	H	H	C_6H_5	C_2H_5	H	–	34–34.7	–	435
C_{13}	$NHCONHSO_2$-$C_6H_4CH_3$-*p*	CH_3	CH_3	H	H	H	–	175–177	–	128

TABLE 20 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{16}	$N{=}CHC_6H_4NO_2$-*p*	H	H	C_6H_5	H	H	–	112–114	–	441
C_{17}	$N{=}CHC_6H_4NO_2$-*p*	H	H	C_6H_5	CH_2OH	H	–	122–123	–	433
C_{18}	$N{=}CHC_6H_4NO_2$-*p*	H	H	C_6H_5	C_2H_5	H	–	83–85	–	435
C_{27}	$NH\dot{P}(C_6H_5)_3$	H	H	C_6H_5	H	H	Br	137–140	–	243

TABLE 21 AZETIDINES WITH OXYGEN SUBSTITUENTS AT N_1

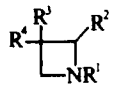


	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_5	CH_3	O	H	H	OCH_3	H	H	H	–	–	90	424, 416
	CH_3	O	H	H	OSO_2CH_3	H	H	H	–	–	77	424, 416
C_6	$CH(CH_3)_2$	O	H	H	Cl	H	H	H	–	–	89.3	424, 416
	$CH(CH_3)_2$	O	H	H	=O		H	H	–	–	87	424, 416
C_7	$OP(OC_2H_5)_2$	–	H	H	H	H	H	H	–	(116/10)	84	180
	H	–	CH_3	CH_3	OH	H	CH_3	CH_3	–	131	–	416
	O	–	CH_3	CH_3	OH	H	CH_3	CH_3	–	–	–	416
C_8	O	C_6H_{11}	H	H	F	H	H	H	–	–	89	424, 416
C_{11}	O	C_6H_{11}	CH_2OCH_3	H	H	H	H	H	–	–	90	424, 416
	O	C_6H_{11}	H	H	OCH_2OCH_3	H	H	H	–	–	89	424, 416
	O	CH_3	H	H	$OCH_2C_6H_5$	H	H	H	–	–	–	424, 416
	O	–	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	CH_3	CH_3	–	–	–	126
	O	–	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	H	CH_3	CH_3	–	–	79	126
	O	$C(CH_3)_3$	C_2H_5	H	=O		$COOCH_3$	H	–	–	95.8	424, 416
C_{12}	O	$CH_2C_6H_5$	H	C_2H_5	H	H	H	H	–	–	91	424, 416
C_{13}	O	$CH(CH_3)_2$	H	H	$OCH_2C_6H_5$	H	H	H	Peroxide	115–117	–	424, 416
	O	$CH(CH_3)_2$	H	H	$OCH_2C_6H_4Cl$-*m*	H	H	H	–	–	91	424, 416
C_{14}	O	$C(CH_3)_3$	H	H	$OCH_2C_6H_5$	H	H	H	–	–	–	424, 416
	O	–	CH_3	CH_3	$OOCC_6H_5$	H	CH_3	CH_3	–	–	86	416
C_{15}	O	$C(CH_3)_3$	H	H	$OCH_2C_6H_5OCH_3$-*p*	H	H	H	–	–	90.7	424, 416
C_{16}	O	C_6H_{11}	H	H	$OCH_2C_6H_5$	H	H	H	Peroxide	126–127	–	424, 416
									Monohydrate	103–104	–	424, 416

TABLE 21 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	O	C_6H_{11}	H	H	$OCH_2C_6H_4NO_2$-*p*	H	H	H	–	–	90	424, 416
C_{17}	O	$CH_2CH_2C_6H_5$	H	H	OC_6H_5	H	H	H	–	–	86	424, 416
	O	$CH(C_6H_5)_2$	H	H	OSO_2CH_3	H	H	H	–	–	92	424, 416
C_{20}	O	$C(CH_3)_3$	C_6H_5	H	$OCH_2C_6H_5$	H	H	H	–	–	85	424, 416
C_{21}	O	$C(CH_3)_3$	$C_6H_4CH_3$-*p*	H	$OCH_2C_6H_5$	H	H	H	–	–	83	424, 416

TABLE 22. AZETIDINES WITH OTHER ELEMENTS AT N_1



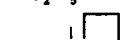
	R^1	R^2	R^3	R^4	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_3	AlH_2	H	H	H	–	–	410
	BH_2	H	H	H	–	–	410
	GaH_2	H	H	H	–	–	410
	SiH_3	H	H	H	–	–	164
C_5	$Al(CH_3)_2$	H	H	H	114–116	–	409
	$Ga(CH_3)_2$	H	H	H	128–131	–	409
	$I(CH_3)_2$	H	H	H	102–104	–	409
	$PO(OCH_3)_2$	H	H	H	(108–109/11)	76.5	181
C_6	$S(CH_3)_3$	H	H	H	114–116	60	419
C_7	$PO(OC_2H_5)_2$	H	H	H	(109/8)	85.5	181
C_8	$P(=O)(OC_2H_5)-N(CH_2)_3$	H	H	H	(82–83/1.2)	73	181
	$(CH_3)_2SN$ 		H	H	(68/5)	–	341
C_9	$P(-N$  $)_2$	H	H	H	(90/2)	54.2	182
	$PO(OC_3H_7\text{-}n)_2$	H	H	H	(133–134/10)	88.5	181
	$PO(OC_3H_7\text{-}i)_2$	H	H	H	(123/15)	80.5	181
	$PO(OC_3H_7\text{-}n)[N(CH_2)_3]$	H	H	H	(102–102.5/1.3)	55	181
	$P(=O)-[N(CH_2)_3]_2$	H	H	H	(124/2.5)	74	181
	$P(=S)-[N(CH_2)_3]_2$	H	H	H	71	90	182

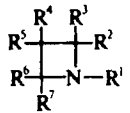
TABLE 22 CONTINUED

	R^1	R^2	R^3	R^4	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	SO_3H	H	C_6H_5	H	185–187	60	441
	$Ti[N(CH_3)_2]_3$	H	H	H	(70/0.1)	–	52
	$P(OC_4H_9)[N(CH_2)_3]$	H	H	H	(96–99/5)	78.5	182
	$PO(OC_4H_9)_2[N(CH_2)_3]$	H	H	H	(103/1)	–	181
	$PS(OC_4H_9)[N(CH_2)_3]$	H	H	H	(132–133/2)	83.1	182
	$Si(CH_3)-[N(CH_2)_3]_2$	H	H	H	(106–110/1)	–	275
C_{11}	$P(OC_4H_9)_2$	H	H	H	(84/1.6)	92	182
	$PO(OC_4H_9\text{-}n)_2$	H	H	H	(158–159/10)	86.5	181
	$PO(OC_4H_9\text{-}i)_2$	H	H	H	(143/10)	86	181
	$PS(OC_4H_9)_2$	H	H	H	(146/4)	86.8	182
	$Si(CH_3)_2C_6H_5$	H	H	H	(65–66/2)	–	275

TABLE 23. REACTIONS AT C_2: MISCELLANEOUS 2-SUBSTITUTED AZETIDINES

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_6	COCl	–	Cl	Cl	H	H	CH_3	CH_3	–	34	–	129
	CH_3	CH_3	D	D	CH_3	CH_3	H	H	–	188–189	–	476
	CD_3	CD_3	D	D	CH_3	CH_3	H	H	–	187–189	–	476
C_7	CHO	–	OCH_3	H	H	H	CH_3	CH_3	–	(52/0.26)	50	312, 311
C_8	COCl	–	Cl	Cl	CH_3	CH_3	CH_3	CH_3	–	96	–	129
C_{10}	COCl	–	Cl	Cl	H	H	C_6H_5	H	–	103 (dec)	–	129
C_{11}	H	–	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	CH_3	CH_3	–	–	80	126
	H	–	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	H	CH_3	CH_3	–	(76–78/10)	40	126
C_{13}	CH_3	–	C_6H_5	CH_3	CH_3	CH_3	H	H	–	–	8	9
									Pic	171–173	–	9
	$CH(C_6H_5)_2$	–	$CH_2C_6H_5$	H	H	H	H	H	–	87.5–89.5	–	175

TABLE 24. REACTIONS AT C_2: AZETIDINE-2-ALKANOLS AND -2-AMINES



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_5	H	$CH_2CH_2NH_2$	H	H	H	H	H	Pic	199	–	423
C_7	$CH(CH_3)_2$	CH_2OH	H	H	H	H	H	–	(47–48/3)	80	379
	$\overset{CH_3}{\underset{\vert}{N}}CONHCH_3$	CH_2OH	H	H	H	H	H	–	–	79	418
C_8	$C(CH_3)_3$	CH_2OH	H	H	H	H	H	–	(54–55/2.4)	85	379, 85, 300
								Pic	190–191 (dec)	–	85
	$C(CH_3)_3$	CH_2NH_2	H	H	H	H	H	–	(53–55/3.7)	61.4	379, 85
								Di-Pic	196.5–197.5	–	85
C_9	$C(CH_3)_3$	$CH_2OSO_2CH_3$	H	H	H	H	H	–	108–109	–	300
								Pic	148.5–149.5 (dec)	–	300
C_{10}	C_6H_{11}	CH_2OH	H	H	H	H	H	–	(67–68/0.35)	88	379
	$C(CH_3)_3$	CH_2OOCCH_3	H	H	H	H	H	–	(89/19)	77	85
								Pic	129–130 (dec)	–	85
C_{11}	$CH_2C_6H_5$	CH_2OH	H	H	H	H	H	–	94–95	87.2	379
	$SO_2C_6H_4CH_3$-*p*	CH_2OH	H	H	H	H	H	–	104–105	30	88, 89
	$\overset{CH_3}{\underset{\vert}{N}}CONHCH_3$	CH_2OH	H	CH_3	CH_3	CH_3	CH_3	–	125–127	77	418
C_{12}	$SO_2C_6H_4CH_3$-*p*	CH_2CH_2OH	H	H	H	H	H	–	42–44	–	423
	$SO_2C_6H_4CH_3$-*p*	$CH_2CH_2NH_2$	H	H	H	H	H	–	(168–190/0.02)	–	423
								Pic	154	–	423
C_{14}	$C(CH_3)_3$	$CH(OH)C_6H_5$	H	H	H	H	H	–	(110–115/0.5)	86.2	377
	$SO_2C_6H_4CH_3$-*p*	$CH_2CH_2OOCCH_3$	H	H	H	H	H	–	(167/0.002)	–	423
C_{15}	$C(CH_3)_3$	$CH_2NHCSNHC_6H_5$	H	H	H	H	H	–	105	–	85

TABLE 24 CONTINUED

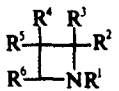
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{16}	N=O	$C(OH)(C_6H_5)_2$	H	H	H	H	H	–	188	65	398
	H	$C(OH)(C_6H_5)_2$	H	H	H	H	H	Cl	195 (dec)	100	398
	$SO_2C_6H_4CH_3$-*p*	1-Succinimidoethyl	H	H	H	H	H	–	45	–	423
C_{19}	$SO_2C_6H_4CH_3$-*p*	$CH_2CH_2NHSO_2C_6H_4CH_3$-*p*	H	H	H	H	H	Pic	113	–	423
	$SO_2C_6H_4NO_2$-*p*	Phthalimidoethyl	H	H	H	H	H	–	185	–	423
	$SO_2C_6H_4CH_3$-*p*	Phthalimidoethyl	H	H	H	H	H	–	146.5–147	–	423
	C_6H_5	$=NC_6H_5$		CF_3	CF_3	$=C(CF_3)_2$		–	66–68	10.8	106
C_{23}	$CH(C_6H_5)_2$	$CH(OH)C_6H_5$	H	H	H	H	H	Cl			
								erythro	182.5–184	–	175
								threo	175–176 (dec)	–	175
	$CH(C_6H_5)_2$	$CH(NH_2)C_6H_5$	H	H	H	H	H	*erythro*	112.5–113	–	175
								threo	101–102	–	175
								Di-Cl			
								erythro	190 (dec)	–	175
								threo	142 (dec)	–	175
	$CH(C_6H_5)_2$	$C(NH)C_6H_5$	H	H	H	H	H	–	123.5–126.5	–	175
C_{24}	$CH(C_6H_5)_2$	$C(NH_2)(C_6H_5)$	H	H	H	H	H	–	–	–	175
	$CH(C_6H_5)_2$	$CH(OH)C_6H_4CF_3$-*m*	H	H	H	H	H	–	145–145.5	–	175
								Cl	144–145.5	–	175

TABLE 24 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$CH(C_6H_5)_2$	CC_6H_5 (OH, OH)	H	H	H	H	H	Cl	152–153.5	–	175
	$CH(C_6H_5)_2$	$CHC_6H_4CF_3$-*m* (NH_2)	H	H	H	H	H	Di-Cl			
								erythro	176 (dec)	–	175
								threo	173.5–175.5 (dec)	–	175
								–	111–113	–	175
	$CH(C_6H_5)_2$	$C(NH)C_6H_4CF_3$-*m*	H	H	H	H	H	–	–	–	175
C_{25}	$CH(C_6H_5)_2$	CHC_6H_5 ($NHCOCH_3$)	H	H	H	H	H	–	183–187	–	175
	$CH(C_6H_5)_2$	CHC_6H_5 ($NHCOCF_3$)	H	H	H	H	H	–	–	–	175
	$CH(C_6H_5)_2$	$C(CH_3)C_6H_5$ ($NHCOCF_3$)	H	H	H	H	H	–	–	–	175

[a] Stereochemical configuration also denoted.

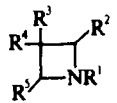
TABLE 25. REACTIONS AT C_2: 2-ACYL- AND 2-ALKYLIDENEAZETIDINES

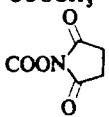


	R^1	R^2	R^3	R^4	R^5	R^6	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_8	$C(CH_3)_3$	CHO	H	H	H	H	–	(59–66/16)	89	116, 115
C_{12}	$C(CH_3)_3$	$=CH-N(CH_2CH_2)_2O$		H	H	H	–	(88/0.3)	69	116
C_{13}	CH_3	$=C(CN)COOH$		$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H				
	CH_3	$=C(CN)CONH_2$		$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	–	190–192	17	364
C_{14}	$C(CH_3)_3$	COC_6H_5	H	H	H	H	–	54–56	42	352
							Pic	189–190	–	352
C_{15}	CH_3	$=C(CN)COOC_2H_5$		C_6H_{11}	H	H	–	121–122	20	364
	CH_3	$=C(CN)COOC_2H_5$		$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	–	77–78	55	364
	C_6H_5	$=O$		CF_3	CF_3	C_6H_5	–	89–91	56.5	389
	CH_3	$=C(CN)COOC_2H_5$		C_2H_5	C_6H_5	H	–	95–96	50	364
C_{19}	CH_3	$=C(CN)COOH$		C_6H_5	C_6H_5	H	–	249–250 (dec)	96	364
C_{21}	CH_3	$=C(CN)COOC_2H_5$		C_6H_5	C_6H_5	H	–	195–196	41	364
C_{22}	C_2H_5	$=C(CN)COOC_2H_5$		C_6H_5	C_6H_5	H	–	156–158	20	364
C_{23}	$CH(C_6H_5)_2$	COC_6H_5	H	H	H	H	–	114–115	–	175
		OCH_3 | CHC_6H_5								
C_{24}	$CH(C_6H_5)_2$	CHC_6H_5	H	H	H	H	*threo*	51–56	–	175
	$CH(C_6H_5)_2$	$COC_6H_4CF_3$-*m*	H	H	H	H	–	–	–	175
		$OOCCH_3$ | CHC_6H_5								
C_{25}	$CH(C_6H_5)_2$	CHC_6H_5	H	H	H	H	–	128–131	–	175
C_{27}	$CH_2C_6H_5$	$=C(CN)COOC_2H_5$		C_6H_5	C_6H_5	H	–	136–151	15	364

[a] Stereochemical configuration also denoted.

TABLE 26. REACTIONS AT C_2: AZETIDINE-2-CARBOXYLATES



	R^1	R^2	R^3	R^4	R^5	Salt[a]	m.p. (°C)	Yield (%)	Ref.
C_8	H	$COOCH_3$	H	H	H	–	–	71.4	361
	H	$COOCH_3$	H	H	H	–	–	100	361
C_{10}	$C(CH_3)_3$	$COOCH_3$	H	H	CH_3	*cis*	–	–	261
						trans	–	–	261
C_{14}	$COOC(CH_3)_3$		H	H	H	–	115–116	80	44
						Cl	127–129	75	44
C_{15}	$COOC(CH_3)_3$	$COOC_6Cl_5$	H	H	H	–	98–99	90	44
						Cl	134–135	89	44
	$COOCOC_6H_4OCOCH_2NH_2$	$COOCH_3$	H	H	H	–	72–74	59.3	43
C_{17}	C_6H_5	$COOCH_3$	H	H	C_6H_5	–	74	30	457
C_{19}	C_6H_5	$COOCH_3$	$COOCH_3$	H	C_6H_5	–	102	74	457
C_{20}	C_6H_5	$COOCH_3$	$COOC_3H_5$	H	C_6H_5	–	60	58	457
C_{24}	C_6H_5	$COOCH_3$	COC_6H_5	H	C_6H_5	–	118	74	457
C_{30}	C_6H_5	$COOCH_3$	Fluorenylidene		C_6H_5	–	192	68	457, 458

[a] Stereochemical configuration also denoted.

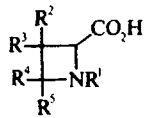
TABLE 27. REACTIONS AT C_2: AZETIDINE-2-CARBOXAMIDES, -2-HYDRAZIDES, AND 2-NITRILES



	R^1	R^2	m.p. (°C)	Yield (%)	Ref.
C_8	$C(CH_3)_3$	CN	(55–56.5/2.5)[a]	71	299, 85
	$C(CH_3)_3$	$CONH_2$	80–81	94	299, 379
	$C(CH_3)_3$	$CONHNH_2$	83–85	~ 100	283
C_{10}	C_6H_{11}	$CONHNH_2$	88	~ 100	283
C_{11}	$CH_2C_6H_5$	$CONHNH_2$	–	–	283
	$C(CH_3)_3$	$CONHN=C(CH_3)_2$	45–47	~ 100	283
C_{12}	$COOCH_2C_6H_5$	$CONH_2$	126–128	75	361
C_{13}	$CH_2C_6H_5$	$CONHN=C(CH_3)_2$	82	~ 100	281
	$COOC(CH_3)_3$		148–152	64	43
C_{15}	$CONHC_6H_5$	$CO\text{-}N(CH_2)_2O$	186–187	25	339
	$CSNHC_6H_5$	$CO\text{-}N(CH_2)_2O$	194–197 (dec)	84	339
C_{17}	$CH(C_6H_5)_2$	$CONHNH_2$	150–152	72	283

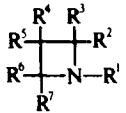
[a] Boiling point, °C/mm Hg.

TABLE 28. REACTIONS AT C_2: AZETIDINE-2-CARBOXYLIC ACIDS



	R^1	R^2	R^3	R^4	R^5	m.p. (°C)	Yield (%)	Ref.
C_4	H	H	H	H	H	> 200	83	361
C_7	$CH(CH_3)_2$	H	H	H	H	177–179	93	379
	$NCONHCH_3$ (N-methylcarbamoyl)	H	H	H	H	181–183 (dec)	83.5	418
C_8	$C(CH_3)_3$	H	H	H	H	173–175	69	375, 376
C_{10}	C_6H_{11}	H	H	H	H	176–178	71	375
C_{11}	$CH_2C_6H_5$	H	H	H	H	159–161	81.8	375
	$SO_2C_6H_4CH_3$-*p*	H	H	H	H	140–141	96	89, 88
	$CSNHC_6H_5$	H	H	H	H	170–182	93	339
	$NCOHHCH_3$ (N-methylcarbamoyl)	CH_3	CH_3	CH_3	CH_3	228–228.5	90	418
C_{14}	1-Adamantyl	H	H	H	H	172–173.5	–	173

TABLE 29. REACTIONS AT C_3: 3-AZETIDINOLS AND DERIVATIVES



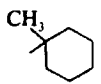
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_4	CH_3	H	H	OH	H	H	H	Cl	93–95	75	237
C_5	C_2H_5	H	H	OH	H	H	H	Cl	–	–	237
C_6	C_2H_5	H	H	OSO_2CH_3	H	H	H	Oxalate	112–113	61	347
	CH_3	CH_3	CH_3	OH	OH	H	H	Cl	–	–	287, 188 189, 190
C_7	$C(CH_3)_3$	H	H	OH	H	H	H	–	–	–	112
	$CH(CH_3)_2$	H	H	OSO_2CH_3	H	H	H	Oxalate	166–168	88	347
C_8	$C(CH_3)_3$	H	H	SO_2CH_3	H	H	H	–	188–190	29	87
	$C(CH_3)_3$	H	H	OSO_2CH_3	H	H	H	Oxalate	116–118	75	347
								Cl	123	–	347
C_9	H	H	H	C_6H_5	OH	H	H	–	157–158.5	–	174
	$C(CH_3)_3$	CH_3	CH_3	OH	H	H	H	Cl	152–153 (dec)	–	287, 188 189, 190
	$C(CH_3)_3$	CH_3	CH_3	OH	OH	H	H	Cl	122–123	–	287, 188 189, 190
C_{10}	COC_6H_5	H	H	OH	H	H	H	–	62–63	–	170
	C_6H_{11}	H	H	OSO_2CH_3	H	H	H	Oxalate	156–157	85	347
								Cl	141	–	347
C_{11}	$C(C_2H_5)_2C{\equiv}CH$	H	H	OSO_2CH_3	H	H	H	–	163	58	146, 73
	C_6H_{11}	H	H	$OSO_2CH_2CH_3$	H	H	H	Oxalate	111.5	32	347
		H	H	OSO_2CH_3	H	H	H	Oxalate	129–140	88	347

TABLE 29 CONTINUED

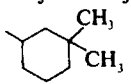
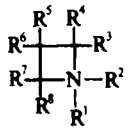
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{12}	$CH(CH_3)C_6H_6$	H	H	OSO_2CH_3	H	H	H	Oxalate	93–94.5	94	347
								Cl	123–124	–	347
	$C(CH_3)_2CH_2C(CH_3)_2CH_3$	H	H	OSO_2CH_3	H	H	H	Oxalate	126	75	347
		H	H	OSO_2CH_3	H	H	H	Oxalate	141–142	97	347
	$-C(CH_2)_5C{\equiv}CH$	H	H	OSO_2CH_3	H	H	H	–	80	87	146, 73
C_{13}	C_2H_5	CH_3	CH_3	C_6H_5	OH	H	H	Cl	210–211 (dec)	–	287, 188 189, 190
C_{14}	$C(CH_3)_3$	H	H	$OSOC_6H_4CH_3$-*p*	H	H	H	–	70–71	78	361, 454
	1-Adamantyl	H	H	OSO_2CH_3	H	H	H	Oxalate	92–93	81	347
	$C(CH_3)_3$	H	H	OSO_2^-	H	H	H	–	55.5–56.5	–	152
	$CH_2C_6H_5$	CH_3	CH_3	OH	H	CH_3	CH_3	–	72	–	416
C_{15}	$C(CH_3)_3$	CH_3	H	$SO_2C_6H_4CH_3$-*p*	H	H	H	–	–	–	207
	$C(CH_3)_3$	CH_3	H	$OSO_2C_6H_4CH_3$-*p*	H	H	H	–	55–56	9	207
	$C(CH_3)_3$	CH_3	CH_3	OH	C_6H_5	H	H	Cl	198 (dec)	–	287, 188 189, 190
C_{16}	COC_6H_5	H	H	C_6H_5	OH	H	H	–	–	–	170
	C_6H_{11}	H	H	$OSO_2CH_2C_6H_5$	H	H	H	Oxalate	159–160	73	347
								Cl	123	–	347
	C_6H_{11}	H	H	$OSO_2C_6H_4CH_3$-*p*	H	H	H	–	–	32	454
C_{17}	$CH(C_6H_5)_2$	H	H	OSO_2CH_3	H	H	H	–	113–114	110	7
	$CH(C_6H_5)_2$	H	H	OSO_2CH_3	H	H	H	–	114.5–116.5	74	347
	$C(CH_2CH_3)_2C{\equiv}CH$	H	H	$OSO_2C_6H_4CH_3$-*p*	H	H	H	Cl	167	40	146, 73
	$CH(C_6H_5)_2$	H	H	OH	CH_3	H	H	–	80	64	82
	$C(CH_2)_5C{\equiv}CH$	H	H	$OSO_2C_6H_4CH_3$-*p*	H	H	H	Cl	171	46	146, 73

TABLE 29 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{22}	$CH(C_6H_5)_2$	H	H	OH	C_6H_5	H	H	–	–	91	337, 82
C_{23}	$CH(C_6H_5)_2$	H	H	$OSOC_6H_4CH_3$-*p*	H	H	H	–	106–107	39	7
	17-Oxo-3-androstanyl	H	H	OSO_2CH_3	H	H	H	3α	(179.5–181)	–	176
								3β	(150.5–151)	–	176
C_{30}	3-Cholestanyl	H	H	OSO_2CH_3	H	H	H	3α	130–136.5	–	176
								3β	135.5	–	176
C_{36}	3-Cholestanyl	H	H	$OSO_2C_6H_4CH_3$-*p*	H	H	H	–	105–109	–	176
C_{37}	$(CH_2)_{17}CH_3$	H	H	$OSO_2(CH_2)_{15}CH_3$	H	H	H	–	73.5–75	–	176
C_{45}	3-Cholestanyl	H	H	$OSO_2(CH_2)_{15}CH_3$	H	H	H	–	64.5–68	–	176

TABLE 30. REACTIONS AT C_3: 3-AMINO-, 3-ALKOXY-, AND 3-ALKYLTHIOAZETIDINES



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_4	$C(CH_3)_3$	–	H	H	$N(CH_2CH_2)_2O$	H	H	H	–	43–45	90	87
C_6	$CH(CH_3)_2$	–	H	H	NH_2	H	H	H	Mes	100–102	36	347
C_7	$C(CH_3)_3$	–	H	H	NH_2	H	H	H	–	(55–60/13)	35	87, 347
									Di-Pic	198–200 (dec)	–	85
C_8	$C(CH_3)_3$	–	H	H	OCH_3	H	H	H	–	(45/10)	71	154
	$C(CH_3)_3$	–	H	H	$NHCH_3$	H	H	H	–	(62–64/10)	66	154
	$C(CH_3)_3$	–	H	H	SCH_3	H	H	H	–	(80–83/13)	74	87
	$C(CH_3)_3$	–	H	H	$NHC(NH)NH_2$	H	H	H	–	210–211	54	347
	H	–	CH_3	CH_3	$=NNHCONH_2$		CH_3	CH_3	–	202	–	416
C_9	$C(CH_3)_3$	–	H	H	OC_2H_5	H	H	H	–	–	20	112
	H	–	H	H	NHC_6H_5	H	H	H	Cl	–	–	415
	C_6H_{11}	–	H	H	NH_2	H	H	H	–	134–137	88	347
	$C(CH_3)_3$	–	H	H	$N(CH_3)_2$	H	H	H	–	(60–64/20)	40	87, 154
	$C(CH_3)_3$	–	H	H	SC_2H_5	H	H	H	–	(95–100/22)	63	87
	$C(CH_3)_3$	–	H	H	$SOCCH_3$	H	H	H	–	(44–55/1.5)	–	87
	$C(CH_3)_3$	–	H	H	$SP(OCH_3)_2$	H	H	H	–	–	76	454
	$C(CH_3)_3$	–	H	H	$COCH_3$	H	H	H	–	(87–89/8)	85	352
									Pic	141–143	–	352
	$C(CH_3)_3$	–	H	H	$COOCH_3$	H	H	H	–	(30–31/0.5)	91	85
									Pic	150.5–152.5	–	85, 152
	C_2H_5	C_2H_5	H	H	$OOCCH_3$	H	H	H	Cl	136–137	40	153

TABLE 30 CONTINUED

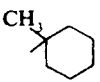
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{10}	$C(CH_3)_3$	–	H	H	CH_2OOCCH_3	H	H	H	–	(57–58/0.5)	–	
									Pic	114	–	85
	C_6H_{11}	–	H	H	$NHC(NH)NH_2$	H	H	H	HSO_4	204–205	44	347
C_{11}	H	–	H	H	$N(C_2H_5)C_6H_5$	H	H	H	–	–	–	415
	CHC_6H_5 (CH$_3$)	–	H	H	NH_2	H	H	H	–	187–189	55	347
	$C(CH_3)_2CH_2(CH_3)_3$	–	H	H	NH_2	H	H	H	Mes	109–110	68	457
	$C(CH_3)_2$	–	H	H	$NHC(CH_3)_3$	H	H	H	–	(59/2)	39	154
		–	H	H	$HNC(NH)NH_2$	H	H	H	HSO_4	218–220	6	347
	$C(CH_3)_3$	–	H	H	$OC(CH_3)_3$	H	H	H	–	(56/4)	64	154
	$C(CH_3)_3$	–	H	H	$SC(CH_3)_3$	H	H	H	–	(68–69/2)	71	154
	$C(CH_3)_3$	–	H	H	$PO(OC_2H_5)_2$ (O)	H	H	H	–	–	56	454
	$C(CH_3)_3$	–	H	H	$PO(OC_2H_5)_2$ (S)	H	H	H	–	–	84	454
	$C(CH_3)_3$	–	H	H	$PS(OC_2H_5)_2$ (S)	H	H	H	–	–	61	454
	$C(CH_3)_3$	–	CH_3	CH_3	$OOCCH_3$	H	H	H	Cl	155–155.5 (dec)	–	287, 188, 189, 190
C_{12}	$C(CH_3)_3$	–	H	H	$N(CH_2)_5$	H	H	H	–	(64–67/1.5)	55	87
	CHC_6H_5 (CH$_3$)	–	H	H	$NHC(NH)NH_2$	H	H	H	HSO_4	190–191	39	347
	$C(CH_3)_2CH_2(CH_3)_3$	–	H	H	$NHC(NH)NH_2$	H	H	H	HSO_4	216–217	19	347
	$C(CH_3)_3$	–	H	H	$CO(CH_2)_3CH_3$	H	H	H	–	(97–100/5)	65	352
									Cl	101–102	–	352

TABLE 30 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCCH_3$	H	H	H	–	134	65	146, 73
	$C(CH_3)_2C{\equiv}CH$	–	H	H	$OOCNH(CH_2)_2CH_3$	H	H	H	Cl	163	60	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHCH_3$	H	H	H	Fumarate	126	60	146, 73
	$C(CH_3)_3$	–	H	H	$SP(O)(OC_2H_5)SCH_2CH_2CH_3$	H	H	H	–	–	59	454
	H	–	H	H	C_6H_5	CH_2OOCCH_3	H	H	Cl	145–147	–	433
C_{13}	$(CH_3)_2C(CH_3)CH_2C(CH_3)_2CH_3$	–	H	H	$OOCCH_3$	H	H	H	–	(78/0.7)	–	152
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	OOC_2H_5	H	H	H	Cl	111	30	146
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCCH_3$	H	H	H	–	200	60	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_2H_5$	H	H	H	Cl	100	46	146, 73
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHCH_3$	H	H	H	Cl	174	65	146, 73
	2-Adamantyl	–	H	H	NH_2	H	H	H	Mes	285–289	73	347
	3,5,5-Trimethylcyclohexyl	–	H	H	$NHC(NH)NH_2$	H	H	H	HSO_4	216–217	20	347
	C_6H_{11}	–	H	H	$SP(O)(OC_2H_5)_2$	H	H	H	–	–	–	454
	C_2H_5	C_2H_5	H	H	$OC_6H_2(NO_2)_3$	H	H	H	–	223–227	–	382
C_{14}	$C(CH_3)_3$	–	H	H	$NHCOC_6H_4NO_2$-*p*	H	H	H	–	163–164	–	87
	C_6H_{11}	–	C_6H_5	H	$OOCCH_3$	H	H	H	–	–	–	348
	$C(CH_3)_3$	–	H	H	$OOCC_6H_4$-NH_2-*p*	H	H	H	–	–	–	301
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHCH_2CH_2CH_3$	H	H	H	Cl	135	68	146, 73
									Fumarate	120	68	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHCH_2CHCH_2$	H	H	H	–	109	60	146, 73

TABLE 30 CONTINUED

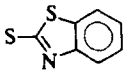
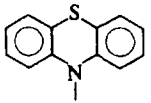
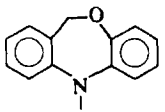
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$C(CH_3)_3$	–	H	H	$NHCSNHC_6H_5$	H	H	H	–	141	–	85
	H	–	H	H	SO_3 	H	H	H	–	55.5–56.5	–	152
	$C(CH_3)_3$	–	H	H		H	H	H	–	48–49	41	87
C_{15}	H	–	H	H		H	H	H	Cl	263	35	306
	2-Adamantyl	–	H	H	$OOCCH_3$	H	H	H	–	(108–111/0.01)	–	171
									Cl	172–182 (dec)	–	171
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNH(CH_2)_3CH_3$	H	H	H	–	121	46	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC(CH_3)_3$	H	H	H	Cl	163	40	146
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHCH_2CH_2CH_3$	H	H	H	Cl	163	75	146, 73
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHCH(CH_3)_2$	H	H	H	–	92	75	146, 73
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHCH_2CH{=}CH_2$	H	H	H	–	84	72	146, 73
	$CH(CH_3)_2$	–	H	H	$OOCCH_2CH_3$	C_6H_5	H	H	–	–	–	170
C_{16}	H	–	H	H		H	H	H	Cl	238–240	57	306
	$CH(C_6H_5)_2$	–	H	H	$NHC(NH)NH_2$	H	H	H	HSO_4	173	36	347
	C_6H_{11}	–	C_6H_5	H	$CONH_2$	H	H	H	–	139–141	–	348
	C_6H_{11}	–	C_6H_5	H	OCH_3	H	H	H	*cis* and *trans*	49–50	–	348
	C_6H_{11}	–	C_6H_5	H	SCH_3	H	H	H	*cis* and *trans*	–	–	348

TABLE 30 CONTINUED

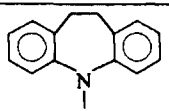
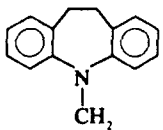
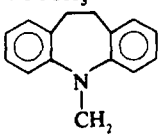
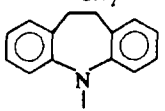
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{17}	H	–	H	H		H	H	H	Cl	271–273	72	306
	H	–	H	H		H	H	H	Cl	140–146	70	306
	$CH(C_6H_5)_2$	–	H	H	OCH_3	H	H	H	–	55–57	51	7
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCC_6H_5$	H	H	H	Cl	162	25	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_{11}$	H	H	H	Cl	170	40	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_5$	H	H	H	Cl	166	50	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_5Cl$-*m*	H	H	H	Cl	167	20	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_4Cl$-*p*	H	H	H	Cl	186	41	146, 73
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_3Cl_2$-3,4	H	H	H	Cl	196	28	146, 73
	C_6H_{11}	–	C_6H_5	H	$OOCCH_3$	H	H	H	–	72–73	–	348
C_{18}	H	–	H	H		H	H	H	Cl	114–148	86	306
	CH_3	–	H	H		H	H	H	H	115–116	62	306
	$CH(C_6H_5)_2$	–	H	H	OC_3H_5	H	H	H	–	65–67	37	306
	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCNHC_6H_4CH_3$-*m*	H	H	H	Cl	153	46	146, 73
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHC_6H_{11}$	H	H	H	–	120	70	146, 73
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHC_6H_5$	H	H	H	–	132	60	146
	$C(CH_2)_5C{\equiv}CH$	–	H	H	$OOCNHC_6H_3Cl_2$-3,4	H	H	H	–	114	70	146, 73
	$SO_2C_6H_4CH_3$-*p*	–	H	H	OCH_2OCH_3	C_6H_5	H	H	–	97–97.5	97	174

TABLE 30 CONTINUED

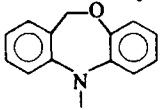
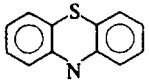
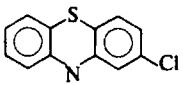
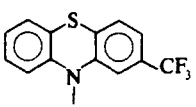
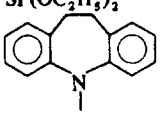
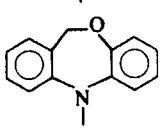
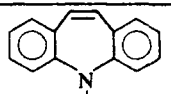
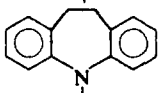
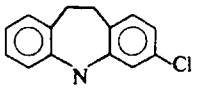
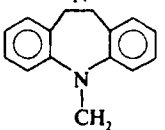
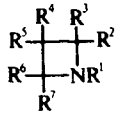
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{19}	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	$OOCCH{=}CHC_6H_5$	H	H	H	Cl	167	29	146, 73
	$CH(CH_3)_2$	–	H	H		H	H	H	Cl	231–233	46	306
	$C(CH_3)_3$	–	H	H		H	H	H	–	155–156	17	306
	$C(CH_3)_3$	–	H	H		H	H	H	–	190–193	28	306
	$C(CH_3)_3$	–	H	H		H	H	H	–	115–118	11	306
C_{20}	$C(CH_3)_2$	–	H	H	$COC_6H_4C_6H_5$-*p*	H	H	H	–	86–87	78	352, 361
	$CH(C_6H_5)_2$	–	H	H	$SP(OC_2H_5)_2$	H	H	H	–	–	84	454
	$CH(CH_3)_2$	–	H	H		H	H	H	Cl	247–250	84	306
	$C(CH_3)_3$	–	H	H		H	H	H	–	108–109	18	306
	$C(CH_3)_3$	–	C_6H_5	H	COC_6H_5	H	H	H	–	–	30	282
C_{21}	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	COONH-1-Naphthyl	H	H	H	–	133	34	146, 73

TABLE 30 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
	$C(CH_3)_3$	–	H	H		H	H	H	–	113–117	12	306
	$C(CH_3)_3$	–	H	H		H	H	H	–	220–223	31	306
	$C(CH_3)_3$	–	H	H		H	H	H	Cl	246–248	42	306
	$CH(CH_3)_2$	–	H	H		H	H	H	Cl	148–150	62	306
	C_6H_{11}	–	C_6H_5	H	SC_6H_5	H	H	H	*cis*	131–132	–	346
									trans	51–59	–	348
	$N{=}C(CF_3)_2$	–	$=NCH_2C_6H_5$		NHC_6H_5	H	CF_3	CF_3	–	84–86	85	60
C_{22}	$CH(C_6H_5)_2$	–	H	H	NHC_6H_5	H	H	H	–	–	–	415
	C_6H_{11}	–	H	H	$COC_6H_4C_6H_5$-*p*	H	H	H	–	112–114	42	361
	$C{\equiv}CH$	–	H	H	OOCNH-1-Naphthyl	H	H	H	Cl	133	34	146, 73
	C_6H_{11}	–	C_6H_5	H	COC_6H_5	H	H	H	–	95–96	22	348
C_{23}	$CH(C_6H_5)_2$	–	H	H	$N(CH_3)C_6H_5$	H	H	H	–	–	–	415
	$CH(C_6H_5)_2$	–	H	H	$N(C_2H_5)C_6H_5$	H	H	H	–	–	–	415
C_{26}	$C(CH_3)_3$	–	C_6H_5	H	COC_6H_5	H	C_6H_5	H	–	–	–	407
C_{28}	C_6H_{11}	–	C_6H_5	H	COC_6H_5	H	C_6H_5	H	–	–	–	407
C_{29}	$C(C_2H_5)_2C{\equiv}CH$	–	H	H	COONH $C_{18}N_{35}$	H	H	H	–	95	45	146, 73

[a] Stereochemical configuration also denoted.

TABLE 31. REACTIONS AT C_3: 3-CYANO- AND 3-CARBOXYAZETIDINES



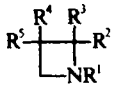
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_8	$C(CH_3)_2$	H	H	CN	H	H	H	–	(66–68/4)	79	154, 85 347
	$C(CH_3)_2$	H	H	COOH	H	H	H	–	189–190	50	347
	H	H	H	$COOC(CH_3)_3$	Cl	H	H	–	–	84	6
C_{10}	C_6H_{11}	H	H	CN	H	H	H	–	83.5–85	67	347, 361
	C_6H_{11}	H	H	COOH	H	H	H	–	163	87	347
	H	H	H	$COOC_6H_5$	H	H	H	Cl	130–135	–	6
C_{11}	$C(C_2H_5)_2C{\equiv}CH$	H	H	CN	H	H	H	Cl	178	37	146
	$COCH_3$	CH_3	CH_3	$COOCH_3$	OH	CH_3	CH_3	–	119–121	94	390
C_{12}	$C(CH_3)_2CH_2C(CH_3)_3$	H	H	CN	H	H	H	–	–	83	347
	CH_3 | CHC_6H_5	H	H	CN	H	H	H	–	(100–107/0.3)	61	347
	$C(CH_3)_2CH_2(CH_3)_3$	H	H	COOH	H	H	H	–	170–172	61	347
	CH_3 | CHC_6H_5	H	H	COOH	H	H	H	–	166–167	57	347
	$(CH_2)_5$-C≡CH	H	H	CN	H	H	H	Cl	212	70	146
C_{14}	1-Adamantyl	H	H	CN	H	H	H	–	94–95	70	347
	1-Adamantyl	H	H	COOH	H	H	H	–	190–192	96	347
	$C(CH_3)_3$	C_6H_5	H	CN	H	H	H	*cis* and *trans*	–	54.6	282
								trans	119–119.5	~ 100	282
								Pic	181–181.5	–	282
	$C(CH_3)_3$	C_6H_5	H	COOH	H	H	H	–	156–157	83	282

TABLE 31 CONTINUED

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt[a]	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{16}	C_6H_{11}	C_6H_5	H	CN	H	H	H	*cis*	123–124	–	348
								trans	89–90	–	348
	COC_6H_5	CH_3	CH_3	$COOCH_3$	OH	CH_3	CH_3	–	173	–	348
C_{17}	$CH(C_6H_5)_2$	H	H	CN	H	H	H	–	152–153	75	7, 347
	$CH(C_6H_5)_2$	H	H	COOH	H	H	H	–	192–195	89	347, 7
	$CH(C_6H_5)_2$	H	H	OH	CH_2OH	H	H	–	175	40	82
C_{18}	$CH(C_6H_5)_2$	H	H	$COOCH_3$	H	H	H	–	67–68	88	6
C_{20}	$CH(C_6H_5)_2$	H	H	$COOCH(CH_3)_2$	H	H	H	–	89–90.5	86	6
C_{21}	$CH(C_6H_5)_2$	H	H	$COOC(CH_3)_3$	H	H	H	–	110–111	68	6
C_{23}	$CH(C_6H_5)_2$	H	H	$COOC_6H_5$	H	H	H	–	93–94	56	6
C_{24}	$CH(C_6H_5)_2$	H	H	$OOCC_5H_5$	CN	H	H	–	215	69	82

[a] Stereochemical configuration also denoted.

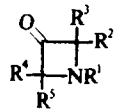
TABLE 32. REACTIONS AT C_3: 3-SUBSTITUTED AZETIDINES FROM 1-AZABICYCLO[1.1.0]BUTANES



	R^1	R^2	R^3	R^4	R^5	Salt	m.p. (°C)	Yield (%)	Ref.
C_9	H	H	H	OH	C_6H_5	–	150–154 (dec)	92	221
	H	H	H	C_6H_5	Cl	Cl	162–163 (dec)	79	221
C_{10}	$CHCH_2COOCH_3$ | $COOCH_3$	H	H	CH_3	H	–	–	83	149
	$C{=}CHCOOCH_3$ | $COOCH_3$	H	H	CH_3	H	–	–	88	149
	H	H	H	C_6H_5	OCH_3	–	30–35/3[a]	> 90	221
	H	CH_3	H	C_6H_5	OH	–	–	–	221
	H	CH_3	H	C_6H_5	Cl	Cl	167 (dec)	> 90	221
C_{11}	$CHCH_2COOCH_3$ | $COOCH_3$	H	H	CH_2CH_3	H	–	–	84	149
	H	CH_3	CH_3	C_6H_5	OH	–	83–85	> 90	221
	H	CH_3	CH_3	C_6H_5	Cl	Cl	197	60	221
C_{15}	$SO_2C_6H_4CH_3$-*p*	H	H	Cl	$COOC(CH_3)_3$	–	106–108	76	6
C_{17}	$COC_6H_4NO_2$-*p*	H	H	C_6H_5	OCH_3	–	119–120	–	221
C_{18}	$CH(C_6H_5)_2$	H	H	$COOCH_3$	H	–	67–68	88	6
C_{20}	$CH(C_6H_5)_2$	H	H	$COOCH(CH_3)_2$	H	–	89–90	86	6
C_{23}	$CH(C_6H_5)_2$	H	H	$COOC_6H_5$	H	–	93–94	56	6

[a] b.p., °C/mm Hg.

TABLE 33. REACTIONS AT C_3: 3-AZETIDINONES



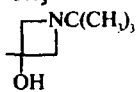
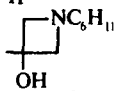
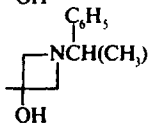
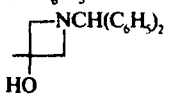
	R^1	R^2	R^3	R^4	R^5	m.p. (°C)	Yield (%)	Ref.
C_7	H	CH_3	CH_3	CH_3	CH_3	198–200	82	100
C_9	C_6H_{11}	H	H	H	H	67	40	82
	$COCH_3$	CH_3	CH_3	CH_3	CH_3	41–42	82	426, 390, 88, 89
C_{10}	COC_6H_5	H	H	H	H	101–101.5	–	170, 172
C_{14}	$CH_2C_6H_5$	CH_3	CH_3	CH_3	CH_3	174–176	96	100, 416
	COC_6H_5	CH_3	CH_3	CH_3	CH_3	61–63	97	100
	$C(CH_3)_3$		H	H	H	76–77	2	337
C_{15}	C_6H_{11}	C_6H_5	H	H	H	–	67	337
C_{16}	$CH(C_6H_5)_2$	H	H	H	H	77–80	80	337, 82
C_{18}	C_6H_5		H	H	H	100–101	33	337
C_{22}	CHC_6H_5 | CH_3		H	H	H	–	30	337
C_{23}	$CH(C_6H_5)_2$	$=CHC_6H_5$		H	H	124–125	63	337
	$CH(C_6H_5)_2$	OH | $CH-C_6H_5$	H	H	H	147–148	43	337
C_{25}	$CH(C_6H_5)_2$	$OCOCH_3$ | CHC_6H_5	H	H	H	145–148	51	337
C_{32}	$CH(C_6H_5)_2$		H	H	H	174–175	–	337

TABLE 34. REACTIONS AT C_3: 3-ALKYLIDENEAZETIDINES



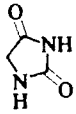
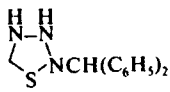
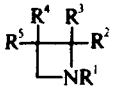
	R^1	R^2	m.p. (°C)	Yield (%)	Ref.
	$COCF_3$	CH_2	50–51	–	34
C_{16}	$CH(C_6H_5)_2$	NOH	169–170	97	337
C_{17}	$CH(C_6H_5)_2$	CH_2	73–74	75	337
	$CH(C_6H_5)_2$	CHCl	64	25	402
C_{18}	$CH(C_6H_4)_2$	CHCN	86	91	402
	$CH(C_6H_5)_2$		238–240	34	337
C_{19}	$CH(C_6H_5)_2$	$CHCOOCH_3$	85	78	402
	$CH(C_6H_5)_2$		105	47	402
C_{32}	$CH(C_6H_5)_2$		211	84	401
	$CH(C_6H_5)_2$		208	83	401
C_{33}	$CH(C_6H_5)_2$		228	78	401
C_{30}	$CH(C_6H_5)_2$		> 194	78	401
	$CH(C_6H_5)_2$		> 212	93	401

TABLE 35. REACTIONS AT C_3: MISCELLANEOUS 3-ALKYL- AND 3-ARYLAZETIDINES



	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_7	$C(CH_3)_3$	H	H	Cl	H	–	(63–64/25)	69	154
	CH_2CH_3	H	H	CH_2Cl	CH_2OH	Cl	142–143	88	308
	CH_2CH_2OH	H	H	CH_2Cl	CH_2OH	Cl	140–151	47	308
C_8	$C(CH_3)_3$	H	H	CH_2OH	H	–	(66–68/0.5)	–	85
						Pic	143–144	–	85
	$C(CH_3)_3$	H	H	CH_2NH_2	H	Di-Pic	230 (dec)	74	85
C_9	$C(CH_3)_3$	CH_3	CH_3	Cl	H	Cl	–	–	287, 190
									188, 189
	$(CH_2)_3CH_3$	H	H	CH_2Cl	CH_2OH	Ts	113–114	66	308
C_{10}	$C(=CHCOOCH_3)COOCH_3$	H	H	CH_3	H	–	(120/0.04)	88	149
	$COCH_3$	H	H	C_6H_4Br-*p*	H	–	82–84	62	41
	$COCH_3$	H	H	C_6H_4Cl-*p*	H	–	82–84	81	41
	$COCH_3$	H	H	C_6H_4OH-*p*	H	–	194–197	78	41
	$COCH_3$	H	H	$C_6H_4NH_2$-*p*	H	–	157–158	69	41
						Di-Cl	232–234	–	41
						Pic	205	–	41
	$COCH_3$	H	H	$C_6H_4NO_2$-*p*	H	–	129–131	68	41
						Cl	162–164	–	41
						Pic	152–154	–	41
C_{11}	$COCH_3$	H	H	$C_6H_3Cl_2$-3,4	H	–	92–94	–	432
	$COCH_3$	H	H	C_6H_3Cl-4-NH_2-3	H	–	99–102	–	432
	$COCH_3$	H	H	C_6H_3Cl-4-NO_2-3	H	–	73–74	–	432
	$COCH_3$	H	H	C_6H_3OH-4-NH_2-3	H	–	175–177	–	432
	$COCH_3$	H	H	C_6H_3OH-4-NO_2-3	H	–	116–118	–	432
	CH_3	H	H	C_6H_4OH-*m*	CH_3	–	154–155	37	37

TABLE 35 CONTINUED

	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{12}	$COCH_3$	H	H	$C_6H_4OCH_3$-*p*	H	–	(145–150/0.1)	–	41
	$COCH_3$	H	H	C_6H_4CN-*p*	H	–	95–98	66	41
	$COCH_3$	H	H	C_6H_4Cl-3-OCH_3-4	H	–	108–110	–	432
	$COCH_3$	H	H	$C_6H_4NH_2$-3-OCH_3-4	H	–	95–96.5	–	432
	$COCH_3$	H	H	$C_6H_4NO_2$-3-OCH_3-4	H	–	118–120	–	432
	$COCH_3$	H	H	C_6H_5	CH_2OH	–	119–121	–	433
	CH_3	H	H	C_6H_5	CH_2OOCNH_2	–	119–122	–	433
	$C(CH_2)_5C{\equiv}CH$	H	H	$C(NOH)NH_2$	H	Cl	202	53	146
C_{13}	$C(CH_3)_3$	H	H	C_6H_{11}	H	–	37–39	20	87
	CH_3	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_3$	–	147–149	85	37
	COC_2H_5	H	H	C_6H_5	CH_2OH	–	76–77	–	433
	CH_2CH_3	H	H	C_6H_5	CH_2OOCNH_2	–	93–95	–	433
						MeI	177–178	–	433
C_{14}	CH_3	H	H	C_6H_5	$CH_2OOCC_2H_5$	Cl	149–151	–	433
	$COCH_3$	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_3$	–	98–100	96	37
	CH_3	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_2CH_3$	–	132–133	53	37
	COC_2H_5	H	H	$C_6H_4NH_2$-*p*	C_2H_5	–	(180–185/0.3)	–	438
						Cl	218–220	–	438
	COC_2H_5	H	H	$C_6H_4NO_2$-*p*	C_2H_5	–	(185–195/0.3)	81	438
	$C(CH_3)_3$	C_6H_5	H	CH_2OH	H	–	–	89	282
C_{15}	$C(CH_3)_3$	H	H	$CH_2NHCSNHC_6H_5$	H	–	99–100.5	–	85
	CH_3	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_2CH_3$	–	153–155	40	37
	CH_3	H	H	$C_6H_4OOCCH_3$-*m*	$CH_2CH_2CH_3$	–	(123/0.8)	95	37
	CH_2CH_3	H	H	C_6H_5	$CH_2OOCC_2H_5$	–	155–157	–	433
	$C(CH_3)_3$	CH_3	CH_3	C_6H_5	H	–	186–189	–	287, 188 189, 190
C_{16}	$CH(C_6H_5)_2$	H	H	Br	H	–	101–102	85	7
C_{17}	$CH(C_6H_5)_2$	H	H	CH_2NH_2	H	–	–	–	7
	$COCH_3$	H	H	C_6H_3OH-4-N=N-C_6H_5-3	H	–	98–100	–	432

TABLE 35 CONTINUED

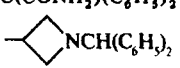
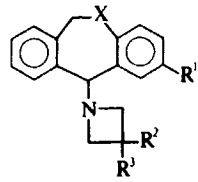
	R^1	R^2	R^3	R^4	R^5	Salt	m.p., °C (b.p., °C/mm Hg)	Yield (%)	Ref.
C_{18}	CH_3	H	H	$C(C_6H_5)_2(CONH_2)$	H	–	171–174	60	474
						Cl	182–185	–	474
	CH_3	H	H	$C(C_6H_5)_3$	H	–	113–115	27	474
	$CH_2C_6H_5$	H	H	C_6H_5	CH_2OOCNH_2	–	101–102	–	433
C_{19}	$CH(CH_3)_2$	H	H	$C(C_6H_5)_2(CONH_2)$(2-Pyr)	H	–	140–141	37	474
	$CH(CH_3)_2$	H	H	$C(C_6H_5)_2$(CN)(2-Pyr)	H	–	78–80	21	474
C_{20}	$CH(CH_3)_2$	H	H	$C(CN)(C_6H_5)_2$	H	–	93–95	56	474
	$CH(CH_3)_2$	H	H	$C(CONH_2)(C_6H_5)_2$	H	–	181–184	59	
	$CH(CH_3)_2$	H	H	6,11-Dihydrodibenz-[b,e]oxepin-11-ylmethyl-	H	–	–	54	306
	$CH_2CH_2C_6H_5$	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_3$	Cl	70–73	50	37
	$CH_2CH_2C_6H_4NH_2$-*p*	H	H	C_6H_4OH-*m*	$CH_2CH_2CH_3$	Di-Cl dihydrate	150 (dec)	60	37
	$CH_2C_6H_5$	H	H	C_6H_5	$CH_2OOCC_2H_5$	–	(160/0.4)	61	433
						Pic	125–127	–	433
C_{21}	$COCH_3$	H	H	$C_6H_4OCH_2C_6H_5$-*m*	$CH_2CH_2CH_3$	–	99–101	92	37
C_{23}	C_6H_{11}	H	H	$C(CN)(C_6H_5)_2$	H	–	111–114	18	474
	$CH_2CH_2C_6H_5$	H	H	$C_6H_4OCH_3$-*m*	$CH_2CH_2CH_2CH_3$	–	75–82	47	37
C_{25}	$CH_2CH_2C_6H_5$	H	H	$C(CN)(C_6H_5)_2$	H	–	122–130	42	474
	$CH_2CH_2C_6H_5$	H	H	$C(CONH_2)(C_6H_5)_2$	H	–	152–153.5	54	474
C_{32}	$CH(C_6H_5)_2$	H	H		H	–	176	–	7

TABLE 36. DERIVATIVES OF 1-AZETIDINODIBENZO[b,f]CYCLOHEPTANE[306]

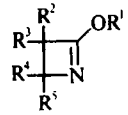


	X	R^1	R^2	R^3	Salt	m.p. (°C)	Yield (%)
C_{17}	CH_2	OCH_3	OH	H	Cl	184–186	54
	S	H	OH	H	Cl	143–148	80
C_{18}	CH_2	H	NH_2	H	Di-HCl	165–170	41
	CH_2	Cl	OH	H	Cl	157–159	38
	CH_2	H	=O		–	96–105	79.8
	O	H	$NHCH_3$	H	–	61–64	36
					Hemifumarate	179–182	74
	O	Cl	$NHCH_3$	H	–	77–80	43
	O	OCH_3	$NHCH_3$	H	–	–	81
	O	H	OSO_2CH_3	H	–	107–109	58
	O	Cl	OSO_2CH_3	H	–	105–110	94
	O	OCH_3	OSO_2CH_3	H	–	–	87
	S	H	$NHCH_3$	H	–	–	86
	S	Cl	$NHCH_3$	H	–	–	49
	S	H	OSO_2CH_3	H	–	–	79
	S	Cl	OSO_2CH_3	H	–	118–127	90
	S	OCH_3	OSO_2CH_3	H	–	–	94
C_{19}	CH	H	$NHCH_3$	H	Di-Cl	156–159	38
	CH_2	Cl	$NHCH_3$	H	Di-Cl	165	65
	CH_2	H	$NHCH_3$	H	–	83–86	68
	CH_2	OCH_3	$NHCH_3$	H	–	–	40
	CH_2	H	CH_2NH_2	H	Di-Cl	135–140	84
	CH_2	H	OH	CH_3	–	100–112	75
	=CH	H	OSO_2CH_3	H	–	96–98	52
	CH_2	H	OSO_2CH_3	H	–	102–104	68
	CH_2	Cl	OSO_2CH_3	H	–	114–118	80
	O	H	NHC_2H_5	H	Fumarate	187–189	55
	O	H	$N(CH_3)_2$	H	Di-Cl	120–125	57
	O	Cl	$N(CH_3)_2$	H	–	105–110	55
	S	H	$N(CH_3)_2$	H	–	–	21
	S	Cl	$N(CH_3)_2$	H	–	–	55
	S	OCH_3	$NHCH_3$	H	–	–	40
C_{20}	CH_2	H	CH_2NHCH_3	H	Di-Cl	90–120	63
	CH_2	H	$N(CH_3)_2$	H	Di-Cl	180	85
	CH_2	Cl	$N(CH_3)_2$	H	Di-Cl	162–167	46
	CH_2	H	NHC_2H_5	H	Di-Cl	138–141	61
	CH_2	H	$N(CH_3)CONH_2$	H	–	105–109	31
	CH_2	H	OSO_2CH_3	H	–	95–98	99
	CH_2	OCH_3	OSO_2CH_3	H	–	–	96
	O	H	$NHCH(CH_3)_2$	H	Fumarate	205–207	50
	O	OCH_3	$N(CH_3)_2$	H	–	–	63
	S	OCH_3	$N(CH_3)_2$	H	–	–	52

TABLE 36 CONTINUED

	X	R^1	R^2	R^3	Salt	m.p. (°C)	Yield (%)
	$-HC=CH-$	H	$NHCH_3$	H	–	95–100	36
	$-HC=CH-$	H	OSO_2CH_3	H	–	183–187	93
	CH_2	H	OSO_2CH_3	CH_3	–	–	58
	CH_2	H	$NHCH_3$	CH_3	–	–	57
	CH_2	H	$NHCH_3$	H	–	–	68
C_{21}	CH_2	H	$NHCH(CH_3)_2$	H	Di-Cl	179–181	40
	CH_2	H	$NCOCH_3$ (CH₃ on N)	H	–	–	91
	$-CH=CH-$	H	$N(CH_3)_2$	H	–	125–130	45
C_{22}	CH_2	H	$NHC(CH_3)_3$	H	Di-Cl	177–179	57
	CH_2	H	1-Imidazolyl	H	–	109–118	40
	CH_2	H	4-Hydroxyethyl-1-piperazinyl	H	Tri-Cl	130	71
	CH_2	H	4-Morpholino	H	–	114–117	71
	CH_2	H	$NHC(CH_3)_2-C\equiv CH$	H	–	108–110	47
C_{24}	CH_2	H	OH	C_6H_5	–	–	45
	CH_2	H	NHC_6H_{11}	H	Di-Cl	140–147	58
	CH_2	H	$N(CH_2C\equiv CH)_2$	H	Di-Cl	170–172	38
C_{25}	CH_2	H	$NHCH_2C_6H_5$	H	Di-Cl	178–180	41
	CH_2	H	$NHCH_3$	C_6H_5	–	–	45
	CH_2	H	OSO_2CH_3	C_6H_5	–	–	82
C_{27}	CH_2	H	$NHCH(CH_3)CH_2C_6H_5$	H	Di-Cl	168–182	44
	CH_2	H	$NCH_2COC_6H_5$ (CH₃ on N)	H	–	120–125	80

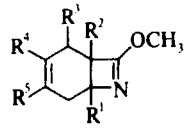
TABLE 37. AZETINES



R^1	R^2	R^3	R^4	R^5	b.p., °C/mm Hg	Yield (%)	Ref.
C_2H_5	n-C_3H_7	n-C_3H_7	H	H	50/0.15	–	363
C_2H_5	C_6H_5	C_2H_5	H	H	80–81/0.1	–	363
C_2H_5	C_6H_5	C_6H_5	H	H	120/0.1	–	363
C_2H_5	H	H	H	CH_3	129/760	68	46
C_2H_5	H	H	H	CH_2=CH	47/10	58	46
C_2H_5	H	H	H	C_6H_5	60/0.1	65	46
C_2H_5	H	H	CH_3	CH_3	82/100	86	46
C_2H_5	H	H	CH_2=CH	CH_3	53/20	82	46
C_2H_5	H	H	C_2H_5	CH_3	58/20	82	46
C_2H_5	H	H	C_3H_7	CH_3	74/20	79	46
C_2H_5	H	H	$C(CH_3)_3$	CH_3	78/20	41	46
C_2H_5	CH_3	CH_3	CH_3	CH_3	80/50	88	46
C_2H_5	CH_3	CH_3	H	H	36/15	54	46
C_2H_5	H (cis)	CH_3	H	CH_3	59/30	76	46
C_2H_5	H (trans)	CH_3	H	CH_3	77/100	72	46
CH_3	H	H	CH_3	CH_3	50/75	78	18
C_2H_5	H	H	CH_3	CH_3	173–142[a]	81	18
CH_3	CH_3	CH_3	CH_3	CH_3	54/28	58	18
C_2H_5	CH_3	CH_3	CH_3	CH_3	68/80	80	18
CH_3	H	CH_3	CH_3	CH_3	50/50	50	18
CH_3	H	C_2H_5	C_2H_5	H	79–80/26	–	359
CH_3	H	C_2H_5	H	C_2H_5	73–74/26	–	359

[a] Melting point, °C.

TABLE 38. 7-AZABICYCLO[4.2.0]OCTA-3,7-DIENES[356]



R^1	R^2	R^3	R^4	R^5	b.p., °C/mm Hg	Yield (%)
H	H	H	H	H	43/0.3	54
CH_3	H	H	H	H	26/0.07	–
CH_3	CH_3	H	H	H	46–47/0.3	80
CH_3	H	CH_3	H	CH_3	52–54/0.3	35
CH_3	CH_3	H	CH_3	CH_3	71–75/0.8	73

X. REFERENCES

1. B. M. Adger, S. Bradbury, M. Keating, C. W. Rees, R. C. Storr, and M. T. Williams, *J. Chem. Soc., Perkin Trans. 1*, 31 (1975).
2. B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 19 (1973).
3. B. M. Adger, K. Keating, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 41 (1975).
4. B. M. Adger, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 45 (1975).
5. M. H. Akhtar and A. C. Oehlschlager, *Tetrahedron*, 26, 3245 (1970).

5a. K. L. Allworth, A. A. El-Hamamy, M. M. Hesbi, and J. Hill, *J. Chem. Soc. Perkin Trans. 1*, 1671 (1980).

6. A. G. Anderson, D. R. Fagerburg, and R. Lok, *J. Heterocyclic Chem.*, 11, 431 (1974).
7. A. G. Anderson and R. Lok, *J. Org. Chem.*, 37, 3953 (1972).
8. A. G. Anderson and M. T. Wills, *J. Org. Chem.*, 32, 3241 (1967).
9. A. G. Anderson and M. T. Wills, *J. Org. Chem.*, 33, 536 (1968).
10. A. G. Anderson and M. T. Wills, *J. Org. Chem.*, 33, 2123 (1968).
11. A. G. Anderson and M. T. Wills, *J. Org. Chem.*, 33, 3046 (1968).

11a. D. J. Anderson and A. Hassner, *J. Chem. Soc., Chem. Commun.*, 45 (1974).

12. D. R. Anderson, J. S. Keute, T. H. Koch, and R. H. Moseley, *J. Am. Chem. Soc.*, 99, 6332 (1977).
13. M. A. Apple and J. V. Formica, U.S. Patent 4,053,460 (1977); *Chem. Abstr.*, 88, 4743j (1978).
14. W. L. F. Armarego, *Stereochemistry of Heterocyclic Compounds*, Part I, Wiley-Interscience, New York, 1977.
15. J. C. Arnould and J. P. Pete, *Tetrahedron Lett.*, 2463 (1975).
16. D. H. Aue, M. T. Bowers, H. M. Webb, and R. T. McIver, *J. Am. Chem. Soc.*, 93, 4314 (1971).
17. D. H. Aue, H. Iwahashi, and D. F. Shellhamer, *Tetrahedron Lett.*, 3719 (1973).
18. D. H. Aue and D. Thomas, *J. Org. Chem.*, 39, 3855 (1974).
19. D. H. Aue and D. Thomas, *J. Org. Chem.*, 40, 1349 (1975).
20. D. H. Aue and D. Thomas, *J. Org. Chem.*, 40, 2356 (1975).
21. D. H. Aue and D. Thomas, *J. Org. Chem.*, 40, 2360 (1975).
22. D. H. Aue and D. Thomas, *J. Org. Chem.*, 40, 2552 (1975).
23. D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, 97, 4137 (1975).
24. W. Aumueller, G. Korger, H. Weber, R. Weyer, A. Baender, and H. Wagner, Ger. Patent 1,182,665 (1964) (in Farbwerke Hoechst A.-G.); *Chem. Abstr.*, 63, 2955 (1965).
25. H. C. Bach, U.S. Patent 3,386,966 (1968) (Monsanto Co.); *Chem. Abstr.*, 69, 28096j (1968).
26. R. E. Banks, M. G. Barlow, and R. N. Haszeldine, *J. Chem. Soc.*, 6149 (1965).
27. R. E. Banks, R. N. Haszeldine, and V. Matthews, *J. Chem. Soc. (C)*, 2263 (1967).
28. A. K. Banthia, E. H. Schacht, and E. J. Goethals, *Makromol. Chem.*, 179, 841 (1978).
29. S. Barak, *Israel J. Chem.*, 6, 471 (1968); *Chem. Abstr.*, 70, 1150a (1969).
30. M. G. Barlow, R. N. Haszeldine, and J. G. Dingwall, *J. Chem. Soc., Perkin Trans. 1*, 1542 (1973).

31. B. J. Baum, R. F. Toxler, H. M. Kagan, J. A. Grasso, B. Faris, and C. Franzblau, *Biochem. Biophys. Res. Commun.*, 53, 1350 (1973).
32. I. Baxter and R. B. Titman, *J. Chem. Soc. (C)*, 2078 (1970).
33. E. Bellasio and C. Cristiani, *J. Med. Chem.*, 12, 196 (1969).
34. G. H. Berezin, U.S. Patent 3,646,010 (E. I. du Pont de Nemours & Co.); *Chem. Abstr.*, 73, 25285s (1970).
35. H. M. Berman, E. L. McGandy, J. W. Burgner, and R. L. Van Etten, *J. Am. Chem. Soc.*, 91, 6177 (1969).
36. R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1215 (1973).
37. D. C. Bishop, J. F. Cavalla, I. M. Lockhart, M. Wright, C. V. Winder, A. Wong, and M. Stephens, *J. Med. Chem.*, 11, 466 (1968).
38. D. S. C. Black, N. A. Blackman, and A. B. Boscacci, *Aust. J. Chem.*, 32, 1775 (1979).
39. D. St. C. Black, R. F. C. Brown, B. T. Dunstan, and S. Sternhell, *Tetrahedron Lett.*, 4283 (1974).
40. D. St. C. Black and K. G. Watson, *Aust. J. Chem.*, 26, 2505 (1973).
41. (a) A. Bonati, G. F. Cristiani, and E. Testa, *Justus Liebigs Ann. Chem.*, 647, 83 (1961); (b) E. Testa, A. Bonati, G. Pagani, and E. Gatti, *ibid.*, 647, 92 (1961).
42. J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, and F. W. Fowler, *J. Am. Chem. Soc.*, 98, 2344 (1976).
43. R. Boni, R. Di Blasi, and A. S. Verdini, *Macromolecules*, 8, 140 (1975).
44. R. Boni, and A. S. Verdini, *J. Chem. Soc., Perkin Trans. 1*, 2173 (1974).
45. D. Bormann, *Chem. Ber.*, 103, 1797 (1970); *Chem. Abstr.*, 73, 25206s (1970).
46. D. Bormann, *Justus Liebigs Ann. Chem.*, 725, 124 (1969); *Chem. Abstr.*, 71, 91180p (1969).
47. A. Botta, *Justus Liebigs Ann. Chem.*, 336 (1976); *Chem. Abstr.*, 84, 164681h (1976).
48. A. T. Bottini and C. P. Nash, *J. Am. Chem. Soc.*, 84, 734 (1962).
49. J. B. Bremner and P. Wiriyachitra, *Aust. J. Chem.*, 26, 437 (1973).
50. Bristol-Myers Co., Fr. Patent 1,580,899 (1969); *Chem. Abstr.*, 73, 14718j (1970).
51. H. Buerger and U. Daemmgen, *Z. Anorg. Allg. Chem.*, 394, 209 (1972); *Chem. Abstr.*, 78, 111098t (1973).
52. H. Buerger and U. Daemmgen, *Z. Anorg. Allg. Chem.*, 407, 201 (1974); *Chem. Abstr.*, 81, 120433n (1974).
53. C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *J. Am. Chem. Soc.*, 85, 97 (1963).
54. C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, 83, 4417 (1961).
55. K. Burger, A. Albanbauer, and F. Manz, *Chem. Ber.*, 107, 1823 (1974); *Chem. Abstr.*, 81, 63427n (1974).
56. K. Burger, J. Fehn, and E. Mueller, *Chem. Ber.*, 106, 1 (1973); *Chem. Abstr.*, 78, 84133s (1973).
57. K. Burger, F. Manz, and A. Braun, *Synthesis*, 250 (1975).
58. K. Burger and R. Ottlinger, *J. Fluorine Chem.*, 12, 519 (1978).
59. K. Burger, W. Thenn, and E. Mueller, *Angew. Chem. Int. Ed. Engl.*, 12, 155 (1973).
60. K. Burger, W. Thenn, and H. Schickaneder, *J. Fluorine Chem.*, 6, 59 (1975).
61. E. M. Burgess and L. McCullagh, *J. Am. Chem. Soc.*, 88, 1580 (1966).
62. E. M. Burgess and J. P. Sanchez, *J. Org. Chem.*, 39, 940 (1974).
63. S. Cabani, G. Conti, and L. Lepori, *J. Phys. Chem.*, 76, 1338 (1972).
64. S. Cabani, G. Conti, and L. Lepori, *Trans. Faraday Soc.*, 67, 1933 (1971).

65. Calanda-Stiftung, Belg. Patent 624,575 (1963); *Chem. Abstr.*, 60, 5460 (1964).
66. A. D. Cale, U.S. Patent 4,144,245 (1979) (A. H. Robins Co., Inc.); *Chem. Abstr.*, 91, 39313h (1979).
67. A. D. Cale and H. Jenkins, Ger. Offen. 2,818,672 (1978) (A. H. Robins Co., Inc.); *Chem. Abstr.*, 90, 87241j (1979).
67a. A. F. Cameron, A. A. Freer, and C. J. Gilmore, *Acta Cryst.*, B37, 1600 (1981).
68. D. W. Cameron and R. G. F. Giles, *J. Chem. Soc. (C)*, 1461 (1968).
69. J. J. A. Campbell, P. Halliwell, and P. W. Manley, *Chem. Ind. (London)*, 842 (1978).
70. T. S. Cantrell, *J. Org. Chem.*, 42, 4238 (1977).
71. L. A. Carreira, R. O. Carter, and J. R. Durig, *J. Chem. Phys.*, 57, 3384 (1977).
72. L. A. Carreira and R. C. Lord, *J. Chem. Phys.*, 51, 2735 (1969).
73. S. A. Castaigne, Fr. Patent 2,280,370 (1976); *Chem. Abstr.*, 85, 159855j (1976).
74. J. Catalan, O. Mo, and M. Yanez, *J. Mol. Struct.*, 43, 251 (1978).
75. J. F. Cavalla and D. C. Bishop, Brit. Patent 1,154,245 (1969) (Parke, Davis and Co.); *Chem. Abstr.*, 70, 81135p (1969).
76. J. F. Cavalla and D. C. Bishop, U.S. Patent 3,491,087 (1970) (Parke, Davis and Co.); *Chem. Abstr.*, 72, 11128ly (1970).
77. R. D. Chambers and J. R. Maslakiewicz, *J. Chem. Soc., Chem. Commun.*, 1005 (1976).
78. R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J. Chem. Soc., Perkin Trans. 1*, 1130 (1975).
79. R. D. Chambers and R. Middleton, *J. Chem. Soc., Chem. Commun.*, 154 (1977).
80. R. D. Chambers and R. Middleton, *J. Chem. Soc., Perkin Trans. 1*, 1500 (1977).
81. J. Charrier, H. Person, and A. Foucaud, *Tetrahedron Lett.*, 1381 (1979); J. Charrier, A. Foucaud, H. Person, and E. Loukakou, *J. Org. Chem.*, in press, 1983.
82. S. S. Chatterjee and A. Shoeb, *Synthesis*, 153 (1973).
83. S. S. Chatterjee and D. J. Triggle, *Chem. Commun.*, 93 (1968).
84. T.-Y. Chen, *Bull. Chem. Soc. Japan*, 41, 2486 (1968); *Chem. Abstr.*, 70, 37572j (1969).
85. T.-Y. Chen, M.-H. Hung, P.-T. Chen, and M. Ohta, *Bull. Chem. Soc. Japan*, 45, 1179 (1972).
86. T.-Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, 40, 1964 (1967); *Chem. Abstr.*, 68, 21754t (1968).
87. T.-Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, 41, 712 (1968); *Chem. Abstr.*, 69, 43698a (1968).
88. T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, 40, 2398 (1967); *Chem. Abstr.*, 68, 49370p (1968).
89. T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, 40, 2401 (1967). *Chem. Abstr.*, 68, 49371q (1968).
90. J. Clark and J. Hill, *J. Chem. Soc., Perkin Trans. 2*, 1514 (1976).
91. P. A. Clark and L. W. Pickett, *J. Chem. Phys.*, 64, 2062 (1976).
92. R. A. Clasen and S. Searles, *Chem. Commun.*, 289 (1966).
93. Copper, McDougall & Robertson, Ltd., Brit. Patent 969,342 (1964); *Chem. Abstr.*, 61, 11976 (1964).
94. A. T. Coscia and J. H. Ross, U.S. Patent 3,634,399 (1972) (American Cyanamid Co); *Chem. Abstr.*, 77, 20789g (1972).
95. A. J. Coulombre and J. L. Coulombre, *Developm. Biol.*, 28, 183 (1972).
95a. D. Greiner, O. V. Dorofeeva, and V. S. Mastryukov, *J. Mol. Struct.*, 75, 225 (1981).

96. N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, 4037 (1966).
97. N. H. Cromwell and B. Phillips, *Chem. Rev.*, 79, 331 (1979).
98. C. R. Crooks, J. Wright, P. S. Callery, and J. E. Moreton, *J. Med. Chem.*, **22**, 210 (1979).
99. F. B. Culp, K. Kurita, and J. A. Moore, *J. Org. Chem.*, 38, 2945 (1973).
100. L. Dall'-Asta and A. Pedrazzoli, *Experientia*, **26**, 1188 (1970); *Chem. Abstr.*, 74, 12905q (1971).
101. W. C. Danen and T. T. Kensler, *Tetrahedron Lett.*, 2247 (1971).
102. L. W. Deady, G. J. Leary, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, 28, 511 (1963).
103. L. W. Deady, R. D. Topsom, R. E. J. Hutchinson, J. Vaughan, and G. J. Wright, *Tetrahedron Lett.*, 1773 (1968).
104. D. P. Del'tsova and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 858 (1976); *Chem. Abstr.*, 85, 123732c (1976).
105. D. P. Del'tsova and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 880 (1979); *Chem. Abstr.*, 89, 42660h (1978).
106. N. I. Delyagina, B. L. Dyatkin and I. L. Knunyants, *Zh. Org. Khim.*, **10**, 935 (1974); *Chem. Abstr.*, 81, 49388u (1974).
107. D. F. DeTar and W. Brooks, *J. Org. Chem.*, 43, 2245 (1978).
108. L. DeVries, *J. Org. Chem.*, 39, 1707 (1974).
109. M. J. S. Dewar, G. P. Ford, J. P. Ritchie, and H. S. Rzepa, *J. Chem. Res. (S)*, 26 (1978).
110. M. J. S. Dewar and N. Trinajstic, *Theor. Chim. Acta*, 17, 235 (1970); *Chem. Abstr.*, 73, 29083x (1970).
111. A. D. de Wit, M. L. M. Pennings, W. P. Trompenaars, D. N. Reinhoudt, S. Harkema, and O. Nevestveit, *J. Chem. Soc., Chem. Commun.*, 993 (1979).
112. J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).
113. J. A. Deyrup, M. M. Vestling, W. V. Hagan, and H. Y. Yun, *Tetrahedron*, **25**, 1467 (1969).
114. E. Doomes and N. H. Cromwell, *J. Org. Chem.*, 34, 310 (1969).
115. L. Duhamel, P. Duhamel, and P. Siret, *Bull. Soc. Chim. France*, 2460 (1973); *Chem. Abstr.*, 79, 136951z (1973).
116. P. Duhamel, L. Duhamel, and P. Siret, *C. R. Acad. Sci. Paris, Ser. C*, 276, 519 (1973).
117. R. A. Dybas, D. W. Graham, and J. E. Brown, U.S. Patent 4,094,976 (1978) (Merck and Co., Inc.); *Chem. Abstr.*, 89, 163395j (1978).
118. M. C. Eagen and N. H. Cromwell, *J. Org. Chem.*, 39, 911 (1974).
119. M. C. Eagen, R. H. Higgins, and N. H. Cromwell, *J. Heterocyclic Chem.*, 8, 851 (1971).
120. N. R. Easton and W. W. Hargrove, U.S. Patent 3,839,415 (1974) (Eli Lilly and Co.); *Chem. Abstr.*, 82, 3816z (1975).
121. A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, 47, 745 (1964).
122. J. M. Eby and J. A. Moore, *J. Org. Chem.*, 32, 1346 (1967).
123. F. Effenberger and R. Maier, *Angew. Chem. Int. Ed. Engl.*, 5, 416 (1966).
124. G. Ege, E. Beisiegel, and P. Arnold, *Chem. Ber.*, 105, 2898 (1972).
125. H. M. El-Namaky and M. A. Salama, *Egypt. J. Chem.*, 18, 1183 (1978); *Chem. Abstr.*, 89, 179758r (1978).
126. J. C. Espie, R. Ramasseul, and A. Rassat, *Tetrahedron Lett.*, 795 (1978).
127. J. C. Espie and A. Rassat, *Bull. Soc. Chim. France*, 4385 (1971); *Chem. Abstr.*, 76, 98736m (1972).

128. Farbwerke Hoechst A.-G., Brit. Patent 1,010,566 (1965); *Chem. Abstr.*, **64**, 5044 (1966).
129. Farbwerke Hoechst A.-G., Fr. Patent 1,548,242 (1968); *Chem. Abstr.*, **71**, 101694a (1969).
130. Farbwerke Hoechst A.-G., Neth. Appl. 6,405,448 (1964); *Chem. Abstr.*, **62**, 16269 (1965).
131. L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *J. Am. Chem. Soc.*, 88, 108 (1966).
132. A. Fischer, H. Hansen, and W. Rohr, Ger. Offen. 2,457,688 (1976) (BASF A.-G.); *Chem. Abstr.*, 85, 108510k (1976).
133. A. Fischer, R. E. J. Hutchinson, R. D. Topsom, and G. J. Wright, *J. Chem. Soc.* (*B*), 544 (1969).
134. M. Fischer, *Chem. Ber.*, **102**, 3495 (1969).
135. M. Fischer and F. Wagner, *Chem. Ber.*, **102**, 3486 (1969).
136. G. Fodor, *J. Am. Chem. Soc.*, 88, 1040 (1966).
137. A. A. Fomochev, I. A. Zon, I. M. Gella, R. G. Kostyanovskii, A. N. Saprin, and V. I. Markov, *Org. Magn. Resonance*, 5, 263 (1973).
138. L. Fowden, *Adv. Enzymol.*, 28, 89 (1967).
139. L. Fowden, *Biochem. J.*, 64, 323 (1956).
140. L. Fowden, *Nature*, 176, 347 (1955).
141. L. Fowden, *Phytochemistry*, 11, 2271 (1972).
142. L. Fowden and M. H. Richmond, *Biochim. Biophys. Acta*, 71, 459 (1963).
143. F. W. Fowler, *J. Org. Chem.*, 37, 1321 (1972).
144. J. P. Freeman and P. J. Mondron, *Synthesis*, 894 (1974).
145. J. P. Freeman, D. G. Pucci, and G. Binsch, *J. Org. Chem.*, 37, 1894 (1972).
146. D. Frehel, A. Heymes, J. P. Maffrand, F. Eloy, D. Aubert, and F. Rolland, *Eur. J. Med. Chem. Chim. Ther.*, 12, 447 (1977).
147. R. Fuks and H. G. Viehe, *Chem. Ber.*, **103**, 573 (1970).
148. W. Funke, *Angew. Chem. Int. Ed. Engl.*, 8, 70 (1969).
149. W. Funke, *Chem. Ber.*, **102**, 3148 (1969).
150. H. Furrer, *Chem. Ber.*, **105**, 2780 (1972).
151. V. R. Gaertner, *J. Heterocyclic Chem.*, 6, 273 (1969).
152. V. R. Gaertner, *J. Org. Chem.*, 32, 2972 (1967).
153. V. R. Gaertner, *J. Org. Chem.*, 33, 523 (1968).
154. V. R. Gaertner, *J. Org. Chem.*, 35, 3952 (1970).
155. V. R. Gaertner, *Tetrahedron*, 23, 2123 (1967).
156. V. R. Gaertner, *Tetrahedron Lett.*, 4691 (1966).
157. V. R. Gaertner, *Tetrahedron Lett.*, 343 (1967).
158. V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968).
159. B. J. Gai and D. R. Moore, *Tetrahedron Lett.*, 2155 (1967).
160. E. J. Gallegos and R. W. Kiser, *J. Phys. Chem.*, 66, 136 (1962).
161. P. G. Gassman and A. Carrasquillo, *Tetrahedron Lett.*, 109 (1971).
162. P. G. Gassman and D. C. Heckert, *Tetrahedron*, 21, 2725 (1965).
163. L. Ghosez and C. De Perez, *Angew. Chem. Int. Ed. Engl.*, 10, 184 (1971).
163a. T. O. Glasbey, P. W. Manley, and R. C. Storr, *J. Chem. Res.* (*S*), 162 (1981).
164. C. Glidewell and D. W. H. Rankin, *J. Chem. Soc.* (*A*), 279 (1970).

165. E. J. Goethals and E. H. Schacht, *J. Polym. Sci., Polym. Lett. Ed.*, 11, 497 (1973).

166. V. N. Gogte, H. M. El-Namaky, M. A. Salama, and B. D. Tilak, *Tetrahedron Lett.*, 3319 (1969).

167. V. N. Gogte, S. B. Kulkarni, and B. D. Tilak, *Tetrahedron Lett.*, 1867 (1973).

168. V. N. Gogte, V. A. Mukhedkar, H. M. El Namaky, M. A. Salama, and B. D. Tilak, *Ind. J. Chem.*, 12, 1234 (1974); *Chem. Abstr.*, 83, 9727p (1975).

169. E. H. Gold, *J. Am. Chem. Soc.*, 93, 2793 (1971).

170. E. H. Gold, Ger. Offen. 1,932,985 (1970) (Scherico Ltd.); *Chem. Abstr.*, 72, 66790a (1970).

171. E. H. Gold, U.S. Patent 3,635,950 (1972) (Schering Corp.); *Chem. Abstr.*, 76, 126762a (1972).

172. E. H. Gold, U.S. Patent 3,898,142 (1975) (Schering A. -G.); *Chem. Abstr.*, 83, 178795q (1975).

173. E. H. Gold, U.S. Patent 3,917,840 (1975) (Schering A. -G.); *Chem. Abstr.*, 84, 59221k (1976).

174. E. H. Gold and E. Babad, *J. Org. Chem.*, 37, 2208 (1972).

175. E. H. Gold and D. M. Solomon, Ger. Offen. 2,548,053 (1976) (Scherico Ltd.); *Chem. Abstr.*, 85, 46359g (1976).

176. E. H. Gold and D. M. Solomon, Ger. Offen. 2,750,300 (1978) (Scherico Ltd.); *Chem. Abstr.*, 89, 109039h (1978).

177. R. Gommper and J. Seybold, *Angew. Chem. Int. Ed. Engl.*, 7, 824 (1968).

178. G. Gondos, K. L. Lang, A. Szeghy, G. Dombi, and G. Bernath, *J. Chem. Soc., Perkin Trans. 1*, 1770 (1979).

179. M. M. Grant, A. S. Brown, L. M. Corwin, R. F. Troxler, and C. Franzblau, *Biochim. Biophys. Acta*, 404, 180 (1975).

180. N. P. Grechkin, *izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1495 (1962); *Chem. Abstr.*, 58, 2418 (1963).

181. N. P. Grechkin and R. N. Khamitov, *Dokl. Akad. Nauk SSSR*, 162, 1063 (1965); *Chem. Abstr.*, 63, 6939 (1965).

182. N. P. Grechkin and R. N. Khamitov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 182 (1967); *Chem. Abstr.*, 66, 94837r (1967).

183. C. A. Grob and V. Krasnobajew, *Helv. Chim. Acta*, 47, 2145 (1964).

184. C. A. Grob, F. Ostermayer, and W. Raudenbusch, *Helv. Chim. Acta*, 45, 1672 (1962).

184a. J. C. Guillemin, J. M. Denis, and A. Lablache-Combier, *J. Am. Chem. Soc.*, 103, 468 (1981).

185. I. Gutman, M. Milun, and N. Trinajstic, *J. Am. Chem. Soc.*, 99, 1692 (1977).

186. H. K. Hall, *J. Org. Chem.*, 29, 3139 (1964).

187. W. W. Hargrove, S. Afr. Patent 6,705,790 (1968) (Eli Lilly and Co.); *Chem. Abstr.*, 70, 87550w (1969).

188. W. W. Hargrove, U.S. Patent 3,481,920 (1969) (Eli Lilly and Co.); *Chem. Abstr.*, 72, 43408t (1970).

189. W. W. Hargrove, U.S. Patent 3,494,964 (1970) (Eli Lilly and Co.); *Chem. Abstr.*, 72, 90256b (1970).

190. W. W. Hargrove, U.S. Patent 3,668,196 (1972) (Eli Lilly and Co.); *Chem. Abstr.*, 77, 126404t (1972).

191. J. Harnisch and G. Szeimies, *Chem. Ber.*, 112, 3914 (1979).

192. H. D. Hartzler, *J. Am. Chem. Soc.*, 95, 4379 (1973).

193. H. D. Hartzler, private communication.

194. H. D. Hartzler, U.S. Patent 3,203,950 (1965) (E. I. du Pont de Nemours & Co., Inc.); *Chem. Abstr.*, **63**, 14813 (1965).

195. A. Hassner, J. O. Currie, A. S. Steinfeld, and R. F. Atkinson, *J. Am. Chem. Soc.*, **95**, 2982 (1973).

196. A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.*, 1015 (1973).

197. A. Hassner and A. B. Levy, *J. Am. Chem. Soc.*, **93**, 2051 (1971).

198. A. Hassner, A. B. Levy, E. E. McEntire, and J. E. Galle, *J. Org. Chem.*, **39**, 585 (1974).

199. R. N. Haszeldine, M. G. Barlow, and J. G. Dingwall, *J. Chem. Soc. (D)*, 1580 (1970).

200. Y. Hata and M. Watanabe, *Tetrahedron*, **30**, 3569 (1974).

201. Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 4659 (1972).

202. M. Heller and S. Bernstein, *J. Org. Chem.*, **36**, 1386 (1971).

203. J. B. Hendrickson and J. R. Sufrin, *Tetrahedron Lett.*, 1513 (1973).

203a. M. M. Hesabi, J. Hill, A. A. El-Hamamy, *J. Chem. Soc. Perkin Trans. 1*, 2371 (1980).

204. B. A. Hess and L. J. Schaad, *J. Org. Chem.*, **41**, 3058 (1976).

205. B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron*, **31**, 295 (1975).

206. R. H. Higgins, F. M. Behlen, D. F. Eggli, J. H. Kreymborg, and N. H. Cromwell, *J. Org. Chem.*, **37**, 524 (1972).

207. R. H. Higgins and N. H. Cromwell, *J. Am. Chem. Soc.*, **95**, 120 (1973).

208. R. H. Higgins and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1059 (1971).

209. R. H. Higgins, N. H. Cromwell, and W. W. Paudler, *J. Heterocyclic Chem.*, **8**, 961 (1971).

210. R. H. Higgins and N. H. Cromwell, *J. Org. Chem.*, **37**, 2918 (1972).

211. R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1063 (1971).

212. J. Hill and J. Townend, *J. Chem. Soc., Chem. Commun.*, 1108 (1972).

213. J. Hill and J. Townend, *J. Chem. Soc. Perkin Trans. 1*, 1210 (1972).

214. J. Hill and J. Townend, *Tetrahedron Lett.*, 4607 (1970).

215. W. Himmele, E. H. Pommer, N. Goetz, and B. Zeeh, Ger. Offen. 2,727,482 (1979) (BASF A. -G); *Chem. Abstr.*, **90**, 152004a (1979).

216. S-i. Hirokami, Y. Hirai, M. Nagata, T. Yamazaki, and T. Date, *J. Org. Chem.*, **44**, 2083 (1979).

217. I. Hoppe and U. Schöllkopf, *Chem. Ber.*, **109**, 482 (1976).

218. B. W. Horrom, U.S. Patent 3,649,618 (1972) (Abbott Laboratories); *Chem. Abstr.*, **76**, 140486g (1972).

219. B. W. Horrom, U.S. Patent 3,733,339 (1973) (Abbott Laboratories); *Chem. Abstr.*, **79**, 18555a (1973).

220. A. G. Hortmann and D. A. Robertson, *J. Am. Chem. Soc.*, **89**, 5974 (1967).

221. A. G. Hortmann and D. A. Robertson, *J. Am. Chem. Soc.*, **94**, 2758 (1972).

222. K. A. Howard and T. H. Koch, *J. Am. Chem. Soc.*, **97**, 7288 (1975).

223. J. A. Hyatt and J. S. Swenton, *Chem. Commun.*, 1144 (1972).

224. K. Ichikawa, *Yuki Gosei Kagaku Kyokai Shi*, **22**, 546 (1964); *Chem. Abstr.*, **64**, 7008 (1966).

225. M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 575 (1975).

226. J. -L. Imbach, E. Doomes, N. H. Cromwell, H. E. Baumgarten, and R. G. Parker, *J. Org. Chem.*, **32**, 3123 (1967).

227. J. -L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

228. G. Impellizzeri, S. Mangiafico, G. Oriente, M. Piatelli, S. Sciuto, E. Fattorusso, S. Magno, C. Santacroce, and D. Sica, *Phytochemistry*, 14, 1549 (1975).

228a. O. V. Isakova, A. M. Sipyagin, and V. V. Kartsev, *Zh. Organ. Khim.*, 17, 1522 (1981).

229. K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, 91, 7490 (1969).

230. K. Isono, S. Funayama, and R. J. Suhadolnik, *Biochemistry*, 14, 2992 (1975).

231. IUPAC, *Nomenclature of Organic Chemistry (1969)*, Sections A and B, 3rd ed., Butterworths, London, 1971.

232. Y. Iwakura, A. Nabeya, T. Nishiguchi, and Y. Ichikawa, *J. Org. Chem.*, 30, 3410 (1965).

233. Y. Iwakura, T. Nishiguchi, and A. Nabeya, *J. Org. Chem.*, 31, 1651 (1966).

234. Y. Iwakura, A. Nabeya, T. Nishiguchi, and K. -H. Ohkawa, *J. Org. Chem.*, 31, 3352 (1966).

235. M. B. Jackson, T. M. Spotswood, and J. H. Bowie, *Org. Mass Spectrom.*, 1, 857 (1968).

236. R. M. Jacob, J. G. Robert, and R. A. Gaillard, U.S. Patent 3,082,210 (1963) (Rhone Poulene S.A.); *Chem. Abstr.*, 60, 1767 (1964).

237. H. Jenkins and A. D. Cale, Ger. Offen. 1,932,219 (1970) (A. H. Robins Co.); *Chem. Abstr.*, 72, 100478s (1970).

238. J. G. Johansson, B. Lindborg, R. Dahlbom, S. B. Ross, and B. Akerman, *Acta Pharm. Suec.*, 10, 199 (1973).

239. F. M. Jones and E. M. Arnett, *Prog. Phys. Org. Chem.*, 11, 263 (1974).

240. L. S. Kaminsky and M. Lamchen, *J. Chem. Soc. (C)*, 2295 (1966).

241. M. J. Kamlet, J. W. Eastes, M. H. Aldridge, and R. R. Minesinger, *J. Org. Chem.*, 36, 3847 (1971).

242. C. Kashima, Y. Aoki, and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 2511 (1975).

243. E. Keschmann and E. Zbiral, *Justus Liebigs Ann. Chem.*, 9, 1445 (1973).

244. K. Kirste, Dissertation, University of Göttingen, 1977.

245. K. Kirste, W. Luettke, and P. Rademacher, *Angew. Chem.*, 90, 726 (1978).

246. Y. Kitaura and T. Matsuura, *Tetrahedron*, 27, 1583 (1971).

247. Y. Kobayashi, A. Ohsawa, M. Baba, T. Sato, and I. Kumadaki, *Chem. Pharm. Bull.*, 24, 2219 (1976).

248. J. Kobor, *Szegedi Pedagog. Foiskola Evk., Masodik Resz.*, 41 (1967); *Chem. Abstr.*, 70, 28809q (1969).

249. J. Kobor, *Szegedi Pedagog. Foiskola Evk., Masodik Resz.*, 51 (1967); *Chem. Abstr.*, 70, 37628g (1969).

250. J. Kobor, *Szegedi Tanarkepzo Foiskola Tud. Kozlem.*, 119 (1973); *Chem. Abstr.*, 80, 47808m (1974).

251. T. H. Koch, D. R. Anderson, J. M. Burns, G. C. Crockett, K. A. Howard, J. S. Keute, R. M. Rodehorst, and R. J. Sluski, *Topics Curr. Chem.*, 75, 65 (1978).

252. T. A. Koch and D. A. Brown, *J. Org. Chem.*, 36, 1034 (1971).

253. T. H. Koch, R. H. Higgins, and H. F. Schuster, *Tetrahedron Lett.*, 431 (1977).

254. T. H. Koch and K. H. Howard, *Tetrahedron Lett.*, 4035 (1972).

255. T. H. Koch and R. M. Rodehorst, *Tetrahedron Lett.*, 4039 (1972).

256. H. Koeppe, W. Kummer, and H. Staehle, *Ger. Offen.* 2,503,222 (1976) (C. H. Boehringer, Sohn); *Chem. Abstr.*, 85, 123572a (1976).

257. H. Kolshorn and H. Meier, *Z. Naturforsch. (A)*, 32A, 780 (1977); *Chem. Abstr.*, 87, 167330r (1977).

258. R. G. Kostyanovskii, I. M. Gella, and Kh. Khafizov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 893 (1971); *Chem. Abstr.*, 75, 62815b (1971).

259. R. G. Kostyanovskii, V. I. Markov, I. M. Gella, Kh. Khafizov, and V. G. Plekhanov, *Org. Mass. Spectrom.*, 6, 661 (1972).

260. R. G. Kostyanovskii, A. V. Prosyanik, A. I. Ermakov, I. A. Zon, Kh. Khafizov, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 119 (1975); *Chem. Abstr.*, 82, 111176g (1975).

261. R. G. Kostyanovskii, A. V. Prosyanik, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 956 (1974); *Chem. Abstr.*, 81, 25476v (1974).

262. I. Kristensen and P. O. Larsen, *Phytochemistry*, 13, 2791 (1974).

263. I. Kristensen, P. O. Larsen, and H. Soerensen, *Phytochemistry*, 13, 2803 (1974).

264. K. Krohn, D. Carboo, and U. Puttfarcken, *Justus Liebigs Ann. Chem.*, 608 (1978); *Chem. Abstr.*, 89, 108861h (1978).

265. E. M. Kryukova, S. B. Davidyants, K. T. Poroshin, R. Dakhte, and I. N. Grigina, *Dokl. Akad. Nauk Tadzh. SSR*, 10, 26 (1967); *Chem. Abstr.*, 68, 3034d (1968).

266. S. B. Kulkarni, R. M. Rodebaugh, and N. H. Cromwell, *J. Heterocyclic Chem.*, 13, 329 (1976).

267. D. L. Ladd and S. T. Ross, U.S. Patent 3,983,245 (1976) (Smithkline Corp.); *Chem. Abstr.*, 86, 43553a (1977).

268. J. B. Lambert, W. L. Oliver, and B. S. Packard, *J. Am. Chem. Soc.*, 93, 933 (1971).

269. J. B. Lambert, B. S. Packard, and W. L. Oliver, *J. Org. Chem.*, 36, 1309 (1971).

270. J. M. Lane, P. Dehm, and D. J. Prockop, *Biochim. Biophys. Acta*, 236, 517 (1971).

271. N. M. Lapshin, M. F. Erykalova, K. A. Kondrat'eva, and A. T. Aidakin, *Zh. Org. Khim.*, 6, 2026 (1970); *Chem. Abstr.*, 74, 12540s (1971).

272. Z. Latajka, H. Ratajczak, W. J. Orville-Thomas, and E. Ratajczak, *J. Mol. Struct.*, 21, 299 (1974).

273. G. J. Leary and R. D. Topsom, *Spectrochim. Acta*, 21, 1161 (1965).

274. J. Le Brumant, J. Hoch, and M. Jaffrain, *C. R. Acad. Sci. Paris, Ser. B.*, 269 (1969); *Chem. Abstr.*, 72, 37472t (1970).

275. L. E. Ledine, V. N. Perchenko, N. S. Nametkin, and A. M. Krapivin, *Dokl. Akad. Nauk SSSR*, 243, 1200 (1978); *Chem. Abstr.*, 90, 121711z (1979).

276. E. Leete, *J. Am. Chem. Soc.*, 86, 3162 (1964).

277. E. Leete, *Phytochemistry*, 14, 1983 (1975).

278. E. Leete, G. E. Davis, C. R. Hutchinson, K. K. Woo, and M. R. Chedekel, *Phytochemistry*, 13, 427 (1974).

279. J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

280. J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968).

281. N. J. Leonard and D. A. Durand, *J. Org. Chem.*, 33, 1322 (1968).

282. H. -K. Leung, S. B. Kulkarni, M. C. Eagen, and N. H. Cromwell, *J. Org. Chem.*, 42, 2094 (1977).

283. K. -K. Leung, B. A. Phillips, and N. H. Cromwell, *J. Heterocyclic Chem.*, 13, 274 (1976).

284. W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, 26, 5137 (1970).

285. W. Lijinsky, K. Y. Lee, L. Tomatis, and W. H. Butler, *Naturwissenschaften*, 54, 518 (1967); *Chem. Abstr.*, 67, 115104n (1967).

286. W. Lijinsky and A. E. Ross, *J. Nat. Cancer Inst.*, 42, 1095 (1969).

287. Eli Lilly and Co., Fr. Patent 1,563,673 (1969); *Chem. Abstr.*, 72, 55231t (1970).

288. K. H. Linke and H. J. Goehausen, *Chem. Ber.*, 104, 301 (1971).

289. E. Lippert and H. Prigge, *Justus Liebigs Ann. Chem.*, 659, 81 (1962).

290. E. Lippert and H. Prigge, *Ber. Bunsenges. Physik. Chem.*, 67, 415 (1963).

291. E. Lippert and H. Prigge, *Ber. Bunsenges. Physik. Chem.*, 67, 555 (1963).
292. C. Lohse, *Tetrahedron Lett.*, 5625 (1968).
293. G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, 69, 3925 (1965).
294. G. Maier and U. Schaefer, *Tetrahedron Lett.*, 1053 (1977).
295. V. G. Mairanowsky, *Angew. Chem. Int. Ed. Engl.*, 15, 281 (1976).
295a. J. Marchand-Brynaert, M. Mora-Portuguez, D. Lesuisse, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 173 (1980).
296. P. Margaretha, *Helv. Chim. Acta*, 58, 929 (1975); *Chem. Abstr.*, 83, 178392f (1975).
297. V. I. Markov, V. A. Doroshenko, O. I. Klimenko, and G. P. Sachko, *Zh. Org. Khim.*, 8, 1717 (1972); *Chem. Abstr.*, 77, 139853p (1972).
298. V. S. Mastryukov, O. V. Dorofeeva, and L. V. Vilkow, *J. Mol. Struct.*, 34, 99 (1976).
299. T. Masuda, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Japan*, 43, 3281 (1970).
300. T. Masuda, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Japan*, 43, 3287 (1970).
301. K. Masuda, T. Okutani, A. Morimoto, T. Kaneko, K. Kikuchi, M. Hirata, Y. Tazima, T. Jimpu, and A. Nagaoka, *Takeda Kenkyusho Ho*, 31, 453 (1972); *Chem. Abstr.*, 78, 135969d (1973).
302. P. H. Mazzocchi and J. J. Thomas, *J. Am. Chem. Soc.*, 94, 8281 (1972).
303. P. H. Mazzocchi, J. Thomas, and F. Danisi, *J. Org. Chem.*, 44, 50 (1979).
304. E. L. McGandy, H. M. Berman, J. W. Burgner, and R. L. Van Etten, *J. Am. Chem. Soc.*, 91, 6173 (1969).
305. P. Melloni, A. Della Torre, V. Gallarate, F. Lauria, N. Passerini, A. Rossi, R. Tommasini, and C. Erba, Ger. Offen. 2,601,540 (1976); *Chem. Abstr.*, 86, 43548c (1977).
306. P. Melloni, A. Della Torre, M. Meroni, A. Ambrosini, and A. Rossi, *J. Med. Chem.*, 22, 183 (1979).
307. A. I. Meyers and H. Singh, *J. Org. Chem.*, 33, 2365 (1968).
308. D. Miller, P. Clark, and T. Melton, Brit. Patent 1,169,027 (1969) (Beecham Group Ltd.); *Chem. Abstr.*, 72, 43409u (1970).
309. D. Miller and T. Melton, Brit. Patent 1,236,078 (1971); *Chem. Abstr.*, 75, 76595s (1971).
310. D. D. Miller, J. Fowble, and P. N. Patil, *J. Med. Chem.*, 16, 177 (1973).
311. M. Mitzlaff, K. Warning, and H. Jensen, *Justus Liebigs Ann. Chem.*, 1713 (1978); *Chem. Abstr.*, 90, 63489v (1979).
312. M. Mitzlaff, K. Warning, and H. Jensen, Ger. Offen. 2,539,777 (1977) (Hoechst A.-G); *Chem. Abstr.*, 87, 5820y (1977).
313. M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chem. Lett.*, 5 (1973).
314. A. L. Mndzhoyan, V. E. Badalvan, and A. G. Samodurova, *Arm. Khim. Zh.*, 27, 516 (1974); *Chem. Abstr.*, 81, 105412m (1974).
315. R. B. Moffett, R. E. Strube, and L. Skaletzky, *J. Med. Chem.*, 14, 1088 (1971).
316. P. D. Mollere and K. N. Houk, *J. Am. Chem. Soc.*, 99, 3226 (1977).
317. T. A. Montzka, Brit. Patent 1,145,255 (1969) (Bristol-Myers Co.); *Chem. Abstr.*, 71, 61242t (1969).
318. T. A. Montzka, S. Afr. Patent 6,801,896 (1968) (Bristol-Myers Co.); *Chem. Abstr.*, 70, 77822x (1969).
319. T. A. Montzka, Swiss Patent 504,439 (1971) (Bristol-Myers Co.); *Chem. Abstr.*, 75, 129685e (1971).
320. T. A. Montzka, U.S. Patent 3,378,561 (1968) (Bristol-Myers Co.); *Chem. Abstr.*, 69, 67244a (1968).

321. T. A. Montzka, U.S. Patent 3,389,140 (1968) (Bristol-Myers Co.); *Chem. Abstr.*, **69**, 86834j (1968).

322. T. A. Montzka, U.S. Patent 3,389,141 (1968) (Bristol-Myers Co.); *Chem. Abstr.*, **69**, 86833h (1968).

323. T. A. Montzka, U.S. Patent 3,452,086 (1969) (Bristol-Myers Co.); *Chem. Abstr.*, **71**, 91118z (1969).

324. (a) J. A. Moore, "Trimethyleneimines," in A. Weissberger, Ed., *Heterocyclic Compounds with Three and Four Membered Rings*, Interscience, New York, 1964; (b) T. A. Montzka, N. M. Cladel, and J. D. Matiskella, *J. Med. Chem.*, **12**, 875 (1969).

325. J. A. Moore, W. J. Freeman, K. Kurita, and M. G. Pleiss, *J. Org. Chem.*, **38**, 2939 (1973).

326. J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962).

327. J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

328. J. A. Moore and L. J. Pandya, *J. Org. Chem.*, **29**, 336 (1964).

329. J. A. Moore and B. Staskun, *J. Org. Chem.*, **43**, 4021 (1978).

330. J. A. Moore, B. Staskun, and J. F. Blount, *J. Org. Chem.*, **41**, 3156 (1976).

331. J. A. Moore, E. J. Volker, and C. M. Kopay, *J. Org. Chem.*, **36**, 2676 (1971).

332. J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *J. Org. Chem.*, **32**, 1353 (1967).

333. J. A. Moore and T. Yamauchi, *J. Org. Chem.*, **31**, 42 (1966).

334. C. L. Moret and L. M. Trefonas, *J. Heterocyclic Chem.*, **5**, 549 (1968).

335. R. M. Moriarty, *Topics Stereochem.*, **8**, 271 (1974).

336. E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966).

337. A. Morimoto, T. Okutani, and K. Masuda, *Chem. Pharm. Bull.*, **21**, 228 (1973).

338. A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).

338a. U. P. Nadir and V. K. Koul, *J. Chem. Soc., Chem. Commun.*, 417 (1981).

339. H. T. Nagasawa, P. S. Fraser, and J. A. Elberling, *J. Org. Chem.*, **37**, 516 (1972).

340. H. T. Nagasawa, P. S. Fraser, and D. L. Yuzon, *J. Med. Chem.*, **16**, 583 (1973).

341. N. S. Nametkin, L. E. Ledina, V. N. Perchenko, and L. G. Batalova, *Dokl. Akad. Nauk SSSR*, **219**, 1130 (1974); *Chem. Abstr.*, **82**, 125440t (1975).

342. N. A. Nelson and Y. Tamura, *Can. J. Chem.*, **43**, 1323 (1965).

343. F. Nerdel, P. Weyerstahl, and K. Zabel, *Chem. Ber.*, **102**, 1606 (1969).

344. M. Noma and M. Noguchi, *Phytochemistry*, **15**, 1701 (1976).

345. M. Noma, M. Noguchi, and E. Tamaki, *Tetrahedron Lett.*, 2017 (1971).

346. Y. Ogata and K. Takagi, *J. Org. Chem.*, **43**, 944 (1978).

347. T. Okutani, T. Kaneko, and K. Masuda, *Chem. Pharm. Bull.*, **22**, 1490 (1974).

348. T. Okutani and K. Masuda, *Chem. Pharm. Bull.*, **22**, 1498 (1974).

349. T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Lett.*, 1115 (1971).

350. A. A. Onishchenko, O. S. Resetova, V. P. Gorelik, O. A. Lik'yanov, and V. A. Tartakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1166 (1976); *Chem. Abstr.*, **85**, 159575t (1976).

351. R. Osman and Y. Shvo, *Tetrahedron*, **34**, 2321 (1978).

352. A. Padwa, F. Albrecht, P. Singh, and E. Vega, *J. Am. Chem. Soc.*, **93**, 2928 (1971).

353. A. Padwa, W. Eisenhardt, R. Gruber, and D. Pashayan, *J. Am. Chem. Soc.*, **93**, 6998 (1971).

354. A. Padwa and R. Gruber, *J. Am. Chem. Soc.*, **92**, 100 (1970).

355. A. Padwa and R. Gruber, *J. Am. Chem. Soc.*, 92, 107 (1970).

356. L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Am. Chem. Soc.*, 93, 152 (1971).

357. L. A. Paquette, T. Kakihana, and J. F. Kelly, *J. Org. Chem.*, 36, 435 (1971).

358. L. A. Paquette and J. F. Kelly, *J. Org. Chem.*, 36, 442 (1971).

359. L. A. Paquette, M. J. Wyvratt, and G. R. Allen, *J. Am. Chem. Soc.*, 92, 1963 (1970).

359a. R. F. Parcell and J. P. Sanchez, *J. Org. Chem.*, 46, 5055 (1981).

360. A. Pedrazzoli, L. Dall'Asta, and A. Degli Angeli, *Arzneim-Forsch.*, 23, 275 (1973).

360a. M. L. M. Pennings, G. Okay, D. N. Reinhoudt, S. Harkema, and G. J. van Hummel, *J. Org. Chem.*, in press, 1983.

360b. M. L. M. Pennings and D. N. Reinhoudt, *J. Org. Chem.*, 47, 1816 (1982).

360c. M. L. M. Pennings, D. M. Reinhoudt, S. Harkema, and G. J. van Hummel, *J. Org. Chem.*, 48, 486 (1983).

360d. M. L. M. Pennings, D. M. Reinhoudt, S. Harkema, and G. J. van Hummel, *J. Org. Chem.*, in press, 1983.

361. B. A. Phillips and N. H. Cromwell, *J. Heterocyclic Chem.*, 10, 795 (1973).

362. L. Pichat, N. L. Phung, and J. P. Guermont, *Bull. Soc. Chim. France*, 4079 (1968); *Chem. Abstr.*, 70, 47829n (1969).

363. G. Pifferi, P. Consonni, G. Pelizza, and E. Testa, *J. Heterocyclic Chem.*, 4, 619 (1967).

364. G. Pifferi, P. Consonni, and E. Testa, *Ann. Chim. (Rome)*, 58, 1283 (1968); *Chem. Abstr.*, 70, 68015j (1969).

365. G. Pifferi, A. Vigevani, and P. Consonni, *Ann. Chim. (Rome)*, 59, 658 (1969); *Chem. Abstr.*, 72, 90159x (1970).

366. C. Pigerol, J. C. Vernieres, M. Broll, P. Eymard, and J. P. Werbenec, *Eur. J. Med. Chem. Chim. Ther.*, 12, 351 (1977); *Chem. Abstr.*, 87, 177801j (1977).

367. T. T. Puck and F. -T. Kao, *Proc. Nat. Acad. Sci. USA*, 60, 561 (1968).

368. C. W. Rees, *New Trends in Heterocyclic Chemistry Stud. Org. Chem.*, 3, Elsevier, Amsterdam, 1979, p. 356.

369. C. W. Rees, R. Somanathan, R. C. Storr, and A. D. Woolhouse, *J. Chem. Soc., Chem. Commun.*, 740 (1975).

370. C. W. Rees, R. C. Storr, and P. J Whittle, *J. Chem. Soc., Chem. Commun.*, 411 (1976).

371. C. W. Rees, R. C. Storr, and P. J. Whittle, *Tetrahedron Lett.*, 4647 (1976).

372. D. N. Reinhoudt, *Adv. Heterocyclic Chem.*, 21, 253 (1977).

373. S. B. Richter and A. A. Levin, U.S. Patent 3,998,808 (1976); *Chem. Abstr.*, 87, 39252e (1977).

374. I. M. Roberts and D. Horvitz, U.S. Patent 3,069,412 (1962) (FMD Corp.); *Chem. Abstr.*, 58, 10172 (1963).

375. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 5, 309 (1968).

376. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 6, 435 (1969).

377. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 6, 439 (1969).

378. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 6, 993 (1969).

379. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 8, 19 (1971).

380. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, 8, 421 (1971).

381. R. M. Rodehorst and T. H. Koch, *J. Am. Chem. Soc.*, 97, 7298 (1975).

382. J. H. Ross, D. Baker, and A. T. Coscia, *J. Org. Chem.*, 29, 824 (1964).

383. J. C. Rosso, C. Caranoni, and L. Carbonnel, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 280, 909 (1975); *Chem. Abstr.*, 83, 205579f (1975).

384. P. D. Rosso, J. Oberdier, and J. S. Swenton, *Tetrahedron Lett.*, 3947 (1971).

385. O. S. Rothenberger and J. A. Moore, *J. Org. Chem.*, 37, 2796 (1972).

386. A. Roubineau and J. C. Pommier, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 281, 47 (1975); *Chem. Abstr.*, 83, 178746z (1975).

387. T. Saegusa, Y. Kimura, S. Sawada, and S. Kobayashi, *Macromolecules*, 7, 956 (1974).

387a. M. D. Rozeboom, K. N. Houk, S. Searles, and S. E. Seyedrezai, *J. Am. Chem. Soc.*, 104, 3448 (1982).

388. T. Saegusa, S. Kobayashi, Y. Kimura, and H. Ikeda, *J. Macromol. Sci., Chem.*, A9, 641 (1975).

389. Z. E. Samoilova, Yu. V. Zeifman, and R. G. Kostyanovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2621 (1968); *Chem. Abstr.*, 70, 68298d (1969).

390. C. Sandriss and G. Ourisson, *Bull. Soc. Chim. France*, 345 (1958).

391. E. H. Schacht, P. K. Bossner, and E. J. Goethals, *Polym. J.*, 9, 329 (1977).

392. E. H. Schacht and E. J. Goethals, *Makromol. Chem.*, 167, 155 (1973).

393. E. H. Schacht and E. J. Goethals, *Makromol. Chem.*, 175, 3447 (1974).

394. E. Schaumann and H. Mrotzek, *Chem. Ber.*, 111, 661 (1978).

394a. E. Schaumann and H. Mrotzek, *Tetrahedron*, 35, 1965 (1979).

395. E. E. Schweizer and M. A. Calcagno, *J. Org. Chem.*, 42, 2641 (1977).

396. S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, 78, 4917 (1956).

397. H. V. Secor and W. B. Edwards, *J. Org. Chem.*, 44, 3136 (1979).

398. D. Seebach, D. Enders, and B. Renger, *Chem. Ber.*, 110, 1852 (1977).

399. J. I. Seeman, H. V. Secor, J. F. Whidby, and R. L. Bassfield, *Tetrahedron Lett.*, 1901 (1978).

400. A. Segre and R. Viterbo, *Experientia*, 14, 54 (1958).

401. G. Seitz and H. Hoffmann, *Arch. Pharm.*, 310, 757 (1977); *Chem. Abstr.*, 88, 37529x (1978).

402. G. Seitz and H. Hoffmann, *Chem.-Ztg.*, 100, 440 (1976); *Chem. Abstr.*, 86, 8942e (1977).

403. G. Seybold, U. Versak, and R. Gompper, *Angew. Chem. Int. Ed. Engl.*, 12, 847 (1973).

404. J. C. Sheehan and R. W. Tulis, *J. Org. Chem.*, 39, 2264 (1974).

405. W. Sliwa, *Rocz. Chem.*, 50, 667 (1976); *Chem. Abstr.*, 86, 55322n (1977).

406. R. L. Snyder, E. L. McGandy, R. L. VanEtten, L. M. Trefonas, and R. L. Towns, *J. Am. Chem. Soc.*, 91, 6187 (1969).

407. M. F. Stevens and N. H. Cromwell, *J. Heterocyclic Chem.*, 8, 253 (1971).

408. V. Stoilova, L. S. Trifonov, and A. Orakhovats, *Synthesis*, 105 (1979).

409. A. Storr and B. S. Thomas, *J. Chem. Soc. (A)*, 3850 (1971).

410. A. Storr, B. S. Thomas, and A. D. Penland, *J. Chem. Soc., Dalton Trans.*, 326 (1972).

411. E. F. W. Su and B. Levenberg, *Acta Chem. Scand.*, 21, 493 (1967); *Chem. Abstr.*, 67, 810x (1967).

412. M. -L. Sung and L. Fowden, *Phytochemistry*, 8, 2095 (1969).

413. M. -L. Sung and L. Fowden, *Phytochemistry*, 10, 1523 (1971).

414. Y. Suzuki, Y. Hasegawa, K. Tsukamoto, Y. Hiramatsu, and K. Miyasaka, U.S. Patent 3,929,765 (1975).

415. Y. Sazuki, K. Tsukamoto, Y. Hasegawa, and Y. Hiramatsu, Japan. Kokai 74,109,369 (1974) (Teikoku Hormone Mfg. Co., Ltd.); *Chem. Abstr.*, 83, 9760u (1975).

416. Y. Suzuki, T. Watanabe, K. Tsukamoto, and Y. Hasegawa, Ger. Offen. 2,317,980 (1973) (Teikoku Hormone Mfg. Co., Ltd.); *Chem. Abstr.*, **80**, 37092j (1974).

417. J. S. Swenton and R. J. Balchunis, *J. Heterocyclic Chem.*, **11**, 453 (1974).

418. J. S. Swenton and J. A. Hyatt, *J. Am. Chem. Soc.*, **96**, 4879 (1974).

419. G. A. Sytov, L. E. Ledina, V. V. Sulima, A. M. Krapivin, V. N. Perchenko, and N. S. Nametkin, *Dokl. Akad. Nauk SSSR*, **212**, 115 (1973); *Chem. Abstr.*, 79, 137227e (1973).

420. G. Sziemies, private communication.

421. G. Sziemies, V. Siefken, and R. Rinck, *Angew. Chem. Int. Ed. Engl.*, **12**, 161 (1973).

421a. J. Szmuszkovicz, M. P. Kane, L. G. Laurina, C. G. Chidester, and T. A. Scahill, *J. Org. Chem.*, **46**, 3562 (1981).

422. T. Takeuchi and D. J. Prockop, *Biochim. Biophys. Acta*, **175**, 142 (1969).

423. H. Taniyama and B. Yasui, *Yakugaku Zasshi*, **81**, 1493, 1497 (1961); *Chem. Abstr.*, **56**, 10070 (1962).

424. Teikoku Hormonme Mfg. Co., Ltd., Ger. Offen. 2,365,391 (1974); *Chem. Abstr.*, **82**, 4236x (1975).

425. E. Testa, L. Fontanella, G. F. Christiani, and L. Mariani, *Helv. Chim. Acta*, **42**, 2370 (1959).

426. E. Testa, A. Bonati, G. Pagani, and E. Gatti, *Justus Liebigs Ann. Chem.*, **647**, 92 (1961).

427. E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **660**, 118 (1962).

428. V. E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **671**, 106 (1964).

429. E. Testa, L. Fontanella, and V. Aresi, *Justus Liebigs Ann. Chem.*, **656**, 114 (1962).

430. E. Testa, L. Fontanella, and V. Aresi, *Justus Liebigs Ann. Chem.*, **673**, 60 (1964).

431. E. Testa, L. Fontanella, and V. Aresi, *Justus Liebigs Ann. Chem.*, **676**, 160 (1964).

432. E. Testa, L. Fontanella, and V. Aresi, *Justus Liebigs Ann. Chem.*, **688**, 165 (1965).

433. E. Testa, L. Fontanella, and M. Bovara, *Justus Liebigs Ann. Chem.*, **671**, 97 (1964).

434. E. Testa, L. Fontanella, and G. F. Christiani, *Justus Liebigs Ann. Chem.*, **626**, 114 (1959).

435. E. Testa, L. Fontanella, G. F. Christiani, and L. Mariani, *Justus Liebigs. Ann. Chem.*, **635**, 119 (1960).

436. E. Testa, L. Fontanella, and G. Maffii, Brit. Patent 858,038 (1958); *Chem. Abstr.*, **56**, 452 (1962).

437. E. Testa, L. Fontanella, and G. Maffii, Brit. Patent 372,446 (1961); *Chem. Abstr.*, **56**, 453 (1962).

438. E. Testa, L. Fontanella, and L. Mariani, *Justus Liebigs Ann. Chem.*, **660**, 135 (1962).

439. E. Testa, L. Fontanella, and L. Mariani, *Farmaco (Pavia), Ed. Sci.*, **19**, 342 (1964).

440. E. Testa, L. Fontanella, L. Mariani, and G. F. Christiani, *Justus Liebigs Ann. Chem.*, **633**, 56 (1960).

441. E. Testa, L. Fontanella, L. Mariani, and G. F. Christiani, *Justus Liebigs Ann. Chem.*, **639**, 157 (1961).

442. E. Testa, A. Wittgens, G. Maffii, and G. Bianchi, in U. Gallo and L. Santamaria, Eds., *Research Progress in Organic-Biological and Medicinal Chemistry*, Vol. 1, Società Editoriale Farmaceutica, Milan, 1964.

443. (a) W. J. Theuer and J. A. Moore, *Chem. Commun.*, 468 (1965); (b) J. -L. Derocque, W. J. Theuer, and J. A. Moore, *J. Org. Chem.*, **33**, 4381 (1968).

444. B. D. Tilak and V. N. Gogte, *Heterocycles*, **7**, 1339 (1977).

445. D. Tourwe, G. Van Binst, S. A. G. De Graff, and U. K. Pandit, *Org. Magn. Reson.*, **7**, 433 (1975).

446. L. M. Trefonas and R. L. Towns, *J. Am. Chem. Soc.*, 93, 1761 (1971).
447. V. I. Trofimov and I. I. Chkheidze, *Khim. Vys. Energ.*, 1, 324 (1967); *Chem. Abstr.*, 68, 12244z (1968).
448. S. Tsuboyama, A. Ohta, and M. Yanagita, *Tetrahedron Lett.*, 3921 (1969).
449. O. Tsuge, K. Oe, and M. Tashiro, *Tetrahedron*, 29, 41 (1973).
450. O. Tsuge, M. Tashiro, and K. Oe, *Tetrahedron Lett.*, 3971 (1968).
451. K. Tsukamoto, Y. Suzuki, A. Izumi, and Y. Hiramatsu, Ger. Offen. 2,058,532 (1972) (Teikoku Hormone, Mfg. Co., Ltd.); *Chem. Abstr.*, 76, 99324n (1972).
452. H. Tucker, Brit. Patent 1,456,525 (1976) (Imperial Chemical Industries Ltd.); *Chem. Abstr.*, 87, 5625p (1977).
453. Union Carbide Corp., Neth. Appl. 6,507,886 (1965); *Chem. Abstr.*, 66, 19630 (1967).
454. P. L. Valint, U.S. Patent 3,665,001 (1972) (Esso Research and Engineering Co.); *Chem. Abstr.*, 77, 114427q (1972).
455. W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 26, 138 (1961).
456. M. Vaultier and R. Carrie, *Tetrahedron Lett.*, 1195 (1978).
457. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *J. Org. Chem.*, 40, 2990 (1975).
458. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *Tetrahedron Lett.*, 1923 (1973).
459. V. V. Volkova, L. E. Gusel'nikov, V. N. Perchenko, V. G. Zaikin, E. I. Eremina, and N. S. Nametkin, *Tetrahedron Lett.*, 577 (1978).
460. V. V. Volkova, V. N. Perchenko, L. E. Gusel'nikov, and N. S. Nametkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2400 (1976); *Chem. Abstr.*, 86, 55212b (1977).
461. D. H. Wadsworth, *J. Org. Chem.*, 32, 1184 (1967).
462. D. H. Wadsworth, *Org. Synth.*, 53, 13 (1973).
463. D. H. Wadsworth and O. E. Schupp, *J. Heterocyclic Chem.*, 3, 230 (1966).
464. H. -V. Wagner, *Angew. Chem. Int. Ed. Engl.*, 12, 848 (1973).
465. K. Wallenfels, and W. Draber, *Justus Liebigs Ann. Chem.*, 667, 55 (1963).
466. M. C. Wani and S. G. Levin, *J. Org. Chem.*, 31, 2564 (1966).
467. R. N. Warrener, G. Ketschmer, and M. N. Paddon-row, *J. Chem. Soc., Chem. Commun.*, 806 (1977).
468. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4613 (1976).
469. H. H. Wasserman, B. H. Lipshutz, and J. S. Wu, *Heterocycles*, 7, 321 (1977).
470. H. H. Wasserman, B. H. Lipshutz, A. W. Tremper, and J. S. Wu, *J. Org. Chem.*, 46, 2992 (1981).
471. R. Watson and L. Fowden, *Phytochemistry*, 12, 617 (1973).
472. J. N. Wells and R. E. Lee, *J. Org. Chem.*, 34, 1477 (1969).
473. J. N. Wells and O. R. Tarwater, *J. Pharm. Sci.*, 60, 156 (1971).
474. W. J. Welstead, U.S. Patent 4,120,969 (1978) (A. H. Robins Co., Inc.); *Chem. Abstr.*, 90, 72066g (1979).
475. J. White and G. McGillivray, *J. Org. Chem.*, 39, 1973 (1974).
476. M. T. Wills, I. E. Wills, L. V. Dollen, B. L. Butler, J. Porter, and A. G. Anderson, *J. Org. Chem.*, 45, 2489 (1980).
477. K. E. Wilzbach and D. J. Rausch, *J. Am. Chem. Soc.*, 92, 2178 (1970).
478. E. Winterfeldt and W. Krohn, *Chem. Ber.*, 102, 2336 (1969).

479. H. Wollweber, H. Wilms, R. Hiltmann, K. Stoepel, and G. Kroneberg, *Arzneim.-Forsch.*, 21, 2089 (1971).

480. D. S. Wulfman and T. F. Steinheimer, *Tetrahedron Lett.*, 3933 (1972).

481. Y. Yamada, T. Emori, S. Kinoshita, and H. Okada, *Agr. Biol. Chem.*, 37, 649 (1973).

482. T. Yamashita, H. Takayaki, J. Hino, and S. Hashimoto, *Polym. J.*, 9, 19 (1977).

483. N. C. Yang, B. Kim, W. Chiang, and T. Hamada, *J. Chem. Soc., Chem. Commun.*, 729 (1976).

484. K. Yoshikawa, M. Hashimoto, and I. Morishima, *J. Am. Chem. Soc.*, 96, 288 (1974).

485. H. M. Zacharis, and L. M. Trefonas, *J. Am. Chem. Soc.*, 93, 2935 (1971).

486. Yu. V. Zeifman, N. P. Gambaryan, L. A. Simonyan, R. B. Minasyan, and I. L. Knunyants, *Zh. Obshch. Khim.*, 37, 2476 (1967); *Chem. Abstr.*, 69, 2919e (1968).

487. Yu. V. Zeifman, E. G. Ter Gabrielyan, L. A. Simonyan, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1813 (1976); *Chem. Abstr.*, 86, 16466t (1977).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

CHAPTER II

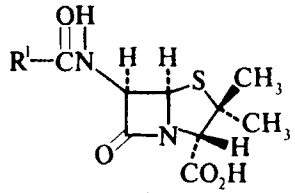
The Synthesis of the β-Lactam Function

GARY A. KOPPEL

Lilly Research Laboratories, Indianapolis, Indiana

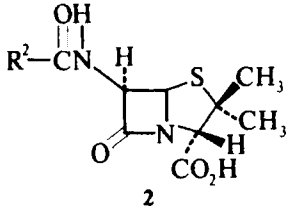
I. Cycloaddition Reactions in the Synthesis of β-Lactams (I + XI → II) 223
1. Ketene–Azomethine Cycloadditions. 223
2. The reaction of Acid Halides with Azomethine Substrates 248
3. [2+2] Cycloaddition Reaction of Isocyanates and Olefins (III + XII → IV) . 302
II. Ring-Closure Reactions 329
1. Formation of the N–C_2 Bond (V → VI) 329
A. Cyclization of β-Amino Acids 329
B. Cyclization of β-Amino Esters: Grignard- and Aluminum-Catalyzed Condensations 337
C. Cyclization of β-Amino Esters: Reformatsky Reaction 346
D. Cyclization of β-Amino Carbonyl Derivatives: Utilization of Titanium Tetrachloride and Transition Metal Complexes in the Construction of β-Lactams 355
2. Formation of the N–C_4 Bond (VII → VI) 359
A. Cyclization of 3-Halopropionamides 359
B. Cyclization of 3-Halocysteinylamides 366
C. Cyclization of Hydroxamic Acids 385
D. Miscellaneous N–C_4 Cyclizations 386
3. Formation of the C_3–C_4 Bond (VIII → VI) 394
A. Cyclization of α-Halocarboxylic Amides 394
B. Azetidinone Formation via Photochemical Cyclizations 401
C. Azetidinone Formation via Transition Metal Carbenes 407
III. Ring-Expansion Reactions (X → XI) 412
IV. Ring-Contraction Reactions (XIII → XIV and XV → XVI) 419
V. Oxidation of Azetidines (XVII → VI) 431
VI. References 433

In 1929 Fleming observed that a *Pencillium* mold inhibited the growth of bacteria.[1] This discovery signaled the onset of one of the most intensive and far-reaching research efforts spanning such scientific disciplines as microbiology, physics, chemistry, and immunology. The initial discovery by Fleming led to the elucidation of the active antibacterial factors – the β-lactams named pencillins (1).[2]

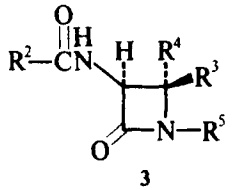


1

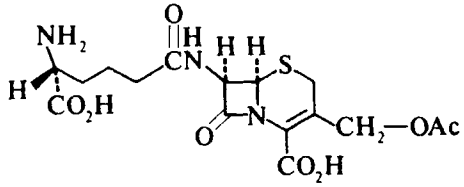
The identification of the β-lactam component as the requisite function for antimicrobial activity stimulated various independent chemical efforts to modify the naturally occurring penicillins (**1** → **2** → **3**) or to prepare novel β-lactam structures by total synthesis. The impetus for the construction of unnatural β-lactam derivatives was generated by a second major discovery in the field of β-lactam antibiotics, namely the isolation and structural determination of cephalosporin C (**4**).[3]



2



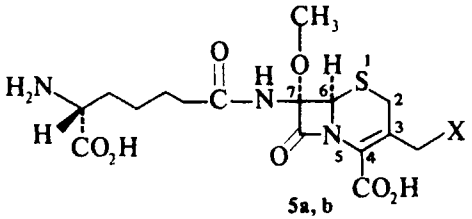
3



4

The clinical effectiveness of these two families of β-lactam antibiotics was the major driving force for research into the structural modification of β-lactams.

A third major breakthrough in the field of the β-lactam antibiotics was achieved in the mid-1960s with the isolation and structural determination of a new family of cephalosporins: the 7-α-methoxycephalosporins (**5**). These were isolated and

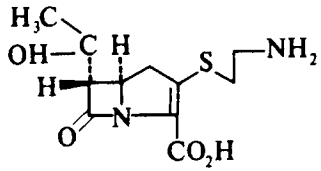


5a, b

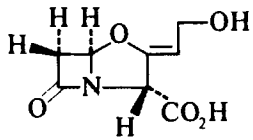
a. X = OAc
b. X = $-OC-NH_2$ (O)

their structures were determined independently at the Lilly Research Laboratories and at Merck Sharp & Dohme.[4] The incorporation of the α-methoxy substituent at C_7 and the enhanced antimicrobial activity of these novel substituted cephalosporins created an additional dimension of difficulty for those architectural adventurers who dared to challenge the power of nature by synthetic methods.

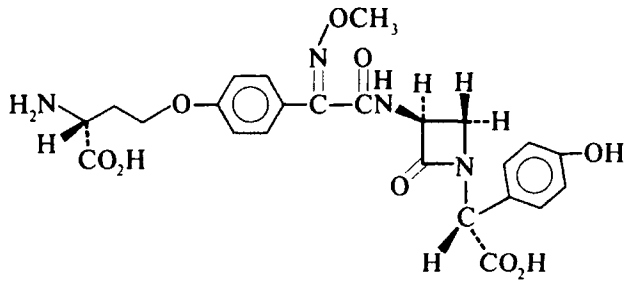
A reaffirmation of the importance of β-lactams occurred in 1976 with the discovery of naturally occurring strained β-lactams with biologically relevant properties. For example, investigators from Merck Sharp & Dohme discovered the fused β-lactam thienamycin (**6**).[5] In addition, researchers from the Glaxo Laboratories isolated the penicillinase inhibitor clavulanic acid (**7**).[6] Finally, a team of investigators from Fujisawa disclosed the structure of the monocyclic β-lactams nocardicin A (**8**).[7]



6



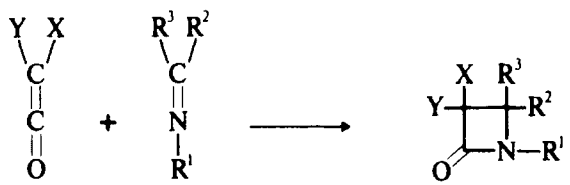
7



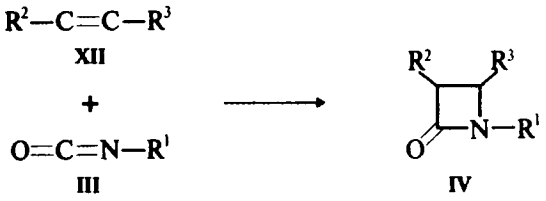
8

The construction of naturally occurring or unnatural β-lactams, with attendent control of functional groups and stereochemistry, has been the goal of synthetic organic chemists for the past 40 years. Thus far, the synthesis of the β-lactams can be differentiated into five fundamental methods:

1. Cycloaddition reactions (**I** + **XI** → **II** or **III** + **XII** → **IV**).

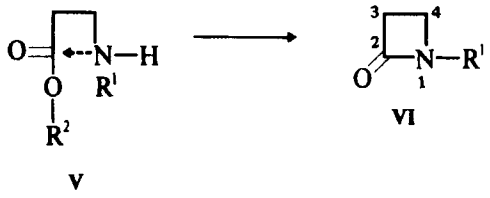


I **XI** **II**

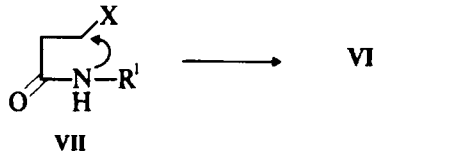


XII + III → IV

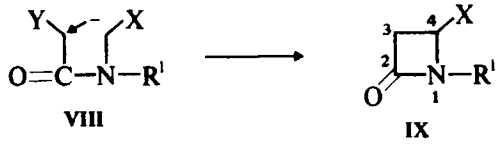
2. Cyclization of the requisite acyclic precursors (**V** → **VI**, **VII** → **VI**, or **VIII** → **IX**).



V → VI

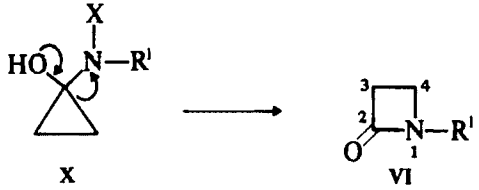


VII → VI



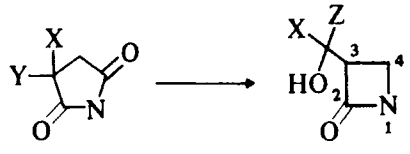
VIII → IX

3. Ring expansions (**X** → **VI**).

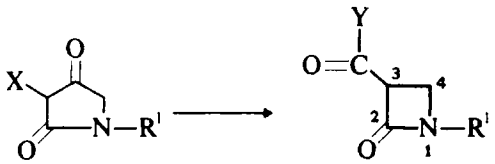


X → VI

4. Ring contractions (**XIII** → **XIV** or **XV** → **XVI**).



XIII → XIV



XV XVI

5. Oxidation of azetidines (**XVII → VI**).

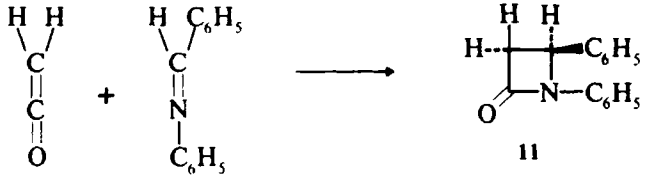


XVII VI

I. CYCLOADDITION REACTIONS IN THE SYNTHESIS OF β-LACTAMS (I + XI → II)

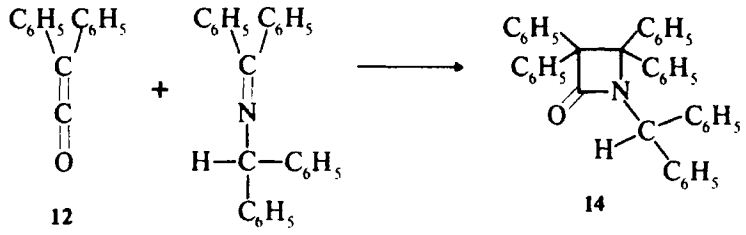
1. Ketene–Azomethine Cycloadditions

The first synthesis of a β-lactam was reported by Staudinger in 1907.[8] In an investigation of the reactivity of azomethine linkages with ketene (**9**), Staudinger discovered that the β-lactam function could be prepared by reacting **9** with a Schiff base (**10**), giving β-lactam **11**.[8–10] The conditions for the formation of **11** were extremely brutal (180–200°C). Nevertheless, this constituted the first synthetic construction of a β-lactam that utilized the [2+2] cycloaddition sequence (**I + XI → II**).



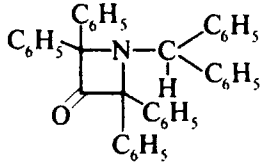
9 10 11

In contrast to the Staudinger synthesis of β-lactams, Rachman et al. reported that *N*-benzhydryl benzophenoneimine (**13**) reacted with diphenylketene (**12**) at room temperature in ether to afford (in 80% yield) β-lactam **14**.[11] The alternate cyclo-



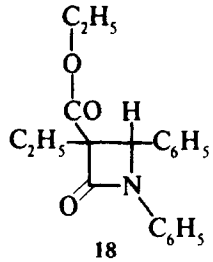
12 13 14

addition product **15** has been ruled out on the basis of its inability to form a quaternary salt.[11]

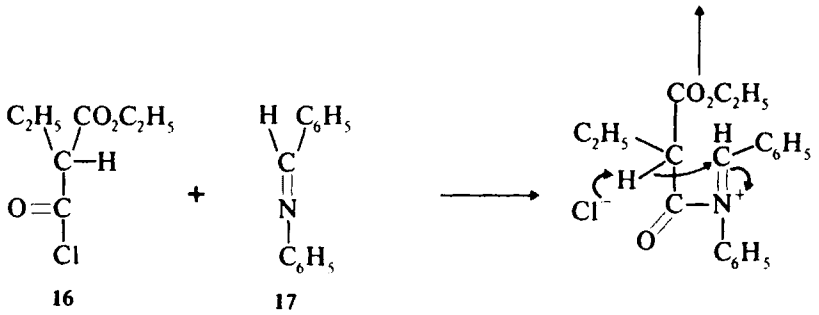


15

Ziegler and Kleineberg reported that the malonyl chloride derivative **16** reacted with Schiff base **17** in refluxing benzene for 4 hours to give **18** in 47% yield.[12] The authors suggested a nonconcerted two-step cycloaddition process for this reaction, as described in Scheme 1.[12]



18



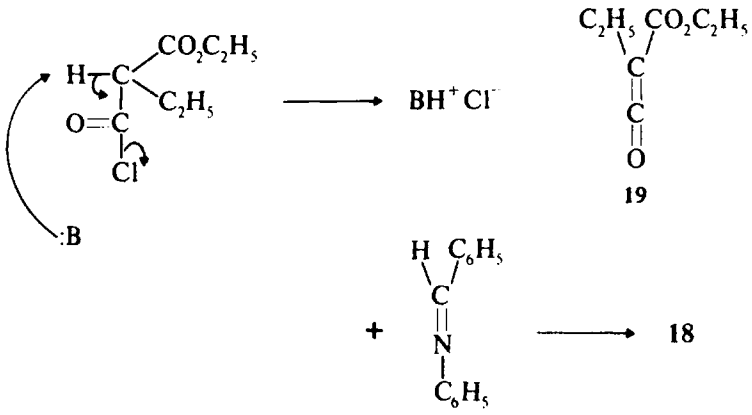
16 **17**

Scheme 1

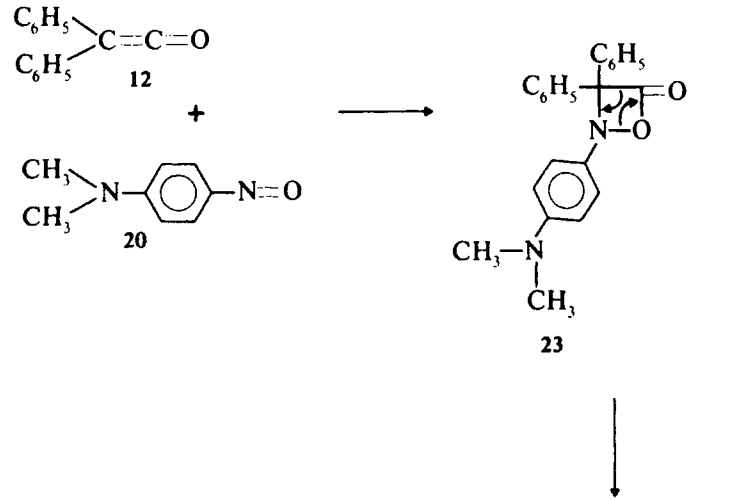
Alternatively, one could propose an initial dehydrohalogenation to afford ketene **19**, which undergoes a concerted cycloaddition to give **18** (Scheme 2).

An interesting variant of the ketene–Schiff base cycloaddition reaction was reported by Staudinger and Jelagin in 1911.[13] They had found that the reaction of the nitrosobenzene **20** with **12** afforded β-lactam **21**. A mechanism for its synthesis was proposed by Staudinger. In involves the formation of 1,2-oxazetidinone **23**, followed by [2+2] retroaddition with concomitant loss of CO_2 and formation of Schiff base **22**, which reacts with **12** to give **21** (Scheme 3).[13]

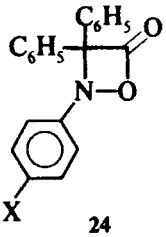
Kresze and Trede reinvestigated the Staudinger nitroso cycloaddition reaction and confirmed that electron-donating groups in the para position (X = $N(CH_3)_2$, OCH_3) give oxazetidinone **24**, whereas electron-withdrawing groups in the para position (X = Cl, Br, H) give the stable isomeric oxazetidinone **25**.[14]



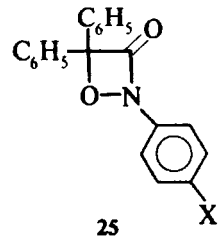
Scheme 2



Scheme 3



24



25

The substitution requirements with respect to ease of formation of the β-lactam from the precursor azomethine and ketene have been reported through the year 1964.[15,16] For example, the ease of β-lactam formation from ketenes and benzophenone anil is presented in Figure 1a.[15] With respect to the azomethine linkage, almost all of the imines have an aromatic group on nitrogen and carbon; with respect to aromatic substitution on nitrogen, electron-donating groups facilitate β-lactam formation and electron-withdrawing substituents retard its formation.[16]

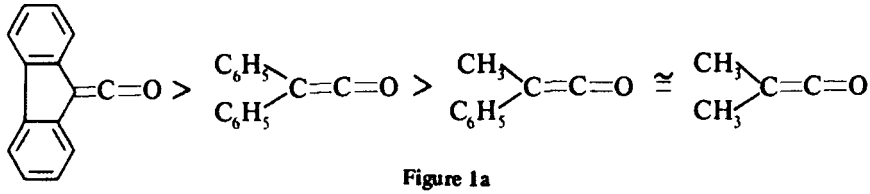
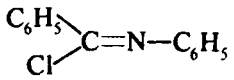
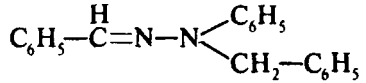


Figure 1a

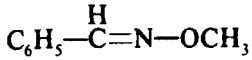
The reactivity of azomethine substrates substituted with heteroatoms at the carbon atom has been investigated with respect to [2+2] reactivity with ketenes. Imino chloride **34**, phenylhydrazone **35** and oxime ether **36** were found to be unreactive.[15] However, thioimidate **37** reacted with dimethylketene to give **38** in 60% yield.[16,19] In addition, the use of thioimidates in the construction of penicillin β-lactam models was successfully demonstrated in the synthesis of fused β-lactams (**39** + **12** → **40**).[15,20] This is presented in Figure 1b.



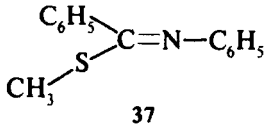
34



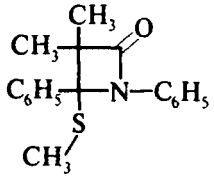
35



36



37



38

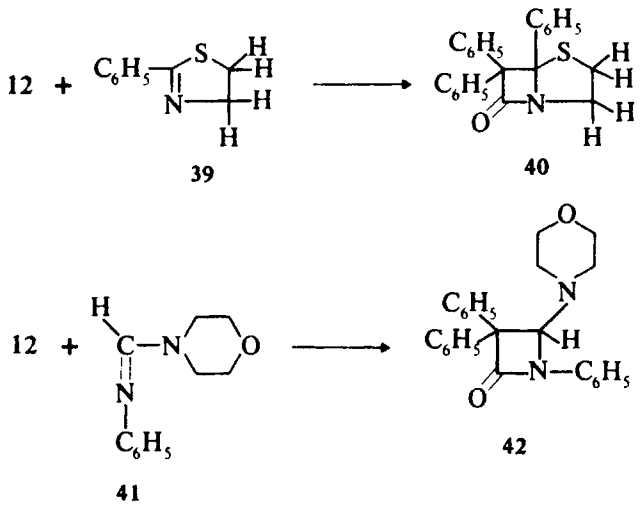
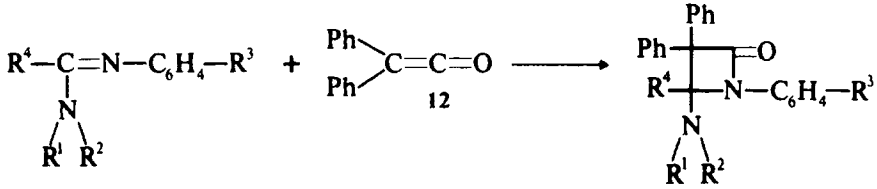


Figure 1b

Bose and Kugajevsky extended the utility of azomethine groups amenable to the [2+2] cycloaddition reaction with the discovery that amidine **41** reacted with diphenyl ketene **12** to give azetidinone **42** in 45% yield.[21] This is illustrated in Figure 1b. A series of nitrogen-substituted azetidinones (**44** through **52**) was prepared according to this procedure (Figure 2).

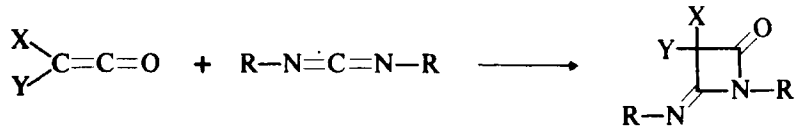


43	$R^1 = R^2 = R^4 = Me$; $R^3 = H$	**44**
45	$R^1 = R^2 = Ph$; $R^3 = H$; $R^4 = Me$	**46**
47	R^1–R^2 = –CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–; $R^3 = R^4 = H$	**48**
49	R^1–R^2 = –CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–; $R^3 = p$-NO_2; $R^4 = H$	**50**
51	R^1–R^2 = –CH_2–CH_2–O–CH_2–CH_2–; $R^3 = p$-OMe; $R^4 = Ph$	**52**

Figure 2

The reactivity of halogenated ketenes with azomethine substrates in β-lactam formation was reported independently by Brady and Hoff and by Hull.[17,18] Fluoroketene **26**, prepared by dehydrohalogenation of fluoracetyl chloride with triethylamine at −78°C, reacted with *N,N'*-diisopropylcarbodiimide **27** in refluxing hexane to give iminoazetidinone **28** in 40% yield.[17] Similarly, the adduct **29**, derived

from chloroketene **30** and **27**, was produced in 60% yield.[17] Dichloroketene **31**, prepared *in situ* by dehydrohalogenation of dichloroacetyl chloride with triethylamine, reacted with dicyclohexylcarbodiimide **32** to give azetidinone **33** in good yield.[18]



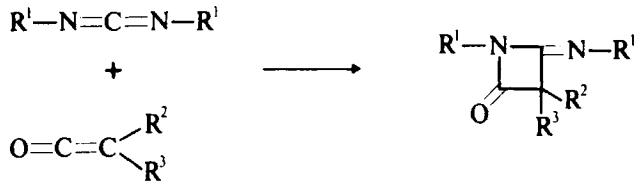
26 X = F; Y = H **27** R = CH(CH$_3$)$_2$ **28** X = F; Y = H; R = *i*-C$_3$H$_7$

29 X = Cl; Y = H; R = *i*-C$_3$H$_7$

30 X = Cl; Y = H **33** X = Y = Cl; R = *n*-C$_6$H$_{13}$

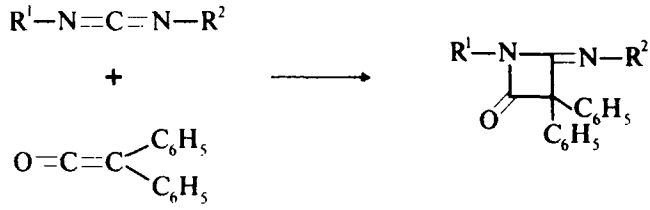
31 X = Y = Cl **32** R = C$_6$H$_{11}$

An extensive investigation of the reaction of substituted ketenes with symmetric and unsymmetric carbodiimides was reported by Metzger and Kurz.[22] The reaction was carried out in refluxing benzene and is illustrated in Figure 3.[22] As can be seen, electron-withdrawing substituents on the ketene reduce the yield of product, as, for example, in compounds **57** (R^3 = H, R^2 = 2-ClC$_6$H$_4$) and **56** (R^3 = R^2 = Cl).[22] With respect to carbodiimide substitution, alkyl substitution enhances the yield of a product (i.e., **53**, **54**, **55**), whereas benzyl and aromatic substitutions reduce the yield (i.e., **59**, **60**, and **61**).[22] The orientation of unsymmetric carbodiimides is illustrated in Figure 4.[22] Quite interestingly, the less sterically hindered nitrogen becomes the β-lactam nitrogen in the dialkyl system (e.g., **62**, **63**, and **64**). In addition, the orientation of substituents differing in electron-donating or electron-



Compound	R^1	R^2	R^3	Yield (%)
53	$(CH_3)_2CH$	C_6H_5	C_6H_5	80
54	$(CH_3)_3C$	C_6H_5	C_6H_5	75
55	*c*-C_6H_{11}	C_6H_5	C_6H_5	88
56	*c*-C_6H_{11}	Cl	Cl	55
57	*c*-C_6H_{11}	2-ClC_6H_4	H	55
58	$C_6H_5CH_2$	C_6H_5	C_6H_5	49
59	C_6H_5	C_6H_5	C_6H_5	60
60	4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	62
61	4-Tolyl	C_6H_5	C_6H_5	48

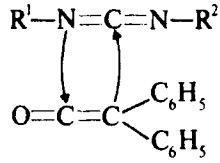
Figure 3



Compound	R^1	R^2	Yield (%)
62	C_2H_5	$(CH_3)_2CH$	30
63	CH_3	$(CH_3)_3C$	70
64	C_2H_5	$(CH_3)_3C$	71
65	$(CH_3)_3C$	C_6H_5	22
66	$(CH_3)_3C$	4-Tolyl	30

Figure 4

withdrawing properties (e.g., **65** and **66**) suggests that the mechanism of the cycloaddition reaction can be described as follows.



The reaction of haloketenes with Schiff bases was reported independently by Duran and Ghosez[23] and by Bose et al.[24] Both groups had discovered that the generation of haloketenes *in situ* afforded very good yields of the appropriate halogenated β-lactams. For example, the reaction of chloroacetyl chloride **67** (in benzene) with Schiff base **68** in the presence of triethylamine at room temperature afforded a quantitative yield of **69**.[23] Similarly, dichloroacetyl chloride **70** reacted with **68** to give **71** in quantitative yield (Figure 5).[23]

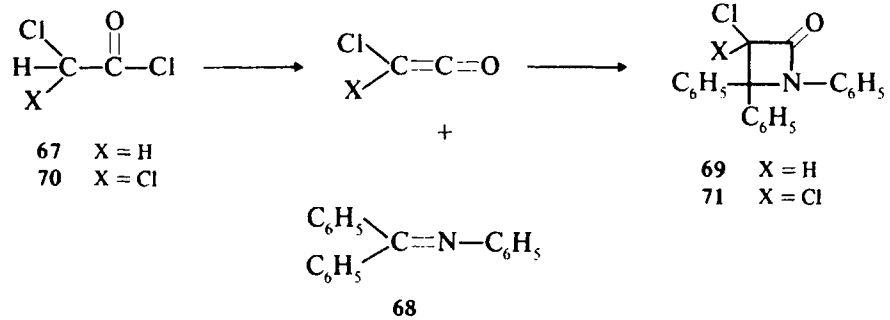
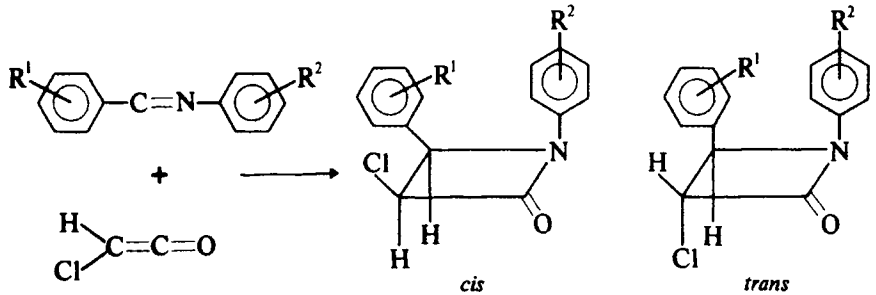


Figure 5

An investigation of the stereochemistry of the cycloaddition reaction of chloroketene with substituted benzalaniline was reported by Nelson.[25] Chloroacetyl chloride was added to a solution of imine and triethylamine at 70–75°C. After 2 hours, the reaction was worked up. The reactants and products with respect to

cis/trans ratios are illustrated in Figure 6.[25] The R^1 group in the ortho position (e.g., **72**, **73**, and **76**) enhanced the formation of the *cis* isomer.[25] In contrast,



Compound	R^1	R^2	Cis/Trans	Yield (%)
72	*o*-Nitro	*p*-Methoxy	50/50	19
73	*o*-Nitro	*p*-Chloro	32/68	6
74	*o*-Nitro	2,4-Dimethyl	22/78	9
75	*o*-Nitro	2-Bromo	20/80	2
76	*o*-Nitro	H	44/56	9
77	*o*-Nitro	*p*-Methoxy	0/100	9
78	*o*-Nitro	*p*-Methoxy	0/100	16
79	*o*-Chloro	*p*-Methoxy	18/82	30
80	*o*-Chloro	H	13/87	28
81	*p*-Chloro	*p*-Methoxy	1/100	7
82	*o*-Methoxy	*p*-Methoxy	10/90	28
83	*o*-Methoxy	H	0/100	25
84	*p*-Methoxy	*p*-Methoxy	0/100	65
85	*o*-Methyl	*p*-Methoxy	10/90	45
86	*o*-Methyl	H	0/100	20
87	*o*-*t*-Butyl	*p*-Methoxy	25/75	10

Figure 6

R^1 substituted in the para positions gave only the trans product (i.e., **77**, **78**, **81**, and **84**).[25] The author proposed a two-step cycloaddition mechanism in which both steric and electronic effects influence the stereochemistry or product (see Figure 7).[25]

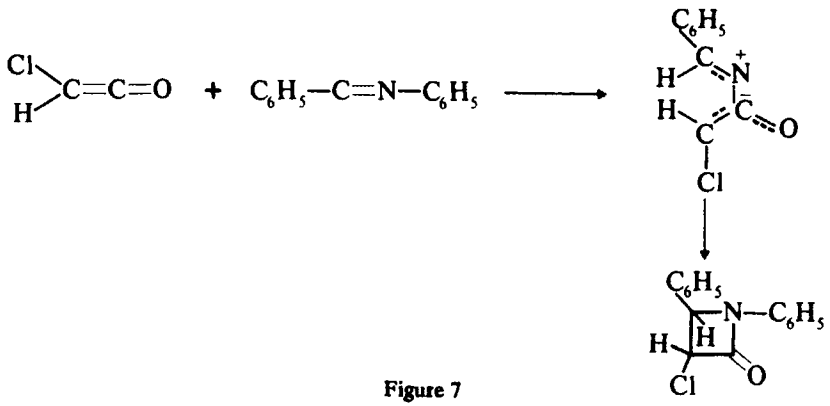
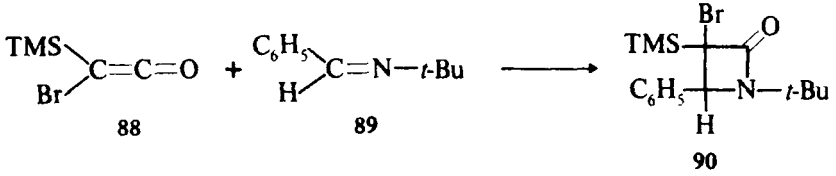


Figure 7

Brady and Owens reported the reaction of trimethylsilylbromoketene (TMS-bromoketene) **88** with *N*-*t*-butylbenzylimine **89** to afford azetidinone **90** in 56% yield.[26] The ketene **88** is produced *in situ* from **91** and triethylamine. If acid bromide **91** is reacted directly with **89** without triethylamine, the nonsilylated azetidinone **92** is produced.[26] The latter product arises through acylation and



subsequent desilylation by another mole of Schiff base, followed by cyclization (Figure 8).[26] The investigators did not describe the stereochemistry of the products.[26]

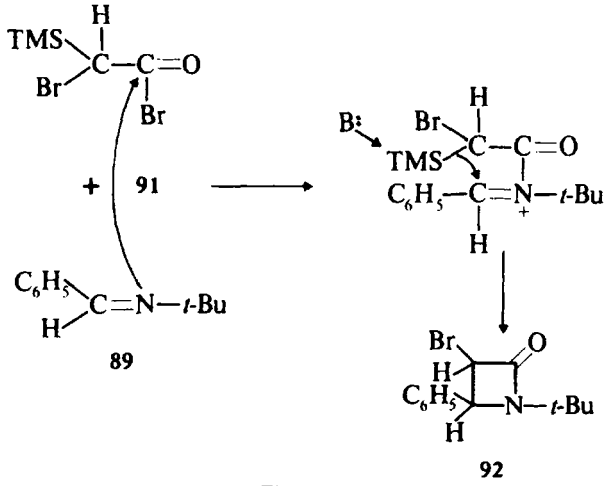
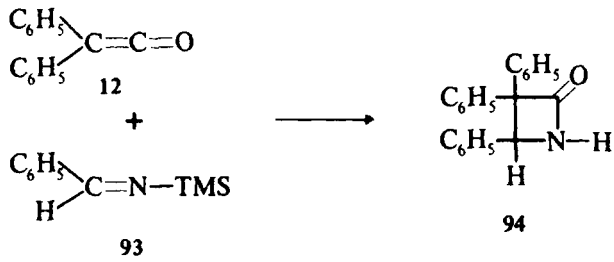
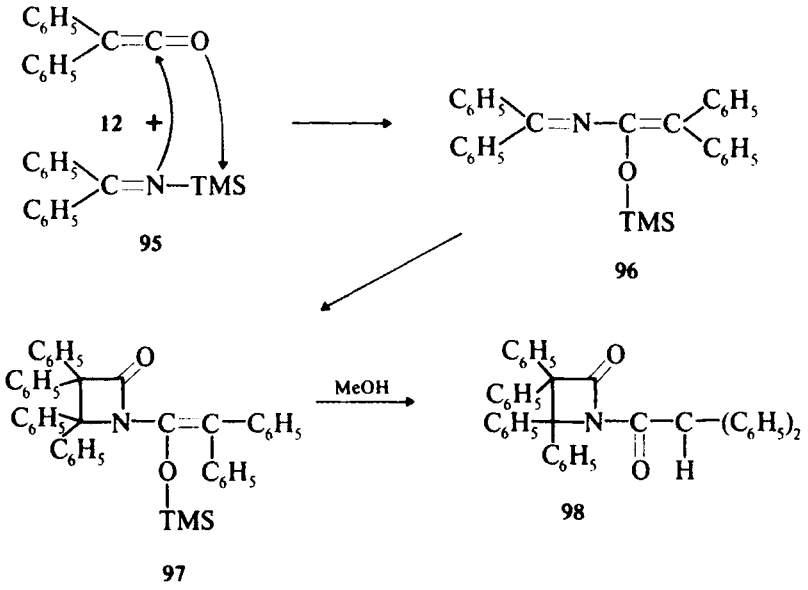


Figure 8

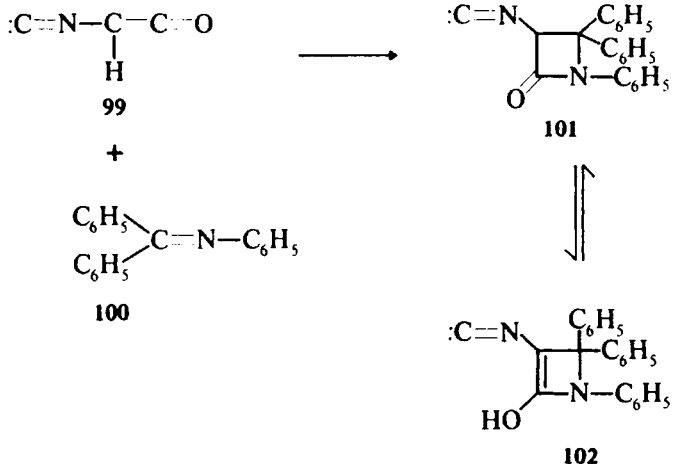
Birkofer and Schramm reported the utility of an azomethine trimethylsilyl group for the direct synthesis of "free N–H" azetidinones employing the [2+2] cycloaddition reaction.[27] For example, the reaction of diphenylketene **12** with *N*-(trimethylsilyl)benzaldimine **93** afforded, upon work up, azetidinone **94** in low yield.[27] In contrast, the reaction of **12** with *N*-(trimethylsilyl)benzophenonimine



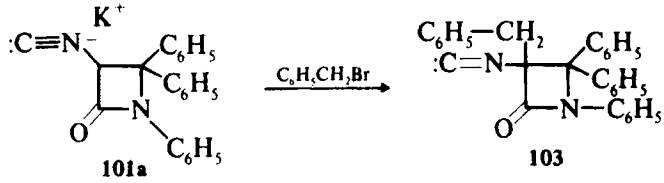
95 yielded the vinylimine **96** in quantitative yield.[27] Interestingly, ketenes **12** and **96** underwent a smooth [2+2] cycloaddition to afford azetidinone **97** in 58% yield.[27] Compound **97** was subsequently converted to the amide **98** in the presence of methanol.[27]



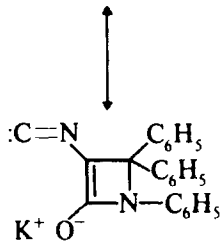
Hoppe and Schöllkopf investigated the reaction of isocyanoketene **99** with benzophenone anil **100** and alkylthioimidate **105**.[28] The reaction of **99** (derived *in situ* from isocyanoacetyl chloride and triethylamine) with **100** afforded a mixture of isocyanoazetidinones (azetidin-2-one **101** and the corresponding enol **102**)[28] in 40% yield.



The virtue of the isocyanazetidinone was demonstrated by these investigators with the incorporation of a variety of electrophiles at C_3.[28] For example, the reaction of anions **101a** or **102a** (produced from the parent azetidinone by treatment with potassium (*t*-butoxide in tetrahydrofuran) with benzyl bromide at room temperature afforded a 90% yield of **103**.

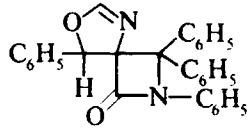


101a **103**

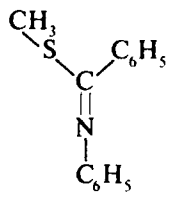


102a

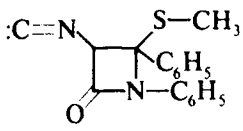
In addition, azetidinone **101** reacted with benzaldehyde in dimethylacetamide (DMAC), with potassium carbonate as the base, to give a 76% yield of oxazoline **104** as a pure diastereomer.[28] Thioimidate **105** reacted with **99** to give **101b** as a 1.3:1 mixture of trans and cis isomers (methylthio to isocyano groups) in 18% yield.[28] The isocyanazetidinone **101b** was converted to the amine tosylate salt **106** (in 55% yield) with *p*-toluenesulfonic acid monohydrate in methylene chloride.[28]



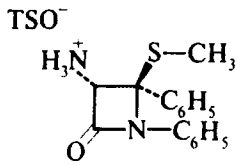
104



105



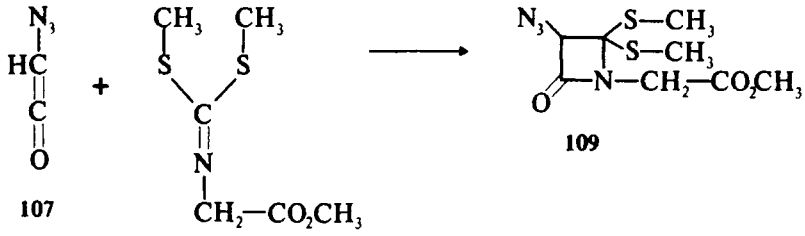
101b



106

The use of azidoketene **107** in the construction of biologically active β-lactams has been reported by a number of investigators.[29] For example, **107** reacts with

108 to give β-lactam **109**.[29] The utilization of **107** and the precursor azidoacetyl chloride in [2+2] cycloadditions will be presented later in a discussion of the *in situ* generation of "ketenes" from acid halides.



107 **108** **109**

One of the more elegant constructions of β-lactams utilizing "latent functionalized ketenes" was reported by Moore and co-workers in a series of investigations into the thermolysis of β-azido-α-chloro-γ-methoxy-$\Delta^{\alpha,\beta}$-crotonolactone **110** and its conversion to chlorocyanoketene **111**.[30] The requisite precursor **110** was prepared as described in Figure 9. When **110** was refluxed in benzene with a stoichiometric amount of dicyclohexylcarbodiimide (DCC; **112**), one obtained an 88%

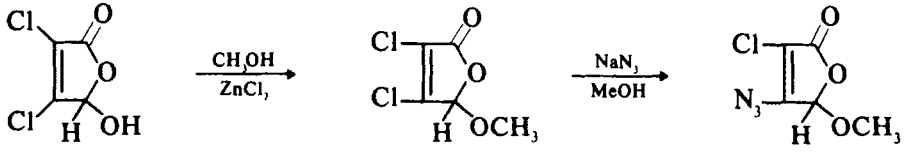


Figure 9 **110**

yield of **113**.[30] Similarly, the reaction of **110** with formimidate **114** produced azetidinone **115** as one diastereomer (with stereochemistry undefined) in 48% yield.[30] The hypothesis of a zwitterion intermediate **116** was supported by the following experiment.[30] Treatment of azidolactam **117** in refluxing benzene afforded β-lactam **119** as one diastereomer (with stereochemistry undefined) in 58% yield. The mechanism for the formation of **119** can best be described as proceeding through zwitterion **118**, as illustrated in Figure 10.[30]

Moore and co-workers expanded the cycloaddition of chlorocyanoketenes and formimidates in the synthesis of β-lactams to include alkylcyanoketenes.[31,32] The latter were derived from substituted quinones by pyrolysis, as described in Figure 11.[31] The experimental procedure was simply to pyrolyze either the butenolide or quinone in benzene or chlorobenzene in the presence of the formimidate or thioformimidate, affording the β-lactam in greater than 80% yield (Figure 11).[31] In addition, these investigators reported an important synthetic use for this series of azetidinones. For example, azetidinone **130** was treated with zinc and acetic acid, giving the dehalogenated β-lactam **150** which could be converted to its anion **150a** and subsequently alkylated with a variety of electrophiles, as described in Figure 12.[31]

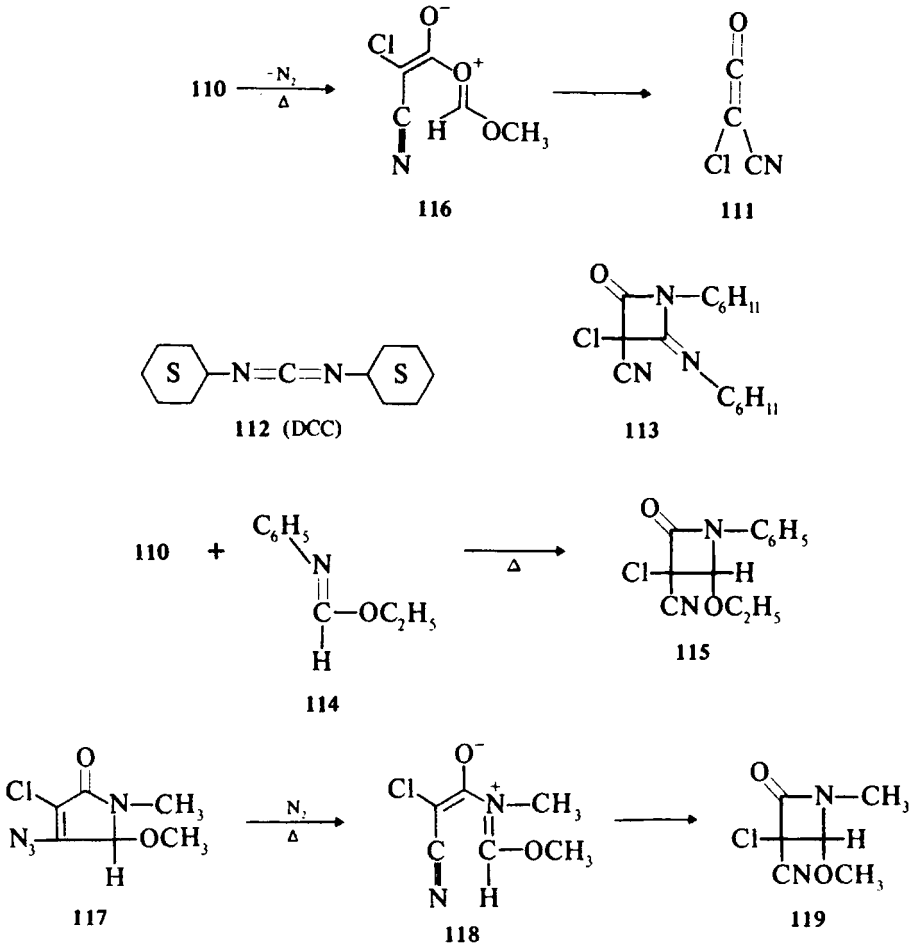
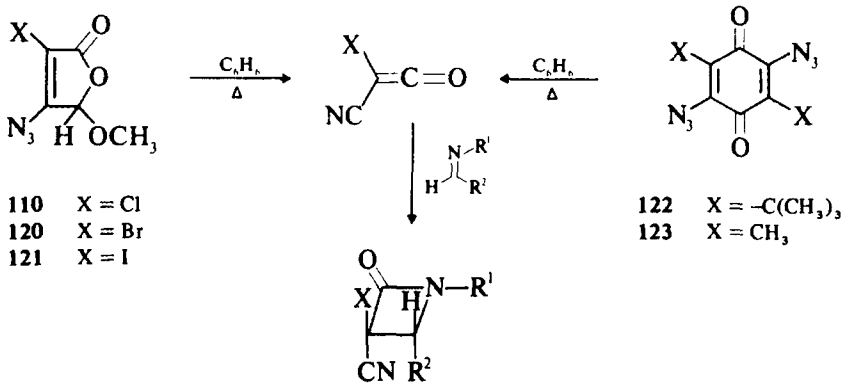


Figure 10

As mentioned earlier, the reaction of halocyanoketenes derived from butenolide is stereospecific. The orientation of the R^2 substituent and of the chloro and cyano groups is represented in structure **161**; this orientation is based on ^{13}C chemical shifts of a variety of compounds derived from chlorocyanoketene **111** and azomethine **160**.[33] The mechanism proposed to account for the specificity is illustrated in the intermediate **162**. The pathway for the formation of β-lactams from lactam **163** was supported by a competitive experiment using **163** and thioimidate **164**.[34] After 96% conversion to product, there was a 1.9:1.0 ratio of **165** to **166**. If **110** was reacted with an equimolar amount of **167** and **164**, after 96% conversion to product the ratio of **165** to **166** was 3.3:1.0. These data support two modes of reaction for **163**: (1) intramolecular cyclization of zwitterion **168** to **166**; (2) conversion of **168** to chlorocyanoketene **111**, which cyclizes intermolecularly to give either **166** or **165**. This pathway is illustrated in Figure 13.[34]



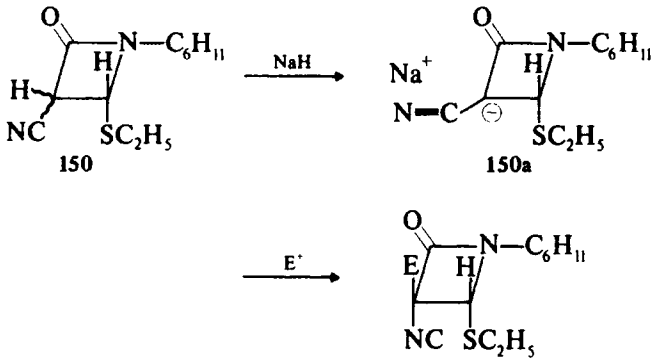
110 X = Cl
120 X = Br
121 X = I

122 X = $-C(CH_3)_3$
123 X = CH_3

	X	R^1	R^2	Yield (%)
124	Cl	C_6H_{11}	OEt	94
125	Br	C_6H_{11}	OEt	85
126	I	C_6H_{11}	SEt	66
127	Cl	C_6H_{11}	SEt	78
128	Br	C_6H_{11}	SEt	63
129	Cl	C_6H_{11}	SMe	85
130	Cl	C_6H_{11}	SiPr	50
131	Cl	C_6H_{11}	StBu	82
132	Cl	C_6H_{11}	SnBu	67
133	Cl	C_6H_{11}	SPh	47
134	Cl	C_6H_5	SMe	70
135	Cl	C_6H_5	SEt	46
136	Cl	C_6H_5	SiPr	56

	X	R^1	R^2	Yield (%)
137	Cl	C_6H_5	S-Bu	72
138	Cl	C_6H_5	S-tBu	56
139	Cl	C_6H_5	SPh	36
140	Me	C_6H_{11}	SMe	40
141	Me	C_6H_{11}	SEt	50
142	Me	C_6H_{11}	S-tBu	28
143	Me	C_6H_5	SEt	80
144	Me	C_6H_5	SPh	59
145	*t*-Bu	C_6H_{11}	SMe	35
146	*t*-Bu	C_6H_{11}	SnBu	29
147	*t*-Bu	C_6H_{11}	S-tBu	34
148	*t*-Bu	C_6H_5	SEt	20
149	*t*-Bu	C_6H_5	SPh	31

Figure 11



Compound	E⁺	E	Yield (%)
151	CH_3I	CH_3	91
152	CH_2=$CHCH_2Br$	CH_2=CH–CH_2	59
153	CH_3COCl	CH_3CO	29
154	C_6H_5COCl	C_6H_5CO	43
155	CH_3OCOCl	CH_3OCO	90
156	C_6H_5CHO	C_6H_5CH | OH	60
157	$(CH_3)_3CN$=C=O	$(CH_3)_3CNHCO$	72
158	CH_2=$CHCN$	NC–CH_2CH_2	63
159	CH_2=$CHCOCH_3$	$CH_3COCH_2CH_2$	92

Figure 12

Joullie et al. reported that *t*-butylcyanoketene **170**, derived from quinone **169** by pyrolysis, reacted smoothly with benzylidinemethylamine **171** in refluxing toluene to give azetidinone **172** in 75% yield.[35] When this reaction was repeated in liquid sulfur dioxide at −78°C, compounds **173** and **174** were obtained in 13 and 22.5% yields, respectively.[35]

Schaumann and Mrotzek reported that the reaction of one equivalent of **170** with three equivalents of **171** at −17°C in toluene afforded a mixture of **175** and **176**, which were fractionally crystallized in yields of 42 and 31%, respectively.[36] Subsequently, compound **175** could be pyrolized to give azetidinone **172** in 15% yield (Figure 13a).[36]

An elegant generation of thioalkyl-substituted ketenes and their application to the construction of β-lactams was reported by Georgian and co-workers.[37] They found that diazomalonate **177** reacted smoothly under photolytic conditions in the presence of *N*-benzylidineaniline **178** to give **179** in quantitative yield. This reaction could also be carried out under thermolytic conditions to afford a quantitative yield of **179**.[37] Similarly, azetidinones **181** and **183** were prepared either under photolytic or pyrolytic conditions.[37] These products and a pathway for their formation are illustrated in Figure 14.[37]

Kagan and co-workers reported the generation of ketenes from the reaction of α-haloacetate esters with zinc.[38–41] For example, the reaction of methyl α-bromoisovalerate **184** with zinc metal in the presence of Schiff base **17** afforded

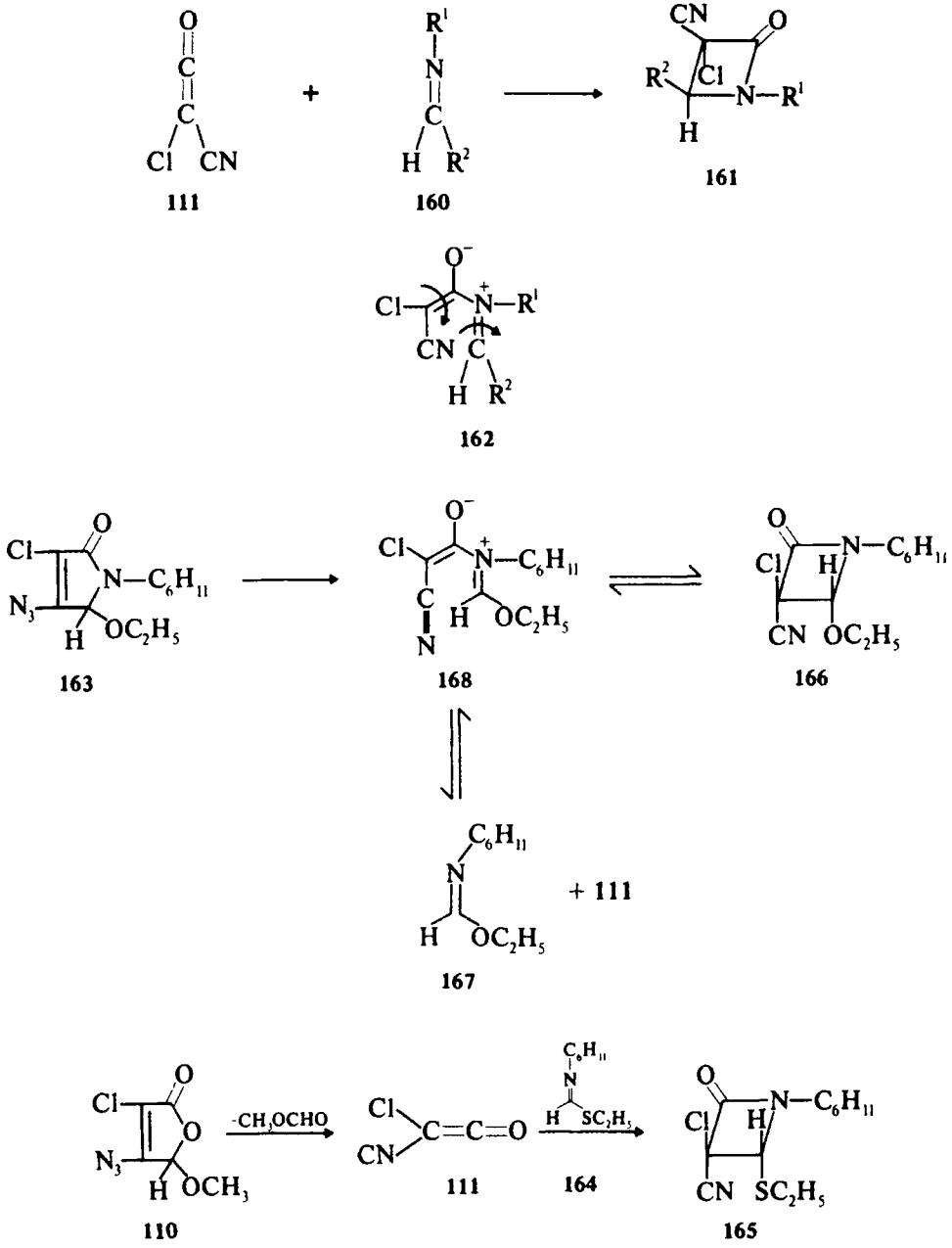
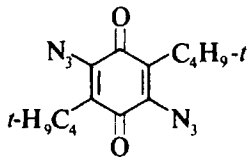
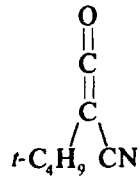


Figure 13

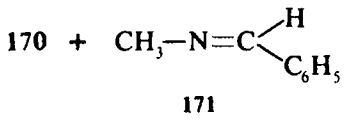
185 and 186 as a 55:45 mixture of *cis/trans* products. Alternately, 186 could be prepared stereospecifically in 78% yield from the pyrolysis of ethoxyacetylene (187), in the presence of 17.[38,42] These data suggest that the zinc-haloester-



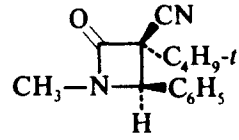
169



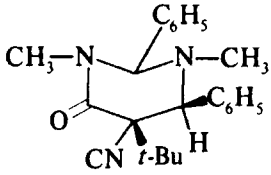
170



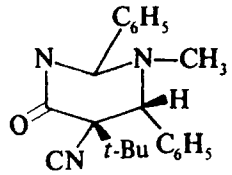
171



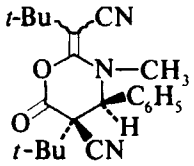
172



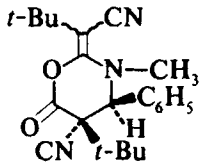
173



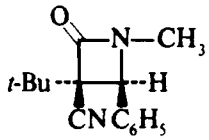
174



175



176



172

Figure 13a

azetidinone formation may proceed by either the ketene [2+2] cycloaddition reaction or a nonconcerted two-step process (Figure 15).

In an attempt to synthesize unnaturally fused β-lactams with antimicrobial activity, Kametani and co-workers reported the construction of tetracyclic azetidinone **190**.[43] They found that phenoxyketene **188**, generated *in situ* from phenoxyacetyl chloride with triethylamine, reacted smoothly with thioimidate

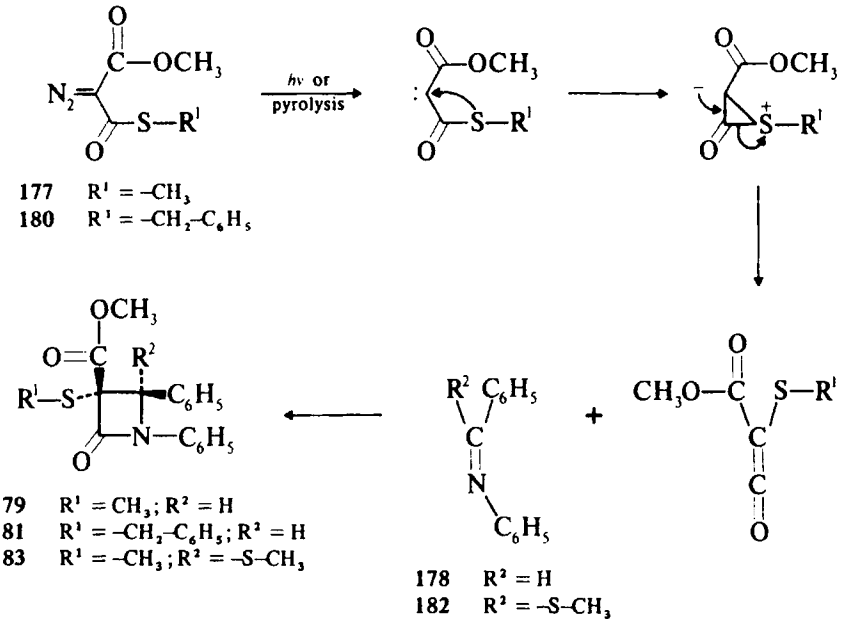


Figure 14

189 in methylene chloride at room temperature to give **190** stereospecifically in 92% yield.[43]

Viehe et al. found that immonium chloride **191** reacted with diphenylketene to give **192** in 72% yield.[44]

Colens and Ghosez reported a fascinating reaction of α-haloenamines affording an exocyclic olefinic azetidinone.[45] These investigators found that **193** reacted with **194** in chloroform at room temperature to afford the azetidinone salt **195**, which was demethylated to **196**. This in turn was hydrolyzed to give the unusual exocyclic olefinic azetidinone **197**.[45] Interestingly, only a catalytic amount of **194** is required for the reaction to proceed, since the fluoride ion that is generated from **196** reacts rapidly with **193** to regenerate **194**. These transformations, as well as a plausible pathway for the formation of **196**, are illustrated in Figure 16.[45]

One of the few benzoazetidinones synthesized and stable enough to be isolated was reported by Olofson and co-workers.[46] They found that the *N-t*-butylanthranilium perchlorate salt (**198**), upon treatment with one equivalent of triethylamine in methylene chloride followed by addition of HN_3, afforded an 84% yield of **199**.[46]

Kretscher and Warrener[48] reported the [2+2] cycloaddition reactions of the strained azetidinone **213**, derived from *N*-methylpyridone **212**.[47] For example, the reaction of **213** with cyclopentadienone **214** afforded in good yield a 1:1 adduct of the *exo-anti* isomer **215** and the minor *endo-anti* isomer **216**. The major isomer **215** was fractionally crystallized from benzene–petroleum ether. Interestingly, irradiation of **215** afforded the decarbonylated product **217**. If compound **217** was exhaustively photolyzed, it fragmented to **218** and the nonisolable azetidinone

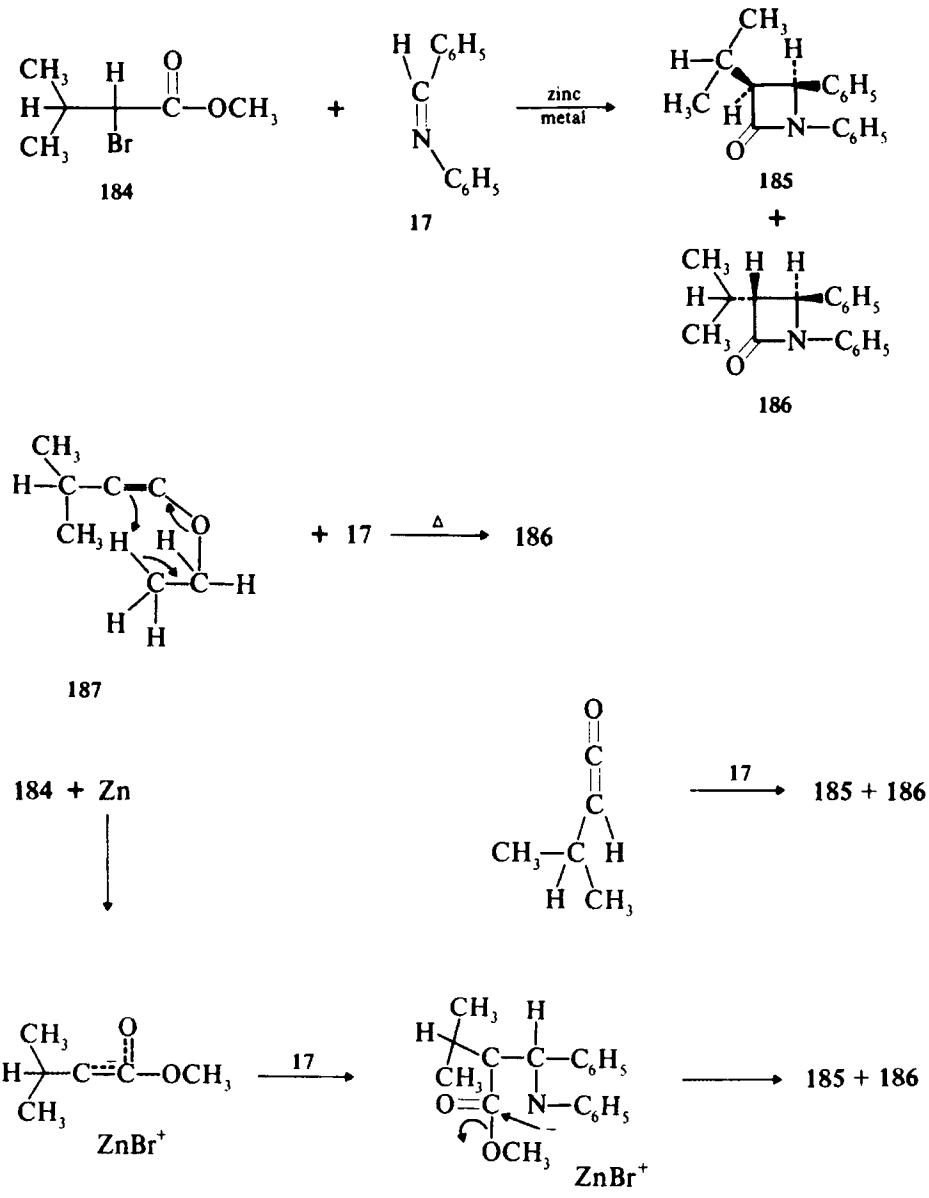
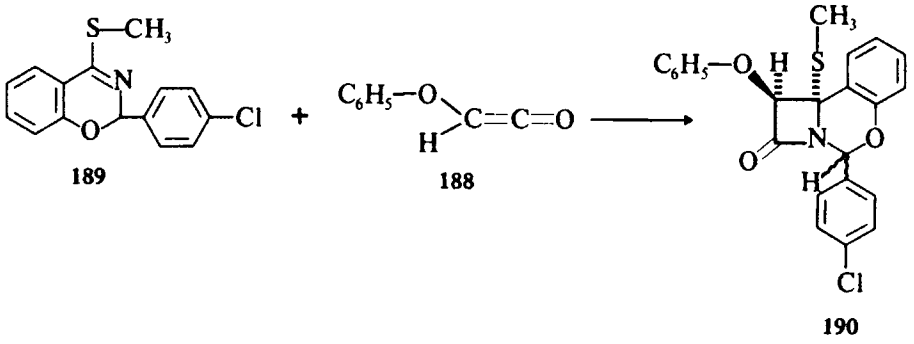
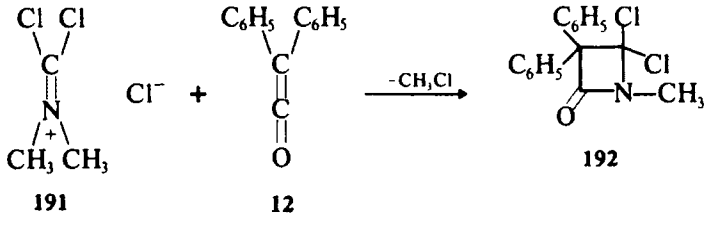


Figure 15

219.[48] Evidence for the formation of **219** arises from the acrylamides **220** and **221**, produced by irradiation **217** with methylamine in tetrahydrofuran. These transformations are illustrated in Figure 17.[48]

A variety of miscellaneous [2+2] cycloaddition reactions utilizing ketenes and unusual aromatic and/or alkyl Schiff bases in a traditional azetidinone synthesis





has been reported. The chromone Schiff base **200** reacted with chloroketene to give azetidinones **201** and **202** in 37 and 35% yields, respectively.[49] The vanillin Schiff base **203** underwent cycloaddition with an excess of diphenylketene **12** to afford **204** in 80% yield.[50] The thiazine **205** reacted with diphenylketene **12** to give **206** in 14% yield.[51] Bachi and Rothfield reported the construction of penicillin and cephalosporin derivatives through the classical ketene–azomethine [2+2] cycloaddition reaction.[52] Representative of their investigation was the reaction of **207** with diphenylketene **12** in refluxing benzene to afford (after chromatography) a 62% yield of **208**.[52] These reactions are illustrated in Figure 17a.

A rather convincing study was carried out by Huisgen, Davis, and Morikawa illustrating the stoichiometric dependence of the [2+2] cycloaddition, ketene–Schiff base reaction on the fundamental substrates **171** and **12**.[54] When ketene **12** was added (in acetonitrile) to an excess of **171** (13 equivalents), 82% of β-lactam **209** and 6% of the 2:1 adduct **210** were obtained. In contrast, when **171** was added to 10 equivalents, of **12** one observed a striking reversal in product distribution, namely an 81% yield of **210** and a 19% yield of **209**. The same result was obtained in benzene. In addition, β-lactam **209** did not undergo reaction with **12** even at 140°C. These results suggest that zwitterion **211** is a common intermediate. With a limited amount of ketene, it closes to the azetidinone, but when there is an excess of ketene, zwitterion **211** is trapped, affording **210**. These compounds and a proposed pathway for their formation are illustrated in Figure 18.[54]

Barr and Storr reported that imidoylazimine **222** reacted with diphenylketene (**12**) in benzene at room temperature to give azetidinone **223** in quantitative yield.[53]

The utilization of nitrones in the construction of β-lactams was first reported by Kinugasa and Hashimoto.[55] These investigators found that copper phenylacetylide

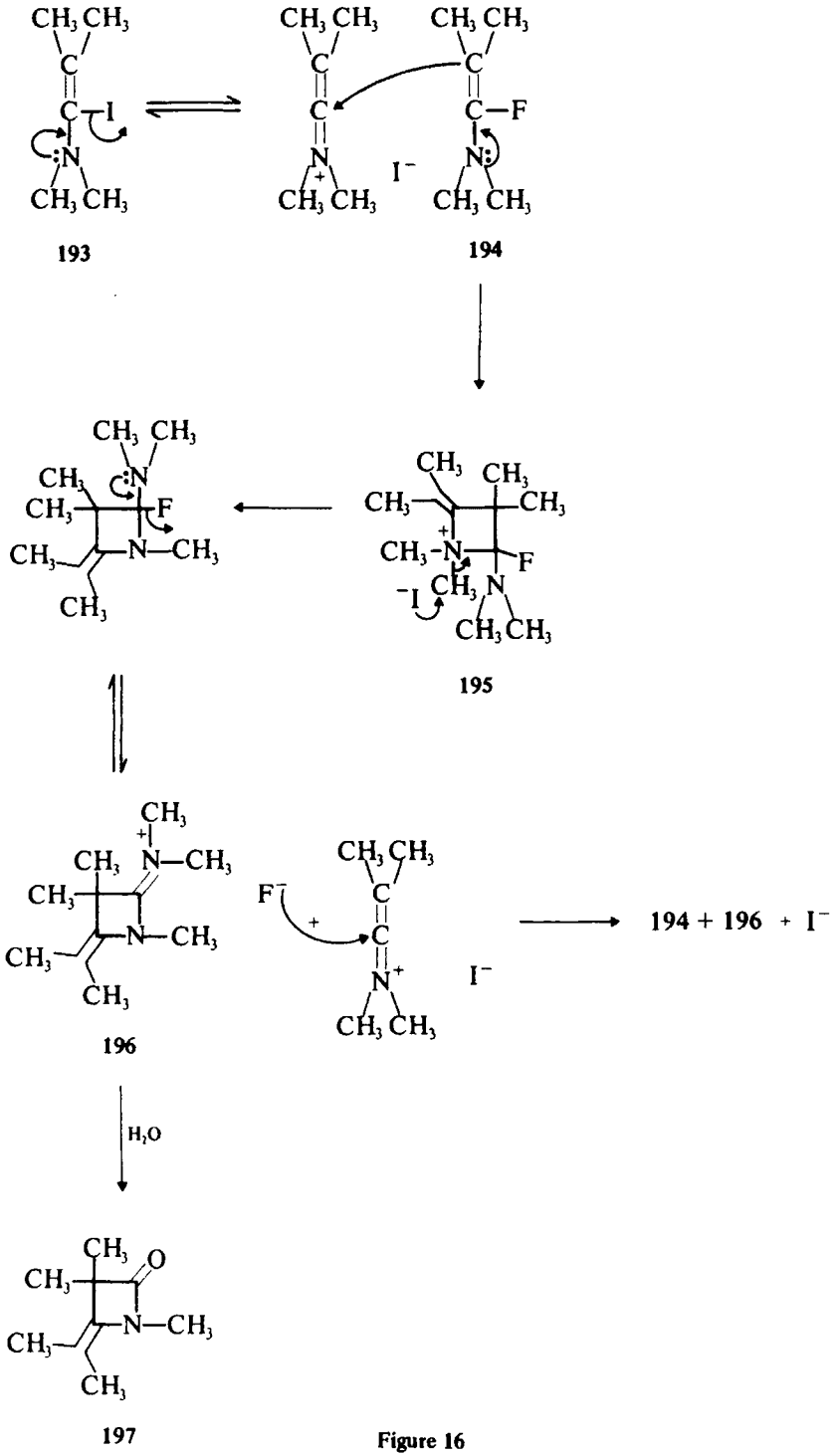
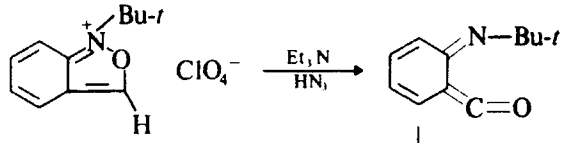
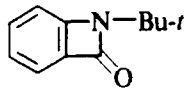


Figure 16

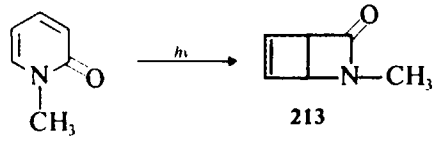


198

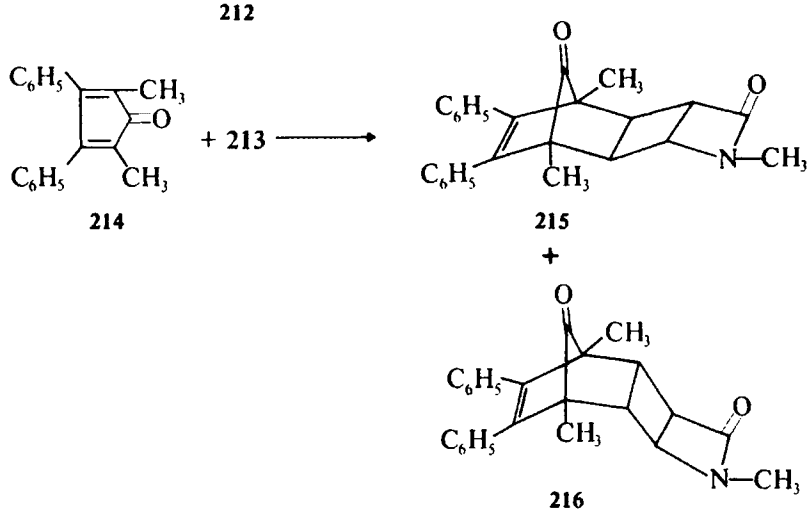


199

224 reacted with *N*-benzylideneaniline-*N*-oxide 225 stereospecifically to give the *cis*-azetidinone 226.[55] Ding and Irwin reported a more extensive study of the reaction of nitrone with copper acetylides.[56] For example, if 224 and 225 were reacted in pyridine 228, one obtained the *cis* and *trans* isomers 226 and 227 in a 5 : 3 ratio.[56] This reaction sequence was amenable to the synthesis of fused β-lactams. Thus the reaction of 224 with tetrahydropyridine-1-oxide 229 afforded 230 as the *cis* isomer. Similarly, the reaction of 224 with 4,5,5-trimethyl-Δ^1-pyrrolin-1-oxide 231 afforded 232 as the trans isomer (Figure 19). These investigators suggested that the initially formed product in the acetylide–nitrone reaction is the *cis*-β-lactam and that, with increased reaction time and with base present, the product undergoes base-catalyzed epimerization, giving the trans product. A plausible pathway for azetidinone formation is illustrated in Figure 19a.[56]



212 213



214 215 216

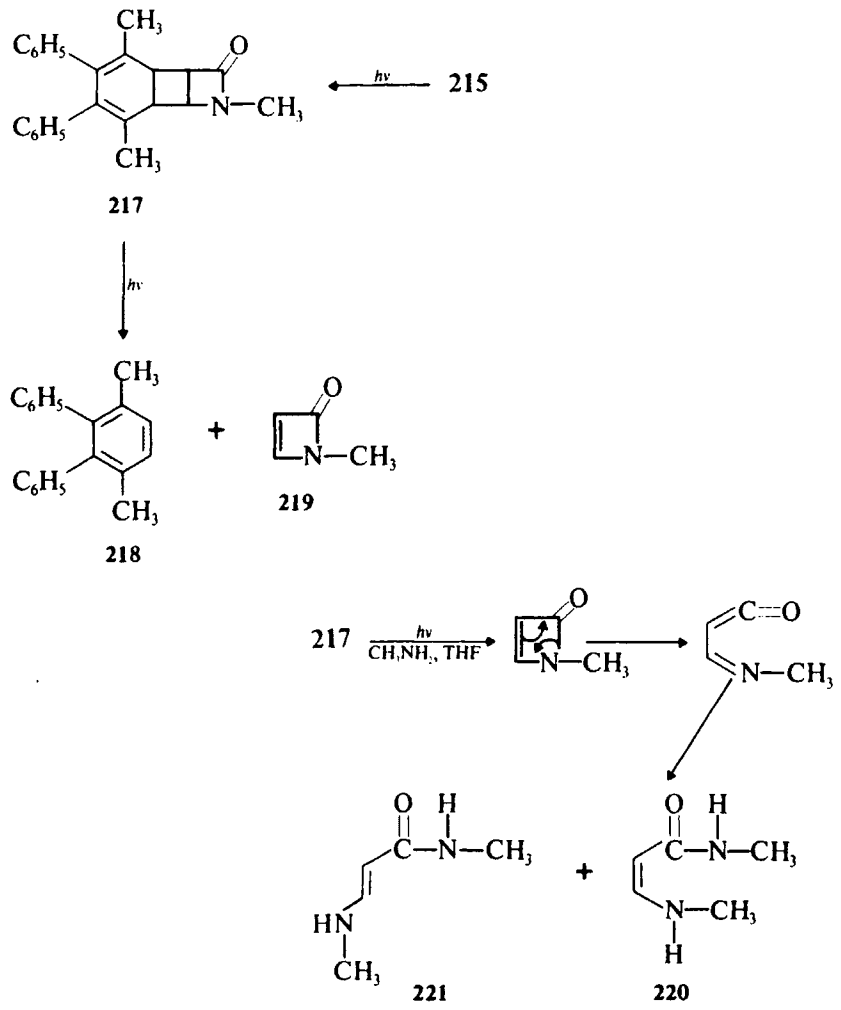
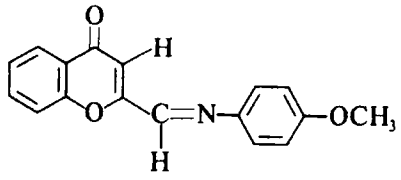


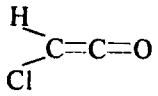
Figure 17

Thus far this review has concentrated on the achievements of investigators in the incorporation of appropriate substituents and functional groups in the control of stereochemistry. An architectural element that nature has integrated into the construction of biologically active compounds is chirality. The exquisite specificity by which natural products carry out their function is the result of this refined spatial order of atoms. The naturally occurring β-lactams (e.g., penicillins, cephalosporin C, 7-α-methoxycephalosporin C., thienamycin, clavulanic acid, and the nocardicins) are no less chirally specific in their biological activity than other families of natural products. Indeed, the unnatural antipodes of penicillins and cephalosporins are biologically inactive. As a result, the control of chirality in the synthesis of β-lactams is a major issue to which investigators have addressed their

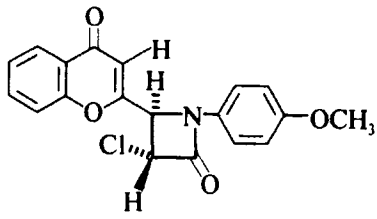


200

+

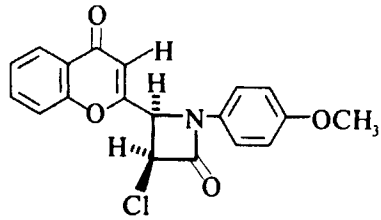


30

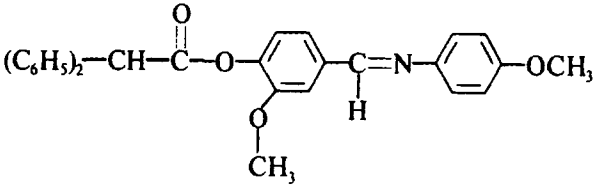


201

+

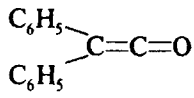


202

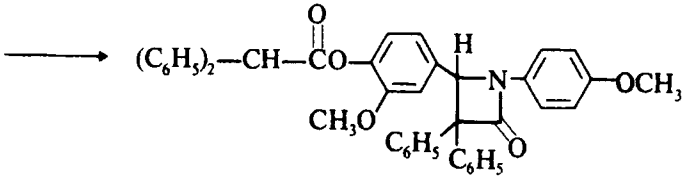


203

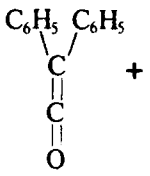
+



12

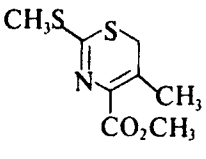


204

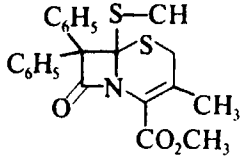


12

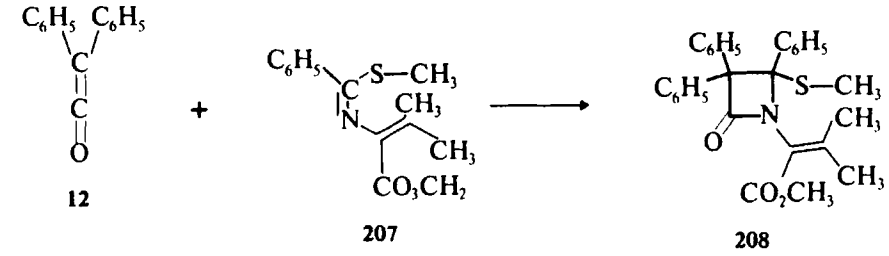
+



205

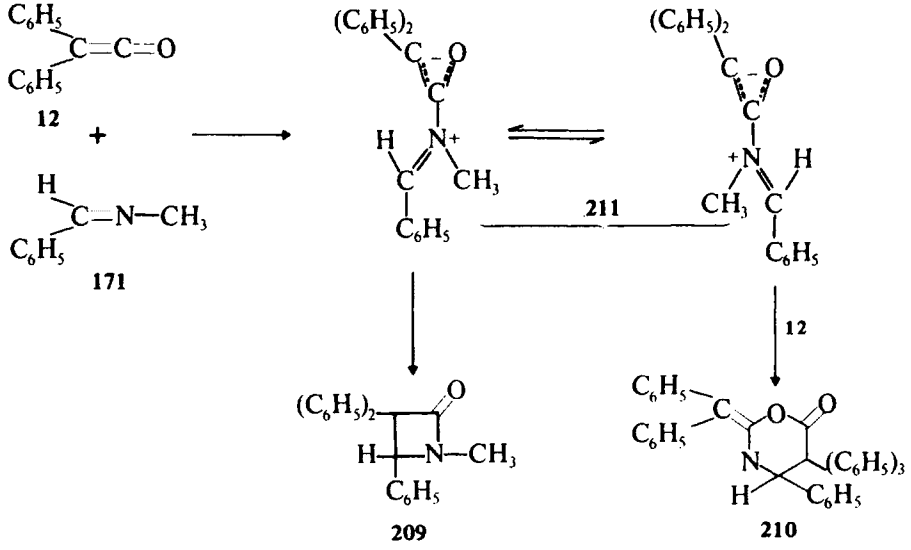


206



12 207 208

Figure 17a

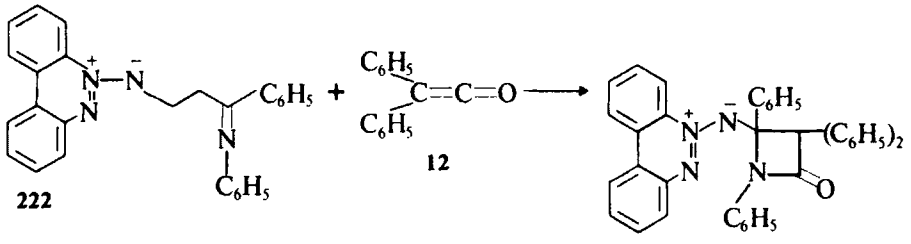


12 171 211 209 210

Figure 18

attention. As will be shown later (Section II), a number of investigators have pioneered chirally specific syntheses of β-lactams.

Efforts have been made at controlling chirality in the [2+2] ketene–azomethine cycloaddition. Belzecki and Krawczyk reported the reaction of chiral carbodiimides with prochiral ketenes to afford chirally selective products.[57,58] For example, the



222 12 223

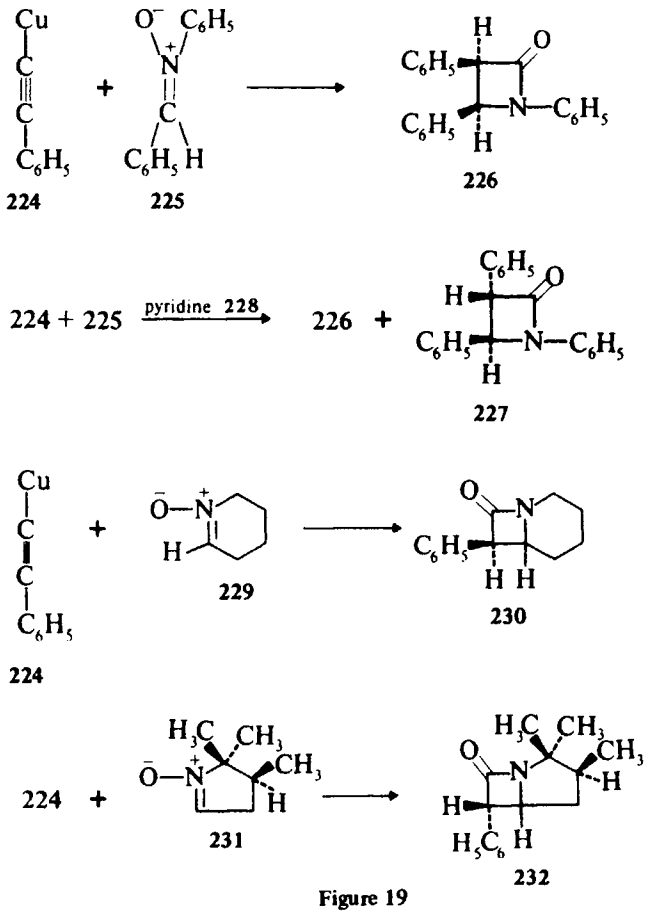


Figure 19

reaction of (−)-menthylcarbodiimide **233** with methylphenylketene **234** afforded 37% of **235** and 3% of the diastereomer **236**, which were separated by silica gel chromatography. Carbethoxyketenes **237** and **238**, upon reaction with carbodiimide **233**, afforded products **239** and **240** in 64 and 74% yield, respectively, with complete asymmetric induction.[57] In addition, asymmetric carbodiimide **241** reacted with **237** to give **242** in a regioselective and chirally selective manner (Figure 19b).[57,58]

2. The Reaction of Acid Halides with Azomethine Substrates

As mentioned earlier, the major impetus for the development of new synthetic methods for the construction of β-lactams was the isolation and structural determination of penicillin **1** and cephalosporin C **4**. Early in the investigation of these naturally occurring β-lactams it became apparent that the β-$C_{6,7}$-amido or amino

substituent was essential for antimicrobial activity. This restricted the utility of the ketene–imine cycloaddition reaction in that an appropriate nitrogen-substituted ketene had to be incorporated in the cycloaddition reaction. This issue was briefly addressed in Section I.1 with the description of the *in situ* generation of isocyanoketene **99** and azidoketene **107** from the appropriate precursor acid halide.[28,29] The most impressive and versatile stratagems made use of the "amino–amido" functional requirement by either generating *in situ* the appropriate ketene from the acid halide for the ketene–imine reaction and/or reacting the acid halide directly with the imine by pathway 2, giving the β-lactam in two steps (Figure 20). It was imperative that the prerequisite amine function (i.e., **243**) be amenable to conversion to the free amino or amido group after cycloaddition (e.g., **244** → **245** → **246** or **244** → **246**) (Figure 20).

Sheehan and Ryan first reported the utilization of phthalimidylacetyl chloride **247** with Schiff base **17** in the presence of triethylamine to give the cycloaddition product **248** in 50% yield.[59] The advantage of the phthalimido substituent was dramatically illustrated by the acid-catalyzed conversion of **248** to the free amine (**249**) and subsequent reacylation to afford the amide **250**.[59] Similarly, thiazoline **251** was reacted with **247** to afford β-lactam **252**.[60] In addition, Sheehan et al. reported the synthesis of 5-phenylpenicillin **256** by the cycloaddition of **253** and **254** to give **255**, which was converted to **256**, as described in Figure 21.[61,62]

The striking incompatibility between the drastic conditions required to hydrolyze the phthalimido group to the free amine and the propensity of the β-lactam function of fused systems as penicillins to undergo hydrolysis necessitated the development

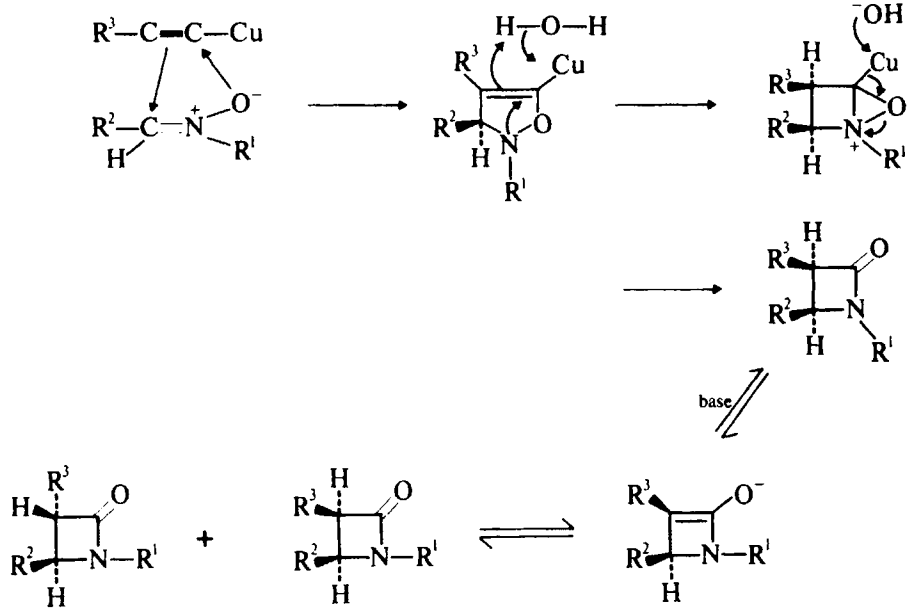
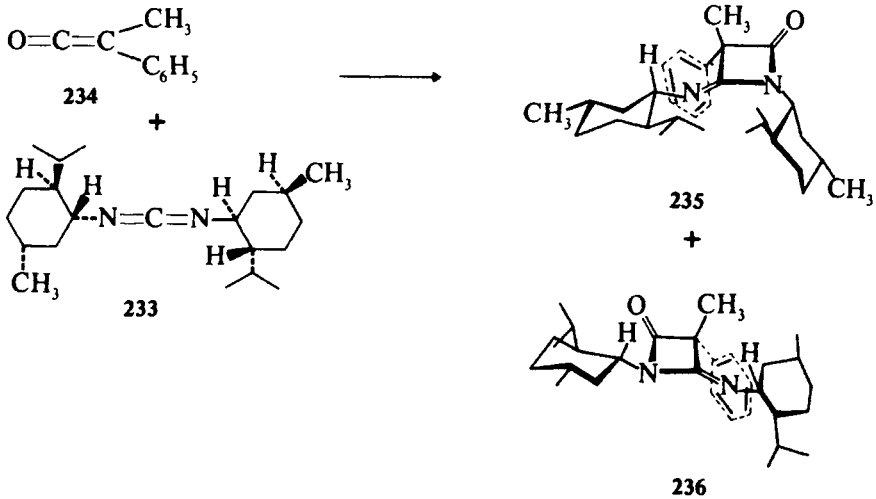
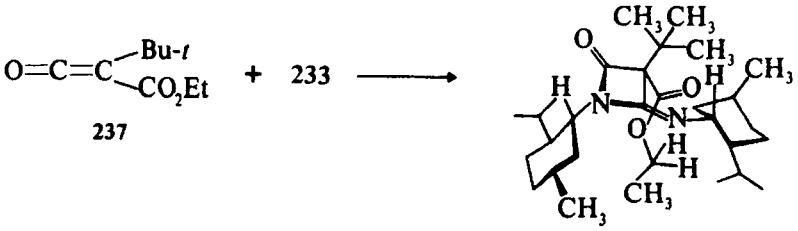
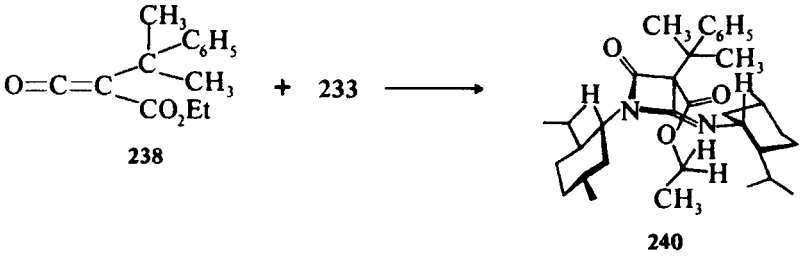


Figure 19a. Pathway for β-lactam formation.







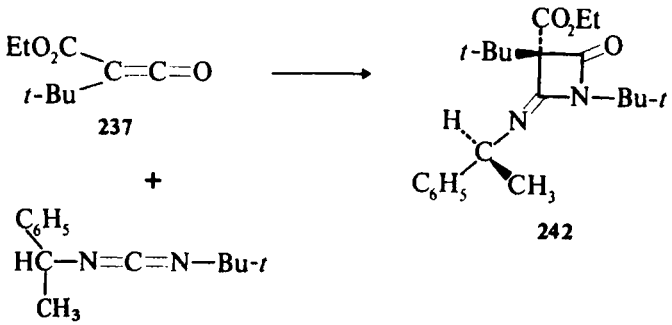


Figure 19b

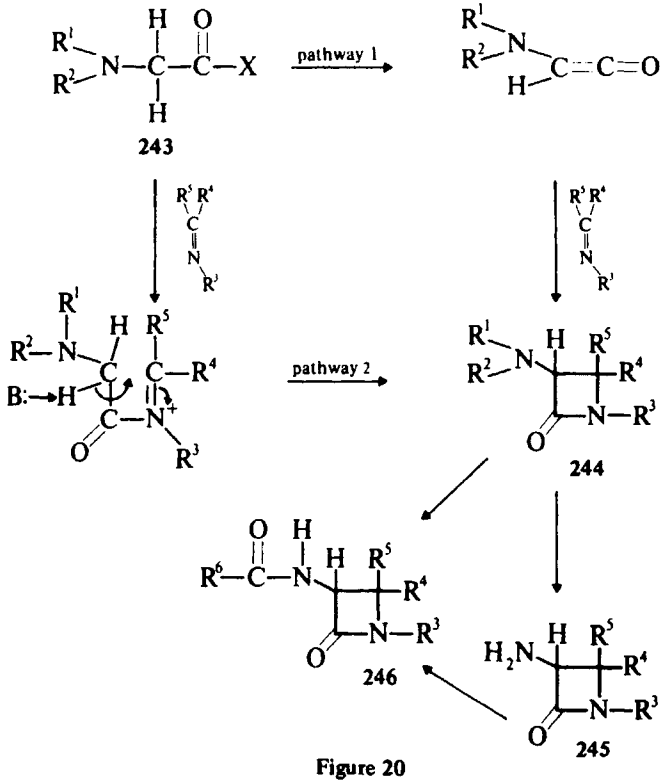


Figure 20

of another "latent amine function" if the cycloaddition route were to lend itself to the ready synthesis of 3-amino- or 3-amidoazetidinones. Bose and co-workers introduced the azido function to the construction of β-lactams via the [2+2] ketene–imine cycloaddition in the elegant synthesis of 6-epiphenoxymethylpenicillin methyl ester **261**.[63] Bose made the important discovery that azidoacetyl chloride **257** reacted with thiazoline **258** to afford only the *trans*-epiazidopenicillin **259** in 8% yield.[63] The azido derivative, in turn, was hydrogenated with Adam's catalyst to give the epipenicillin nucleus **260**, which was acylated with phenoxyacetyl chloride to produce **261** (Figure 22).[63] The low yield of the cycloaddition step (**257** + **258** → **259**) did not diminish the immense impact that this simple cycloaddition had on the chemistry of β-lactams. In one step the second synthesis of penicillin was recorded; the azido function was recognized as the preferred amine precursor; and, most important, a pathway was established for the rapid construction of synthetic β-lactams with the greatest potential for antimicrobial activity.[63]

In an attempt to prepare the isomeric penicillin skeleton **290**, thiazoline **289**, derived from α-mercaptoisobutyraldehyde **287**, ammonia, and *t*-butyl glyoxylate **288**, was reacted with **257**. Surprisingly, under the conditions that afford epipenicilin **259**, there was no evidence for isomeric penicillin **290** being formed. This failure may have been the result of steric interaction with the *t*-butyl ester

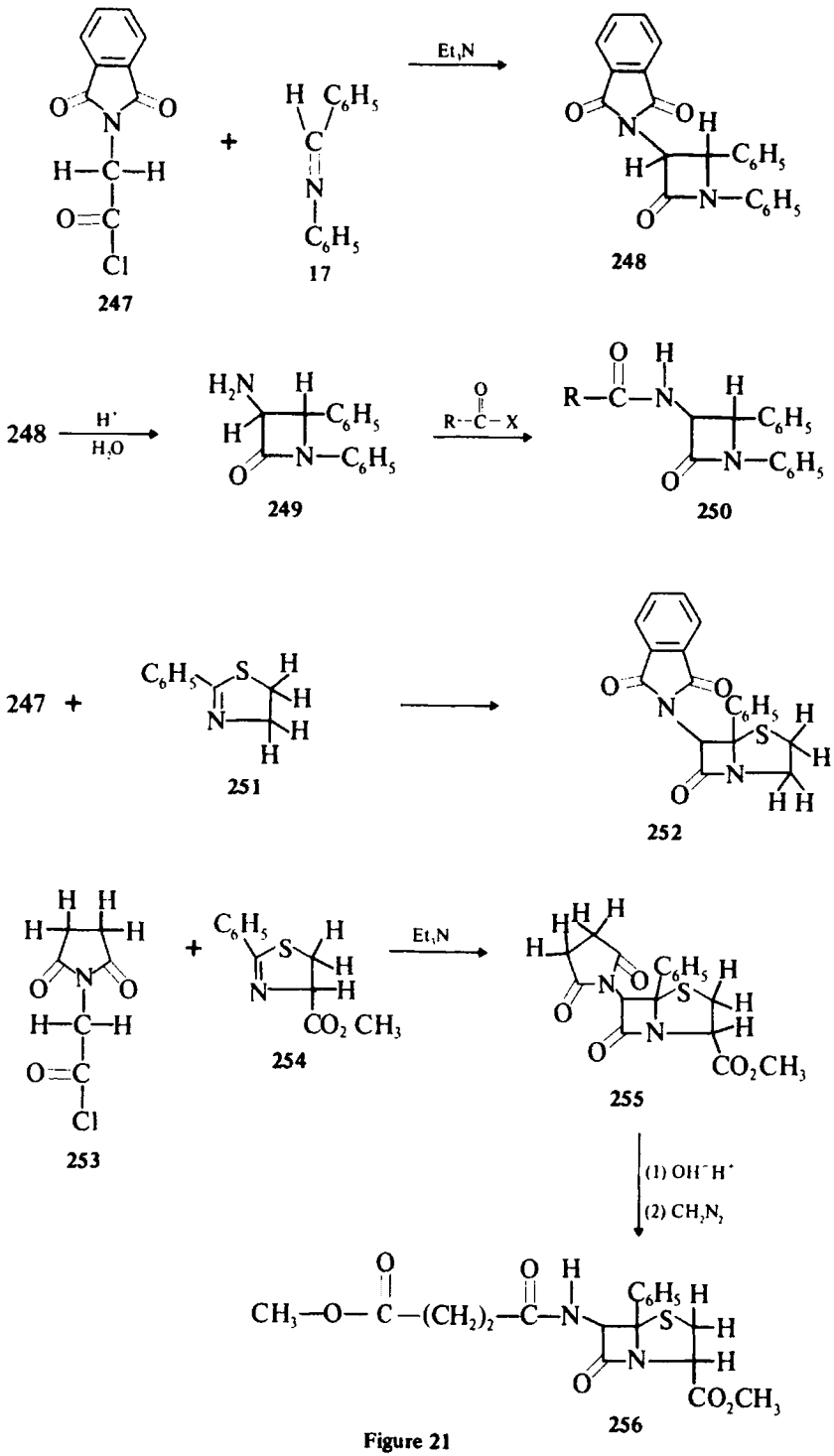

Et3N
247
17
248
H+
H2O
249
250
251
252
253
254
255
(1) OH⁻ H⁺
(2) CH2N2
256

Figure 21

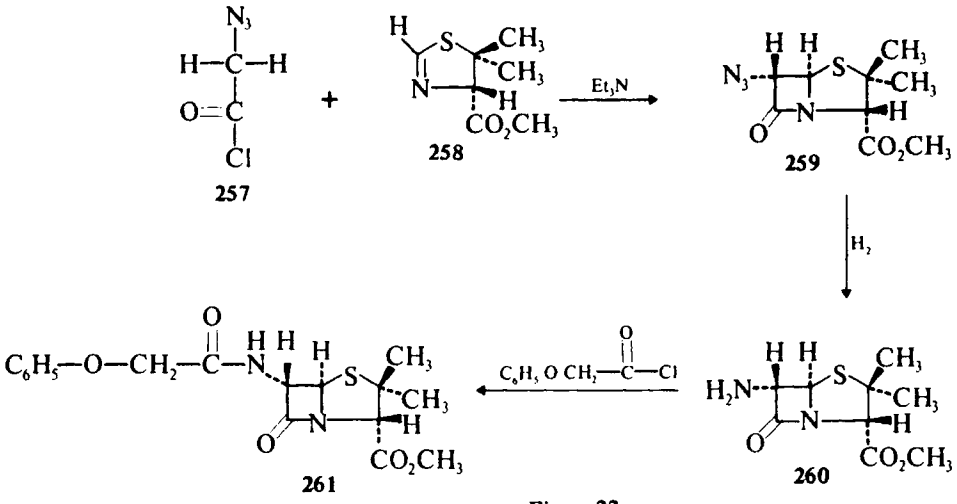


Figure 22

and the "ortho" *gem*-dimethyl group.[64] These transformations are illustrated in Figure 23.

Bose and co-workers pursued the azidoacetyl chloride reaction with cyclic azomethines in the hope of developing a synthetic analog of penicillins and cephalosporins with antimicrobial activity.[65] These investigators reacted thioimidate **291** with **257** to afford **292** in 31% yield.[65] Similarly, azathioimidate **293** was treated with **257** to give **294** in 60% yield.[66] More recently, Bose and co-workers reported the reaction of aromatic thioimidate **295** with **257** to afford **296** in 60% yield.[67] This azidoazetidinone was reduced to the amine **297** and reacetylated with phenoxyacetyl chloride to give **298**[67] (Figure 24). Finally thiazoline **258a** was reacted with **257** to afford the fused β-lactam **299**.[68] The advantage of an adduct such as **299** is its potential for desulfurization with Raney nickel to give a monocyclic azetidinone with cis stereochemistry about C_3 and C_4.[68] However, desul-

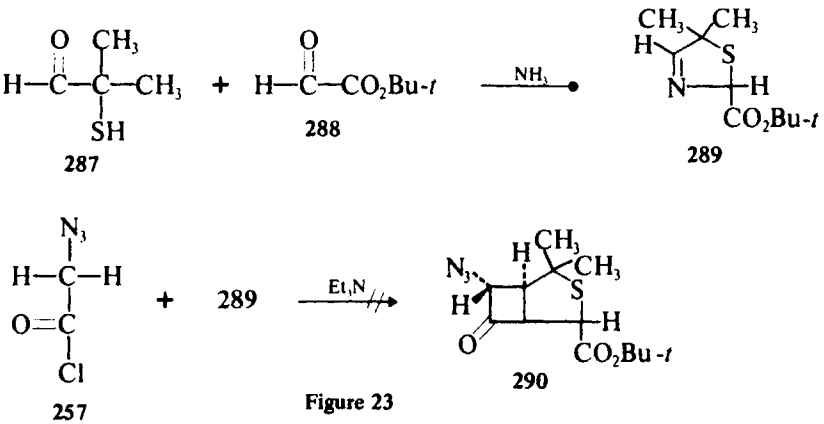


Figure 23

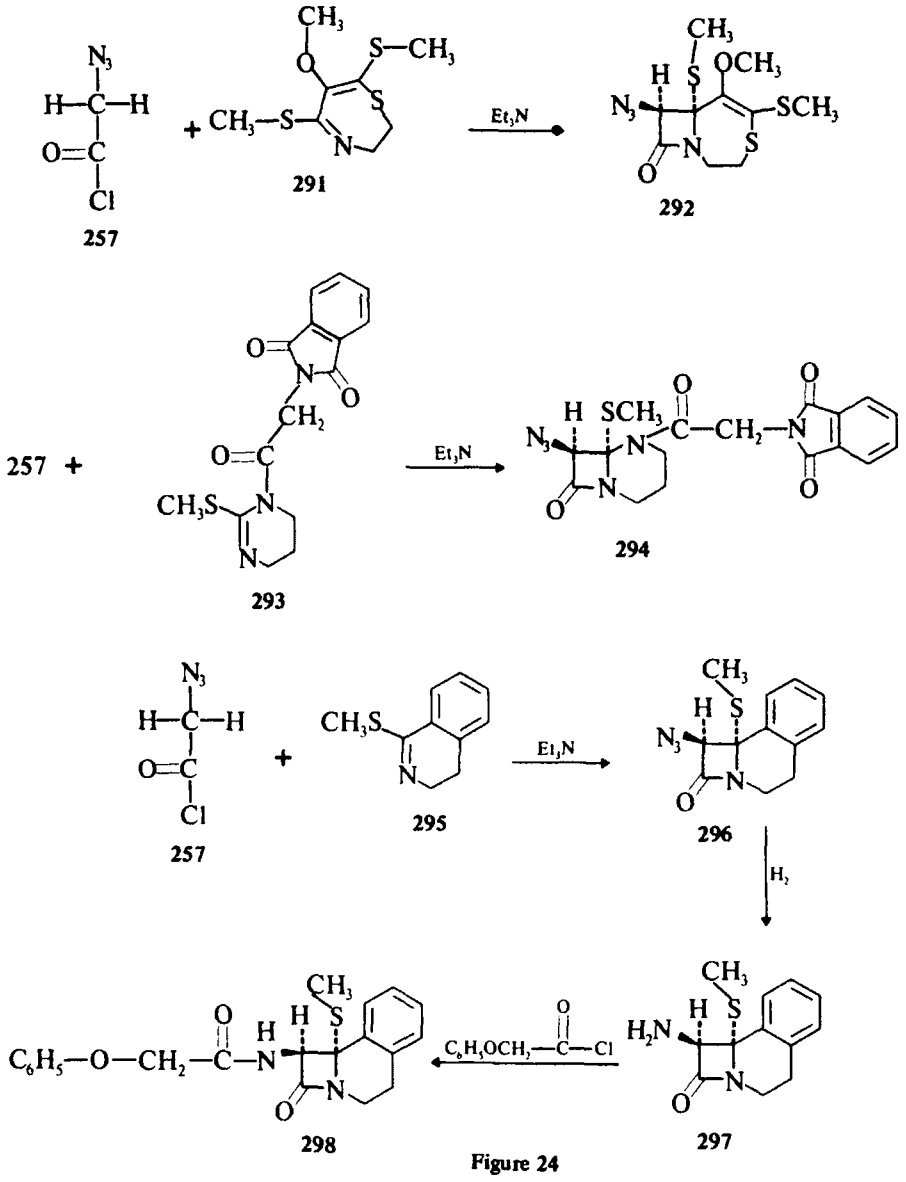
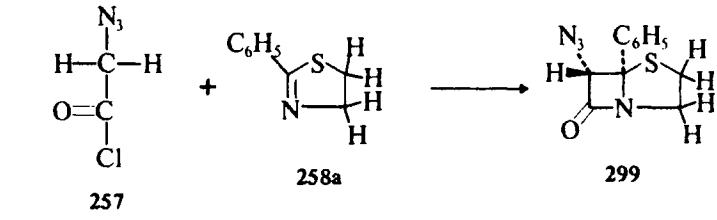


Figure 24

furization of **299** was not reported, no doubt because of azido reduction complications. Nevertheless, methoxy azetidinone **300** underwent desulfurization to afford **301** with inversion of configuration, as depicted in Figure 25.[68]

Bose et al. found that the yield of product could be improved and, more important, that the stereochemistry of the azetidinone (*cis* or *trans*) could be effectively controlled by altering the experimental conditions.[69] If triethylamine and the Schiff base were first placed in the reaction vessel and azidoacetyl chloride **257** was added later, the product distribution favored the *cis* over the *trans* isomer



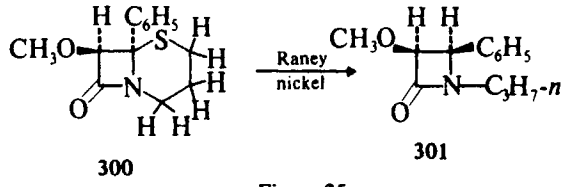


Figure 25

by a ratio of 3:1 (addition 1). Conversely, if **257** was first placed in the reaction vessel and the Schiff base and triethylamine were added dropwise, the product ratio of *cis* to *trans* was 1:3 (addition 2).[69] For example, the reaction of **257** with Schiff base **262** under the former conditions afforded crystalline *cis*-azetidinone **263** in 30% yield. The same reactants under the latter conditions gave *trans*-azetidinone **264** in 65% yield, as illustrated in Figure 26.[69] A variety of azetidinones prepared in this manner are illustrated in Figure 27.[69]

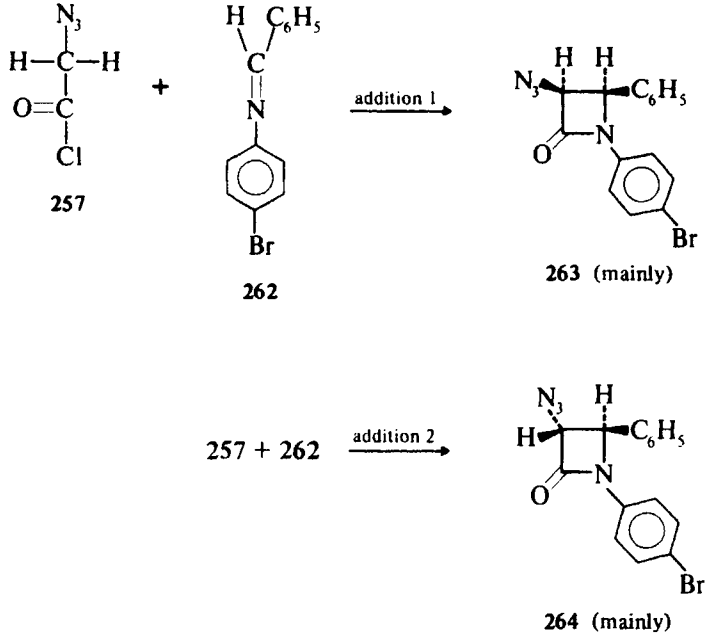
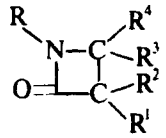


Figure 26



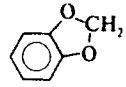
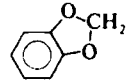
Compound	R	R^1	R^2	R^3	R^4	Stereochemistry
263	*p*-BrC_6H_4	H	N_3	H	Ph	*cis*
264	*p*-BrC_6H_4	H	N_3	H	Ph	*trans*
265	Ph	H	N_3	H	Ph	*cis*
266	Ph	H	N_3	H	Ph	*trans*
267	Ph	H	N_3	H	*p*-$NO_2C_6H_4$	*cis*
268	Ph	H	N_3	H	*p*-$MeOC_6H_4$	*cis*
269	Ph	H	N_3	H	*p*-$MeOC_6H_4$	*trans*
270	*p*-BrC_6H_4	H	N_3	H		*cis*
271	*p*-BrC_6H_4	H	N_3	H		*trans*
272	Ph	H	N_3	H	OEt	*trans*
273	*p*-FC_6H_4	H	N_3	H	Ph	*cis*
274	Ph	H	N_3	H	*p*-BrC_6H_4	*cis*
275	Ph	H	N_3	H	*p*-FC_6H_4	*cis*
276	Ph	H	N_3	Me	Ph	
277	Ph	H	N_3	Ph	Ph	
278	Ph	Me	N_3	H	Ph	
279	Ph	Et	N_3	H	Ph	
280	Ph	Ph	N_3	H	Ph	

Figure 27

The stereochemistry and the experimental factors determining the enhancement of either the *cis* or the *trans* forms of azetidinone have been investigated by Bose and others. The contrast between the stereochemistry of preformed ketene cycloaddition products (*trans*) and that of acid halide–base cycloaddition products (*cis–trans* mixture) led Bose to suggest that the stereochemical distribution of products reflected a competition between the appropriate pathways. In support of this hypothesis, Bose reported an nmr experiment in which the reaction of acetyl chloride **281** with benzalaniline **17** was monitored. From the chemical shift of the benzal hydrogen, the intermediate formed was not the acylimmonium ion **282** but rather the chloroadduct **283**, as shown in Figure 28.[70]

This experiment supported the contention that the "intimate ion" was implicated in the acid chloride–Schiff base cycloaddition. Additional data in support of this hypothesis were reported in the investigation of the products of the azido-substituted acid chloride–Schiff base reaction.[71] For example, **257** reacted with Schiff base **17** (addition 1 or addition 2; see Figure 26) to give azetidinones **263** and **264**, respectively. In sharp contrast, under the identical conditions, β-azidopropionyl chloride **257** and **17** gave no azetidinone product. These results are rationalized in

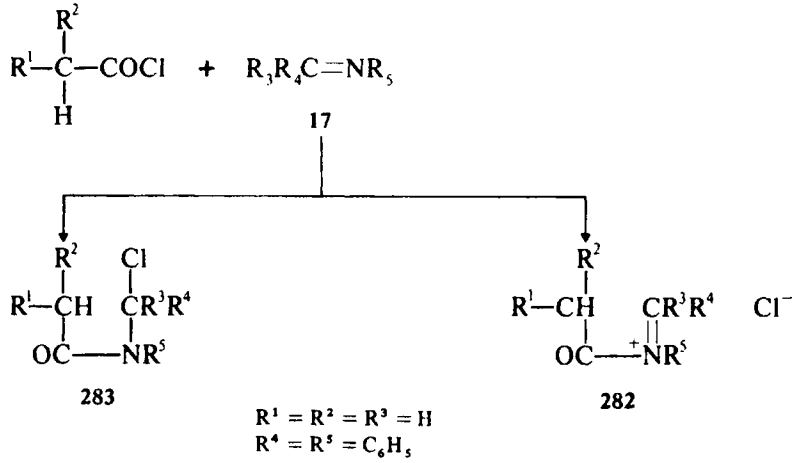


Figure 28

terms of a cyclic ion pair **284**. The azido substrate **257** forms a five-membered ion pair with the C_4-carbon so that collapse to the β-lactam (C_3–C_4 bond formation) is sterically accessible, as shown in Figure 29. However, the β-azido analog **285** forms a six-membered transition ion **286**, which sterically and electronically precludes β-lactam formation, as shown in Figure 30.[71]

A series of C_4-spiro-β-lactams were prepared by the reaction of **257** with the appropriate cyclic ketone Schiff base, as is shown in Figure 31.[69] Surprisingly, triethylamine would not effect azetidinone formation in this series; however, substitution of triethylamine with tripropylamine afforded the spiro-β-lactams in

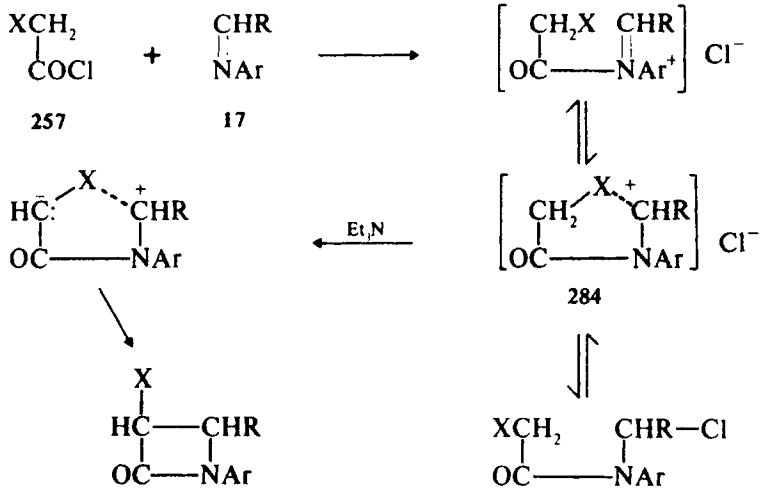


Figure 29

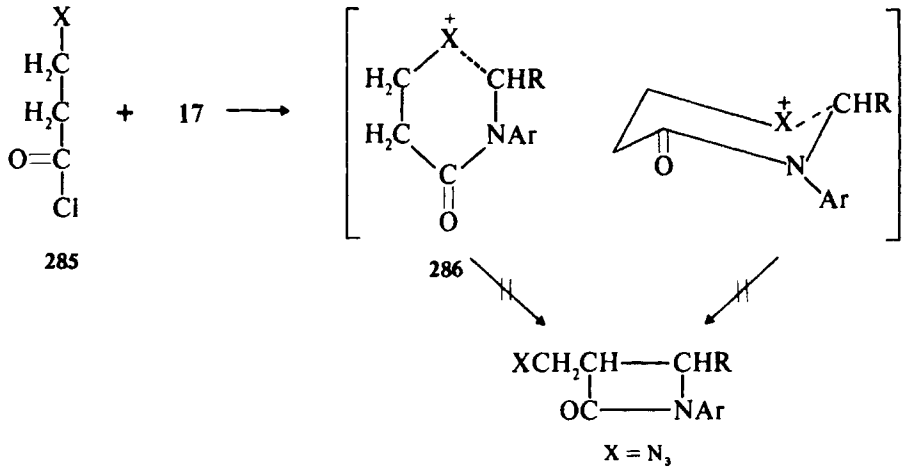


Figure 30

good yield. The various azidoazedidinones, as well as the 3-amino and 3-amido derivatives produced by hydrogenation of the azide function, are illustrated in Figure 32.[69]

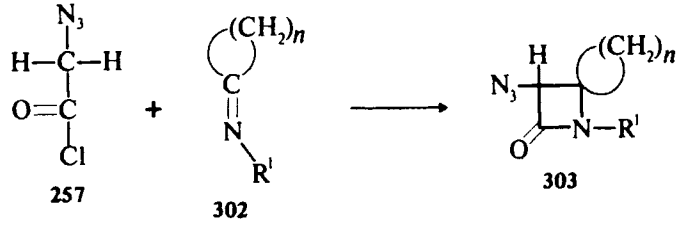
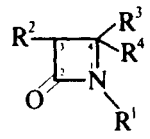


Figure 31

A useful application of the acid chloride–Schiff base cyclization was discovered with the utilization of the trimethylsilyl (TMS) protecting group, affording the free acid function after azetidinone formation.[70] For example, reaction of *p*-aminobenzoic acid **304** with trimethylsilyl chloride and triethylamine afforded the TMS ester **305**, which reacted with *p*-methoxybenzaldehyde to give Schiff base **306**. This in turn reacted with **257** in the presence of triethylamine and methanol to give azetidinone **307** in 80% yield. These transformations are presented in Figure 33.[70]

The versatility of the azidoazetidinone as an intermediate in the synthesis of biologically relevant β-lactams was effectively demonstrated by Bose and coworkers in the conversion of 3-azido-4-thioazetidinones to the corresponding 3-azido-4-methoxyazetidinones.[71] For example, the reaction of azidoacetyl chloride **257** with thioimidate **308** afforded azetidinone **309**, which in turn was treated at −78°C with bromine and methanol to afford a 60% yield of methoxyazetidinone **310**.[71] These reactions, as well as a plausible mechanism for the halogenation sequence, are illustrated in Figure 34.[71] This investigation was signifi-



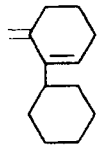
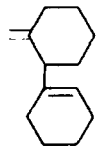
R^1	R^2	R^3	R^4	Yield (%)
C_6H_{11}	N_3	$(CH_2)_5$		20
C_6H_5	N_3	$(CH_2)_6$		30
p-$CH_3OC_6H_4$	N_3	$(CH_2)_5$		16
p-$CH_3OC_6H_4$	NH_2	$(CH_2)_5$		35
p-$CH_3C_6H_4$	N_3	$(CH_2)_5$		30
p-$CH_3C_6H_4$	NH_2	$(CH_2)_5$		20
p-ClC_6H_4	N_3	$(CH_2)_5$		14
o-$CH_3C_6H_4$	N_3	$(CH_2)_5$		31
p-BrC_6H_4	N_3			–
p-BrC_6H_4	N_3			–

Figure 32

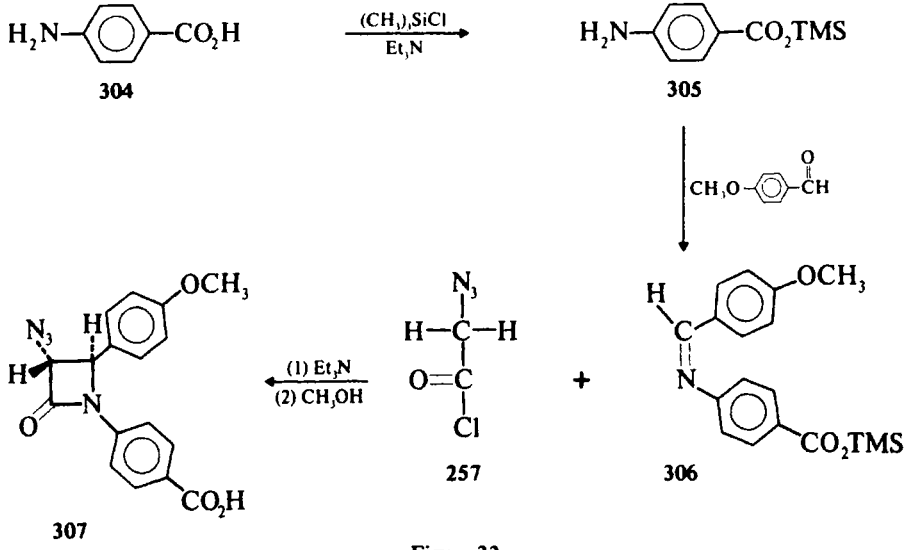


Figure 33

cant not only because it expanded the arsenal of synthetic azetidinones, but, more importantly, it demonstrated that the azido group was stable to electrophilic attack by halogens. Future syntheses requiring halogenation could employ a strategy in which the C_4-amine function could be masked as the C_4-azido group.

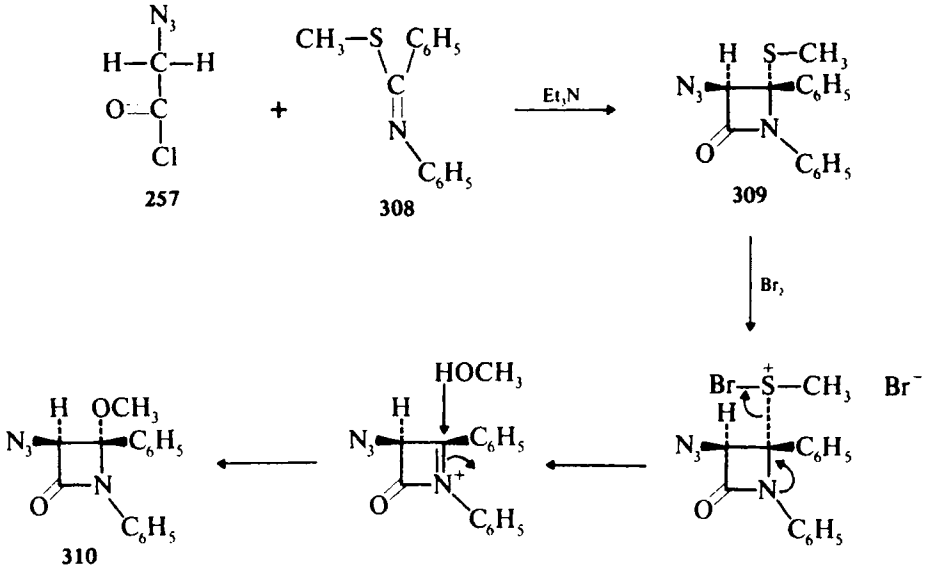


Figure 34

Azidoacetyl chloride has been shown to be a very useful reagent in the construction of biologically relevant synthetic β-lactams. However, this reagent is not without problems. It is corrosive, hazardous, and violently explosive if appropriate precautions are not observed. In an attempt to obviate the cumbersome and dangerous step of preparing azidoacetyl chloride, Bose and colleagues investigated the feasibility of the *in situ* generation of acid chloride equivalents of **257**.[75] These investigators found that pretreatment of azidoacetic acid **311** in methylene chloride with trifluoroacetic anhydride (TFAA) and triethylamine, followed by the addition of Schiff base **17** and triethylamine, afforded the *cis*- and *trans*-azetidinones **265** and **266**, respectively, in comparable yields and in the same ratio as the acid chloride–Schiff base reaction (Figure 35).[75]

An interesting modification of the *in situ* acyl activation is the use of diethylphosphorochloridate **312** and **311**.[76] For example, the pretreatment of **312** and **311** in methylene chloride followed by the addition of triethylamine and Schiff base **17** afforded a 65% yield of **265** and **266** in a strikingly surprising ratio of 9:1.[69] The same reaction sequence with Schiff base **313** afforded only the *cis*-azetidinone **314** in 66% yield.[76] These reactions are illustrated in Figure 36. A summary of azetidinones prepared by the phosphorochloridate method is presented in Figure 37.[76]

The utilization of the Manhas–Bose phosphorylation procedure for the synthesis of monocyclic azetidinones was recently reported by Kametani et al.[77] The synthesis

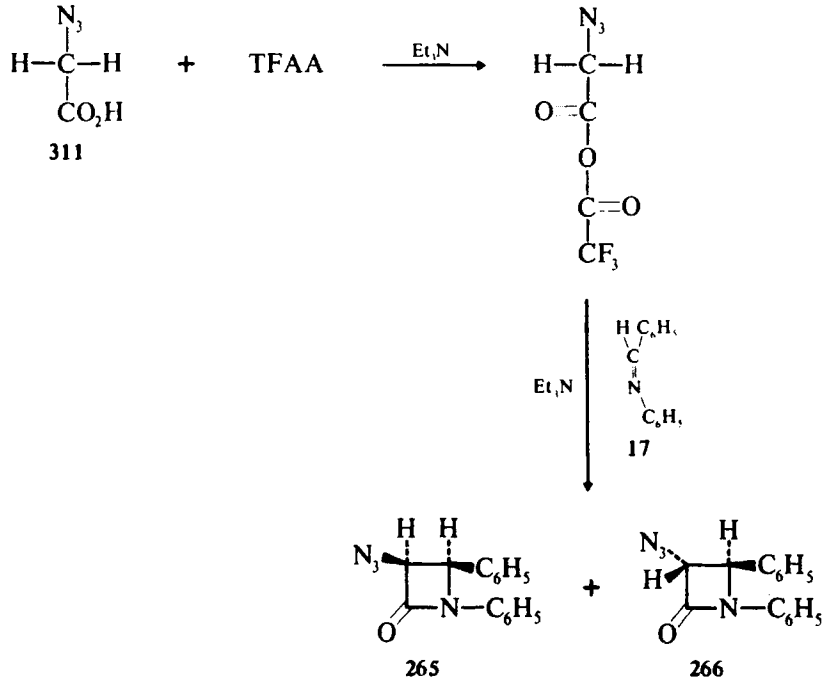


Figure 35

and a summary of the azetidinones produced by this method are presented in Figure 38.[77] A modification of this procedure was reported by Sharma et al.[78] by using phosphorous oxychloride, as described by Ziegler et al.[79] and Nelson.[80]

An extremely mild variant of the phosphorylation method for the acyl–imine azetidinone construction was disclosed by Bose and colleagues.[81] These researchers found that triphenylphosphine, carbon tetrabromide, and the appropriately substituted acid could react directly with the Schiff base and triethylamine at −78°C to give the azetidinone in excellent yield. A proposed mechanism for acyl activation is presented in Figure 39. A summary of the azetidinones prepared by this method is presented in Figure 40.

Another acyl-activating method whose discovery was stimulated by the need to circumvent the requirement of azidoacetyl chloride in the synthesis of azetidinones was reported by Manhas and co-workers.[82] They found that azidoacetic acid **311** reacted *in situ* with saccharyl chloride **337**, affording the acylimidate, which underwent cycloaddition with thioimidate **308** to afford azetidinone **309** in 50% yield. These data are presented in Figure 41.[82] An alternative "acid chloride equivalent" was reported by Ami , Glazer, and Manhas.[83] For example, treatment of azidoacetic acid **311** with *N*-methylpyridinium iodide **338** in the presence of triethylamine afforded the acylpyridinium intermediate **339**, which reacted with Schiff base **340** to give *cis*-β-lactam **341** in 35% yield.[83] This is illustrated in Figure 42. Additional monocyclic azetidinones synthesized by this method are listed in Figure 43.[83]

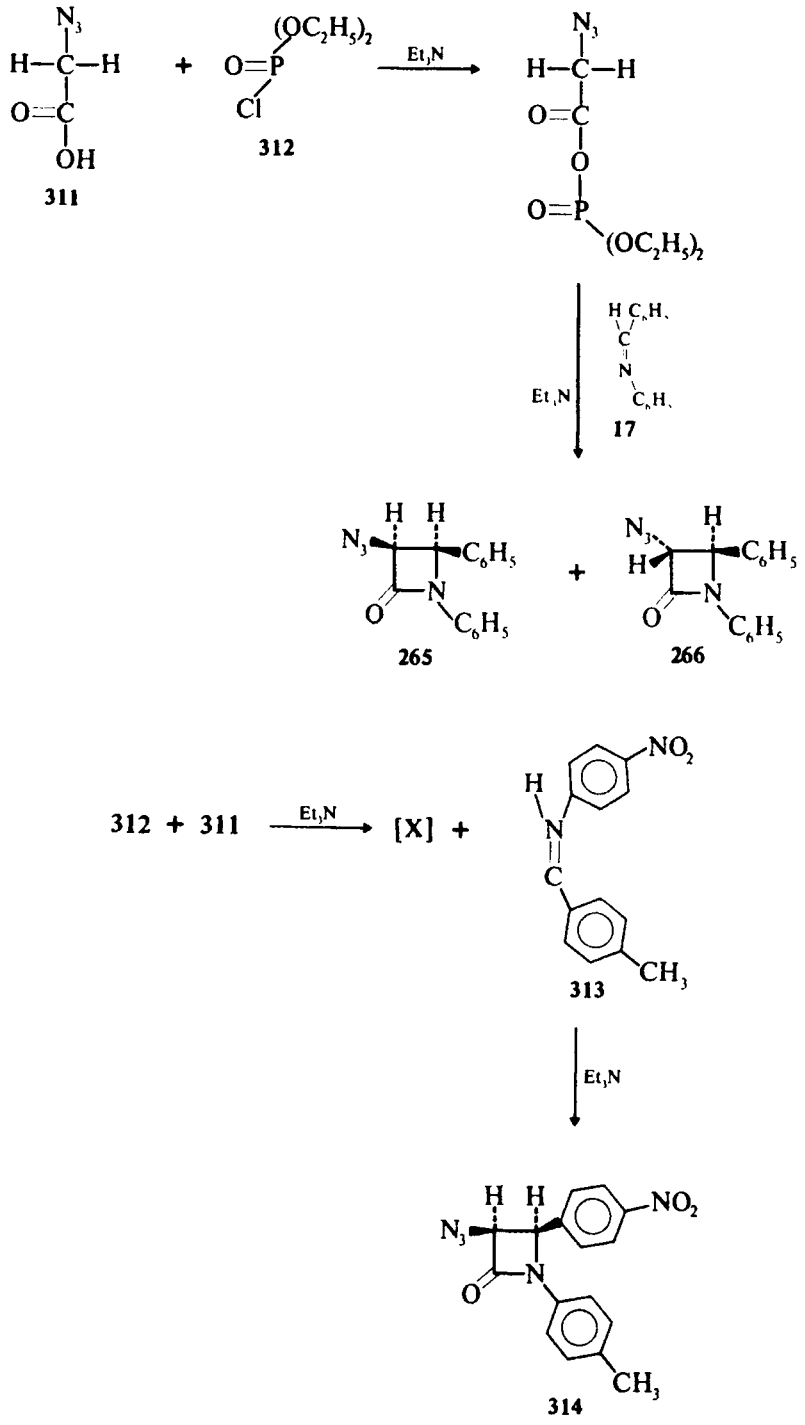
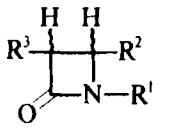


Figure 36



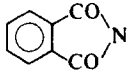
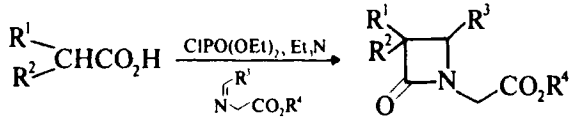
Compound	R^1	R^2	R^3	Yield (%)	Stereochemistry
315	Ph	Ph	Ph	75	*trans*
316, 317	Ph	Ph	OCH_3	70	*cis*, 85% *trans*, 15%
265, 266	Ph	Ph	N_3	65	*cis*, 90% *trans*, 10%
318	Ph	Ph	SCH_2Ph	80	*trans*
319	Ph	Ph	Br	50	*trans*
314	*p*-$CH_3C_6H_4$	*p*-$NO_2C_6H_4$	N_3	60	*cis*
320	*p*-$CH_3OC_6H_4$		N_3	50	*cis*
321	Ph	*o*-$NO_2C_6H_4$	N_3	60	*cis*
322	*p*-$CH_3C_6H_4$	*p*-$NO_2C_6H_4$		70	*trans*

Figure 37

The azido group functioning as an amine equivalent in the construction of 3-amidoazetidinones had indeed served its purpose well. Nevertheless, other avenues of approach to the synthesis of biologically relevant β-lactams (i.e., 3-β-amino substituent and C_3–C_4 *cis* configuration, utilizing "latent 3-amino substitution") were conceived. One such creative approach was discovered by Bose and co-wokers.[84] These investigators found that the reaction of benzyloxycarbonylglycyl chloride **349**, prepared *in situ*, with Schiff base **340** in the presence of triethylamine afforded *cis*-β-lactam **350**, as shown in Figure 44.[84] The utility of this discovery can best be demonstrated by exemplifying the product of the reaction of an acetamido acetyl halide with a Schiff base. The product is the imidazolidone **353**.



Compound	R^1	R^2	R^3	R^4	Yield (%)	Stereochemistry
323	Ph	H	Ph	Et	48.9	*trans*
324	Ph	H		Et	69.2	*trans*
325	Cl	H	Ph	Et	3.8	*trans*
326	SPh	H		Et	4.5	*trans*

Figure 38. Synthesis of β-lactams by the phosphate anhydride–imine method.

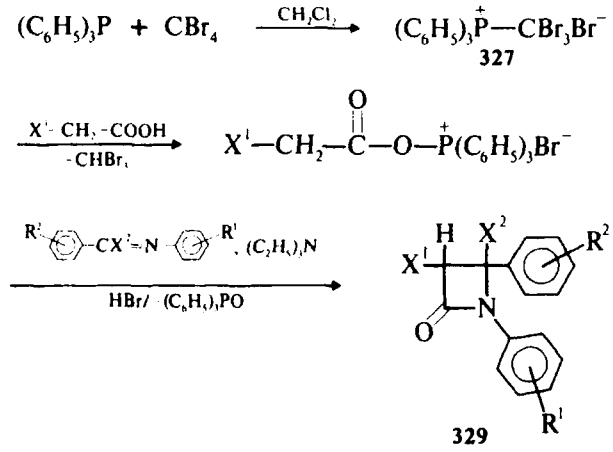
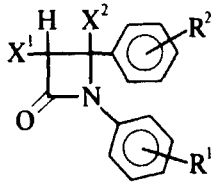


Figure 39

This product arises by formation of oxazolone **352** followed by the reaction with Schiff base and subsequent conversion to imidazolidone, as illustrated in Figure 45. In sharp contrast, the acid chloride **349** does not form oxazolone but reacts directly with the Schiff base to give azetidinone (see Figure 44).[84] The conversion of **350** to the free amine **351** was carried out with hydrobromic acid in acetic acid solution (Figure 44). A summary of monocyclic azetidinones prepared by this procedure is illustrated in Figure 46.[84] Quite surprisingly, the reaction of thiazoline **354** with *p*-nitrobenzyloxycarbonylglycyl chloride **355** and triethylamine did not produce the expected fused β-lactam **356** but rather the imidazolidone **357**.[84,85] If one substituted the phenylthiazoline **298** in this sequence, the β-lactam **358** was produced in good yield. This is illustrated in Figure 47.[84,85]

As has been described in Section I.1 Zeigler and Kleinberg[12] disclosed that the reaction of malonyl chloride **16** with Schiff base **17** afforded the azetidinone **18**



Compound	R^1	R^2	X^1	X^2	Yield (%)
330	4-CH_3	4-OCH_3	$C_6H_5CH_2O$	H	80
331	4-CH_3	H	$C_6H_5CH_2O$	H	85
332	H	H	C_6H_5O	H	50
333	4-CH_3	4-OCH_3	H_3CO	H	85
334	4-CH_3	4-OCH_3	C_6H_5O	H	70
335	4-CH_3	4-OCH_3	$C_6H_5CH_2S$	H	30
336	H	H	H_3CO	SCH_3	65

Figure 40

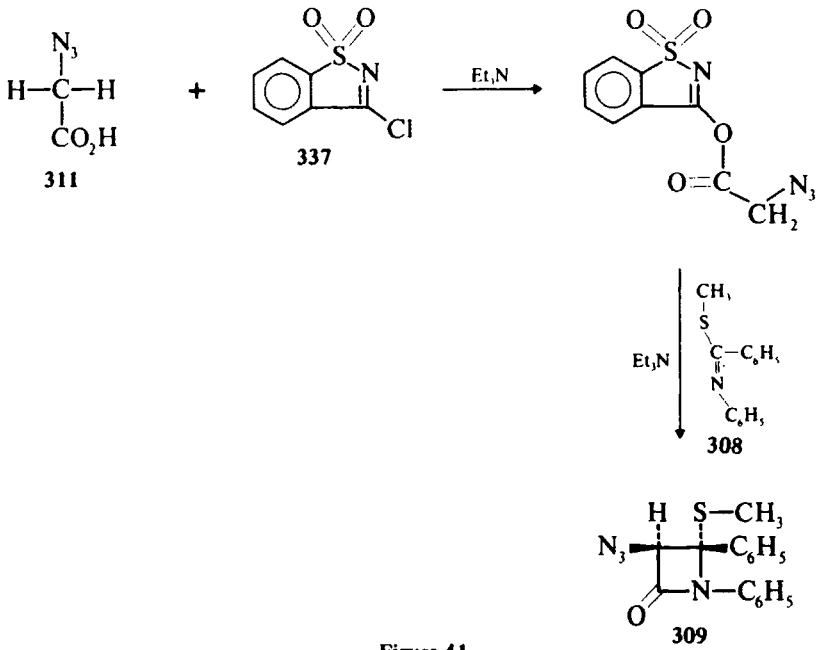


Figure 41

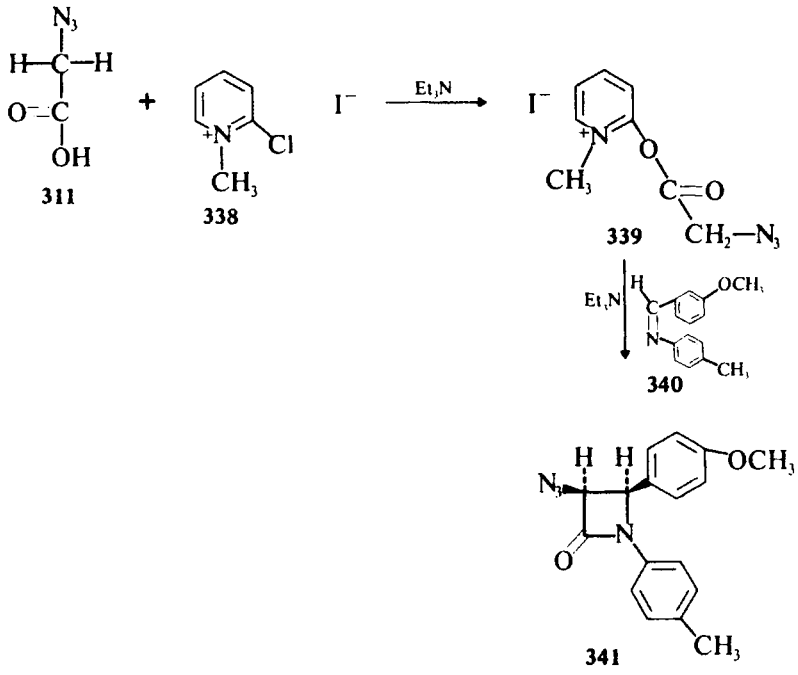
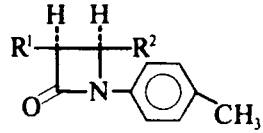


Figure 42



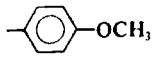
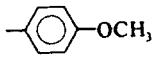
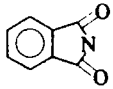
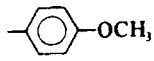
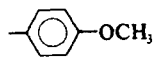
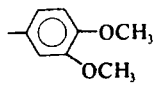
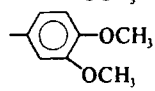
Compound	R^1	R^2	Yield (%)
341	N_3		35
342	C_6H_5S		34
343			21
344	H_3CCOO		25
345	H_3CO		45
346	$(H_3C)_3CO$		50
347	C_6H_5O		48
348	C_6H_5O		55

Figure 43

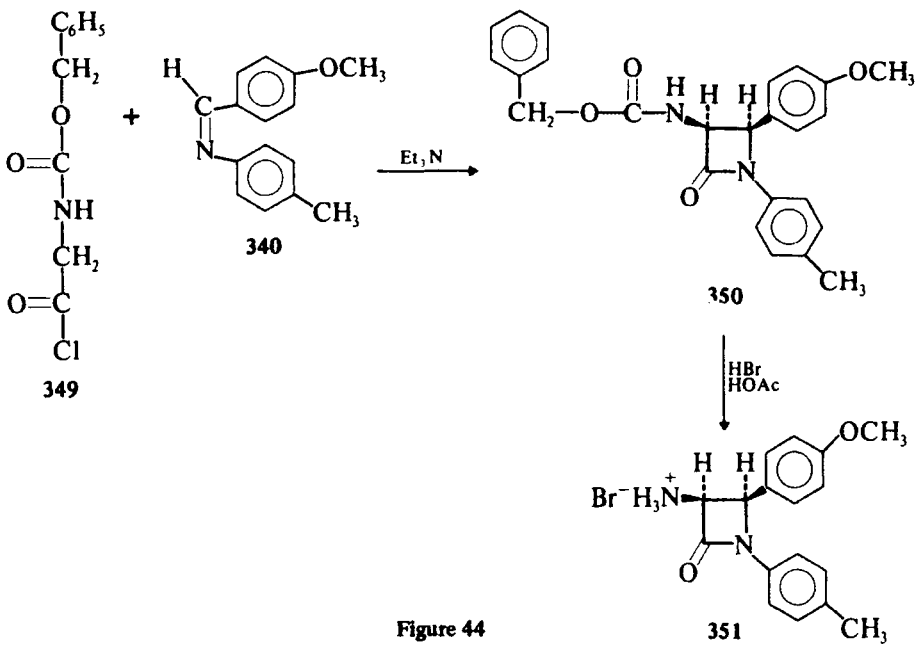


Figure 44

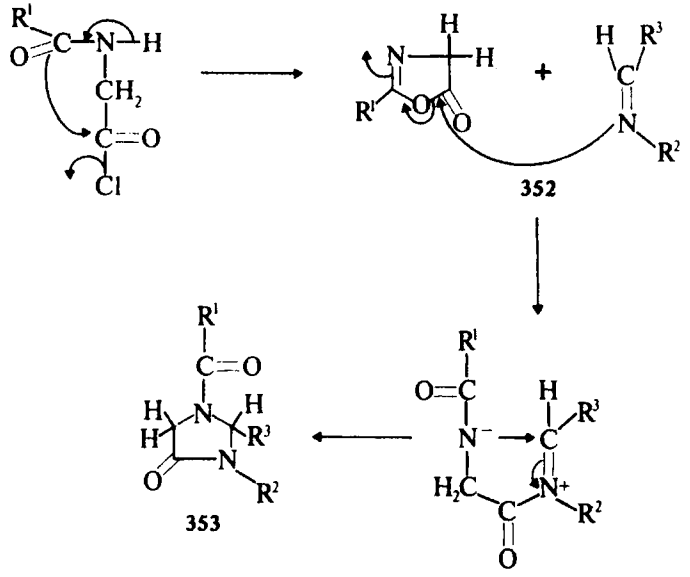
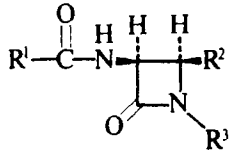


Figure 45

in 47% yield. Bose and co-workers had envisioned a C_3–acyl halide as being an appropriate precursor for the acyl azide Curtius rearrangement, giving the C_3-isocyanate, as conceptually described in Figure 48.[86] To test the reality of this architectural scheme in the synthesis of 3-amidoazetidinone, these investigators reacted phenylmalonyl chloride **359** with Schiff base **17**, producing **360** in high yield. The acid chloride was not isolated but was converted directly to the acyl azide **361** in 55% yield. The azide in turn was heated in benzene to afford the isocyanate **362**, as shown in Figure 49.[86]

The versatility of isocyanate **362** was most effectively demonstrated in its multifunctional conversions. For example, **362**, upon treatment with *p*-anisyl alcohol **363**, was converted to the urethan **364**. In addition, phenoxyacetic acid reacted with **362** in the presence of a catalytic amount of pyridine in refluxing benzene to



Compound	R^1	R^2	R^3
350	$C_6H_5CH_2O$	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$
350a	*p*-$NO_2C_6H_4CH_2O$	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$
350b	$C_6H_5CH_2O$	*p*-$CH_3OC_6H_4$	

Figure 46

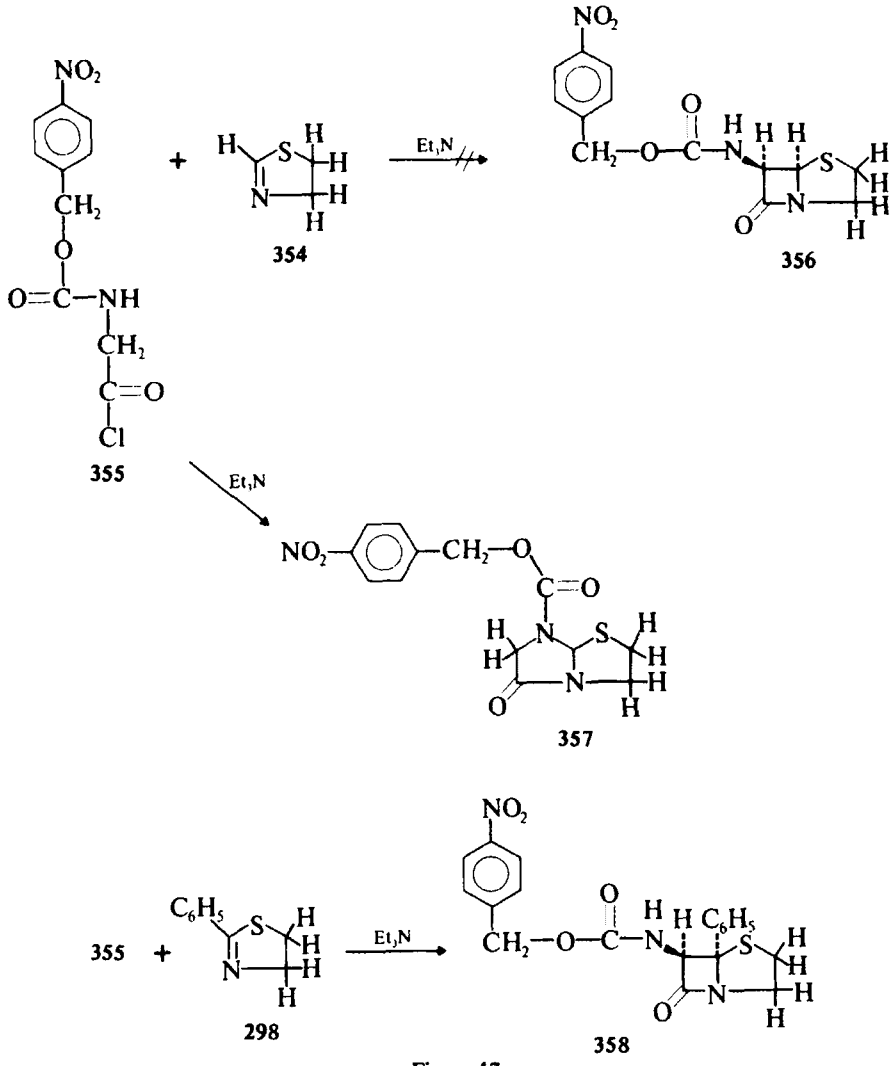


Figure 47

produce **365** in 65% yield. These reactions are depicted in Figure 50.[86] The compatibility of the acid halide with other functionalities was clearly illustrated by the reaction of phenylmalonyl chloride **359** with thioimidate **308** to give acid chloride **366**, which was converted to its methyl ester **367**, as illustrated in Figure 51.[88] A summary of the azetidinones synthesized from malonyl chloride is presented in Figure 52.[87]

An elegant amine-protecting group utilized in the acid chloride–Schiff base cycloaddition sequence was disclosed by Sharma and Gupta.[88] These investigators found that the enamino potassium salt **376** reacted with Schiff base **17**, phosphorus oxychloride, and triethylamine to give *cis*-azetidinone **377** in 45% yield.[88,89] The

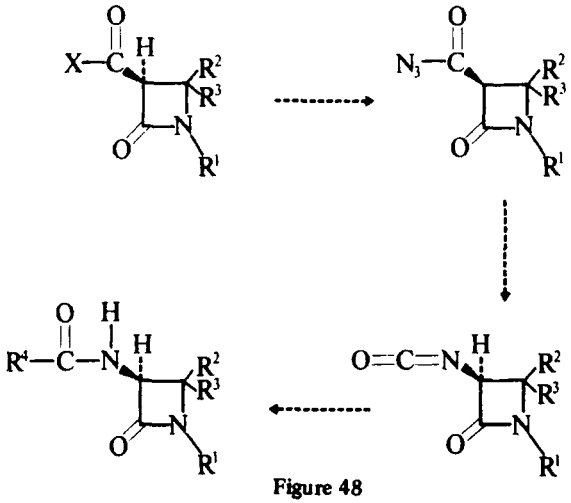


Figure 48

enaminoazetidinone **377** was hydrolyzed with ethanol–HCl to afford the free amino derivative **378**, which was subsequently reacetylated with phenoxyacetyl chloride to give **365**.[88] These transformations are illustrated in Figure 53. A summary of the azetidinones prepared by this method is presented in Figure 54.[88,89]

Thus far the cycloaddition reactions of ketenes or acid halides with azomethine substrates to produce azetidinones have utilized *N*-alkyl or *N*-aryl Schiff bases, imidates, or thioimidates. Wells and Lee reported the first total synthesis of a biologically relevant *N*-unsubstituted azetidinone (such as β-lactam **386**).[90] These researchers disclosed that hydrobenzamide **387** underwent cycloaddition with

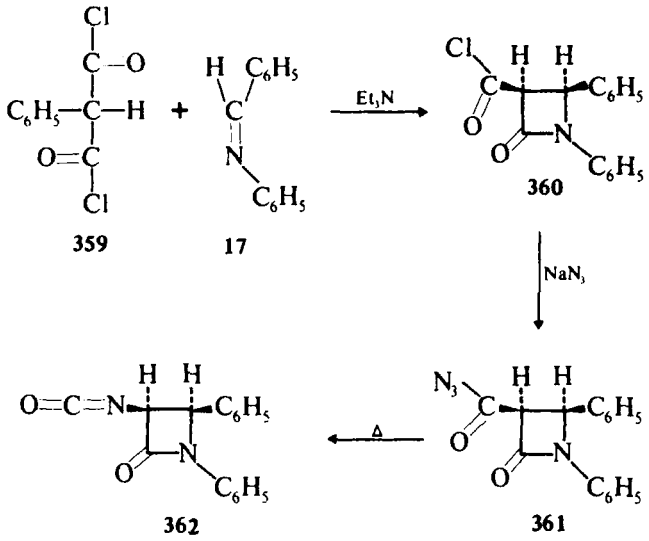


Figure 49

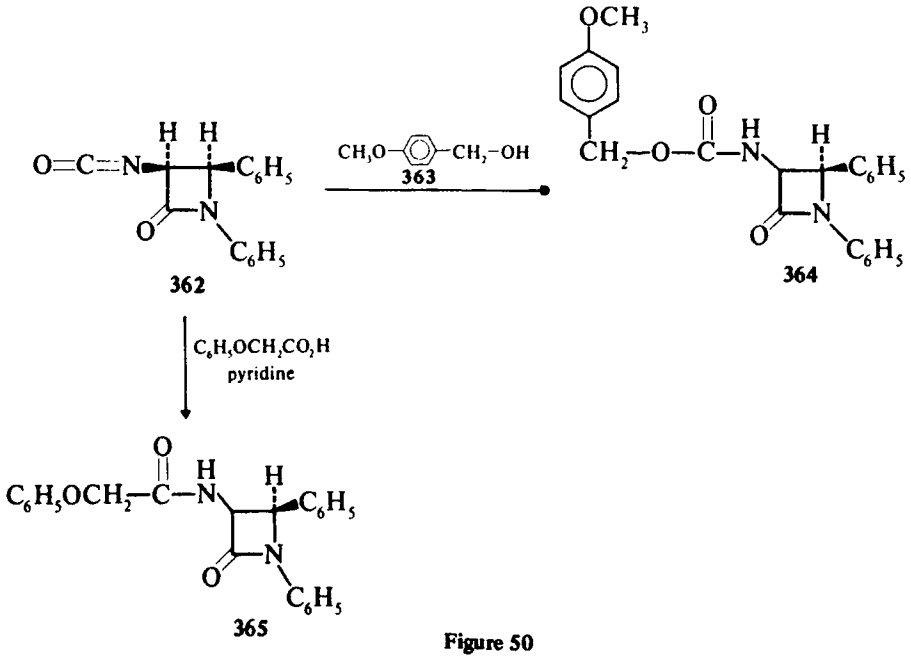


Figure 50

azidoacetyl chloride **257** under the Bose conditions to give, after work-up with aqueous acid, a 40% yield of **388**. This is shown in Figure 55.

Bose and co-workers reported that the enamino potassium salt **389**, after mixed anhydride formation with ethyl chloroformate, underwent cycloaddition with Schiff base **390** (derived from benzaldehyde and veratrylamine) to produce azetidinone

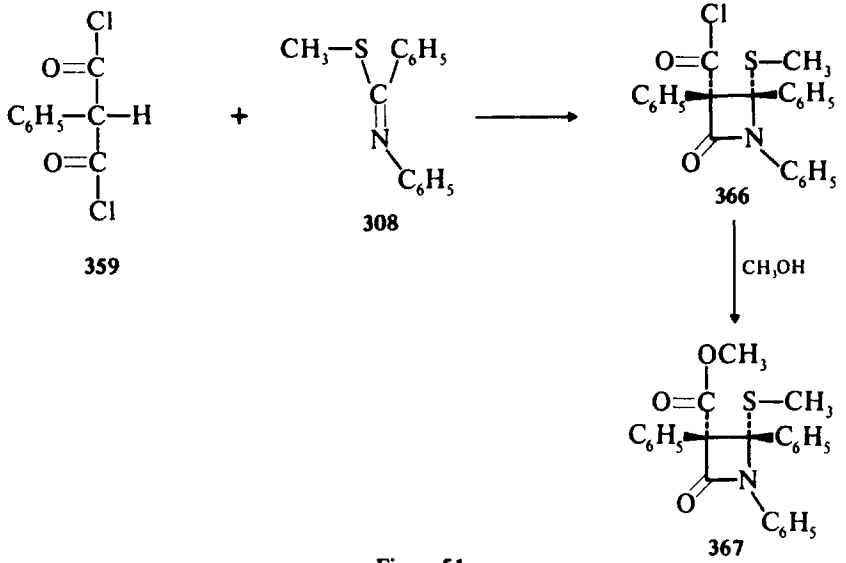
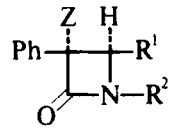


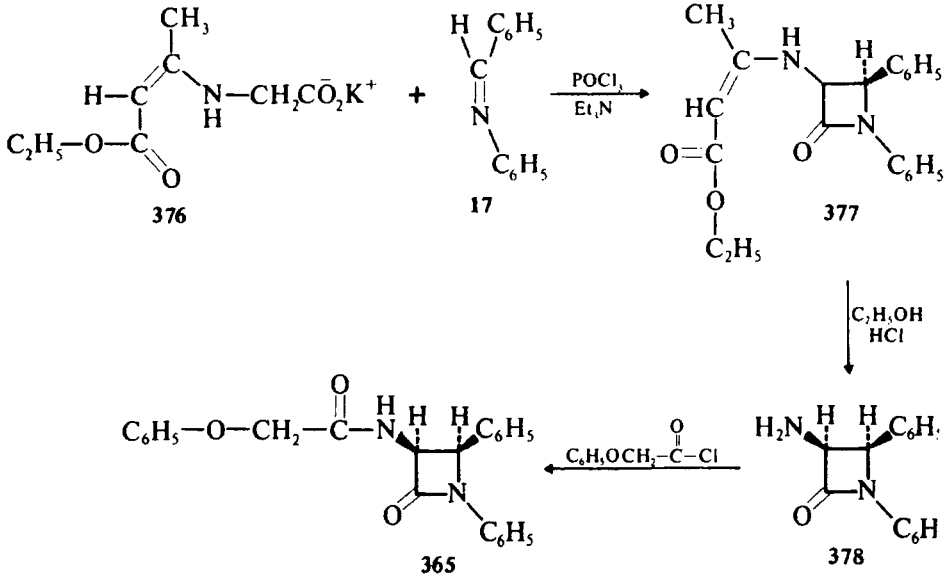
Figure 51



Compound	Z	R^1	R^2
360	COCl	Ph	Ph
368	CO_2Me	Ph	Ph
369	CO_2CH_2Ph	Ph	Ph
370	CO_2H	Ph	Ph
371	COCl	*p*-C_6H_4OMe	*p*-C_6H_4Me
372	COCl	*p*-C_6H_4OMe	β-Naphthyl
373	COCl	Ph	α-Naphthyl
361	CON_3	Ph	Ph
362	NCO	Ph	Ph
364	$NHCO_2CH_2C_6H_4OMe$-*p*	Ph	Ph
374	$NHCO_2Et$	Ph	Ph
365	$NHCOCH_2OPh$	Ph	Ph
375	$NHCOCH_2Ph$	Ph	Ph

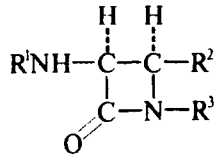
Figure 52

391 in 65% yield.[91] The enaminoazetidinone was subsequently hydrolyzed with water and *p*-toluenesulfonic acid to give the tosylate salt **392**, which was acylated with phenoxyacetyl chloride to give azetidinone **393**. The *N*-veratryl β-lactam **393** was then converted to the *N*-unsubstituted azetidinone **394** in 25% yield under buffered acid (potassium persulfate–disodium hydrogen phosphate) conditions.[96] This reaction sequence is described in Figure 56.



376 **17** **377** **365** **378**

Figure 53



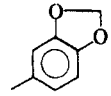
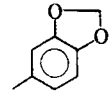
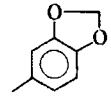
Compound	R^1	R^2	R^3
377	$-C(CH_3)=CHCOOC_2H_5$	C_6H_5	C_6H_5
378	H	C_6H_5	C_6H_5
379	$-C(CH_3)=CHCOOC_2H_5$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
380	H	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
381	$PhOCH_2CO$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
382	$-C(CH_3)=CHCOOC_2H_5$		p-$CH_3C_6H_4$
383	H		p-$CH_3C_6H_4$
384	$PhOCH_2CO$		p-$CH_3C_6H_4$
385	$-C(CH_3)=CHCOCH_3$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$

Figure 54

The field of β-lactam antibiotics (i.e., pencillins and cephalosporins) was created, in part, to meet the needs of humanity. As one pursues the goal of utilizing synthetic methods for the construction of β-lactams, the driving force must always be to create what is needed; indeed, this has been an important consideration in the various azetidinones reviewed thus far.

Although the review has so far included mostly monocyclic azetidinones, the author has, at his discretion, incorporated the synthesis of fused β-lactams as a relevant application of cycloaddition chemistry. The contributions to be reviewed at this point apply the "current state of the art" of ketene or acid halide–azomethine cycloadditions to the total synthesis of biologically relevant β-lactam antiobiotics.

As has been previously described, Bose and co-workers[63] had reported the total synthesis of 6-epipenicillin methyl ester by the cycloaddition of **257** with the thiazoline **258** (see Figure 22). In order to establish the relevance of this synthetic sequence to the production of useful β-lactam antiobiotics, an appropriate C_3-carboxy protecting group would be required to afford the free acid without concomitant rupture of the β-lactam ring and, most important, a means of converting the biologically inactive 6-epipenicillin to the active 6-β-amido derivative would have to be developed.

Firestone and co-workers reported the total synthesis of penicillin G **395** utiliz-

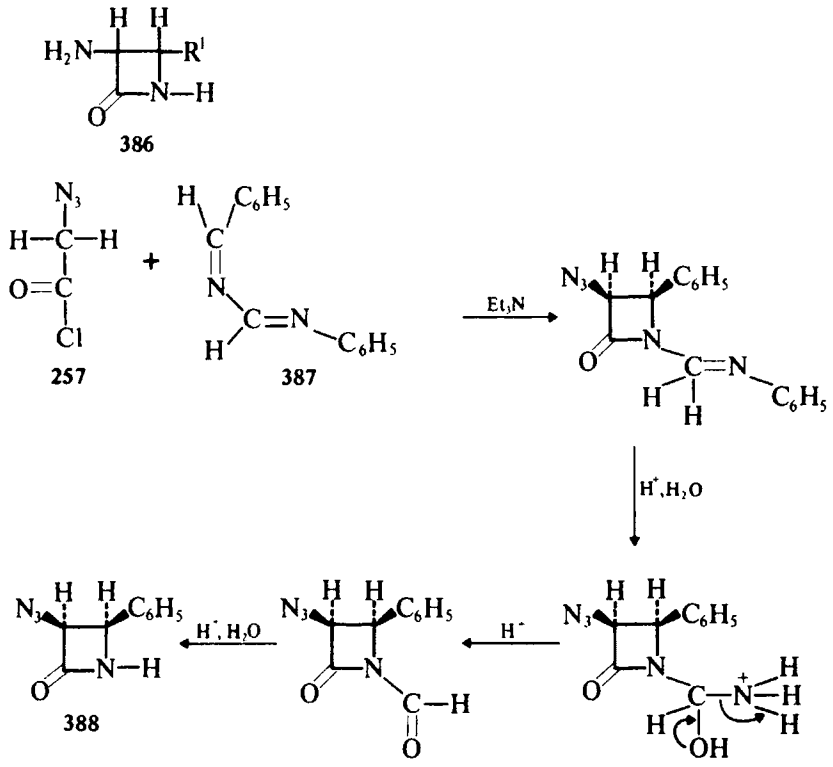


Figure 55

ing the cycloaddition reaction with azidoacetyl chloride **257**.[92] These investigators found that thiazoline **396** underwent cycloaddition with **257** to produce the 6-α-azidopenam **397**. The azidopenam was then hydrogenated with platinum oxide in benzene to afford the 6-α-aminopenam **398**. The important conversion of the 6-epipenam **398** to the natural configuration, i.e., 6-β-aminopenam **401**, was effected in the following sequence: the amine **398** was converted to its *p*-nitrobenzaldehyde Schiff base **399** and then treated at −78°C with phenyllithium in tetrahydrofuran (THF) and a small amount of dimethylformamide. The anion **399** was kinetically protonated with THF and acetic acid at −78°C, affording the 6-β-amino Schiff base **400** in 75% yield. The Schiff base **400** was converted to the free amine **401** and was subsequently reacylated with phenylacetyl chloride to give the pencillin G benzyl ester **402**. The conversion of **402** to penicillin G **395** was accomplished by hydrogenation with 10% Pd/C in methanol–water.[92] This synthetic sequence is illustrated in Figure 57

An important "synthetic bridge" joining the discovery of the azidoacetyl chloride cycloaddition reaction with azomethine to the construction of the biologically important cephems was reported by Ratcliffe and Christensen.[93,94] These investigators found that thioformamide **403** reacted with 1-chloro-3-acetoxy-2-propanone **404** in the presence of base to afford thiazine **405**. The cycloaddition of **257** and

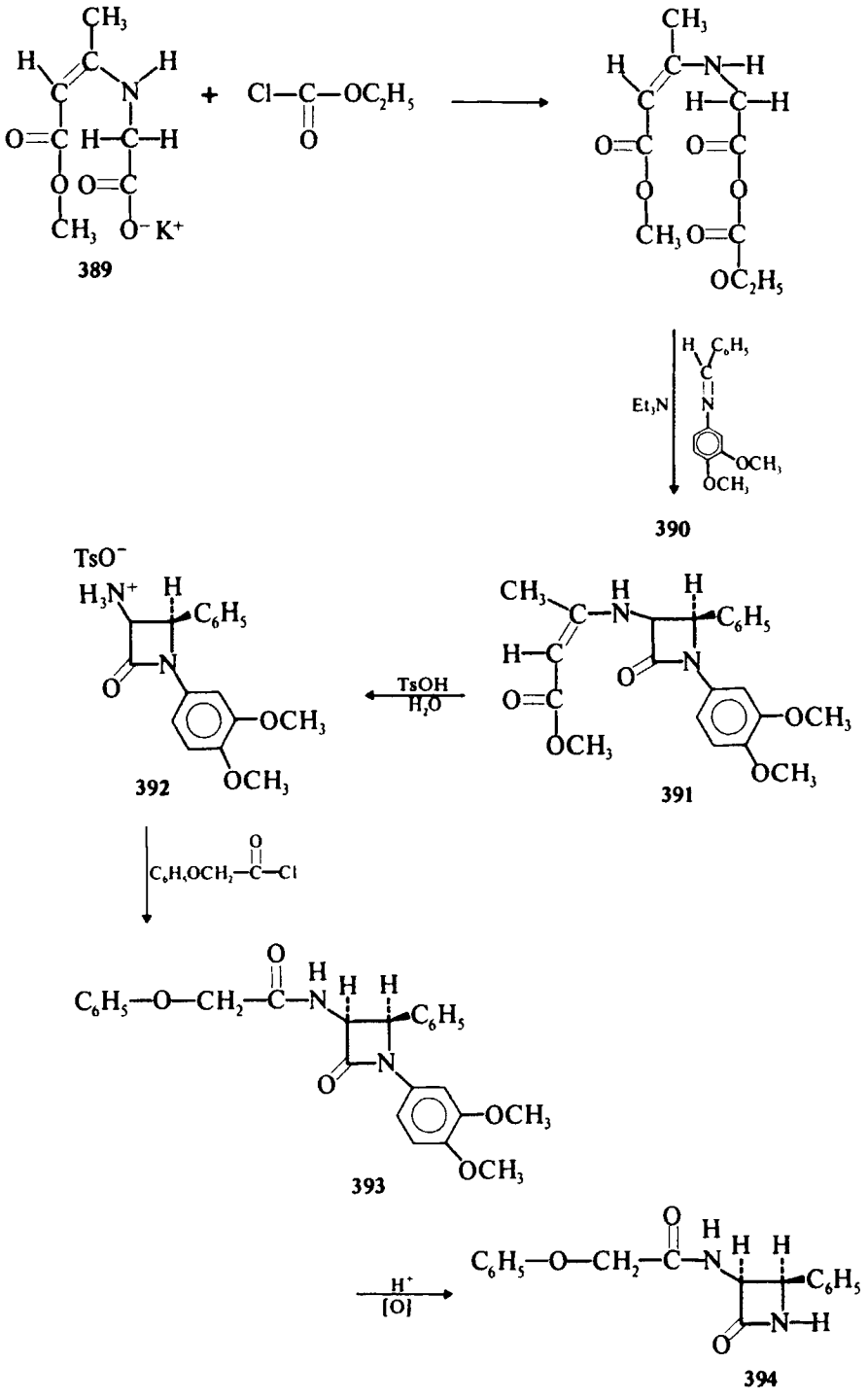


Figure 56

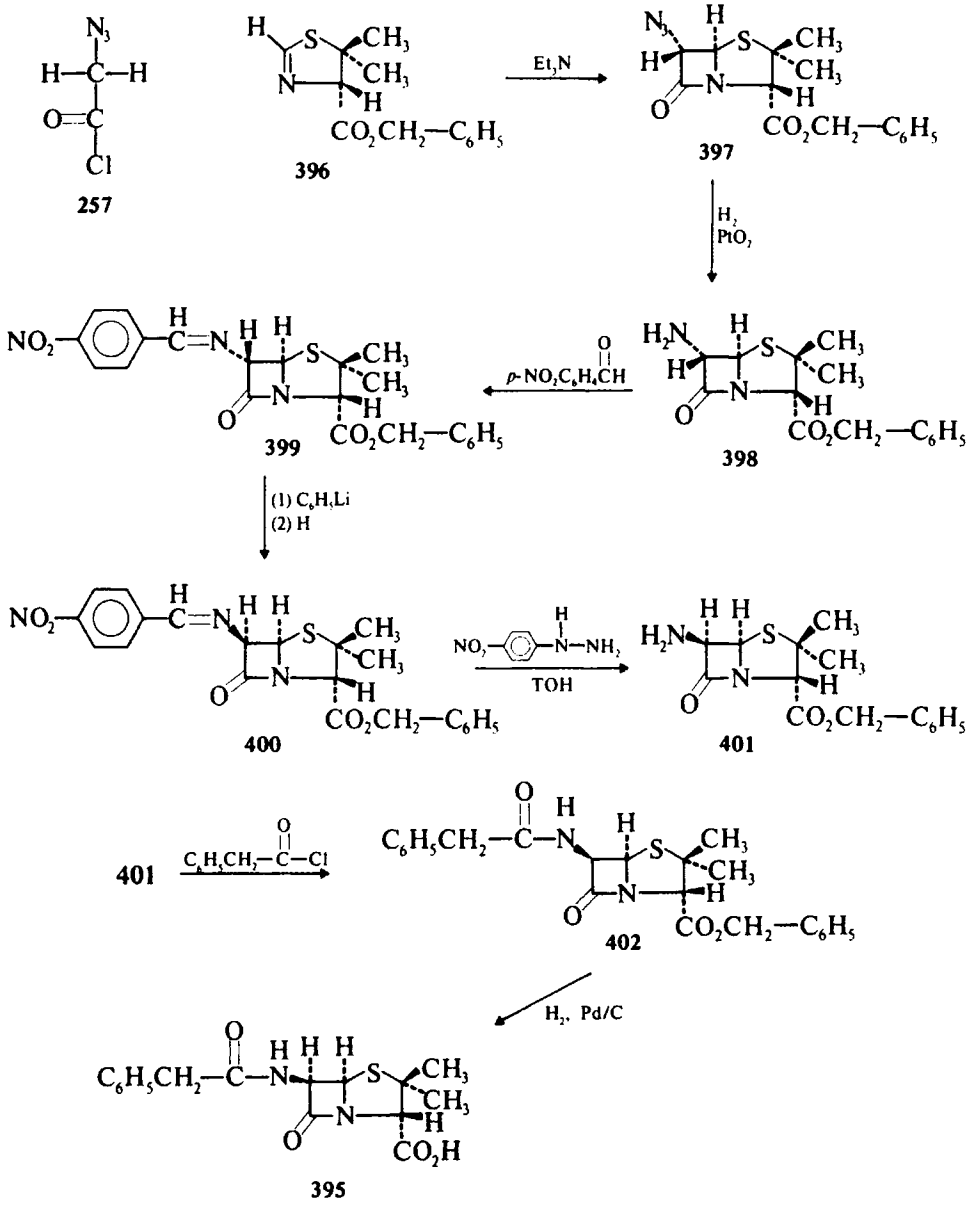


Figure 57

405 to produce **406** was achieved in 56% yield. The azidocephem **406** was hydrogenated to **407** and converted to the Schiff base **408**, which was subsequently epimerized to **409**.[92] Schiff base **409** was hydrolyzed to the 7-β-aminocephem **410** which was reacylated with thienylchloride to give **411**. Conversion to *dl*-cephalothin **412** was completed by ester removal with trifluoroacetic acid (TFA) and anisole.[94] This sequence is illustrated in Figure 58.

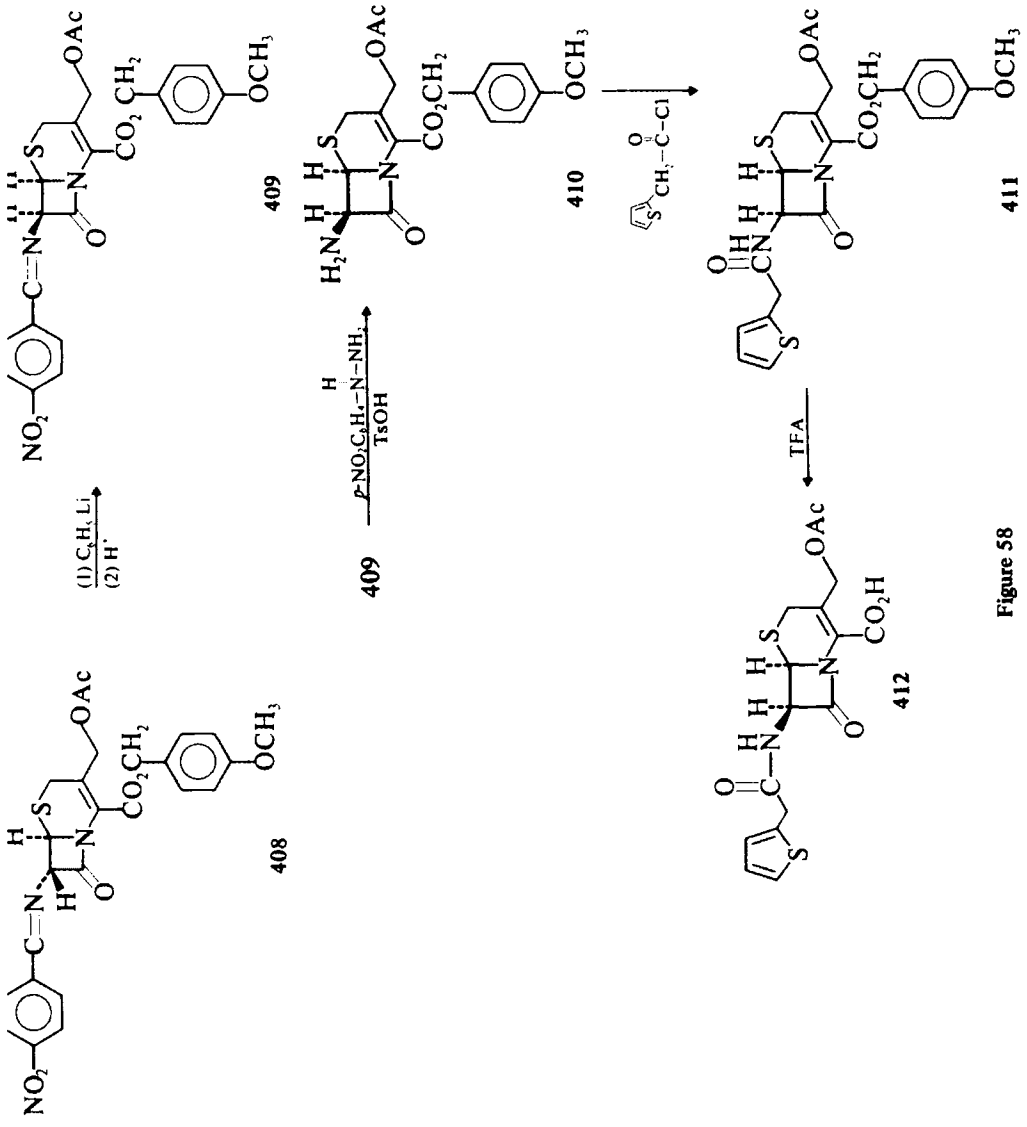


Figure 58

In a similar manner, Steinberg, Ratcliffe, and Christensen reported the synthesis of 3′-methylcephalothin **416**.[95] The required thiazine **413**, derived from thioformamide **403** and 1-chloro-3-acetoxy-2-butanone **404**, reacted with **257** to produce azidocephem **414**. This was converted to the desired cephem **416**, as outlined in Figure 59.[95]

Ratcliffe and Christensen utilized the azidoacetyl chloride–thiazine cycloaddition sequence in the total synthesis of the 7-α-methoxycephem **420**.[96] The

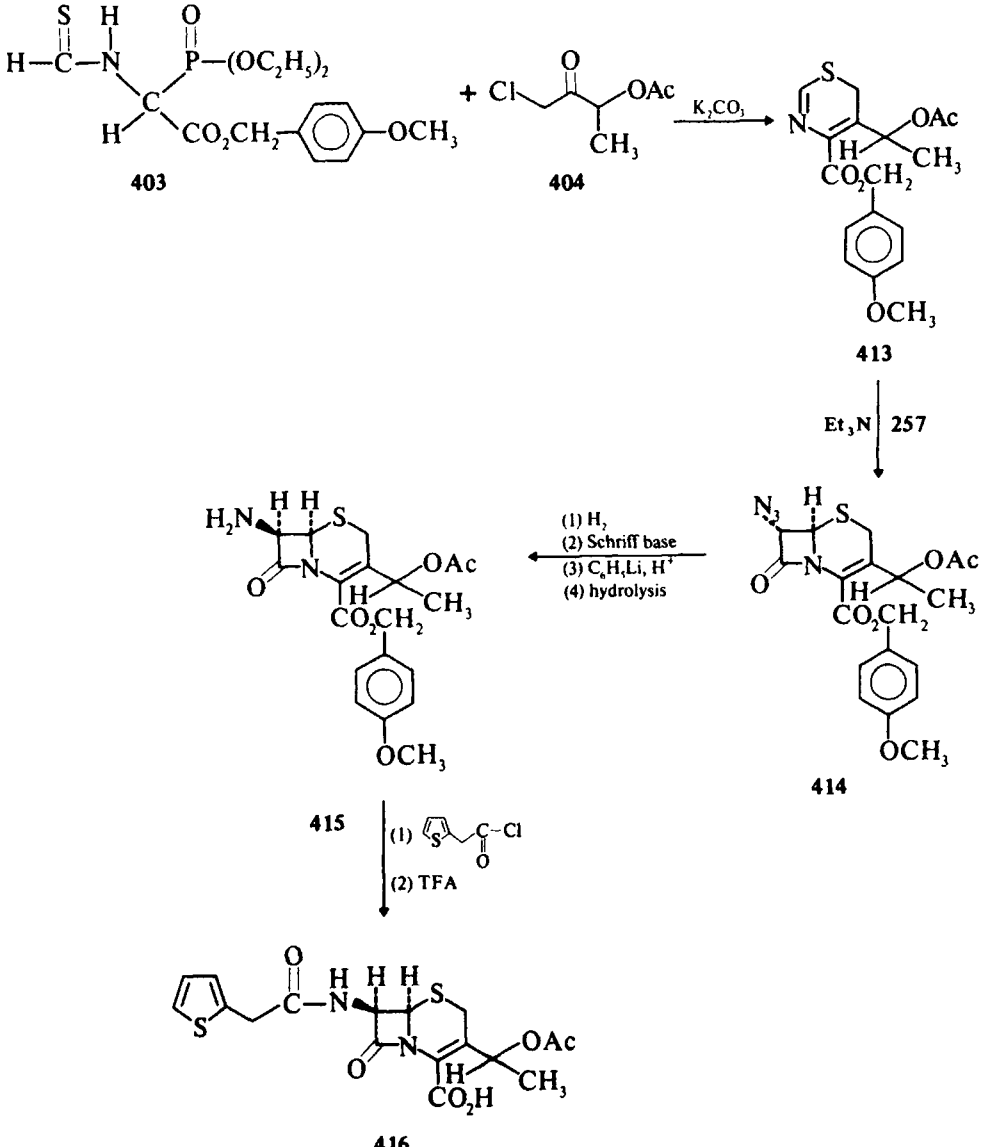


Figure 59

Schiff base **408** (for its synthesis see Figure 58) was treated with phenyllithium and methylsulphenyl chloride to give the 7-α-methylthiocephem **417**, which was hydrolyzed to the nucleus **418**. This in turn was reacylated with thienyl chloride and converted to the 7-α-methoxycephem **419**. The subsequent deblocking of the ester protecting group with TFA-anisole produced *dl*-7-α-methoxycephem **420**.[96] This series of reactions is summarized in Figure 60.

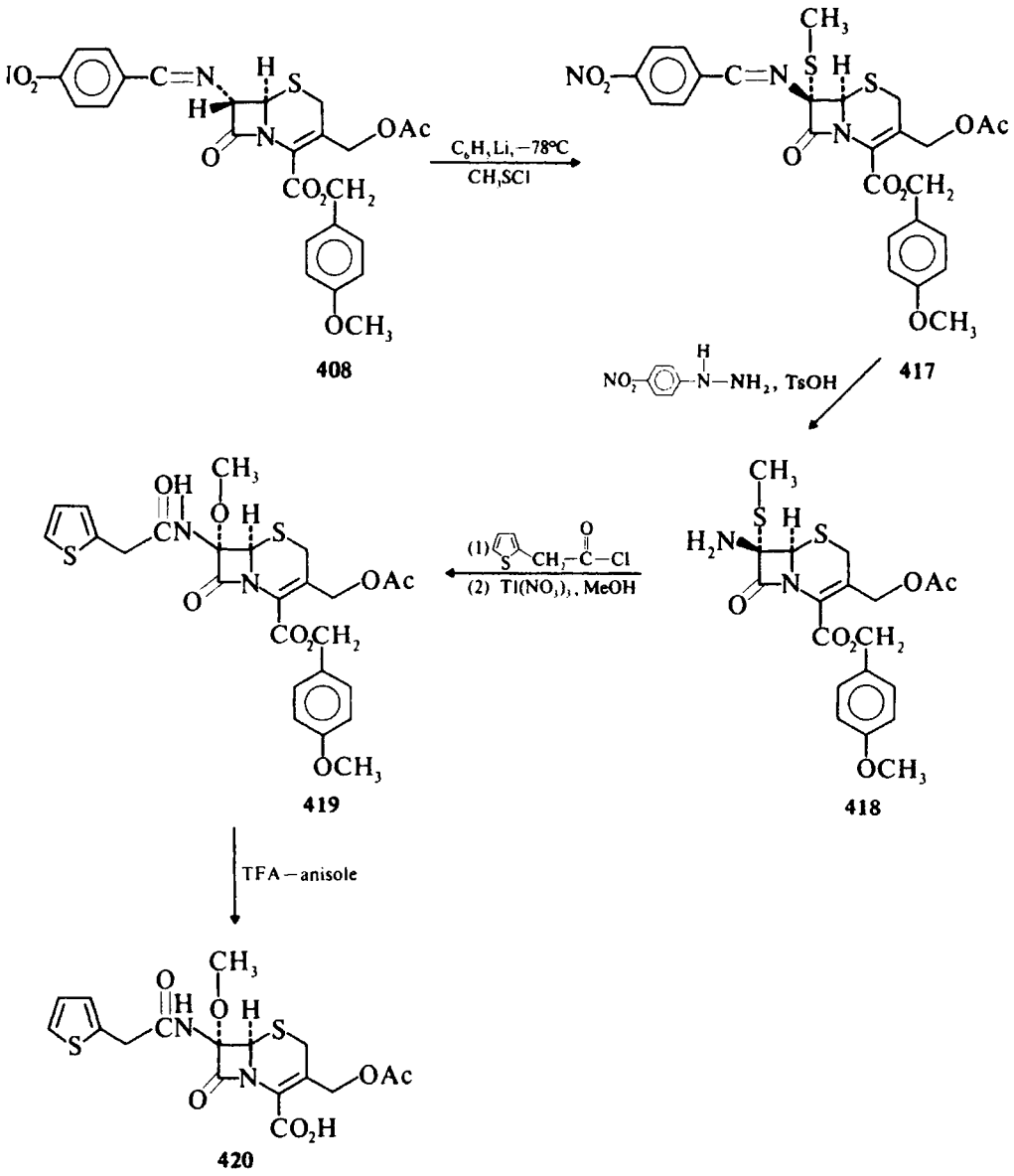


Figure 60

This important sequence of reactions conceived by Ratcliffe for the construction of naturally derived cephems was elegantly applied to the synthesis of the unnatural 1-oxacephalothin **428** and 1-carbacephalothin **437**.[97,98] Cama and Christensen reported the synthesis of 1-oxacephalothin utilizing thioformamide **403**.[97] Treatment of **421** with methyl iodide and base afforded the methylthioimidate **422**, which underwent smooth cycloaddition with azidoacetyl chloride **257**, affording *trans*-azetidinone **423** in 42% yield.[97] Subsequent chlorination of **423** gave **424** as a cis and trans mixture of isomers. This was reacted with 1-hydroxy-3-acetoxy-2-propane to give **425** as a 1 : 1 mixture of cis–trans isomers. Intramolecular Emmons cyclization was achieved with sodium hydride, affording a 1 : 1 mixture of 7-azidocephem **426**. The 7-β isomer was separated and hydrogenated to the 7-β-aminocephalosporanic acid **427**. This in turn was reacylated with thienyl chloride, giving *dl*-1-oxacehalothin **428**.[97] This reaction sequence is illustrated in Figure 61.

The synthesis of 1-carbacephalothin **437** was carried out by Guthiconda and co-workers.[98] For example, the reaction of Schiff base **431** (derived from aldehyde **429** and aminophosphorate **430**) with **257** in triethylamine at −78°C gave *cis*-azetidinone **432** in 30% yield. The ketal function was hydrolyzed with 10% H_2SO_4 (with the undesired attendant hydrolysis of the acetate) to give **433**. This was reacylated with acetyl chloride to give **434**, which was cyclized with base to give cephem **435**. The azidocephem **435** was hydrogenated to the 7-β-aminocephalosporanic acid **436**, which was acylated with thienyl chloride, giving *dl*-1-carbacephalothin **437**.[98] This series of reactions is presented in Figure 62.

The use of azidoacetic acid **311** (via its mixed anhydride) in the synthesis of β-lactams was reported by Huffman and co-workers[99] in their synthesis of β-lactam **446**. The reaction of azidoacetic acid **311** with trifluoroacetic anhydride produced the mixed anhydride, which reacted smoothly with Schiff base **438** in the presence of triethylamine, affording *cis*-azetidinone **439** in 58% yield. Azetidinone **439** was hydrogenated to **440**, which was reacylated with phenoxyacetyl chloride to give **441**. The 3,4-dimethoxybenzyl protecting group of **441** was removed, quite elegantly, with buffered potassium persulfate in aqueous acetonitrile to give the unsubstituted azetidinone **442** in 69% yield. The ester of **442** was reduced with sodium borohydride, tosylated, exchanged with iodide, and reacted with sodium azide to give **443** in 75% yield. Hydrogenation of **443**, followed by conversion to its Schiff base with benzylglyoxalate, afforded **444**, which was cyclized to **445** upon acylation with acetyl chloride. Finally, catalytic hydrogenation gave the *dl* free acid **446**.[99] These transformations are illustrated in Figure 63.

Bryan and co-workers reported the synthesis of cephem **447** utilizing technology similar to that outlined above.[100] For example, the azide **439** was reduced with sodium borohydride to give the alcohol, which was converted to tosylate.[99,100] This in turn was reduced to the amine and reacylated with thienyl chloride to give **442a**. The latter was converted to the iodide, displaced with tritylmercaptan, and deblocked with silver nitrate in methanol to give the mercaptomethylazetidinone **442b**. The final sequence was completed by reacting **442b** with benzhydryl β-bromopyruvate **443** to give the carbinolamide **444a**, which was dehydrated with thionyl chloride and pyridine to give isocephem **445a**. Ester deblocking with

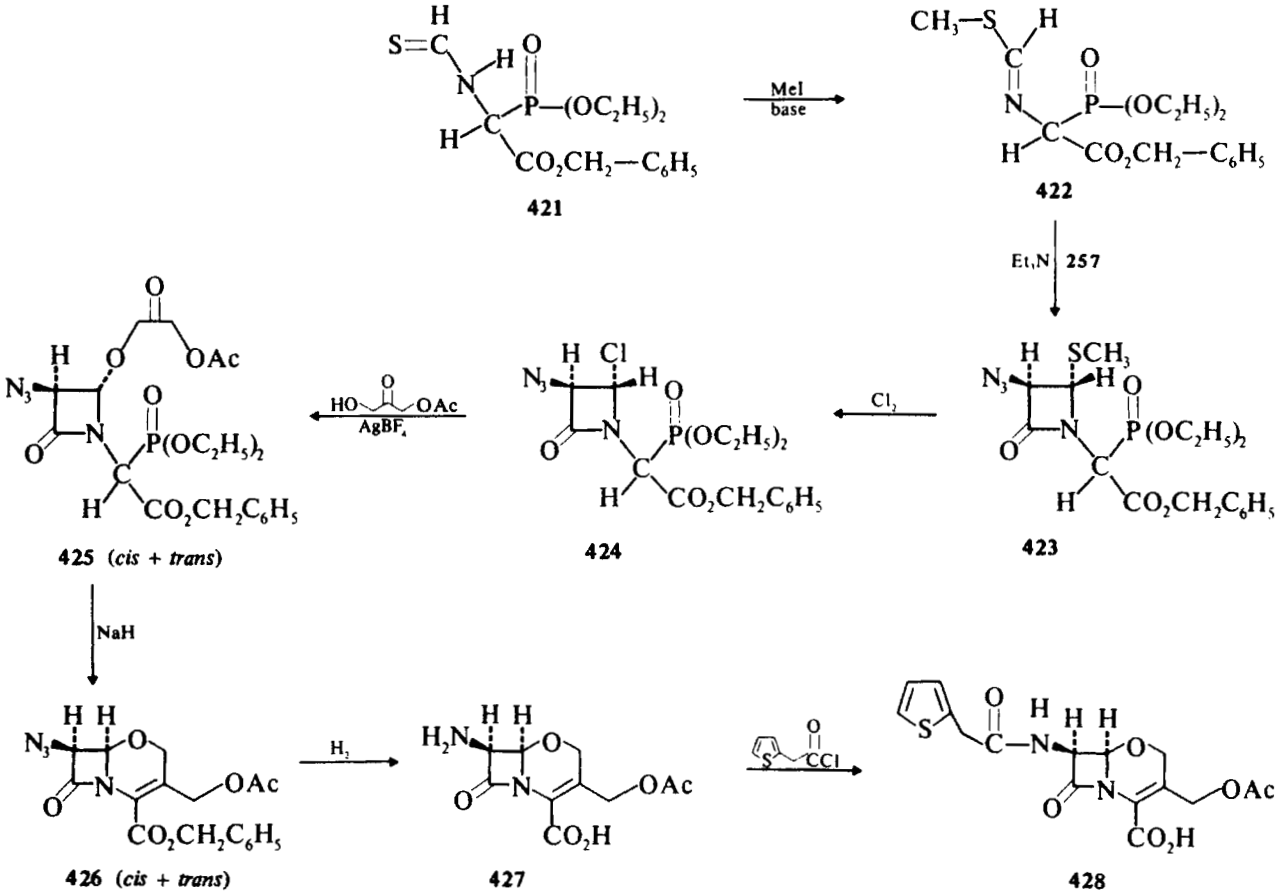

421
MeI
base
422
Et3N 257
423
Cl2
424
HO OAc
AgBF4
425 (cis + trans)
NaH
426 (cis + trans)
H2
427
428

Figure 61

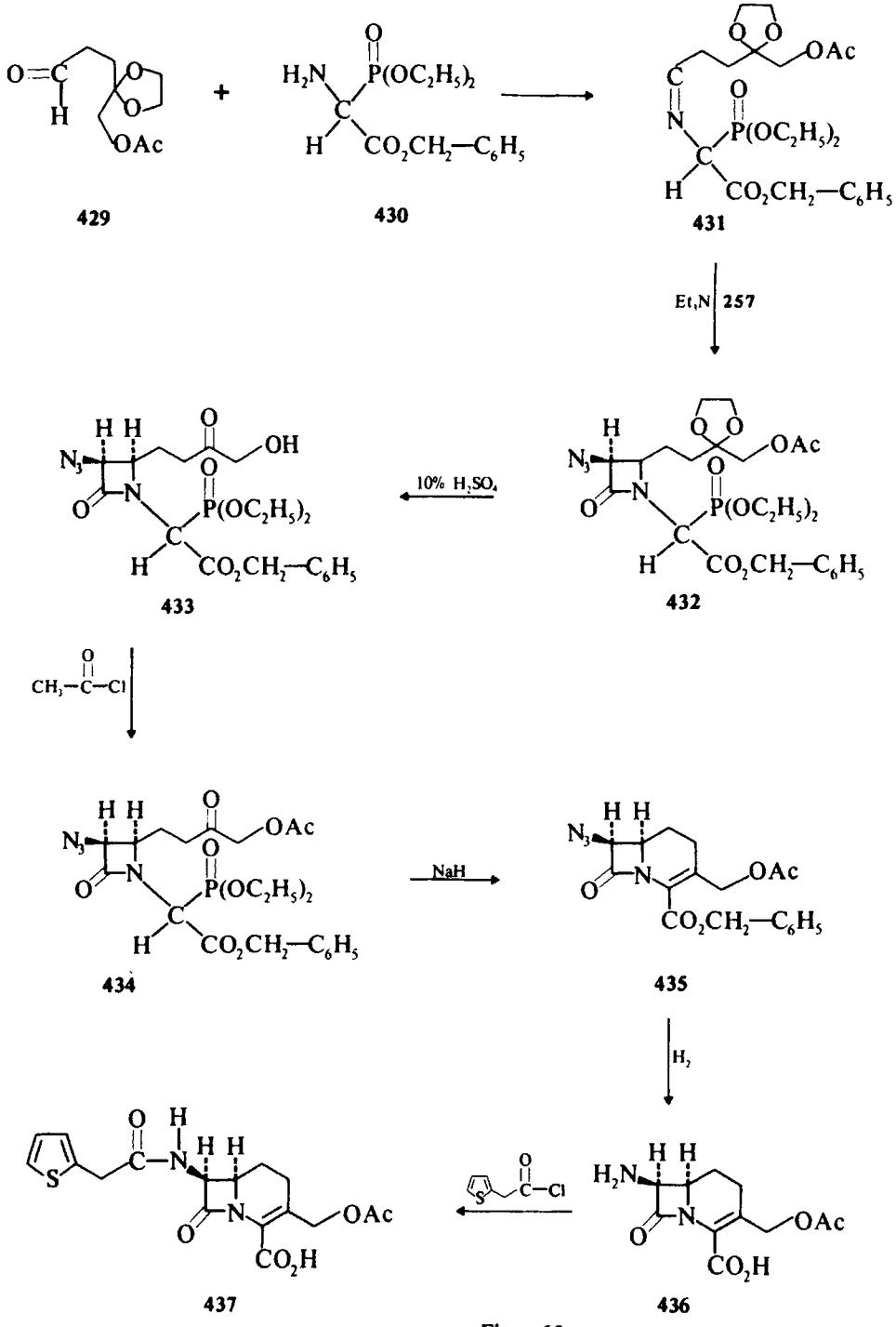

429
430
431
Et3N 257
10% H2SO4
433
432
CH3—C—Cl
434
NaH
435
H2
437
436

Figure 62

trifluoroacetic acid gave *dl*-**447**.[100] A summary of these reactions is presented in Figure 64.

Doyle and co-workers disclosed the reaction of azidoacetyl chloride **257** with a cinnamylidene Schiff base **448**, giving stereospecifically the *cis*-azetidinone **449** in 98% yield.[101] This β-lactam can be envisioned as an appropriate precursor for the unnatural oxacephem **455**. The reaction of **449** with sodium hydroxide produced crystalline acid **450** in 86% yield. This acid was converted to its benzyl ester **451** in 99% yield. The olefin of **451** was ozonized at −78°C, reduced with sodium borohydride, mesylated, and hydrolyzed with trifluoroacetic acid to give **452** in 42% overall yield. Cyclization of **452** was achieved with triethylamine in refluxing methylene chloride to give the oxacephem **453** in 80% yield. The azide function of **453** was reduced by catalytic hydrogenation to give the nucleus **454**, which was reacylated with phenoxyacetyl chloride to give *dl*-oxacephem **455** in 30% overall yield. Conversion to the free acid was carried out by hydrogenation, affording oxacephem **456** in 84% yield.[101] The importance of the cycloaddition reaction affording the azetidinone with the requisite C_3-amido function is demonstrated by the enhanced antimicrobial activity of *dl*-**456** as compared to cephem **457**, derived from natural caphalosporin C.[101] These transformations are illustrated in Figure 65.

Just and Zamboni reported the stereospecific synthesis of azetidinones **464** and **473**, in which the $C_{6,7}$-amido and the $C_{3,4}$-carboxyl (or its acid equivalent) of penicillins and cephalosporins, respectively, were incorporated into the given azetidinones.[102,103] These investigators found that cinnamylidene Schiff base **458** reacted with azidoacetyl chloride **257** in the presence of triethylamine to give a 74% yield of *cis*-azetidinone **459**.[102] The azide function was reduced with hydrogen sulfide–triethylamine to afford amine **460**, which was acylated with phenylacetyl chloride to give **461** in 60% yield. The amide **461** was ozonized, reduced with sodium borohydride at −50°C, and alkylated with diazomethane to give methyl ether **462**. The silyl protecting group of **462** was removed with trifluoroacetic acid to afford the alcohol **463**, which was oxidized to the aldehyde with pyridinium chlorochromate and finally to the acid **464** with silver oxide–sodium cyanide in methanol.[102] This sequence is illustrated in Figure 66.

In a similar manner, Just and Zamboni found that Schiff base **465** reacted with azidoacetyl chloride **257** to give *cis*-azetidinone **466** in 81% yield.[103] Ozonolysis of **466**, followed by reduction with sodium borohydride and reaction with methane sulfonyl chloride and triethylamine, afforded mesylate **467**. This was treated with potassium fluoride and 18-crown-6 ether to give **468** in 95% yield. The silyl ether **468** was treated with trifluoroacetic acid to give the alcohol (**469**) which was oxidized with chromium trioxide–acetic acid to the free acid (**470**). This in turn was converted to its benzhydryl ester **471**, which was reduced to the amine and acylated with phenylacetyl chloride to give amide **472**. Conversion to the free acid **473** was achieved by hydrogenation. This is presented in Figure 67. Unfortunately, neither **464** nor **473** showed any antimicrobial activity.[102,103]

An important observation associating the relative basicity of the nitrogen of Schiff base **474** and the stereochemistry of the azetidinones derived from the reaction of **474** with azidoacetyl chloride **257** was made by Just and co-workers.[104] For

TFAA
Et3N
H2
C6H5OCH2-C-Cl
311
438
439
440
441

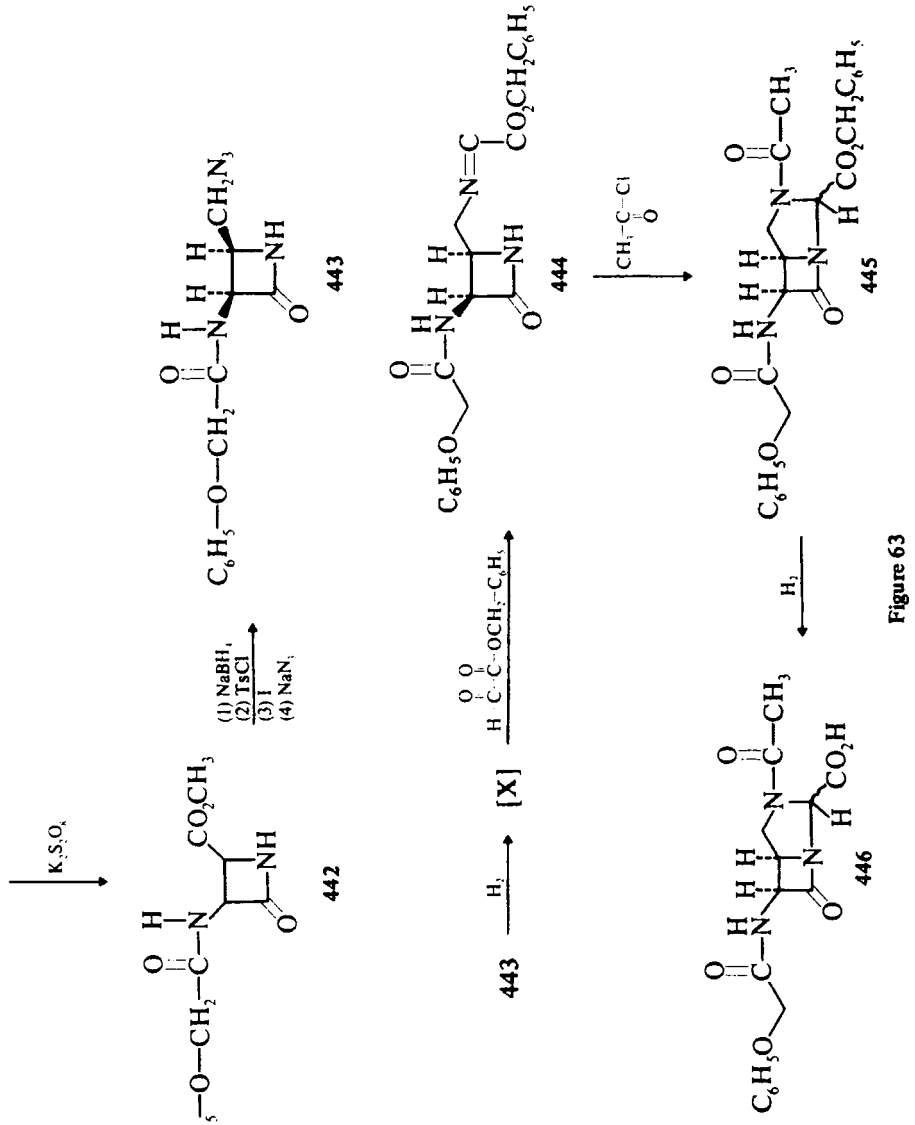


Figure 63

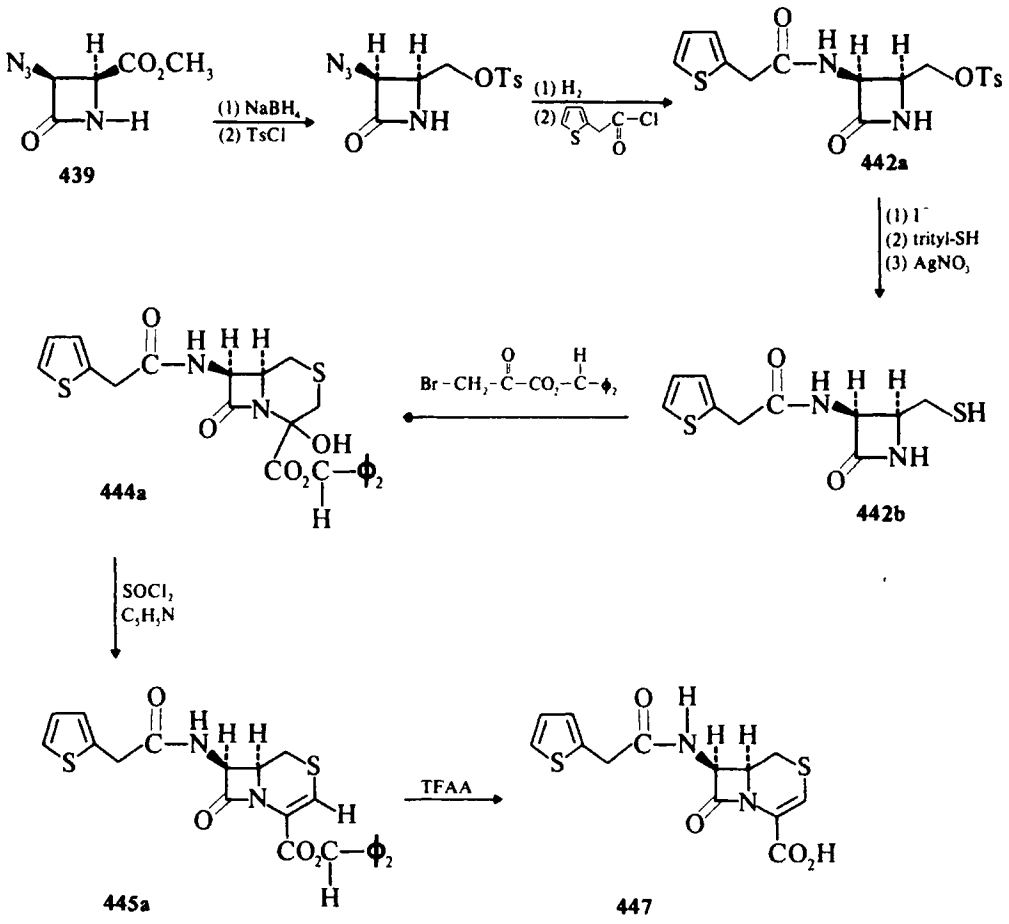


Figure 64

example, if the pK_a of the nitrogen of **474** was greater than 2.05, *cis*-azetidinones were formed exclusively. However, when the pK_a of the nitrogen was less than 2.05, varying amounts of *trans*-azetidinones were produced.[104] A summary of these data is presented in Figure 68.

Bachi and Vaya reported a synthetic method for the conversion of 3-azido-azetidinone to 3-amidoazetidinone that obviated the cumbersome problem of azide reduction.[105] For example, these investigators reacted azidoacetyl chloride **257** with thioimidate **489** to give *trans*-azetidinone **490** in 83% yield along with *cis*-azetidinone **491**, isolated in 6% yield. Treatment of **490** with triphenylphosphine **492** afforded iminophosphorane **493** in 90% yield. The iminophosphorane was subsequently acylated with phenoxyacetyl chloride to give amide **494** in 75% yield (based on azide **490**).[105] These reactions are shown in Figure 69.

The synthesis of cephalothin lactone **501**, utilizing the activated acyl–azomethine cyclization was reported by Edwards and co-workers.[106] These investigators found

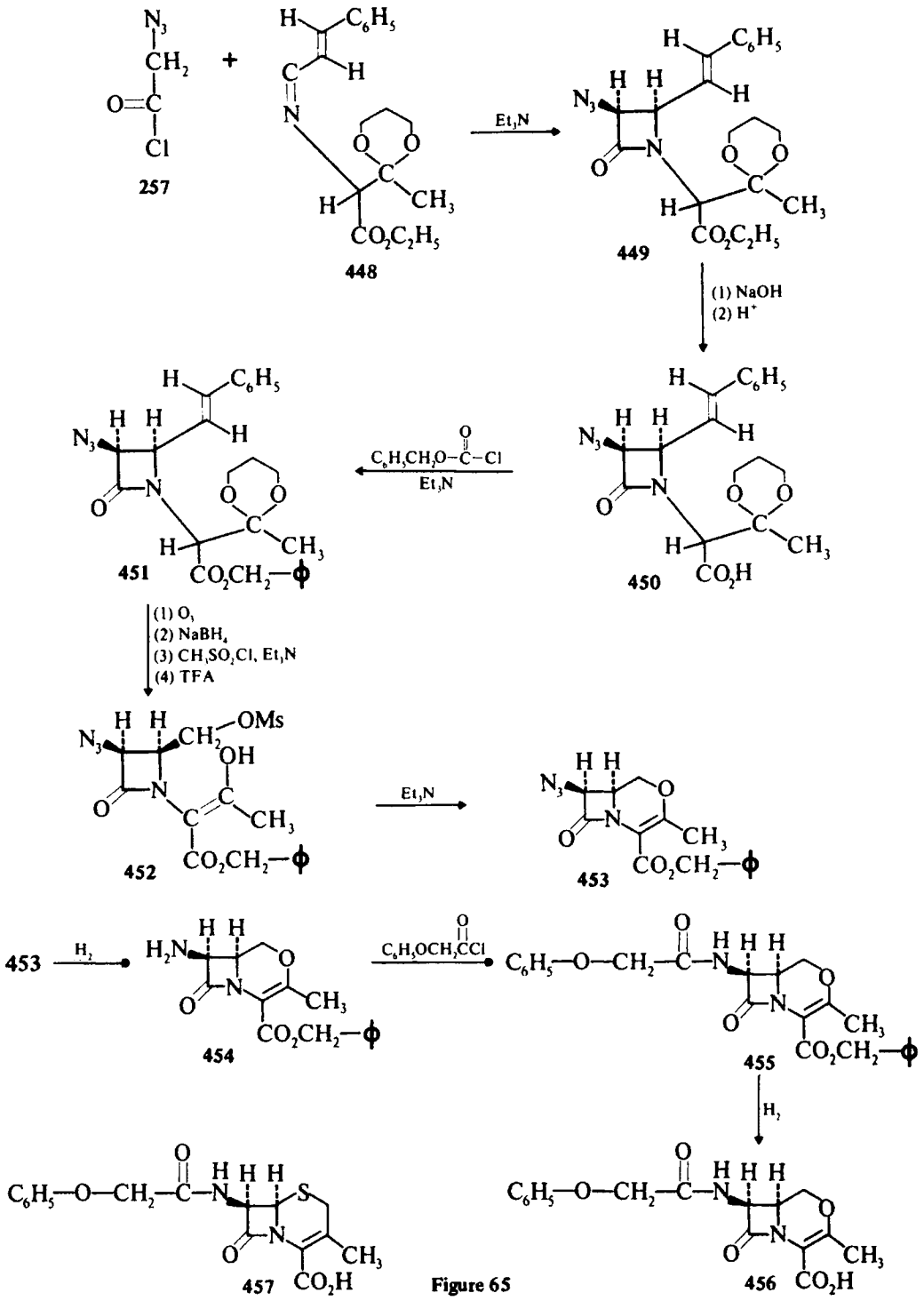

257
448
Et3N
449
(1) NaOH
(2) H+
450
C6H5CH2O–C–Cl
Et3N
451
(1) O3
(2) NaBH4
(3) CH3SO2Cl, Et3N
(4) TFA
452
Et3N
453
453
H2
454
C6H5OCH2CCl
455
H2
456
457

Figure 65

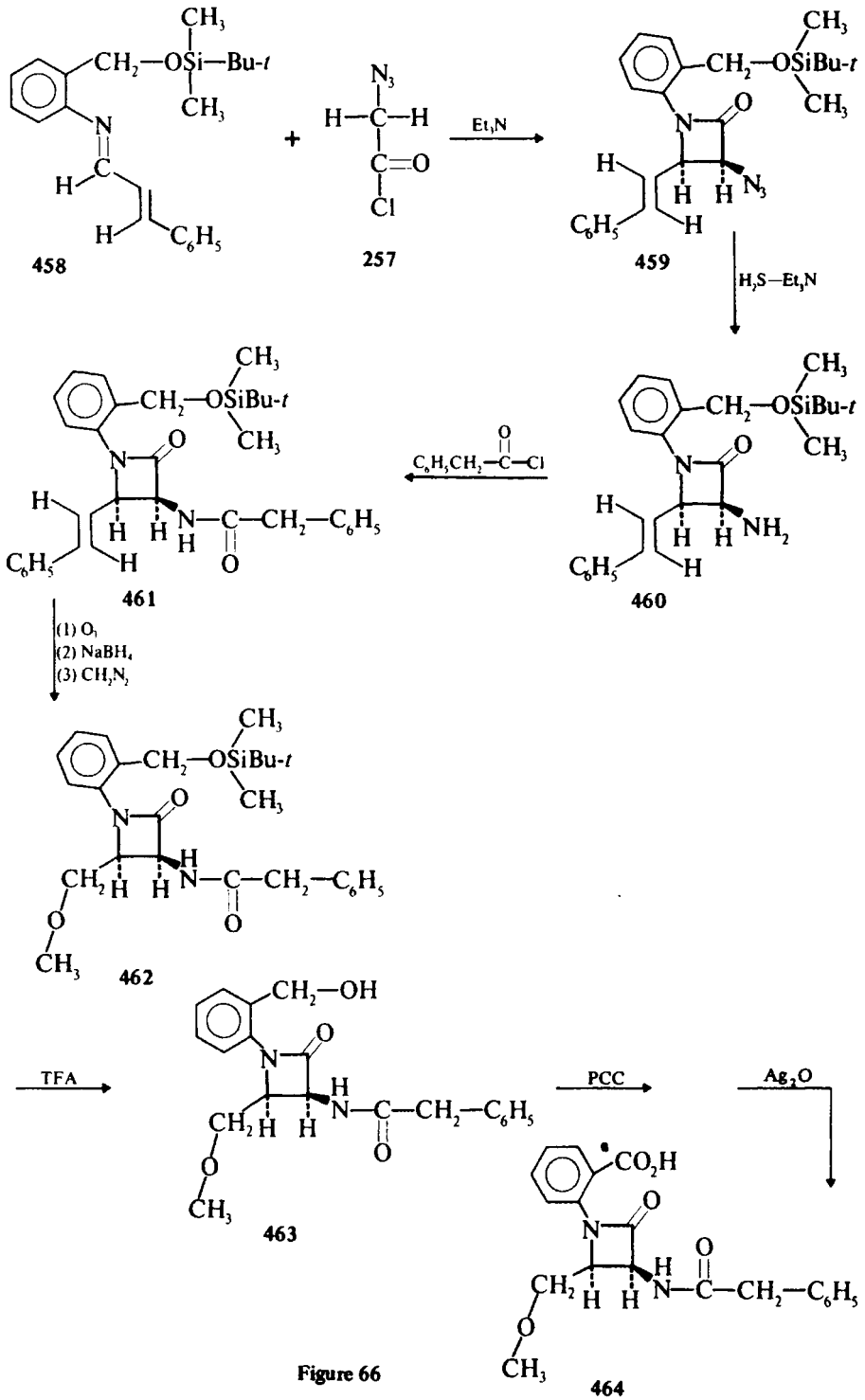

458
257
Et3N
459
H2S—Et3N
460
C6H5CH2—C—Cl
461
(1) O3
(2) NaBH4
(3) CH2N2
462
TFA
463
PCC
Ag2O
464

Figure 66

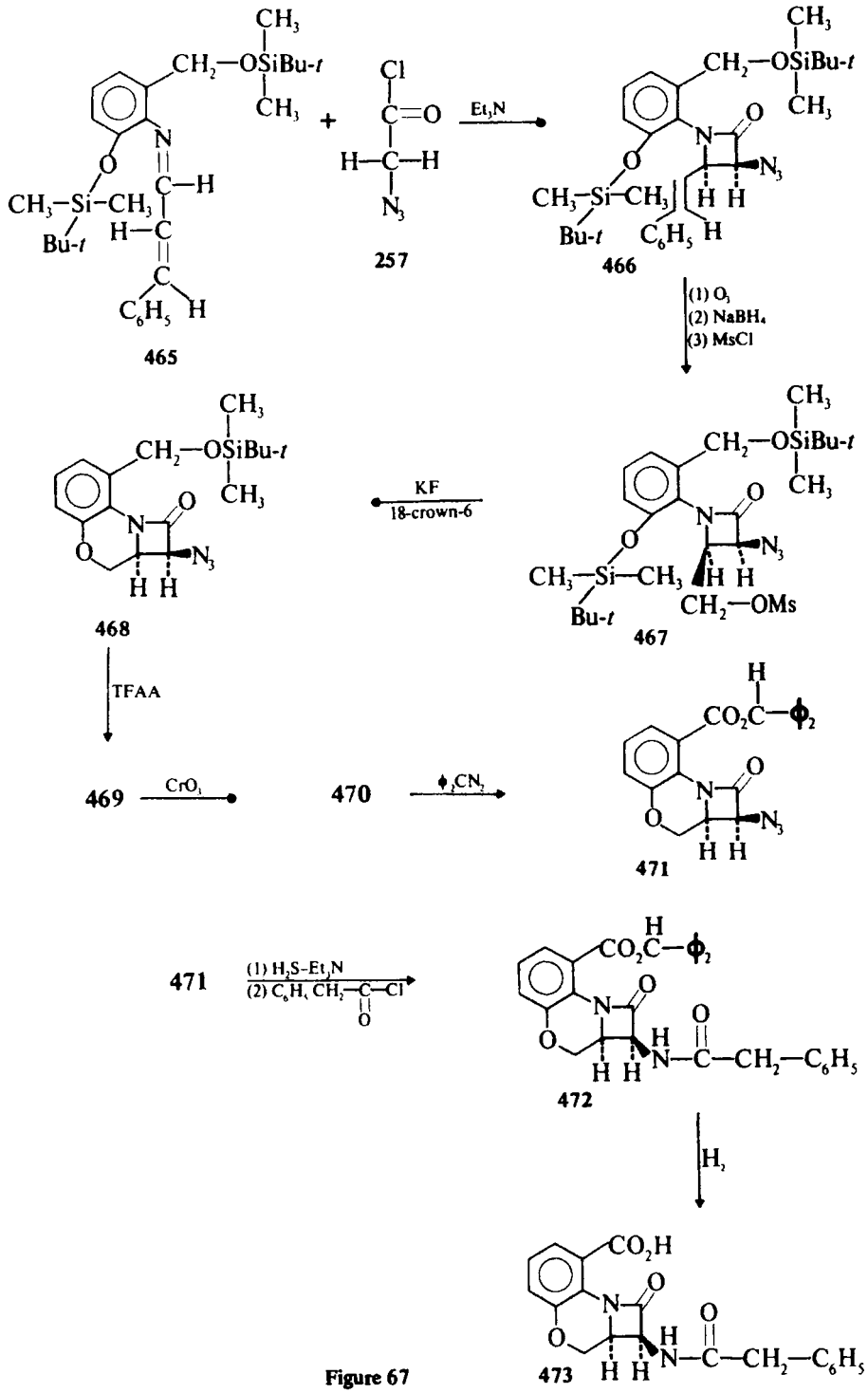
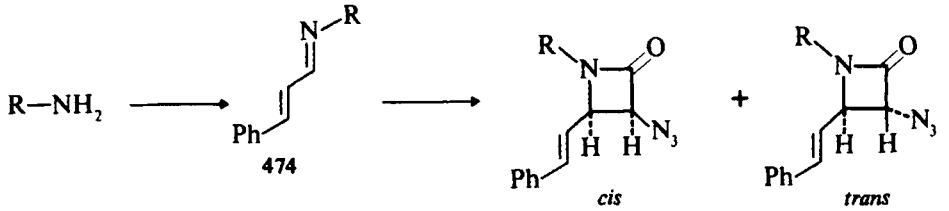
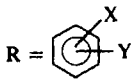

465
257
466
(1) O3
(2) NaBH4
(3) MsCl
467
KF
18-crown-6
468
TFAA
469
CrO3
470
471
(1) H2S-Et3N
(2) C6H5CH2—C—Cl
472
H2
473

Figure 67



Compound	R = 	pK_a	Yield of *cis* Isomer (%) Isolated by Nmr	Yield of *trans* Isomer (%) Isolated by Nmr
475	X = Y = H	4.6	50 90	
476	X = *p*-Cl; Y = H	3.98	40 90	
477	X = *o*-CH_2OTBDMS;[e] Y = H	> 3[a]	70 95	
478	X = *o*-TBDMS; Y = H	> 3[a]	60 90	
479	X = *o*-CH_2OTBDMS; Y = *o*-TBDMS	> 3[a]	65 80	
480	X = Y = *o*-OTBDMS	> 3[a]	40 > 73	
481	X = *m*-NO_2; Y = H	2.46	80	
482	X = *o*-OMe; Y = *p*-COOMe	2.4[b]	85	
483	X = *p*-Cl; Y = *o*-Cl	2.05	60	15
484	X = *o*-COOH; Y = *o'*-OMe	2.0[c]	15	15
485	X = *o*-COOH; Y = H	2.2		30
486	X = *o*-TBDMS; Y = *p*-NO_2	< 1.5		2[d] 70
487	X = *p*-NO_2; Y = H	1	50	25
488	X = *p*-NO_2; Y = *o*-CH_3	~ 1	5	50

[a] estimated
[b] measured
[c] measured on corresponding methyl esters
[d] In THF.
[e] TBDMS = *t*-butyldimethylsilyl

Figure 68

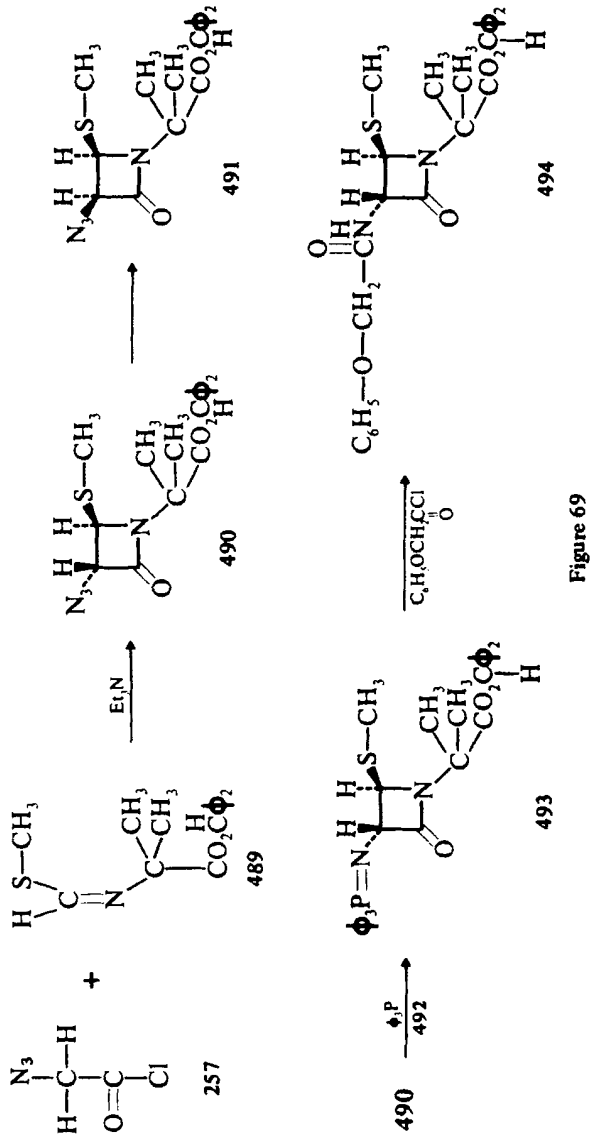


Figure 69

that furanothiazine **495** underwent cycloaddition with azidoacetyl chloride **257** to give *trans*-azetidinone **496** in 45% yield. Reduction of the azide function with ammonium sulfide afforded the amine **497**, which was epimerized by conversion to its *p*-nitrobenzaldehyde Schiff base and treated with base to afford a 4 : 1 mixture of *trans* and *cis* isomers, **498** and **499** respectively. The 7-β isomer **499** was isolated, hydrolyzed, and acylated with thienyl chloride to give β-lactam **500**. Conversion of **500** to cephalothin lactone **501** was completed by bromination in acetic acid followed by rearrangement with *p*-toluenesulfonic acid in refluxing chloroform.[106] This sequence is illustrated in Figure 70.

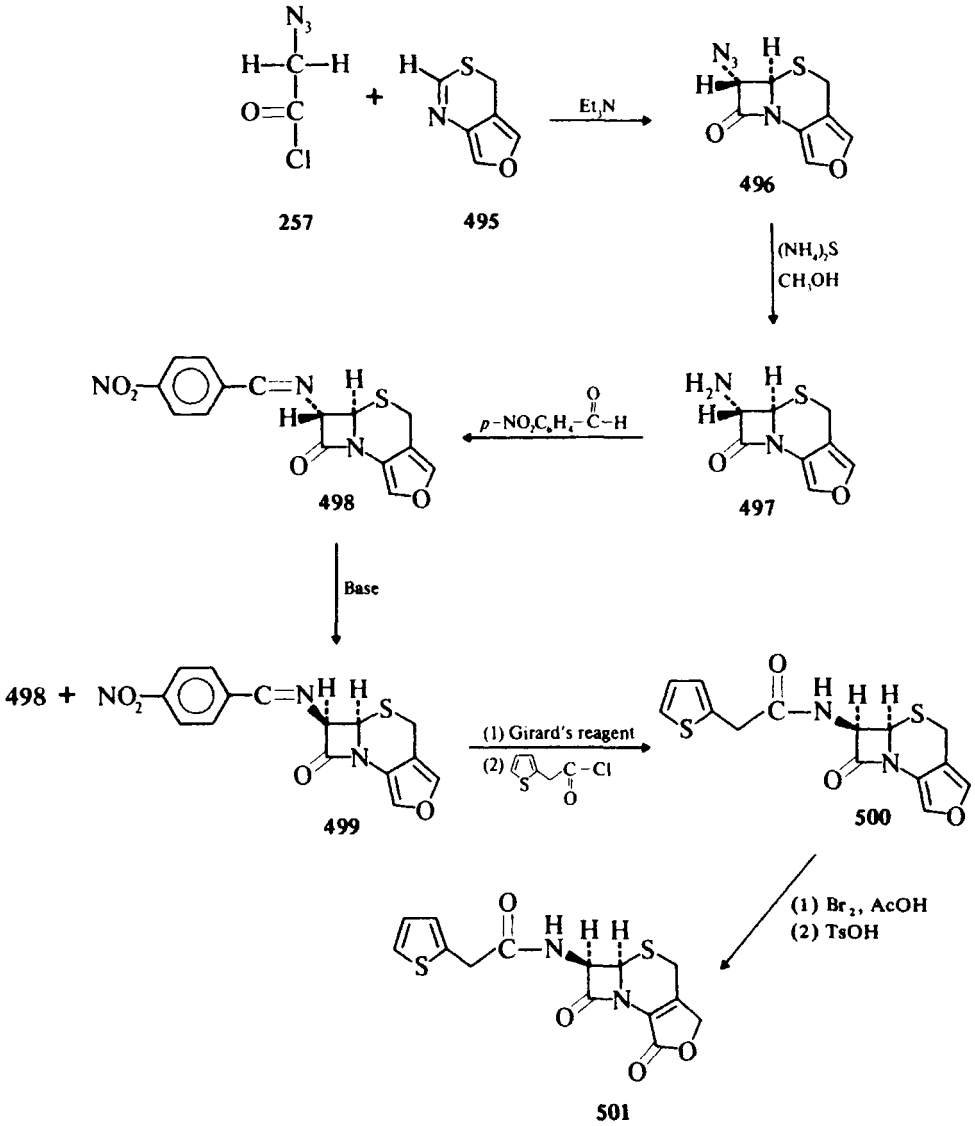


Figure 70

The very elegant contruction of nocardicin A **504**, utilizing the acid chloride-Schiff base sequence and chiral induction, has been reported by Kamiya and co-workers.[107] The reaction of hexahydro-*s*-triazine **502** with phthalimidoacetyl chloride **253**, pyridine, and $BF_3 \cdot OEt_2$ in methylene chloride at $-78°C$, followed by warming to $0°C$, gave a 3 : 1 mixture of epimers of **503** in 87% yield. Epimer **503** was crystallized and converted to nocardicin A (Figure 71).[100]

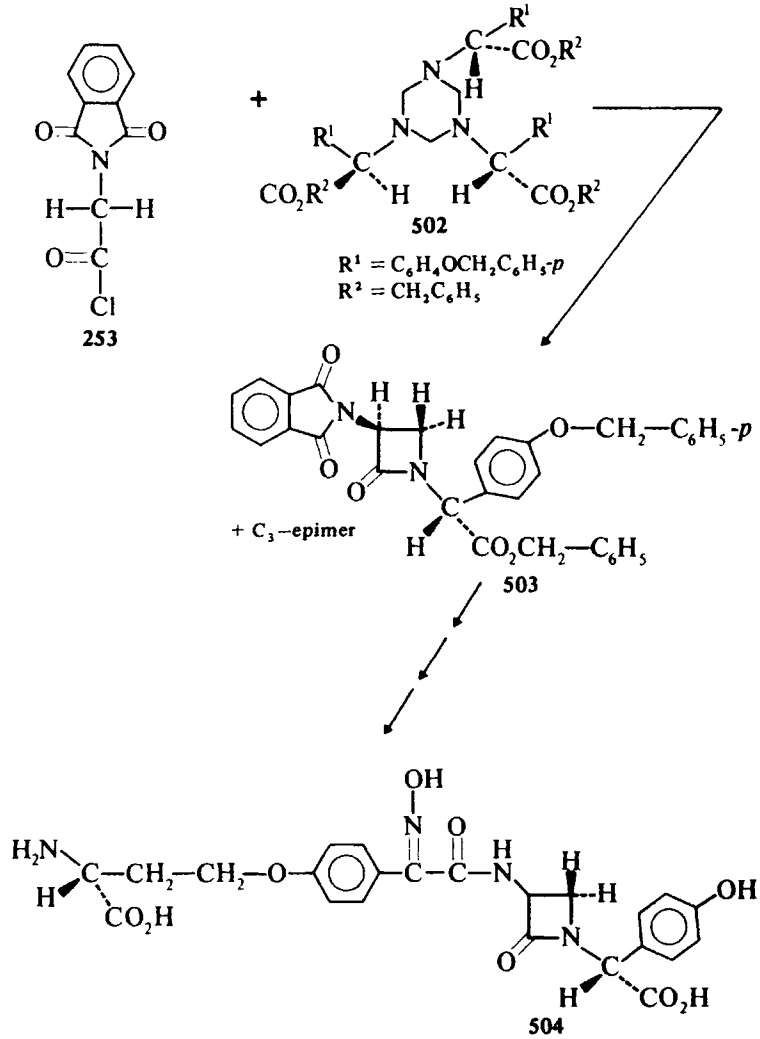


Figure 71

Other reactions utilizing ketene–azomethine [2+2] concerted cycloadditions or activated acyl–azomethine nonconcerted cycloadditions in the synthesis of β-lactams are variations of the basic theme that has been described. The representative reactants and azetidinones produced are presented in Table 1.

TABLE 1. FORMATION OF AZETIDINONES BY KETENE–AZOMETHINE CYCLOADDITIONS

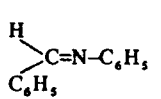
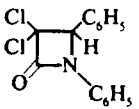
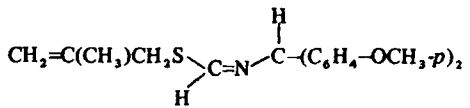
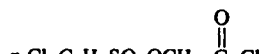
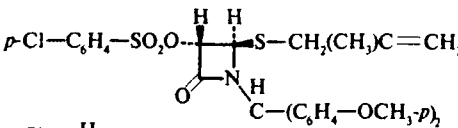
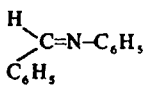
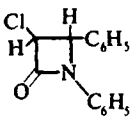
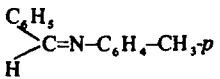
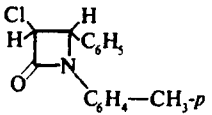
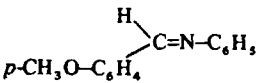
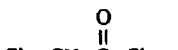
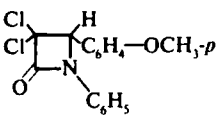
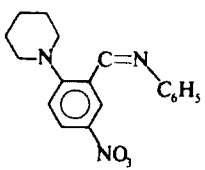
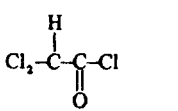
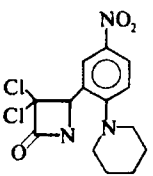
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			83	108
			87	109
			59	110
			52	111
			87	112
			85	113

TABLE 1 CONTINUED

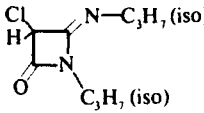
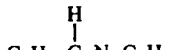
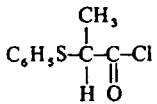
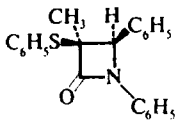
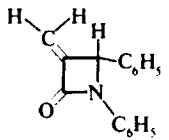
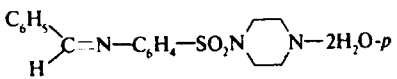
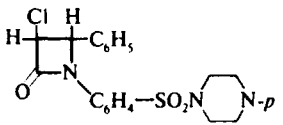
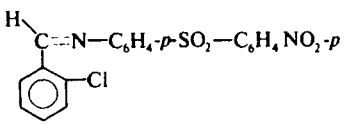
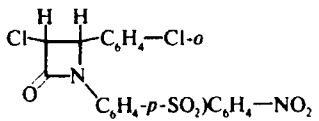
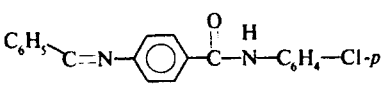
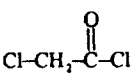
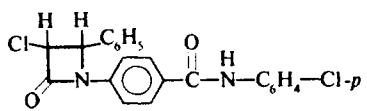
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
(iso)C_3H_7–N=C=N–C_3H_7(iso)	Cl–CH_2–C(=O)–Cl		65	114
			58	115
"	"		72	116
	Cl–CH_2–C(=O)–Cl		20	117
	Cl–CH_2–C(=O)–Cl		60	118
			75	119

TABLE I CONTINUED

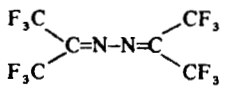
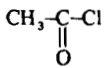
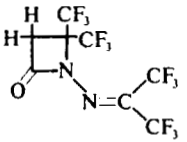
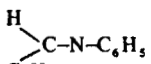
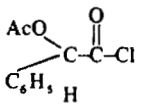
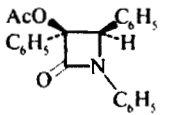
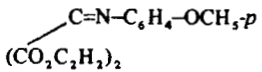
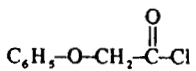
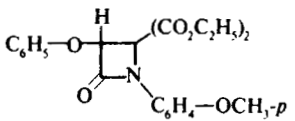
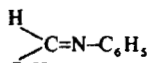
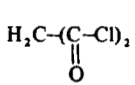
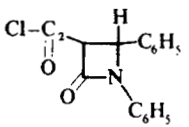
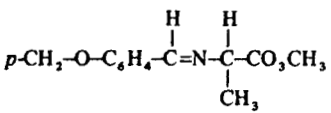
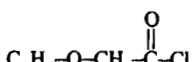
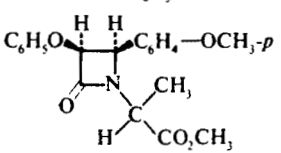
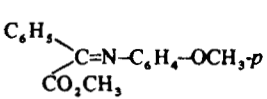
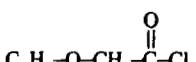
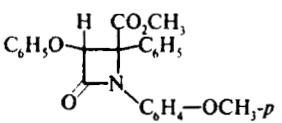
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			75	120
			90	121
			–	122
			–	123
			32	124
			73	125

TABLE 1 CONTINUED

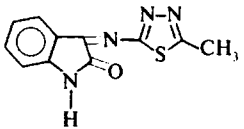
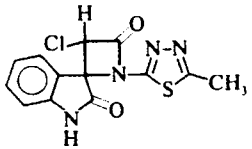
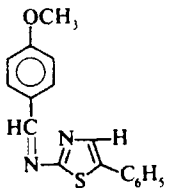
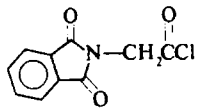
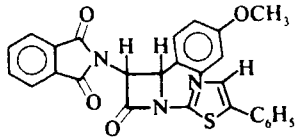
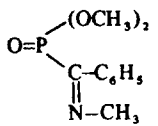
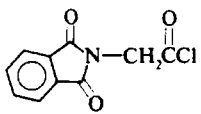
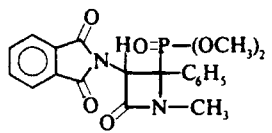
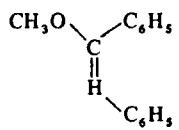
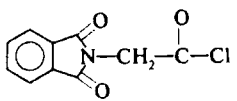
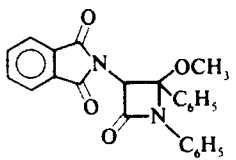
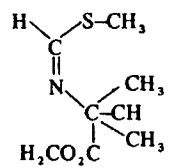
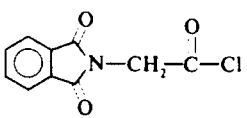
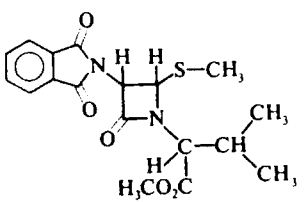
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			–	126
			64	127
			18	128
			70	129
			40	130

TABLE 1 CONTINUED

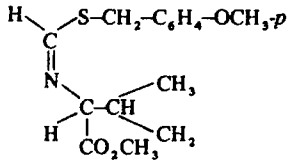
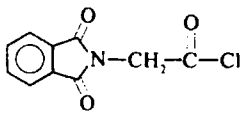
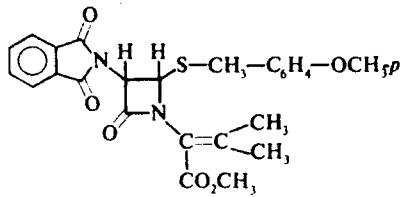
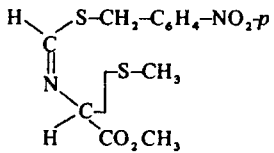
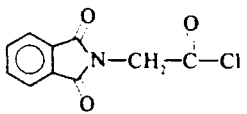
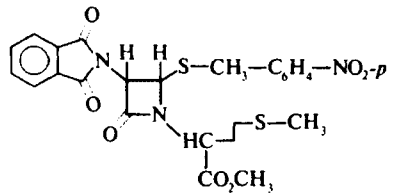
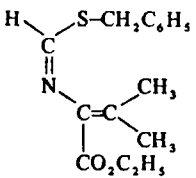
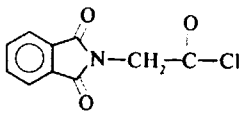
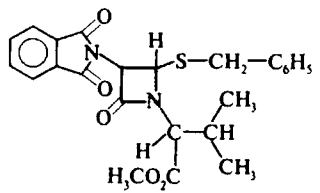
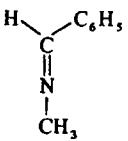
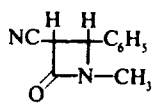
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			30	131
			22	132
			39	133
			42	134

TABLE 1 CONTINUED

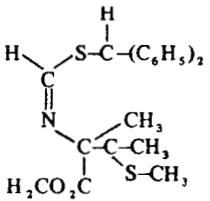
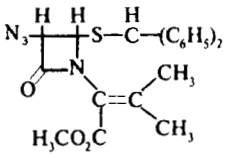
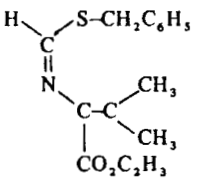
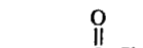
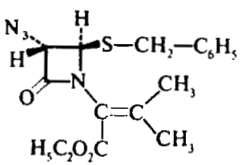
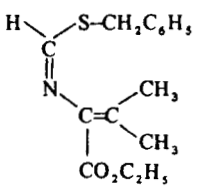
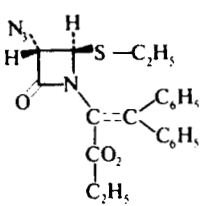
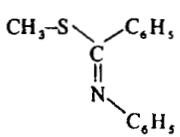
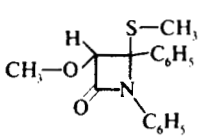
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			–	135
			25	136
			94	137
			–	138

TABLE 1 CONTINUED

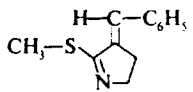
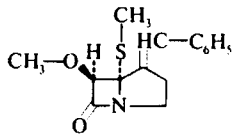
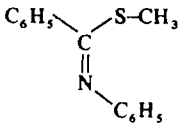
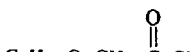
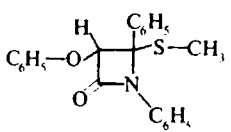
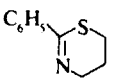
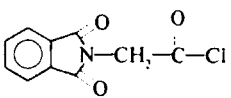
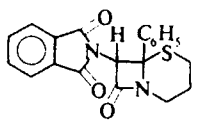
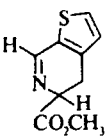
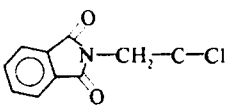
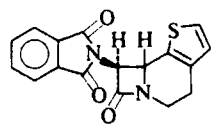
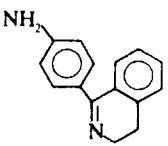
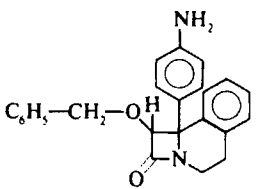
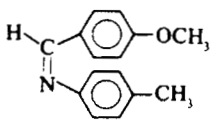
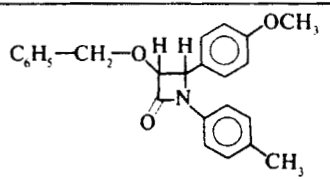
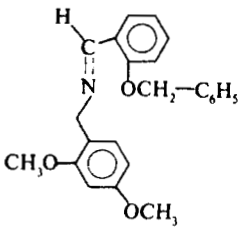
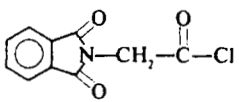
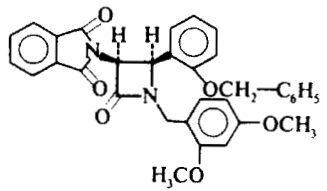
Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			68	139
			90	140
			71	147
			24	148
			80	149

TABLE 1 CONTINUED

Azomethine Group	Acyl Group	Azetidinone	Yield (%)	Reference
			56	150
			77	151

3. [2+2] Cycloaddition Reaction of Isocyanates and Olefins III + XII → IV

The [2+2] cycloaddition reaction between azomethine substrates and ketenes to give the corresponding azetidinone has been extensively reviewed in the previous sections. The importance of the (I + XI → II)[9] cycloaddition in the construction of biologically active β-lactams was clearly demonstrated in several synthetic examples (see Figures 57–71). The limitations of this sequence are: (1) the substituent destined to become joined to the azetidinone at C_3 must be incorporated into the activated acyl group or the ketene; (2) the variability in C_4 substitution is dependent upon the ability to prepare the precursor azomethine substrates; (3) the established stereochemistry at C_3 and C_4 is controlled by the mode of [2+2] cycloaddition (i.e., "free ketene" or activated acyl–azomethine cyclization).

An important contribution that extended both the versatility and the utility of the [2+2] cycloaddition reaction in the synthesis of azetidinones was reported by Perelman and Mizsak.[145] These investigators discovered that phenyl isocyanate **505** reacted with *N,N*-dimethylisobutenylamine **506** to give azetidinone **507**, which was unstable and decomposed in water very rapidly to **508**. In contrast to the instability of **507**, azetidinone **510**, derived from the reaction of **505** and *N*-methyl-*N*-phenylisobutenylamine **509**, was stable to water and acid. However, after several days of exposure to moist air, azetidinone **510** underwent hydrolysis to give **508**.[145] The synthetic sequences are illustrated in Figure 72.

This first construction of azetidinones by the cycloaddition of an isocyanate and an enamine served as a precedent for the synthesis of a large number of azetidinones from isocyanates and various substituted olefins. The advantage of this mode of [2+2] cycloaddition was the potential for controlling the stereochemistry at C_3 and C_4. For examples, *cis*-olefin **511** reacted with isocyanate **512** to give *cis*-azetidinone **513**, and *trans*-olefin **514** reacted with **512** to give *trans*-azetidinone **515**. These reactions are illustrated in Figure 73. The important question of regioselectivity in olefin–isocyanate cycloaddition has been avoided in Figure 73 but will be dealt with as this section unfolds.

Shortly after disclosure of the enamine–isocyanate reaction, Opitz and Koch reported their results of the reaction of enamines with phenyl isocyante **505**.[146] They found that 1-pyrrolidinoisobutene **516** reacted with **505** to give azetidinone **517**, in 84% yield. This was subsequently hydrolyzed with 0.1 *N* hydrochloric acid to give the aldehyde **508**. In addition, both 1-morpholinoisobutene **518** and 1-piperidinoisobutene **519** reacted with phenyl isocyanate **505** to give azetidinones **520** and **521**, in 95 and 92% yields, respectively.[146] These data are presented in Figure 74.

Most recently, Abdulla and Fuhr reported their investigation of the cycloaddition reaction of aryl isocyanates and enamines to afford β-aminoazetidinones.[147] These investigators found that aryl-substituted isocyanates **522** reacted with various 1-aminoisobutene substrates **523** to afford the corresponding azetidinones **524**. Interestingly, Abdulla and Fuhr found that the antimicrobial activity of these azetidinones was dependent upon the availability of the lone pair electrons of the amino substituent. For example, the conversion of **526** to its methylated salt **527**

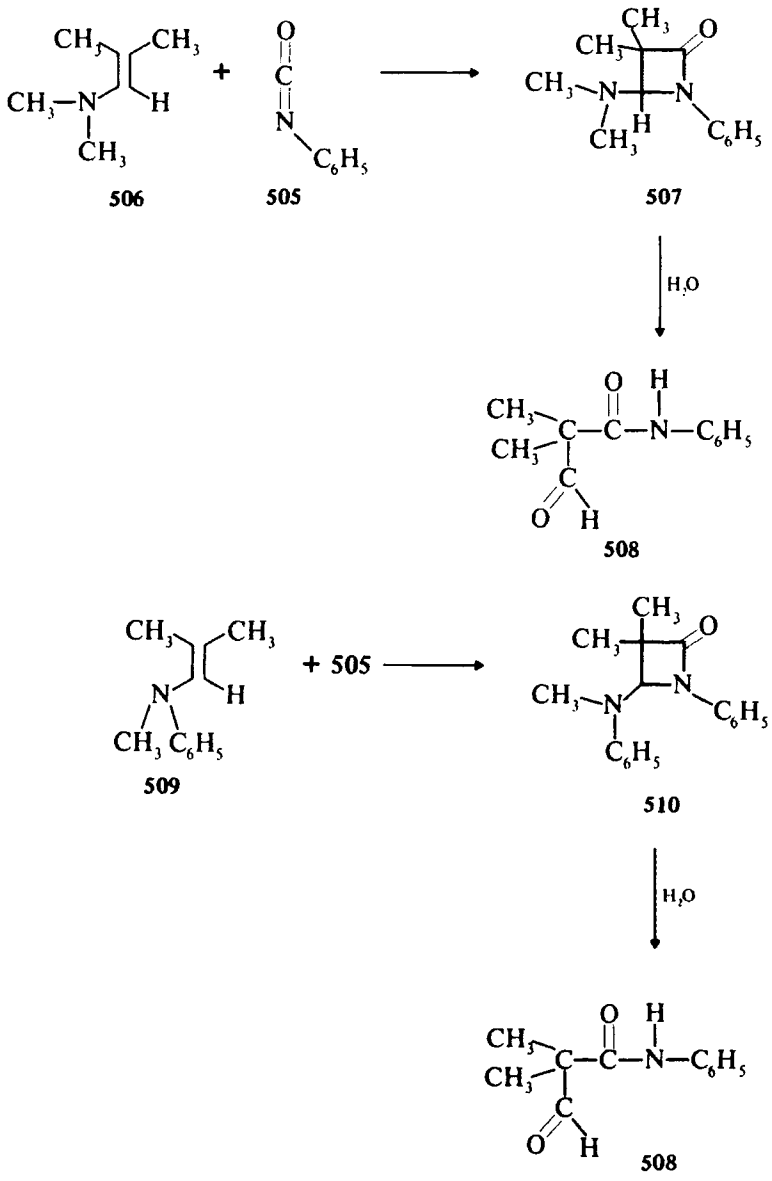


Figure 72

removed the antimicrobial activity of **526** and enhanced the physical stability of azetidinone **527** as compared to **526**.[147] The mechanism of the conversion of the azetidinone **524** to its aldehyde **525** and the methylation of **526** are illustrated in Figure 75. A summary of the aminoazetidinones prepared by this procedure, as well as their antimicrobial activity, is presented in Figure 76.

A major breakthrough in the utilization of olefin–isocyanate cycloaddition in

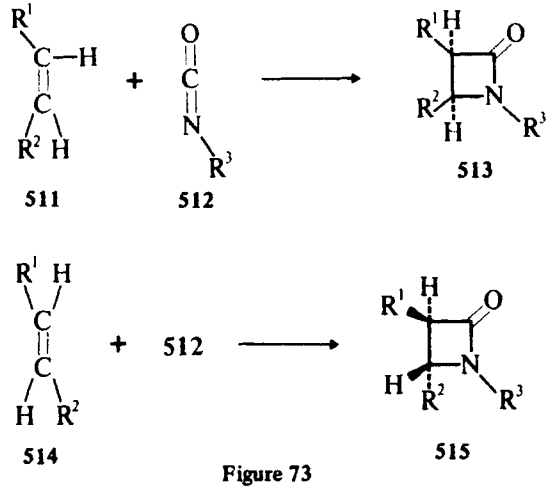


Figure 73

the construction of azetidinones occurred with the dramatic disclosure by Graf that chlorosulfonyl isocyanate (CSI) underwent smooth cycloaddition with variously substituted olefins to give the corresponding azetidinones.[148] For example, CSI **533** reacted with isobutylene **534** to afford a 70% yield of azetidinone **535** and a 30% yield of the sulfonylamide **536**.[148a] The mechanism proposed by Graf for the formation of **535** is a two-step cycloaddition process in which initial bond formation occurs between the isocyanate carbon and the olefinic carbon that produces the more stable carboniun ion, as depicted in zwitterionic transition state **537**.[148] Graf suggested that **537** can undergo the requisite bond formation to give **535** or undergo a prototropic shift to give **536**. An alternate pathway for the formation of **536**, which has been overlooked by investigators, is the simple "ene" reaction, which may, in fact, compete with transition state **537**. The "ene" reaction, being the exclusive pathway for the formation of **536**, would imply that zwitterion **537** collapses selectively by azetidinone **535** formation. The mechanism for the formation of azetidinone **535** and sulfonylamide **536** via the zwitterion **537** is illustrated in Figure 77, and the alternative "ene" pathway for the conversion to **536** is presented in Figure 78. Some additional azetidinones produced by the CSI–olefin route are presented in Figure 79.[148b]

The disclosure by Graf initiated an avalanche of investigations conceived to test the limitations of the sulfonyl isocyanate reaction with a variety of olefins. Soon after Graf's publication, Effenberger and Fleiter reported that enol ether **545** reacted with *p*-tolylsulfonyl isocyanate **546** to give azetidinone **547**.[149,150] In contrast to the singular formation of **547**, enol ether **548** reacted with isocyanate **546** to give azetidinone **549** along with the sulfonylamide **550**. These transformations are illustrated in Figure 80, and a summary of azetidinones synthesized by this procedure is presented in Figure 81.

Moriconi and Mazzocchi found that CSI **533** reacted with dihydronaphthalene **551** to give the β-lactam **552** in excellent yield.[151] This is represented in Figure 82. In addition to expanding the scope of the CSI–olefin cycloaddition reaction,

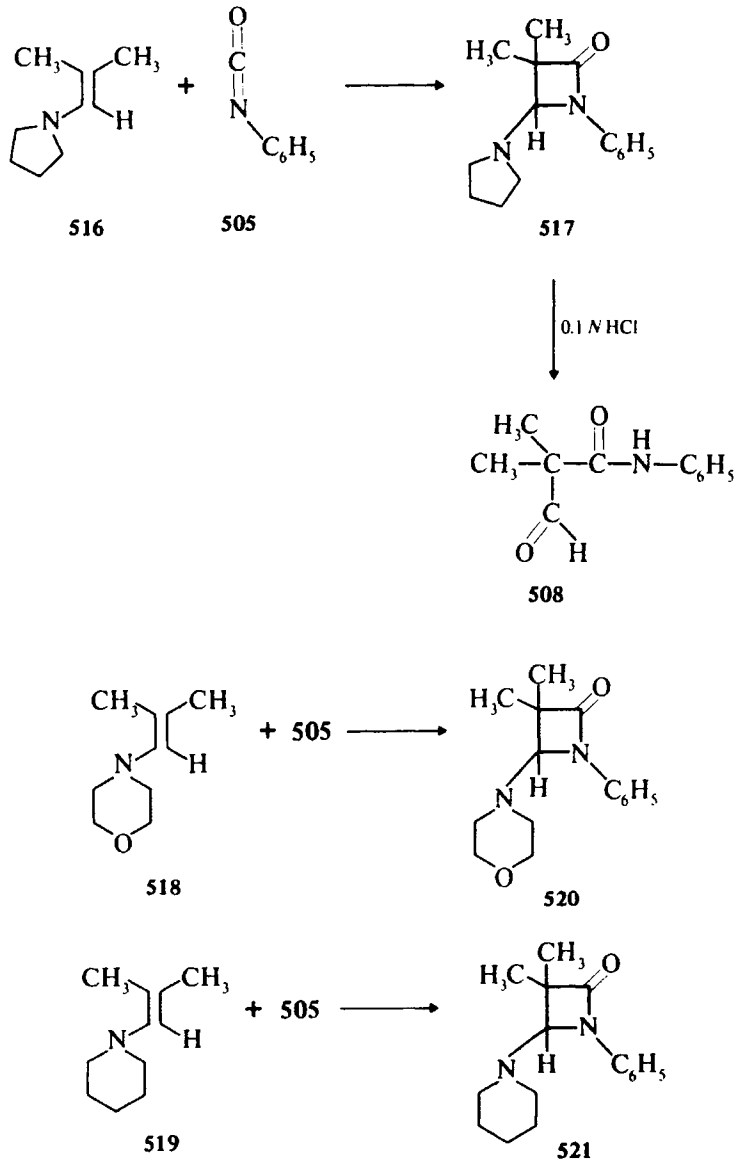


Figure 74

the regioselective formation of **552** supported the Graf hypothesis of the two-step "zwitterion intermediate" mechanism.

Moriconi and Kelly investigated the reaction of CSI **533** with a variety of allene systems.[152] For example, these investigators found that **533** reacted with 3-methyl-1,2-butadiene **553** to give azetidinone **554** in 21% yield and the carboxamide **555** in 36% yield. The orientation of functionality (i.e., the exoolefin adjacent to the carbonyl carbon) of azetidinone **554** agains supports the zwitterion pathway.[152]

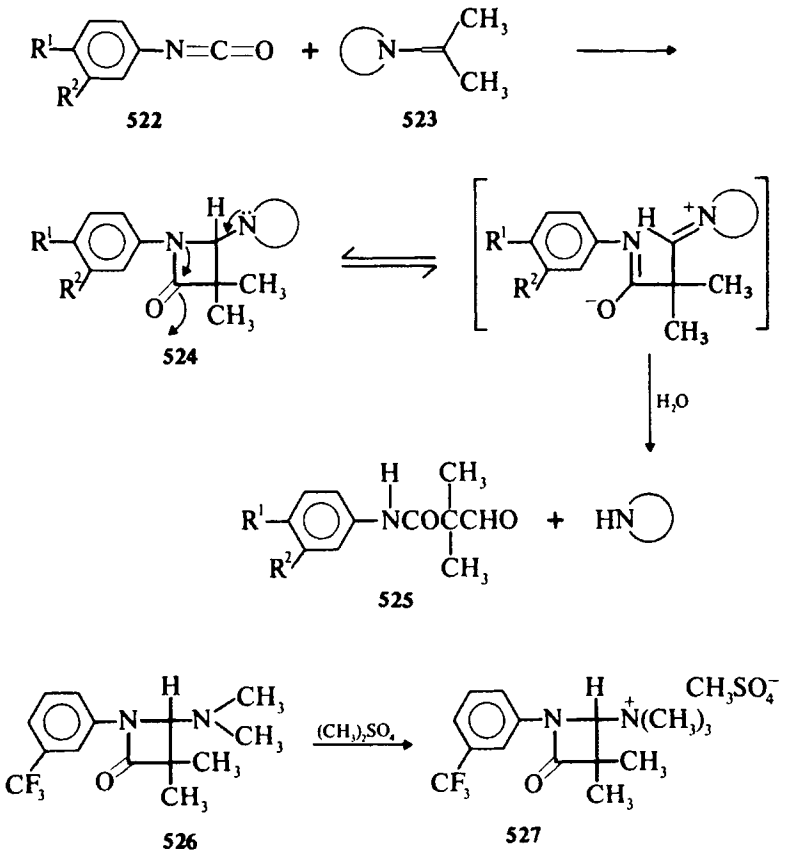
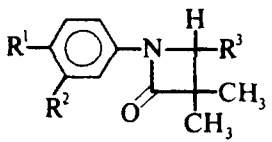


Figure 75

These reactions are presented in Figure 83 and a summary of exoolefinic azetidinones synthesized by CSI–allene cyclization is illustrated in Figure 84.

The investigations presented thus far support the contention of a "zwitterion intermediate" in the construction of azetidinones via the sulfonyl isocyanate–olefin cyclization. The strategically important question of stereochemistry has heretofore remained unanswered. There can be no doubt that without its attendant stereospecificity this powerful cycloaddition reaction would be reduced to a modestly important exercise in azetidinone formation. Indeed, there was good reason to fear the loss of stereochemical control; for if the lifetime of zwitterion intermediate **537** (see Figure 77) were greater than the rotational time about the developing carbonium ion, potentially constructive methods for the synthesis of biologically important β-lactams would have been lost.

Moriconi and Crawford made the important discovery that CSI **533** underwent cycloaddition reactions with systems susceptible to rearrangement, such as norbornene (**559**) and norbornadiene **560**, to produce the corresponding azetidinones without concomitant skeletal rearrangement.[153] For example, **533** reacted with **559** to produce **561** in 86% yield. Similarly **533** underwent smooth cycloaddition



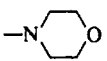
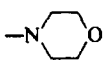
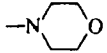
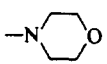
Compound	R^1	R^2	R^3	Yield (%)	Antimicrobial Activity: Microorganism	MIC (μg/ml)
526	H	CF_3	NMe_2	100	*Staphylococcus aureus* 3055	10
					S. aureus 3074	10
					Streptcoccus fecalis X66	10
					Bordetella bronchiseptica	100
528	H	Cl	NMe_2	100	*S. aureus* 3055	10
					S. aureus 3074	100
					S. fecalis X66	100
					B. bronchiseptica	100
529	H	CF_3		96.2	*S. aureus* 3055	10
					S. aureus 3074	100
					S. fecalis X66	100
530	CH_3	Cl		95.0	*S. aureus* 3055	10
531	H	Cl		93.0	*S. aureus* 3074	10
					S. fecalis X66	100
					B. bronchiseptica	100
532	Cl	Cl		91.3	*S. aureus* 3055	10
					S. aureus 3074	10
					B. bronchiseptica	100

Figure 76

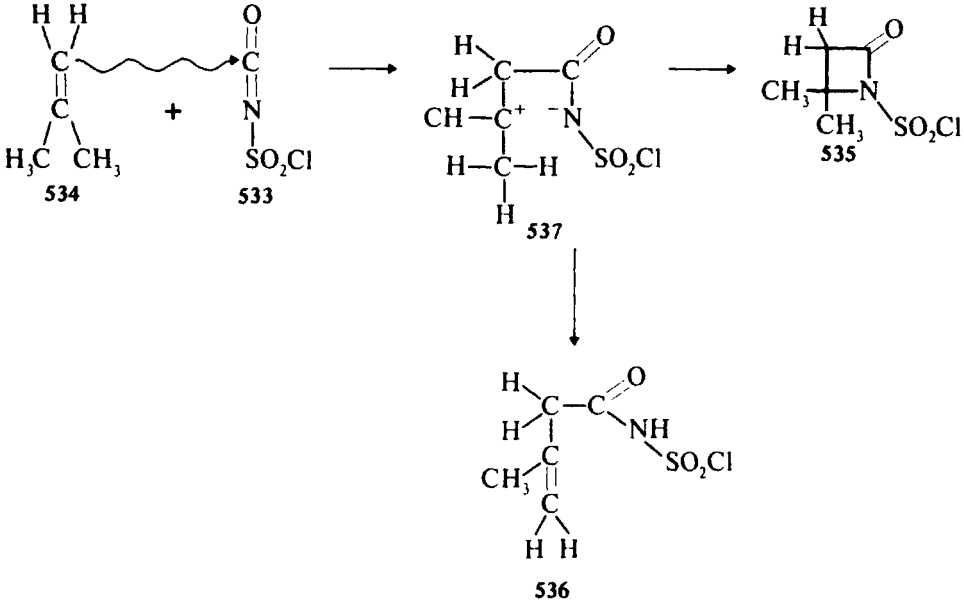


Figure 77

with **560** to afford azetidinone **562** in 94% yield. In addition, **533** underwent cycloaddition with both endodicyclopentadiene **563** and exodicyclopentadiene **564** to afford azetidinones **565** and **566** in 78 and 71% yields, respectively. Finally, bicyclo[2.2.2]octene **567** underwent smooth cycloaddition with **533** to give azetidinone **568** in 63% yield.[153] Each of these examples supports the hypothesis that the cycloaddition mechanism proceeds through a two-step zwitterionic process in which the bond-formation step (i.e., N → C) is the fast step, precluding any rapidly equilibrating bridgehead nonclassical carbonium ion skeletal rearrangement. Because the Woodward–Hoffman rules[154] forbid a concerted [2+2] cycloaddition mechanism, Moriconi and Crawford postulated a "reasonably concerted" cycloaddition mechanism in which there is an uneven rate of sigma-bond formation. This mechanism is clearly discernible in the reaction of norbornene **559** with CSI **533**. Initially, a π-complex **569** is formed from the more accessible exoface. This rearranges to the 1,4-dipole of the "Graf zwitterion intermediate" **570**, which

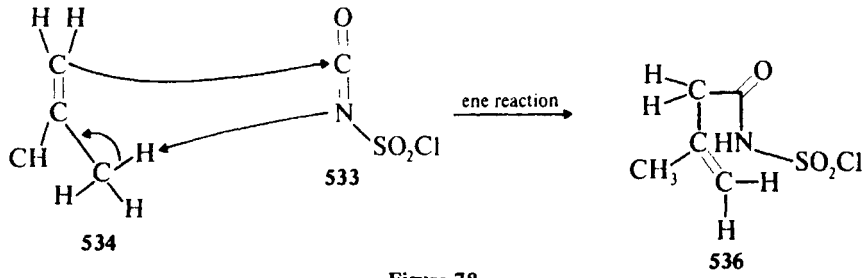
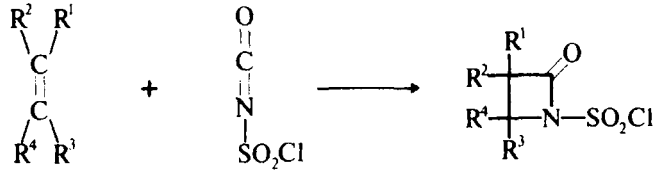


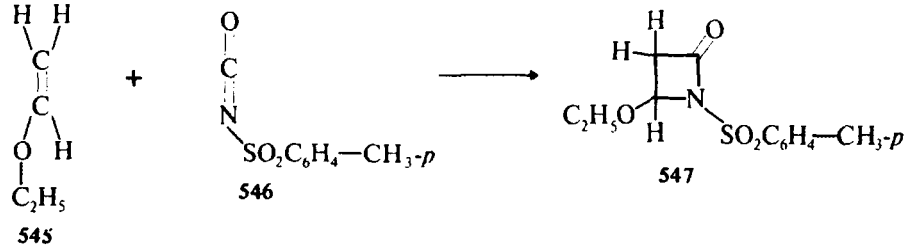
Figure 78



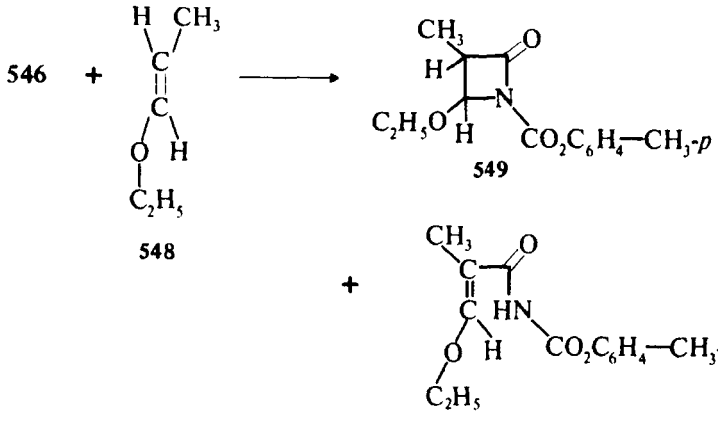
Compound	R^1	R^2	R^3	R^4	Yield (%)
535	H	H	CH_3	CH_3	69
538	H	H	CH_3	C_2H_5	65
539	H	H	CH_3	n-C_3H_7	65
540	H	H	C_2H_5	C_2H_5	65
541	H	H	CH_3	Isobutyl	50
542	H	CH_3	CH_3	CH_3	80
543	CH_3	CH_3	CH_3	CH_3	100
544	H		H		100

Figure 79

rapidly collapses to **561** with the requisite N–C bond formation.[153] The reactions of the appropriate bridged-ring olefinic systems with CSI **533** are depicted in Figure 85. The [2+2] CSI–olefin cycloaddition mechanism proposed by Moriconi and Crawford is illustrated in Figure 86.

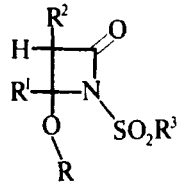


545 **546** **547**

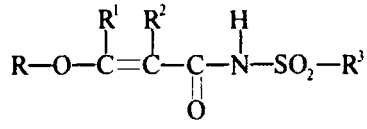


548 **549** **550**

Figure 80



a

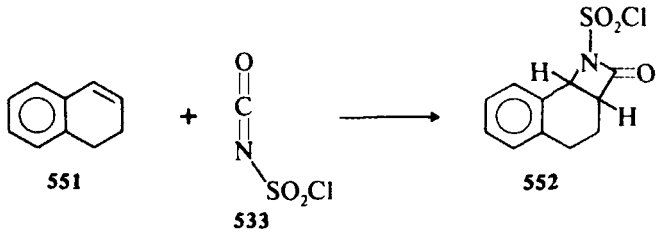


b

R	R^1	R^2	R^3	Reaction Temperature (°C)	Product
C_2H_5	H	H	p-$CH_3C_6H_4$	20	a
C_2H_5	H	CH_3	p-$CH_3C_6H_4$	20	a + b
C_2H_5	H	C_2H_5	p-$CH_3C_6H_4$	20	a
C_2H_5	H	C_2H_5	p-$CH_3C_6H_4$	80	b
C_4H_9	H	H	p-$CH_3C_6H_4$	20	a + b
C_2H_5	H	C_2H_5	Cl	15–70	b
	Dihydropyran		p-$CH_3C_6H_4$	20	a + b
	Dihydropyran		p-$CH_3C_6H_4$	80	a + b
	Dihydropyran		Cl	15–20	b

Figure 81

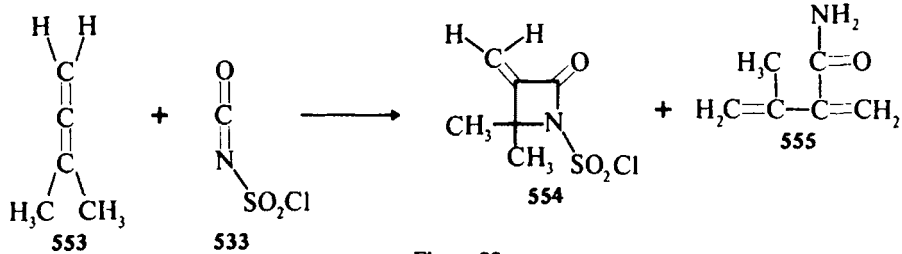
Moriconi and Jalandoni[155] found that norbornene derivative **570** reacted with **533** (regioselectively with the exoolefin) to give **571** in 85% yield. Treatment of **571** with thiophenol–pyridine in acetone removed the sulfonyl protecting group, affording azetidinone **572** in 36% yield.[155] This sequence is presented in Figure 87.



551 533 552

Figure 82

Durst and O'Sullivan reported a method for removing the chlorosulfonate protecting group of azetidinones that is superior to the thiophenol–pyridine method.[156] For example, the reaction of **574** with sodium sulfite afforded a 98% yield of azetidinone **575**.[156] This is illustrated in Figure 88.



553 533 554 555

Figure 83

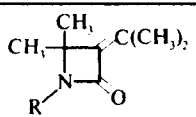
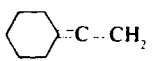
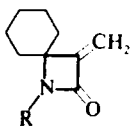
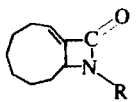
Compound	Allene	β-Lactam	R	Yield (%)
556	$(CH_3)_2C{=}C{=}C(CH_3)_2$		SO_2Cl	73
557			SO_2Cl	38
558			SO_2Cl	89

Figure 84

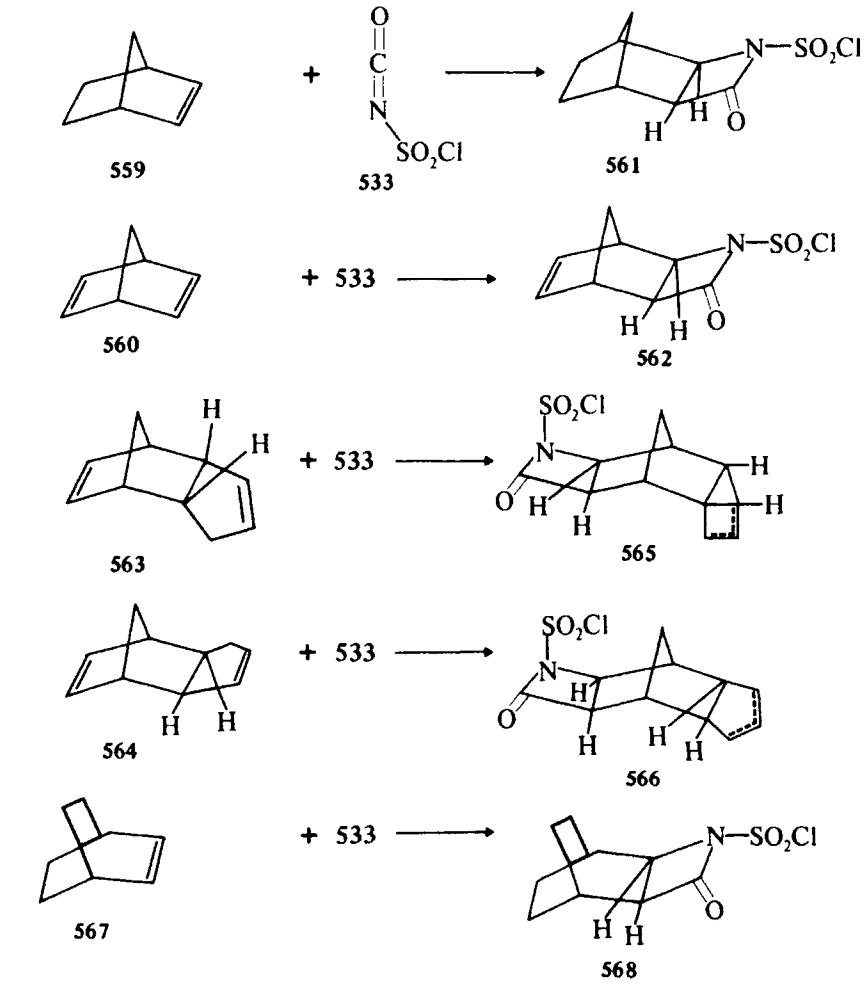


Figure 85

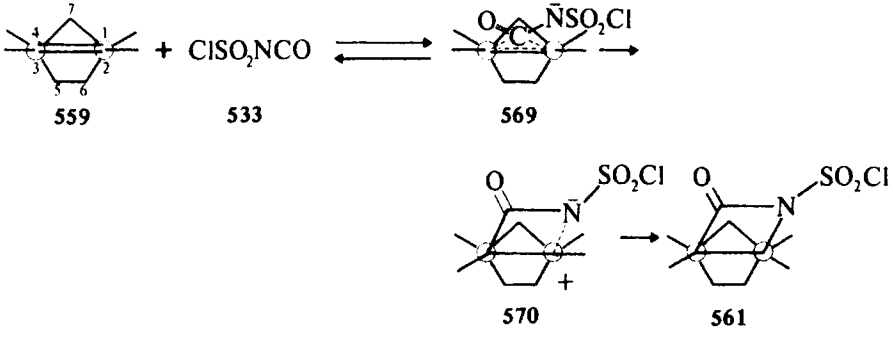


Figure 86

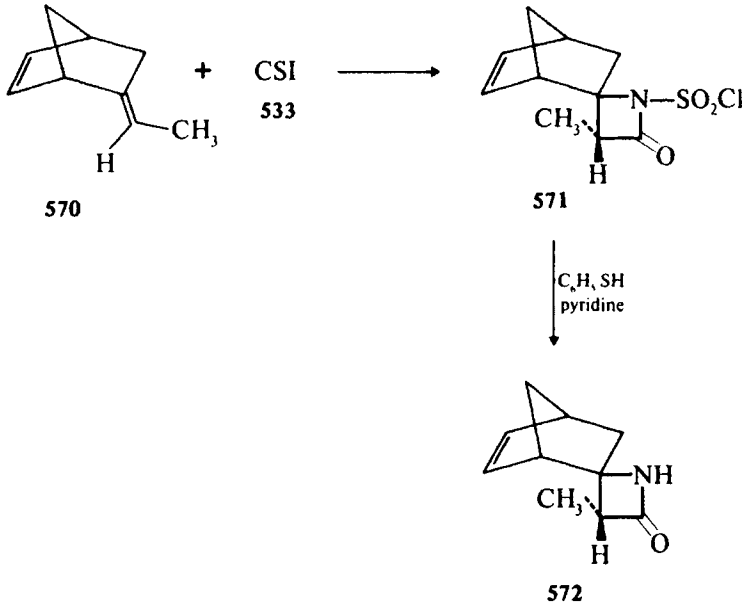


Figure 87

Bestian and co-workers reported the results of their investigation on the stereospecificity of the CSI–olefin cycloaddition reaction.[157] Indeed, the complete potential of this cycloaddition sequence in the construction of azetidinones was realized in their investigation. For example, *cis*-butene-2 **576** reacted with CSI **533** to give *cis*-azetidinone **577** in 85% yield. Similarly, *trans*-butene-2 **578** underwent cycloaddition with **533** to give *trans*-azetidinone **579**.[157] These two classical experiments unequivically support the contention that the lifetime of the Graf zwitterion intermediate **537** (see Figure 77) is significantly shorter than the

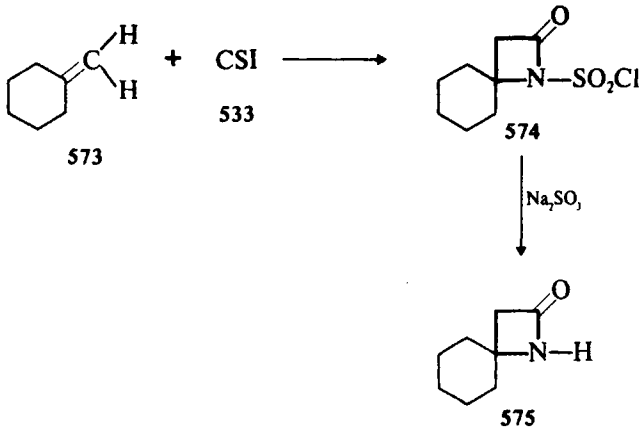


Figure 88

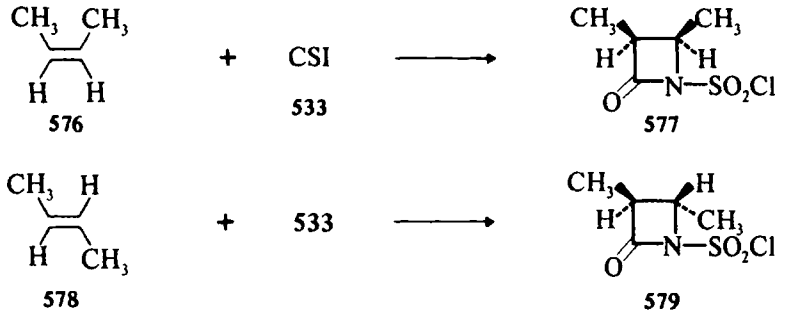
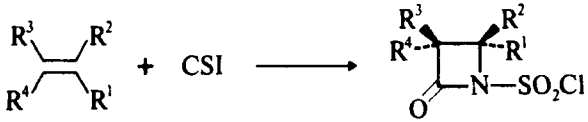


Figure 89

rotational time about the developing carbonium ion in **537**. These transformations are represented in Figure 89. A summary of the azetidinones derived from the CSI–olefin cyclization is given in Figure 90.

Haug and co-workers investigated the reaction of CSI with conjugated dienes.[158] They reported that isoprene **584** reacted with CSI **533** to give azetidinone **585**. However, the vinyl azetidinone **585** was unstable and, under acid catalysis, underwent rearrangement to pyran **586** and lactam **587**.[157] This sequence is illustrated in Figure 91.

Goebel and Clauss[159] confirmed the findings of Haug and co-workers.[158] In addition, they discovered that butadiene **588** reacted with CSI **533** to give the stable azetidinone **589** in 89% yield. Compound **589** could be hydrolyzed to the azetidinone **590** without an acid-catalyzed rearrangement. These investigators also found that isoprene **584** reacted with **533** in a regioselective manner to afford the stable azetidinone **592** in 55% yield. However, diene **591** reacted with **533** to afford the rearranged pyran **586** in 81% yield, thus confirming the report of Haug and co-workers.[158] The construction of azetidinones **589**, **590** and **592** is presented in Figure 92. A summary of the pyrans produced by the reaction of substituted butadienes with **533** is presented in Figure 93.



Olefin	β-Lactam	R^1	R^2	R^3	R^4	Yield (%)
cis-Butene-2	577	H	CH_3	CH_3	H	85
trans-Butene-2	579	CH_3	H	CH_3	H	85
cis-Hexene-2	580	H	CH_3	n-C_3H_7	H	55
trans-Hexene-2	581	CH_3	H	n-C_3H_7	H	55
cis-Heptene-2	582	H	CH_3	n-C_4H_9	H	75
cis-Heptene-3	583	H	C_2H_5	n-C_3H_7	H	65

Figure 90

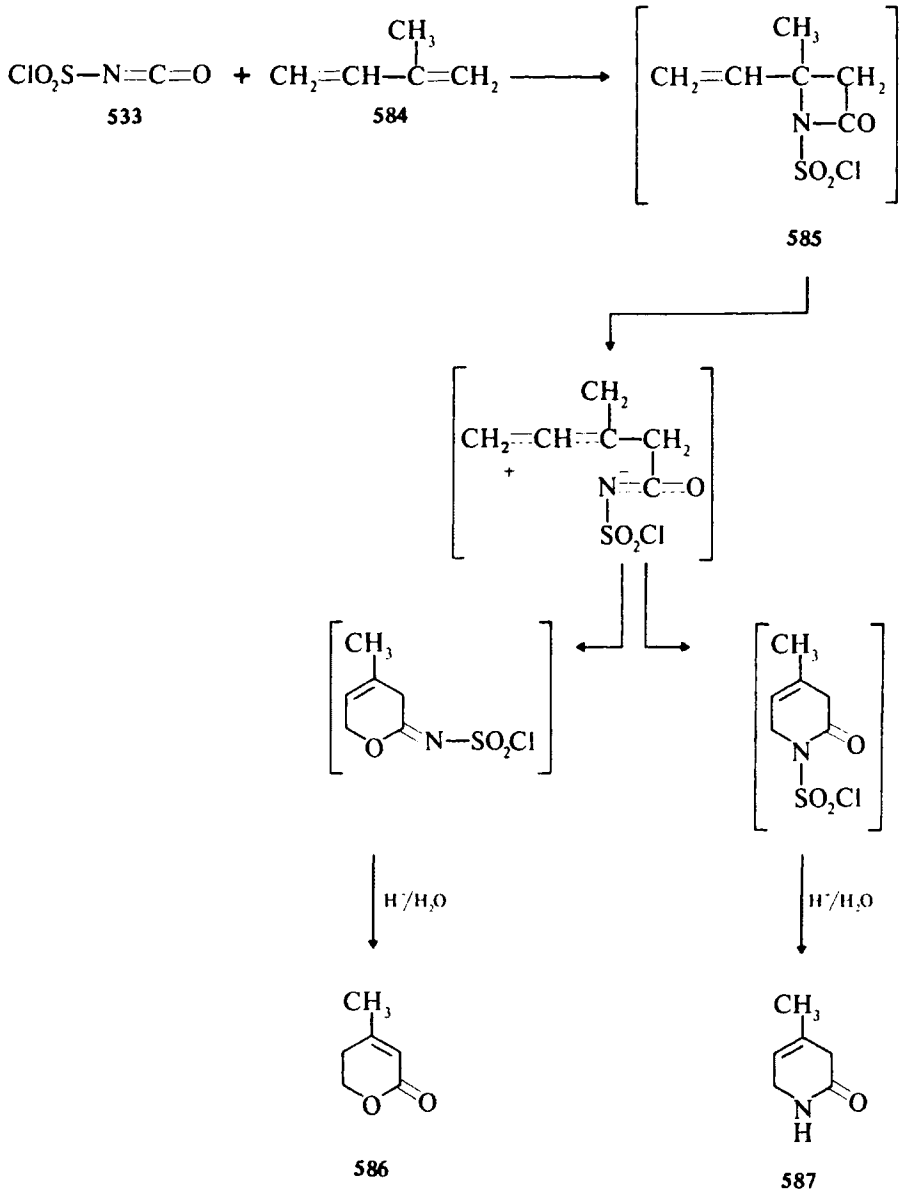


Figure 91

The kinetics of the sulfonyl isocyanate cycloaddition reaction with olefins was investigated by Clauss,[160] who studied the rate of this reaction as a function of the type of isocyanate, olefin, and solvent used. The reaction rate was determined from the infrared absorption of the azetidinone carbonyl. Clauss found that CSI (X = Cl) reacted faster than other sulfonyl isocyanates in the cycloaddition with 2-ethylhexene-1 **600** in methylene chloride (Figure 94). The rates dropped off

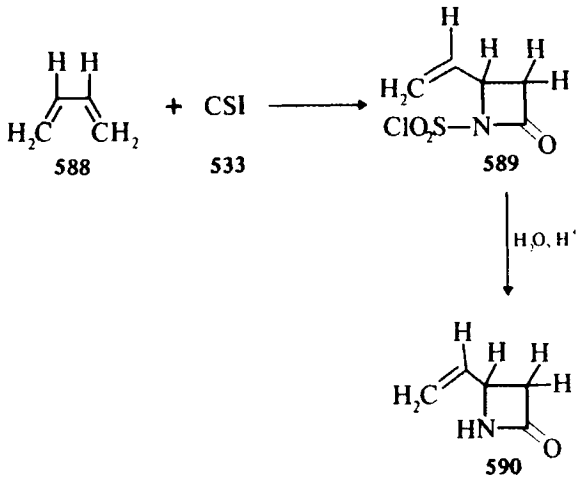
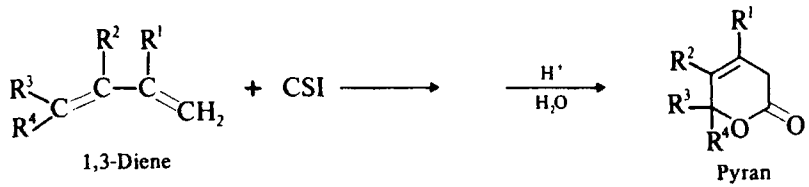
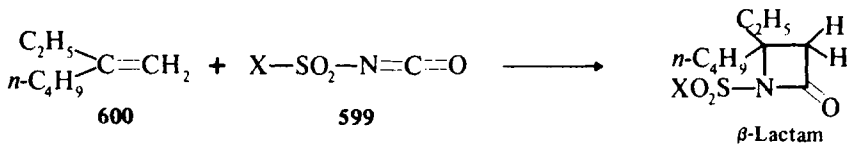


Figure 92



Pyran	R^1	R^2	R^3	R^4	Yield (%)
586	CH_3	CH_3	H	H	81
593	$CH_2CH_2CH_2CH_2$		H	H	43
594	C_6H_5	H	H	H	50
595	CH_3	H	CH_3	H	42
596	CH_3	H	CH_3	CH_3	45
597	C_6H_5	H	CH_3	CH_3	12
598	H	H	CH_3	H	21

Figure 93



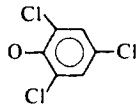
β-Lactam	X	k_2 (liter · mole^{-1} · sec^{-1})
601	Cl	$(6-7.5) \times 10^{-2}$
602	F	$(2-2.5) \times 10^{-2}$
603	N=C=O	$(6-7.5) \times 10^{-3}$
604		$(2.5-3) \times 10^{-4}$
605	*p*-Tolyloxy	$(1.2-1.5) \times 10^{-5}$
606	CH_2-$CHCl_2$	$(1-1.2) \times 10^{-5}$
607	CH=CHCl	$(6.5-8) \times 10^{-6}$
608	OCH_3	$(1.2-1.5) \times 10^{-6}$
609	$CH=CH_2$	$(5-8) \times 10^{-7}$
610	CH_2-CH_2Cl	$(5-8) \times 10^{-7}$
611	*p*-Tolyl	$(2-3) \times 10^{-7}$

Figure 94

significantly as halogen groups were replaced by nitrogen, oxygen, and carbon groups, as depicted in Figure 94. When various acyclic olefins were reacted with CSI **533**, the rate of azetidinone formation was not affected. It is interesting to note that the k_2 value for the reaction of *cis*-heptene-3 with **533** was $(1-1.2) \times 10^{-6}$, while that of *trans*-heptene-3 was $(5-7) \times 10^{-7}$ (Figure 95). The reaction of 1,3-dienes with CSI **533** was significantly enhanced from butadiene [$k_2 = (2-2.5) \times 10^{-5}$] to isoprene [$k_2 = (1.2-1.5) \times 10^{-2}$] (Figure 96). The reaction rate of 2-ethylhexene-1 with CSI was studied in a number of solvents. The more polar solvents enhanced the rate of the reaction.[148b] For example, the k_2 value in nitromethane was 0.5–1.0, while the k_2 value in *n*-hexane was $(3-5) \times 10^{-5}$ (Figure 97).

Lattrell reported the kinetics of the reaction of alkoxy olefins with sulfonyl isocyanates.[161] For example, he reported that cyclic olefin **612** reacted at different rates with various sulfonyl isocyanates. The most rapid rate was with CSI, and the slowest reaction was with *p*-tolyl isocyanate. These data support the findings of Clauss.[160] The rates of azetidinone formation from the reaction of **612** with sulfonyl isocyanates are illustrated in Figure 98.

Effenberger and co-workers investigated the stereochemistry and the kinetics of the cycloaddition reaction of enol ethers with *p*-tolysulfonyl isocyanate **546**.[162] They found that the *cis*-enol ether **614** reacted with sulfonyl isocyanate **546** to give *cis*-azetidinone **615** in quantitative yield. Similarly, the *trans*-enol ether **616** underwent cycloaddition with **546** to afford *trans*-azetidinone **617** in 52% yield.[162] These transformations are illustrated in Figure 99. A series of azetidinones synthesized from enol ethers and **546** is presented in Figure 100. An important obser-

Olefin	k_2 (liter · mole^{-1} · sec^{-1})	Heptene	k_2 (liter · mole^{-1} · sec^{-1})
Butene-1	$(1.2–1.5) \times 10^{-2}$	Heptene-1	1.5×10^{-6}
Pentene-1	1.2×10^{-6}	Heptene-2,*cis*	1.2×10^{-6}
Hexene-1	$(1.2–1.5) \times 10^{-6}$	Heptene-3,*cis*	$(1–1.2) \times 10^{-6}$
Octene-1	$(1.2–1.5) \times 10^{-6}$	Heptene-3,*trans*	$(5–7) \times 10^{-7}$
Decene-1	$(1.2–1.5) \times 10^{-6}$	Heptene-2,*trans*	$(3–4) \times 10^{-7}$
Dodecene-1	$(1.1–1.5) \times 10^{-6}$		

Figure 95. The rates of azetidinone formation from the reaction of CSI 533 with olefins in methylene chloride (1 *M* solution).

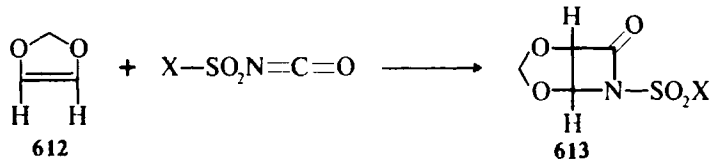
Diene	k_2 (liter · mole^{-1} · sec^{-1})	Heptene	k_2 (liter · mole^{-1} · sec^{-1})
Butadiene	$(2–2.5) \times 10^{-3}$	Styrene	$(0.8–1) \times 10^{-3}$
Isoprene	$(1.2–1.5) \times 10^{-2}$	α-Methylstyrene	$> 1.2 \times 10^{-1}$
cis-Pentadiene-1,3	$(3–4) \times 10^{-3}$	*cis*-β-Methylstyrene	$(7–8) \times 10^{-5}$
trans-Pentadiene-1,3	$(1.2–1.5) \times 10^{-2}$	*trans*-β-Methylstyrene	$(7–8) \times 10^{-5}$

Figure 96. The rates of azetidinone formation from the reaction of CSI (533) with 1,3-dienes in methylene chloride.

Solvent	Concentration (M)	k_2 (liter · mole^{-1} · sec^{-1})	Dielectric Constant
Nitromethane	0.05	0.5–1	38.6[a]
Nitrobenzene	0.05	$(1.2–2.5) \times 10^{-1}$	34.6
Methylene chloride	0.05	$(6–7.5) \times 10^{-2}$	8.93
o-Dichlorobenzene	0.05	$(1.5–2.5) \times 10^{-2}$	9.82
Chlorobenzene	0.05	$(1.2–1.5) \times 10^{-2}$	5.61
Chloroform	0.1	1.0×10^{-2}	4.70
1-Chloropropane	0.1	$(0.8–1) \times 10^{-2}$	~ 8[a]
Toluene	0.1	$(3–3.5) \times 10^{-3}$	2.38
Diethyl ether	0.2	$(1–1.5) \times 10^{-3}$	4.22
CCl_4	0.2	$(1–1.5) \times 10^{-4}$	2.23
Cyclohexane	0.2	$(6–8) \times 10^{-5}$	2.02[a]
n-Hexane	0.2	$(3–5) \times 10^{-5}$	1.90

[a] At 20°C.

Figure 97. The rates of azetidnone formation from the reaction of CSI 533 with 2-ethylhexene-1 600 at 25°C in various solvents.



Isocyanate	k_2 (liter · mole^{-1} · sec^{-1})
4-$CH_3C_6H_4SO_2NCO$	9×10^{-5}
CH_3OSO_2NCO	6.3×10^{-4}
4-CH_3O-C_6H_4-OSO_2NCO	2×10^{-3}
$CCl_3CH_2OSO_2NCO$	6×10^{-3}
2,4,6-$Cl_3C_6H_2OSO_2NCO$	1×10^{-2}
FSO_2NCO	5×10^{-1}
$ClSO_2NCO$	1.2

Figure 98. The rates of azetidinone formation from the reaction of sulfonyl isocyanate with compound 612 in methylene chloride at 20°C.

vation made by these investigators was that the azetidinones (e.g., **615** and **617**) were synthesized stereospecifically at a temperature range of −20 to +20°C. When the azetidinone solutions were stirred for long periods of time at room temperature, a slow cis–trans equilibration took place. If the azetidinones were heated to 80°C, they underwent conversion to the acrylamides **625** and **626**. This sequence is presented in Figure 101.

Effenberger, Prossel, and Fischer did an elegant nmr study of the enol ether–isocyanate cycloaddition reaction, determining the rates of azetidinone formation in both carbon tetrachloride and deuterated acetonitrile.[163] They found that the rates of azetidinone formation from the *cis*-enol ethers were significantly greater than those from the *trans*-enol ethers. A summary of the data is given in Figure 102.[163]

Friedrich reported an interesting study of the reaction of CSI with *cis*- and *trans*-stilbenes.[164] He found that, at room temperature, *cis*-stilbene **633** reacted with **533**

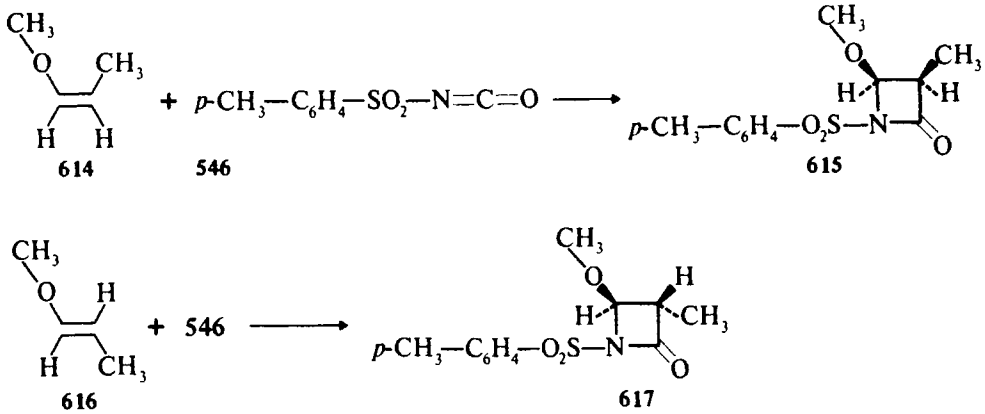
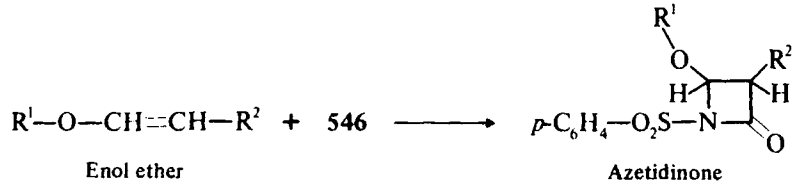


Figure 99



Azetidinone	R^1	R^2	Stereochemistry	Yield (%)
615	CH_3	CH_3	*cis*	Quant.
617	CH_3	CH_3	*trans*	52
618	CH_3	C_2H_5	*cis*	53
619	CH_3	C_2H_5	*trans*	45
620	C_2H_5	CH_3	*cis*	70
621	C_2H_5	CH_3	*trans*	33
622	C_2H_5	C_2H_5	*cis*	76
623	C_2H_5	C_2H_5	*trans*	67

Figure 100

to give *cis*-azetidinone **635** and that *trans*-stilbene **634** underwent cycloaddition with **533** to afford *trans*-azetidinone **636**. Quite remarkably, as the reaction temperature increased, higher concentrations of the initial stilbene were obtained. This information is summarized in Figure 103. In addition, Friedrich discovered that

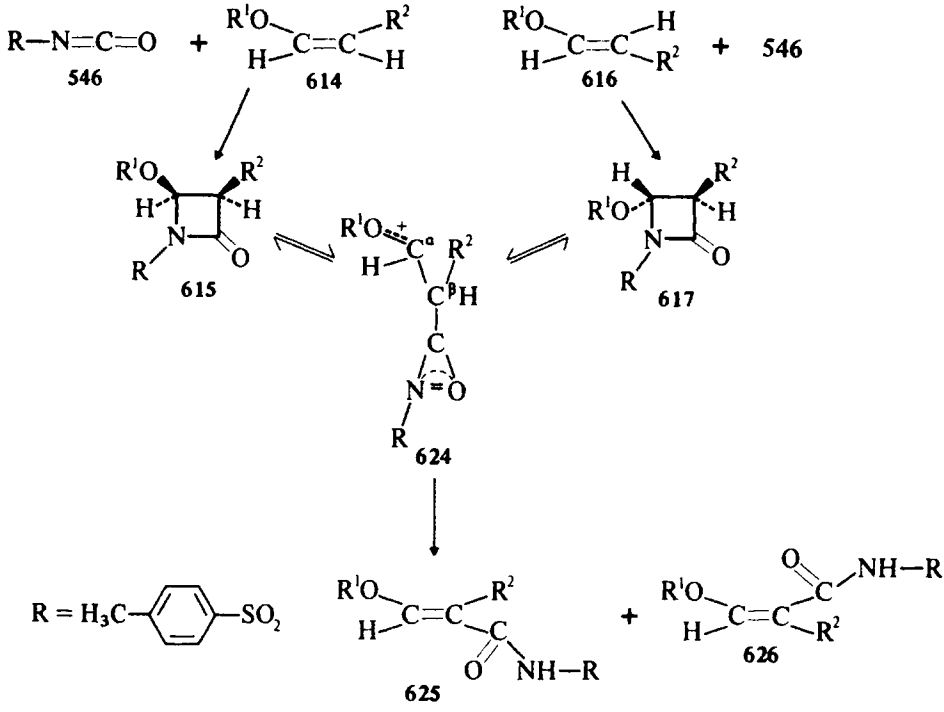
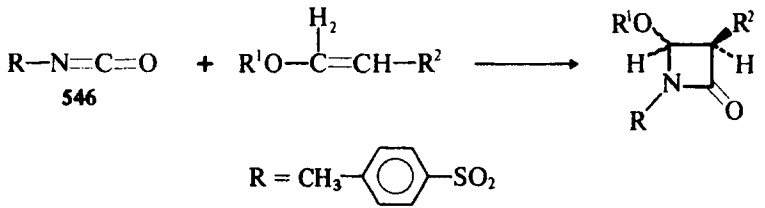


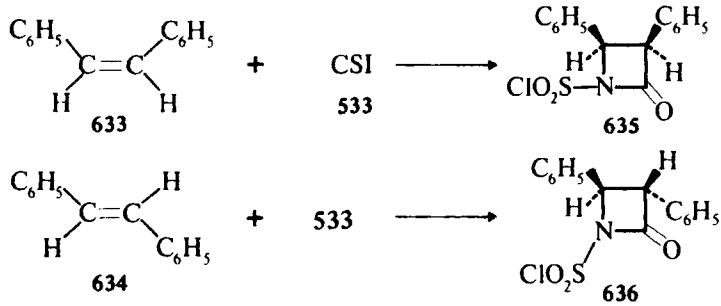
Figure 101



Cis	R^1	R^2	Trans
614	CH_3	CH_3	616
627	CH_3	C_2H_5	628
629	C_2H_5	CH_3	630
631	C_2H_5	C_2H_5	632

	CCl_4		CD_3CN	
Enol ether	k_2 (liter · mole^{-1} · sec^{-1})	k_{cis}/k_{trans}	k_2 (liter · mole^{-1} · sec^{-1})	k_{cis}/k_{trans}
614	$(1.96 \pm 0.01) \times 10^{-2}$		$(9.2 \pm 0.5) \times 10^{-1}$	
		5.6		4.4
616	$(3.5 \pm 0.3) \times 10^{-3}$		$(2.08 \pm 0.09) \times 10^{-1}$	
627	$(1.58 \pm 0.05) \times 10^{-2}$		$1.2 \pm 0.25 \times 10^{0}$	
		5.9		3.8
628	$(2.69 \pm 0.07) \times 10^{-3}$		$(3.15 \pm 0.1) \times 10^{-1}$	
629	$(1.77 \pm 0.07) \times 10^{-1}$		2.6 ± 0.6	
		10.0		1.7
630	$(1.77 \pm 0.07) \times 10^{-2}$		1.5 ± 0.3	
631	$(6.0 \pm 0.35) \times 10^{-2}$		2.3 ± 0.6	
		8.3		2.8
632	$(8.3 \pm 0.4) \times 10^{-3}$		$(8.1 \pm 1.5) \times 10^{-1}$	

Figure 102. The rates of azetidinone formation from the reactions of enol ethers 614–632 and *p*-toluenesulfonyl isocyanate 546 in CCl_4 and CD_3CN at 23°C.



Temperature (°C)	636 (mole %)	634 (mole %)
100	25	75
90	33	67
80	40	60
70	47	53

Figure 103

cis- and *trans*-azetidinones **637** and **638**, respectively, underwent interconversion with potassium amide in liquid ammonia to afford a 1 : 1 mixture of **637** and **638**. This transformation is illustrated in Figure 104.

An important application of the Graf[148] CSI–olefin cycloaddition reaction (see Figures 77–79) was reported by Johnston and co-workers in the first total synthesis of thienamycin.[165] This research group found that CSI **533** reacted smoothly with 1-acetoxybutadiene **639** at −20°C in ether to give, regioselectively, azetidinone **640** in 42% yield. This was deblocked with sodium sulfite, hydrogenated, and subsequently deacetylated with methanol and sodium methoxide to give **641** in 95% yield. Azetidinone **641** was converted to its acetonide **642**, which in turn was transformed (in 89% yield) to **643** as a mixture of epimers about the hydroxyl-bearing carbon. Alcohol **643** was acylated with *p*-nitrobenzoyl chloride to afford ester **644**, which was hydrolyzed to azetidinone **647**. The alcohol of **647** was converted to the thioenol ether **648** in a series of steps outlined in Figure 105. The cyclization of **648** was carried out with bromine followed by triethylamine to afford **649**. This was dehydrohalogenated with silver fluoride and pyridine to give **650** which was decarboxylated and hydrogenated to thienamycin (**651**), as described in Figure 105. Other isocyanate–olefin cycloadditions affording azetidinones are summarized in Table 2.

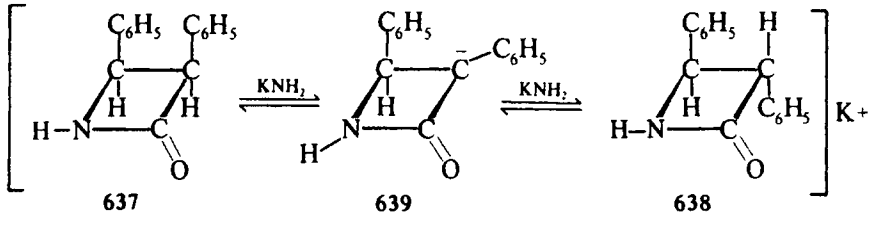
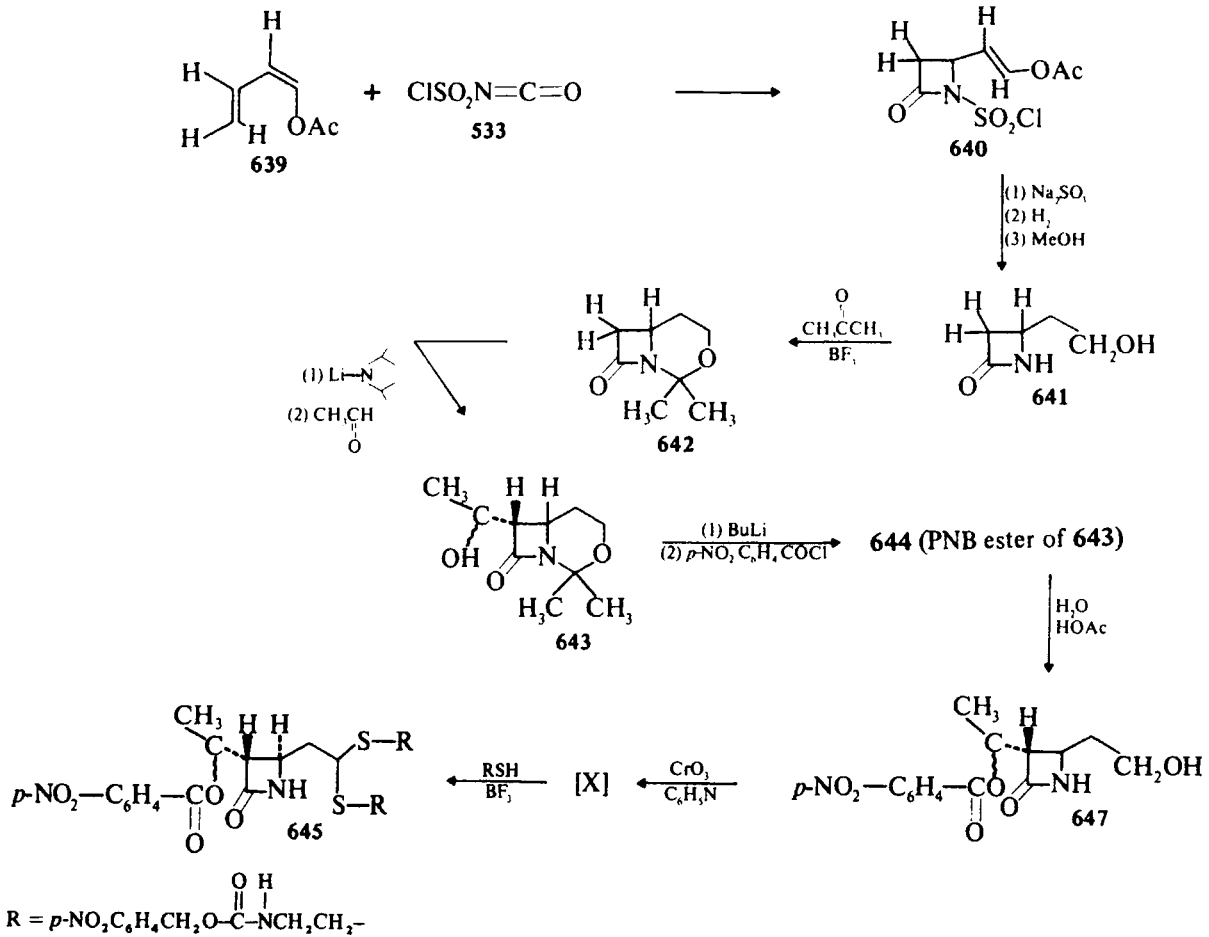


Figure 104


639
533
640
(1) Na2SO3
(2) H2
(3) MeOH
641
642
643
644 (PNB ester of 643)
647
645
[X]
R = p-NO2C6H4CH2O-C-NCH2CH2-

645
(1) Br2
(2) Et3N
646
(1) PNBO2C—C—CO2PNB
(2) SOCl2
(3) P(Bu)3
(CO2PNB)2
648
(1) Br2
(2) Et3N
649
AgF, C5H5N
650
(1) LiI, collidine
(2) HN
(3) H2
651

Figure 105

TABLE 2. AZETIDINONES BY ISOCYANATE–OLEFIN CYCLOADDITIONS

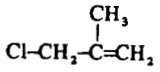
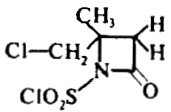
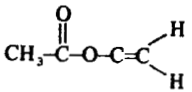
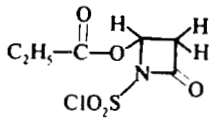
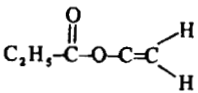
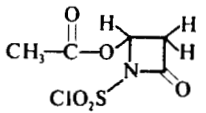
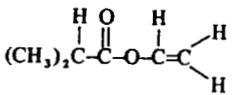
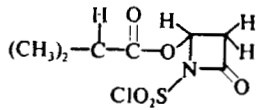
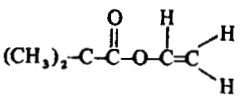
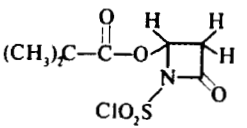
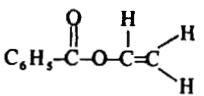
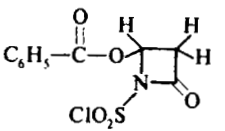
Isocyanate Group	Olefin	Azetidinone	Yield (%)	Reference
$Cl–SO_2–N=C=O$			75	166
$Cl–SO_2–N=C=O$			43	167
$Cl–SO_2–N=C=O$			56	167
$Cl–SO_2–N=C=O$			48	167
$Cl–SO_2–N=C=O$			65	167
$Cl–SO_2–N=C=O$			51	167

TABLE 2 CONTINUED

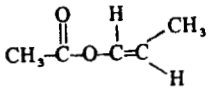
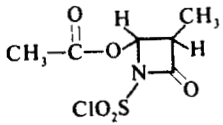
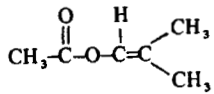
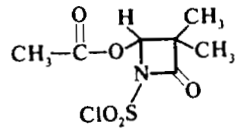
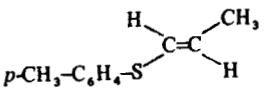
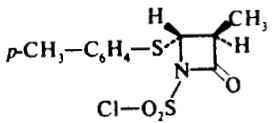
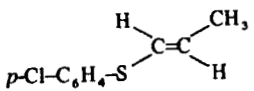
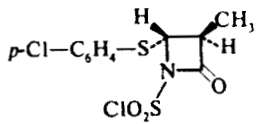
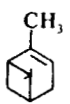
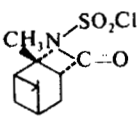
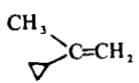
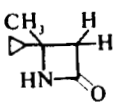
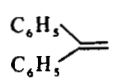
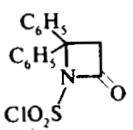
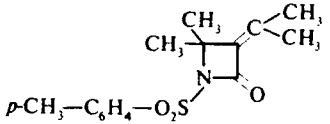
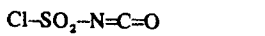
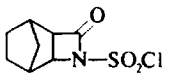
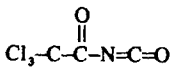
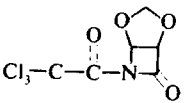
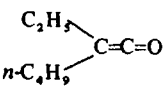
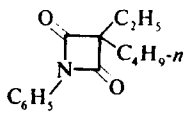
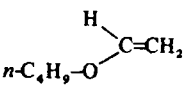
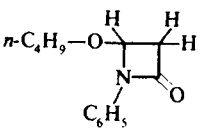
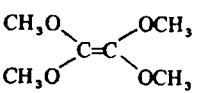
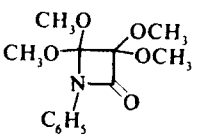
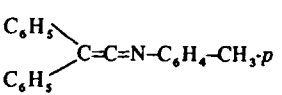
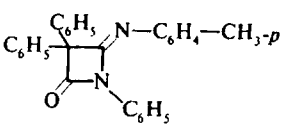
Isocyanate Group	Olefin	Azetidinone	Yield (%)	Reference
$Cl–SO_2–N=C=O$			33	167
$Cl–SO_2–N=C=O$			55	167
$Cl–SO_2–N=C=O$			66	168
$Cl–SO_2–N=C=O$			60	169
$Cl–SO_2–N=C=O$			75	170
$Cl–SO_2–N=C=O$			53	171
$Cl–SO_2–N=C=O$			45	172

TABLE 2 CONTINUED

Isocyanate Group	Olefin	Azetidinone	Yield (%)	Reference
			67	173
			85	174
			6	175
			70	176
			44	177
			76	178
			83	179

II. RING-CLOSURE REACTIONS

1. Formation of the N-C_2 Bond (V → VI)

A. *Cyclization of β-Amino Acids*

The first construction of an azetidinone utilizing a precursor β-amino acid (V → VI, R^2 = H) was reported by Staudinger, Klever, and Kober.[180] In an effort to confirm the structural assignment of azetidinone **654**, derived from the cycloaddition reaction of dimethylketene **652** and Schiff base **653**, these investigators treated β-amino acid **651** with acetyl chloride and obtained β-lactam **654** in 60% yield. These transformations are illustrated in Figure 106. In addition, Staudinger

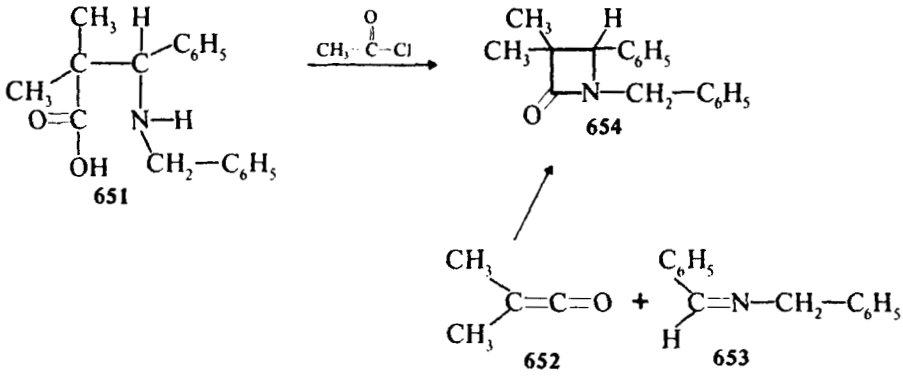


Figure 106

found that isobutyryl amides of β-amino acids cyclized, when heated, to the *N*-unsubstituted azetidinones with concomitant loss of isobutyric acid.[180] Sheehan and Corey have postulated a "cyclic *ortho*-amide", transition state to justify this facile conversion to β-lactams.[15] This pathway is presented in Figure 106a.

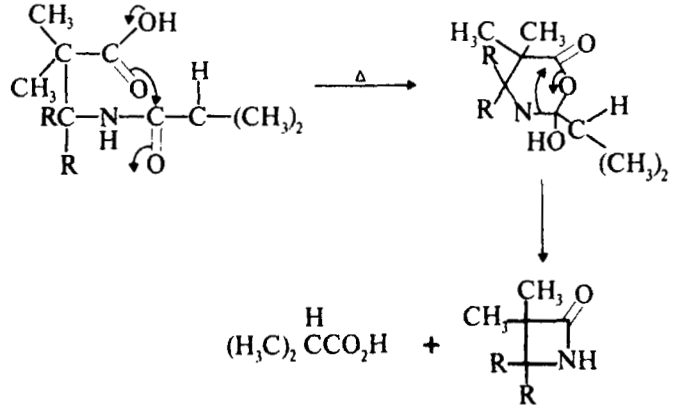
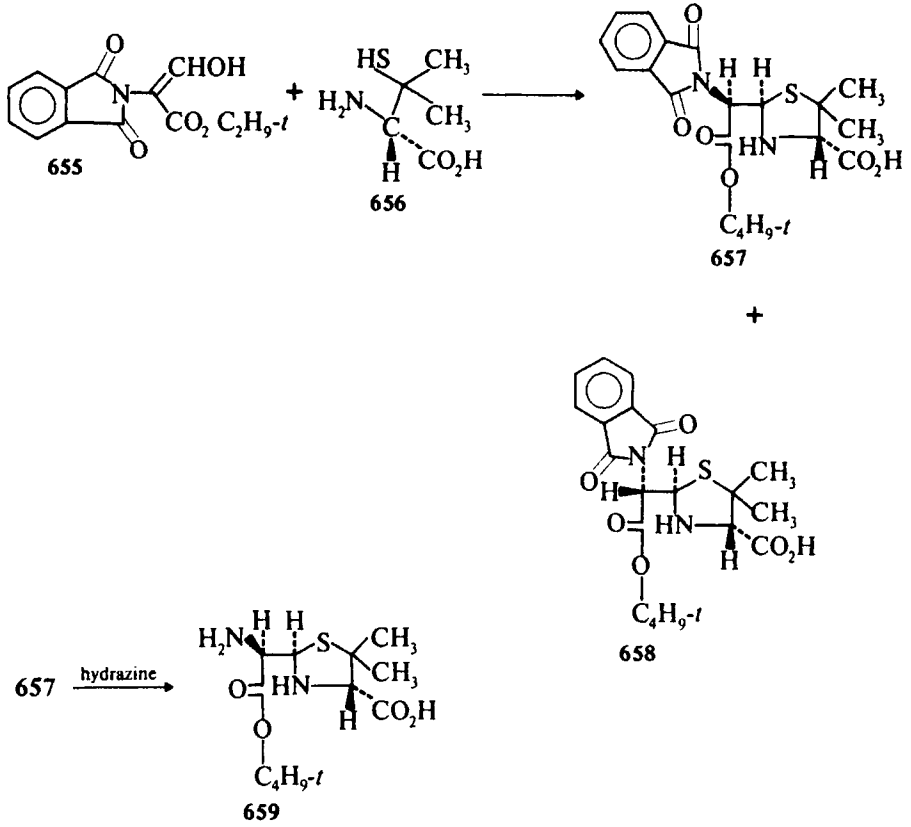


Figure 106a

There were no further reports in the literature of β-lactam synthesis via N–C_2 bond formation until the structure of penicillin **1** was determined. Sheehan and Henery-Logan[181,182] completed the first total synthesis of phenoxymethyl penicillin by elegantly constructing the fused β-lactam via N–C_2 bond formation.[181,182] They found that phthalimidoaldehyde **655** condensed with D-penicillamine **656** to give a mixture of diasteromers **657** and **658** in 24 and 30% yields, respectively.[181] The isomer **657**, which corresponded to the natural configuration of penicillin at the three asymmetric centers, was separated from **658** and used in the synthetic pathway. Because of the susceptibility of the β-lactam function to rupture under the conditions required for phthalimide removal, the nitrogen-protecting group was removed with hydrazine at the penicilloate **657** stage, affording **659**, which was reacylated with phenoxyacetyl chloride to produce **660**. The penicilloate **660** was treated with formic acid, affording penicilloic acid **661**. Heretofore, all attempts at the cyclization of **661** to penicillin **665** (by the use of thionyl chloride, mixed anhydride, etc.), were unsuccessful, affording only oxazolone **663** as the major product. Sheehan found that the monosodium salt **664** reacted with dicyclohexylcarbodiimide (DCC) to afford a 5.4% yield of phenoxymethyl penicillin **665**. This constituted the first total synthesis of penicillin.[181] The synthesis sequence is illustrated in Figure 107.



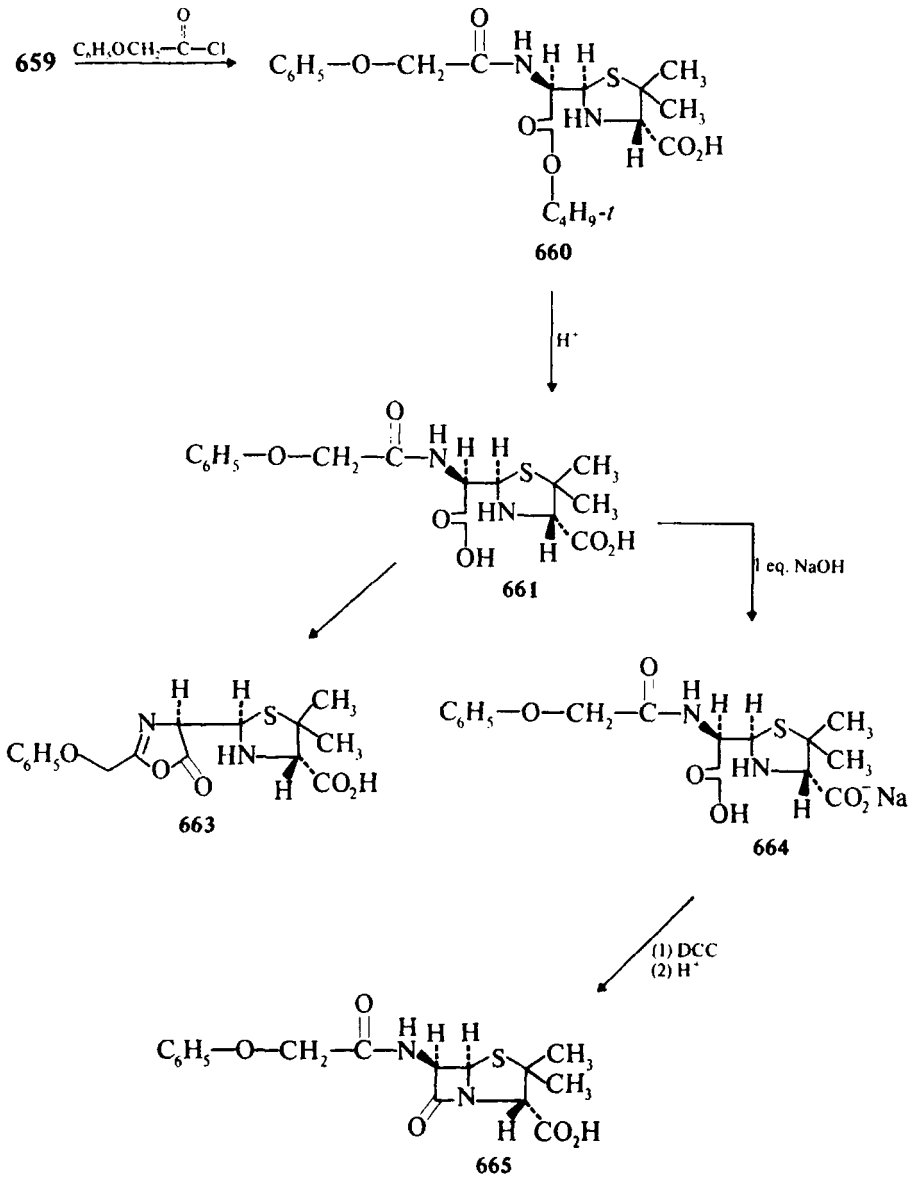


Figure 107

Sheehan and Henery-Logan,[182] continuing their investigation of the carbodiimide-mediated cyclizations of penicilloates to the corresponding penicillins, found that *N*-titrylbenzyl penicilloate **666** reacted with diisopropylcarbodiimide to give the titryl penicillin **667** in 67% yield. Penicillin **667** could subsequently be converted to the 6-β-aminopenicillanic acid **668**, which was reacylated with phenoxyacetyl chloride to give **665**. These transformations are described in Figure 108.

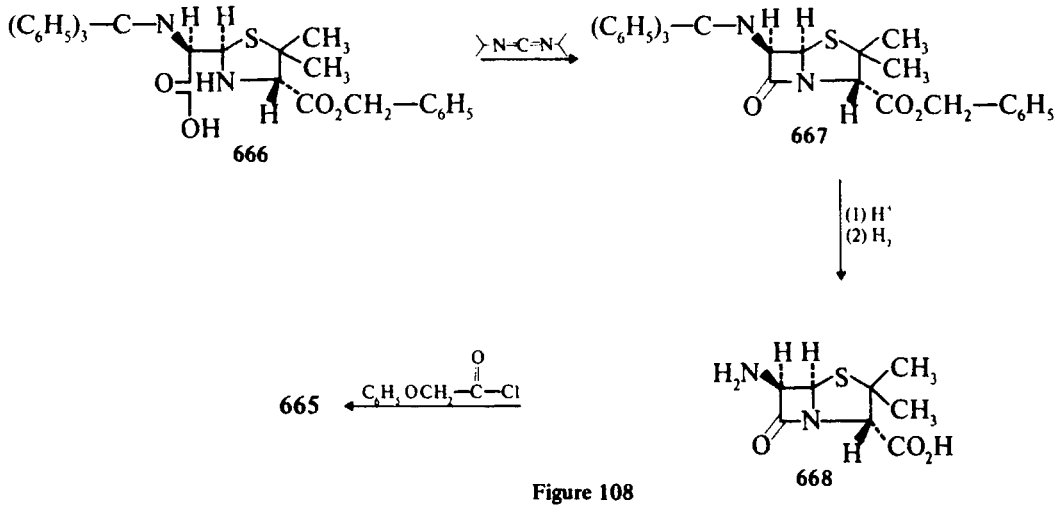
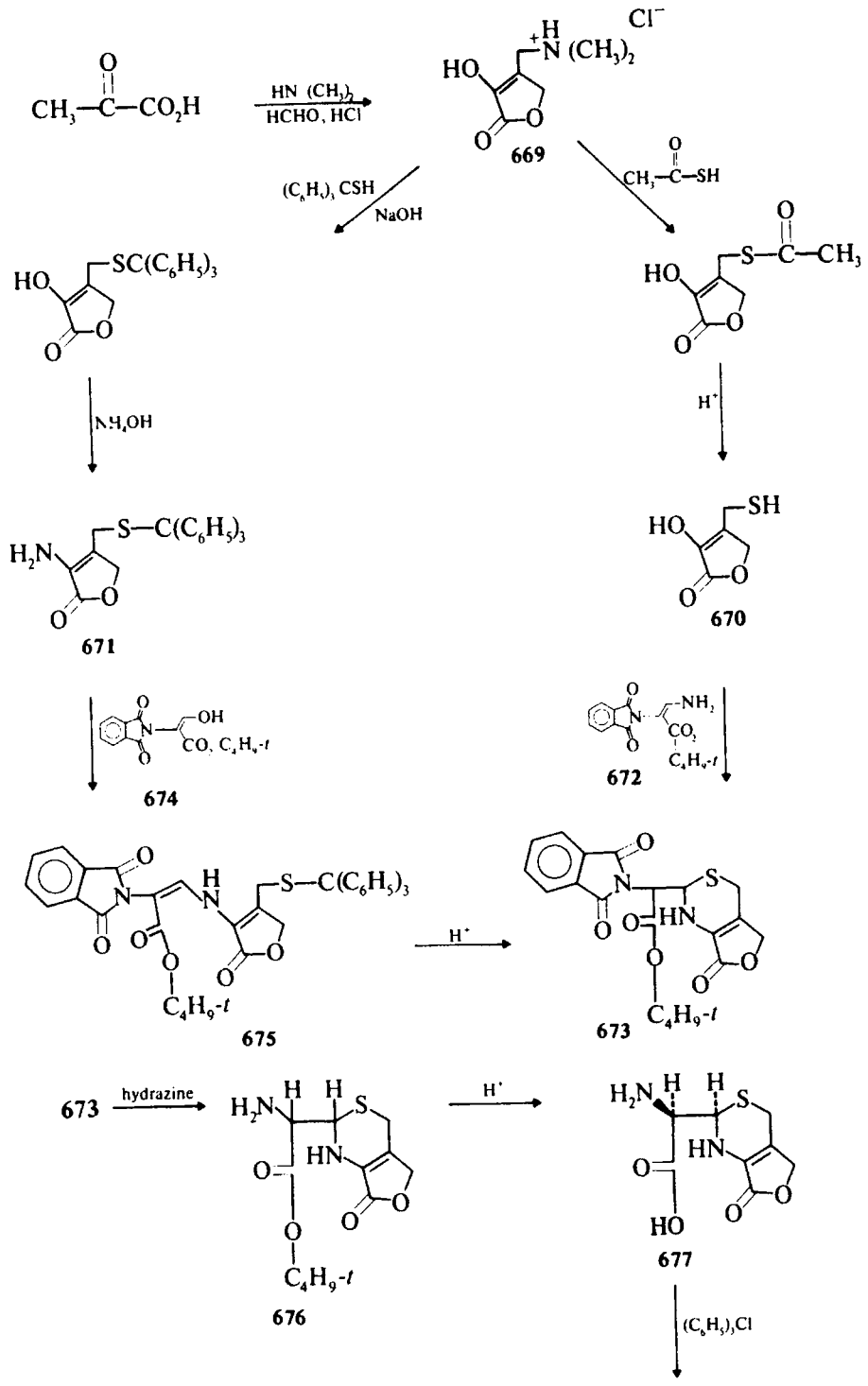


Figure 108

The Sheehan carbodiimide method was independently adapted to the synthesis of cephalothin lactone **501** by Dolfini et al.[183] and by Heymes et al.[184] These investigators found that lactone **669** could be treated with thiolacetic acid to give, after acid hydrolysis, sulfhydryl lactone **670** (Heymes et al.).[184] Alternatively, lactone **669** could be transformed with trityl mercaptan and ammonium hydroxide to lactone **671** (Dolfini et al.).[183] The sulfhydryl lactone **670** reacted with the phthalimide enamine **672** to give the dihydrothiazine lactone **673** in 65% yield.[184] Similarly, lactone **671** underwent condensation with phthalimide aldehyde **674** to give enamine **675**, which was subsequently converted to **673** by acid-catalyzed detritylation.[183] The phthalimido group of **673** was removed with hydrazine to give **676** as a mixture of diastereomers. When the amino ester **676** was treated with hydrochloric acid to give the amino acid **677**, only one diastereomer, corresponding to the natural configuration at C_6 and C_7, was isolated.[184] After tritylation of **677**, the Sheehan closure of **678** was effected with DCC in nitromethane to afford **679** in 70% yield.[184,185] The trityl group of **679** was removed to give the nucleus **680**, which was resolved with *l*-tartaric acid and reacylated with thienyl chloride to afford cephalothin lactone **501**.[185] This series of transformations is summarized in Figure 109.

The carbodiimide-mediated cyclization of β-amino acids to azetidinones was very elegantly utilized in the stereospecific construction of *dl*-thienamycin by Melillo and co-workers.[186] These investigators reacted the acetone dicarboxylate ester **681** with benzylamine to afford the enamine, which was acylated with ketene gas to give **682**. The enamine **682** was reduced with $NaCNBH_3$ to give the "cis" amino alcohol **683** in 61% yield. The carboxyl groups of **683** were differentiated by conversion of the diester to the lactone acid **684** with aqueous hydrochloric acid. At this stage, the benzyl protecting group of **684** was removed by hydrogenation to give the free amino lactone, which was solvolyzed with benzyl alcohol to give the amino acid hydrochloride **685** in good yield. The conversion of **685** to azetidinone


HN (CH3)2
HCHO, HCl
669
(C6H5)3CSH
NaOH
NH4OH
671
674
672
675
673
H+
hydrazine
676
677
(C6H5)3Cl

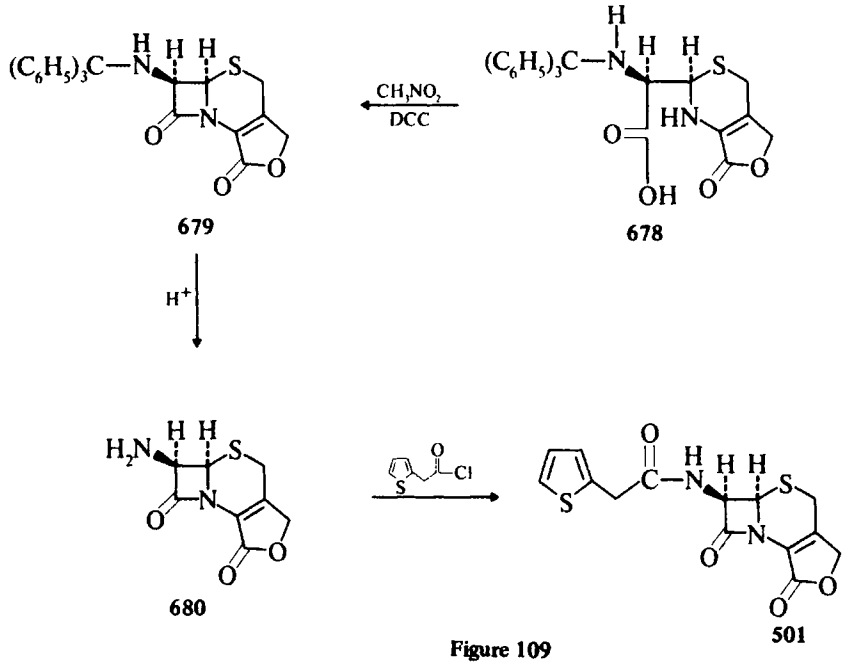


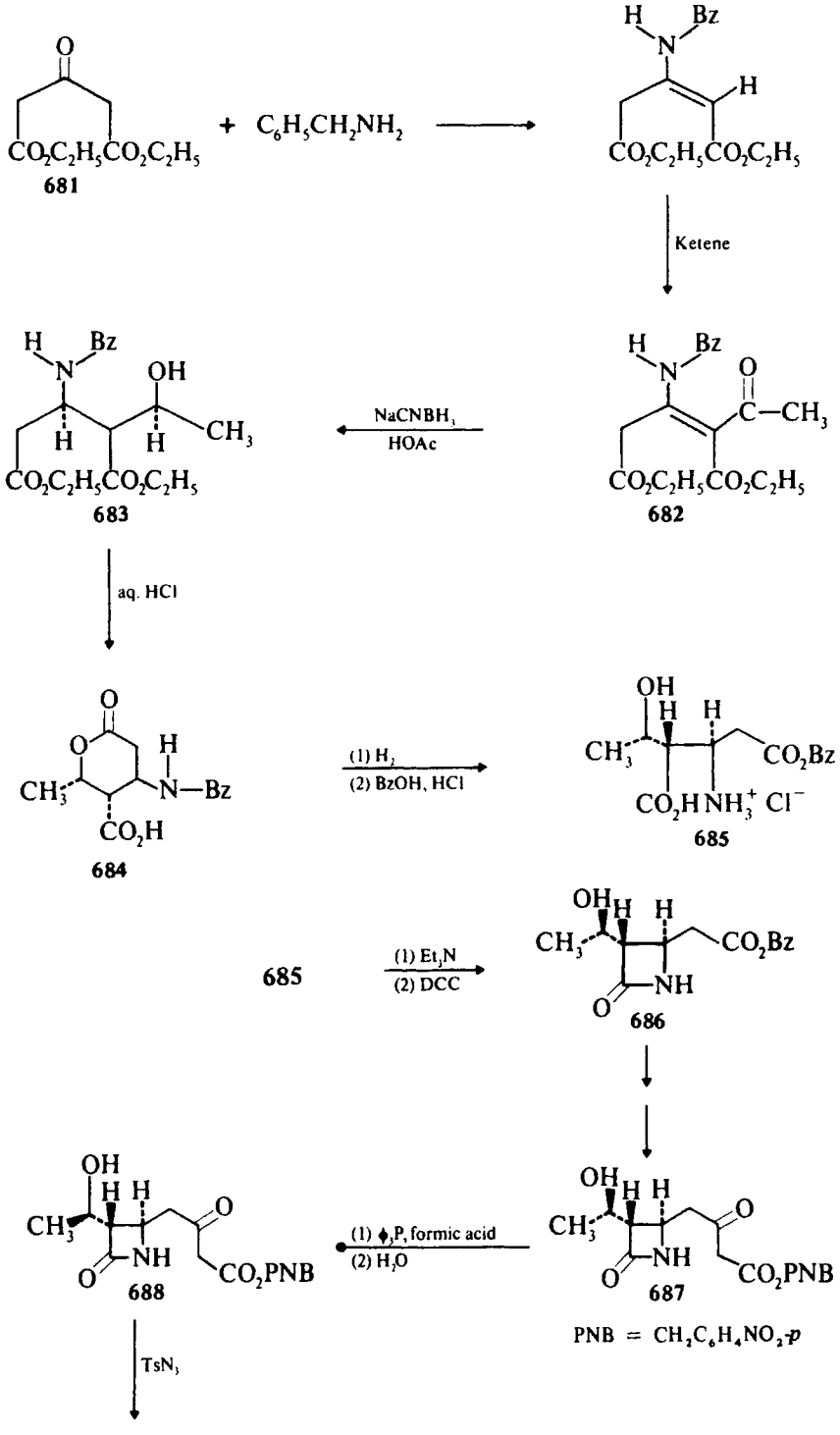
Figure 109

686 (in 93% yield) was achieved with triethylamine and DCC. Azetidinone **686** was converted to the β-keto ester **687**, which was selectively converted to the epimer **688**, in high yield, with triphenylphosphine and formic acid. The β-keto ester **688** was diazotized and then reacted with $Rh_2(OAc)_2$ to give **689**. The transfomation of **689** to thienamycin **651** was achieved by the conversion to its enol phosphate **690**, followed by reaction with thiol **691**, and finally by hydrogenation at pH 7.0. This sequence of reactions is illustrated in Figure 110.

In contrast to the difficulty encountered by investigators in the construction of fused β-lactams of the penicillin and cephalosporin family by $N–C_2$ bond formation from precursor β-amino acids, the synthesis of simple azetidinones without C_3-amido side chains was quite amenable to traditional activated acyl cyclization. For example, Simova and Kurtev[187] reported that threo-3-anilino-2,3-diphenylpropanoic acid **692** underwent condensation with benzenesulfonyl chloride and base to give azetidinone **693** in 70% yield. This sequence is illustrated in Figure 111.

Dobrev and Ivanov reported that acetic anhydride reacted with β-amidopropanoic acids to give the corresponding 1-acylazetidinones in good yield.[188,189] For example, 3-benzamido-2,3,3-triphenylpropanoic acid **694** reacted smoothly with acetic anhydride under reflux to give azetidinone **695** in 98% yield. This reaction is presented in Figure 112, and a summary of azetidinones prepared by this method is illustrated in Figure 113.

Prasad and Petrizilka disclosed an elegant synthesis of azetidinones utilizing an "oxazolone-activated" acyl group.[190] These investigators found that oxazolone **710**, which was derived from acid **709** and acetic anhydride in 90% yield, reacted


681
+ C6H5CH2NH2
Ketene
NaCNBH3
HOAc
682
683
aq. HCl
684
(1) H2
(2) BzOH, HCl
685
685
(1) Et3N
(2) DCC
686
(1) Ph3P, formic acid
(2) H2O
687
688
TsN3
PNB = CH2C6H4NO2-p

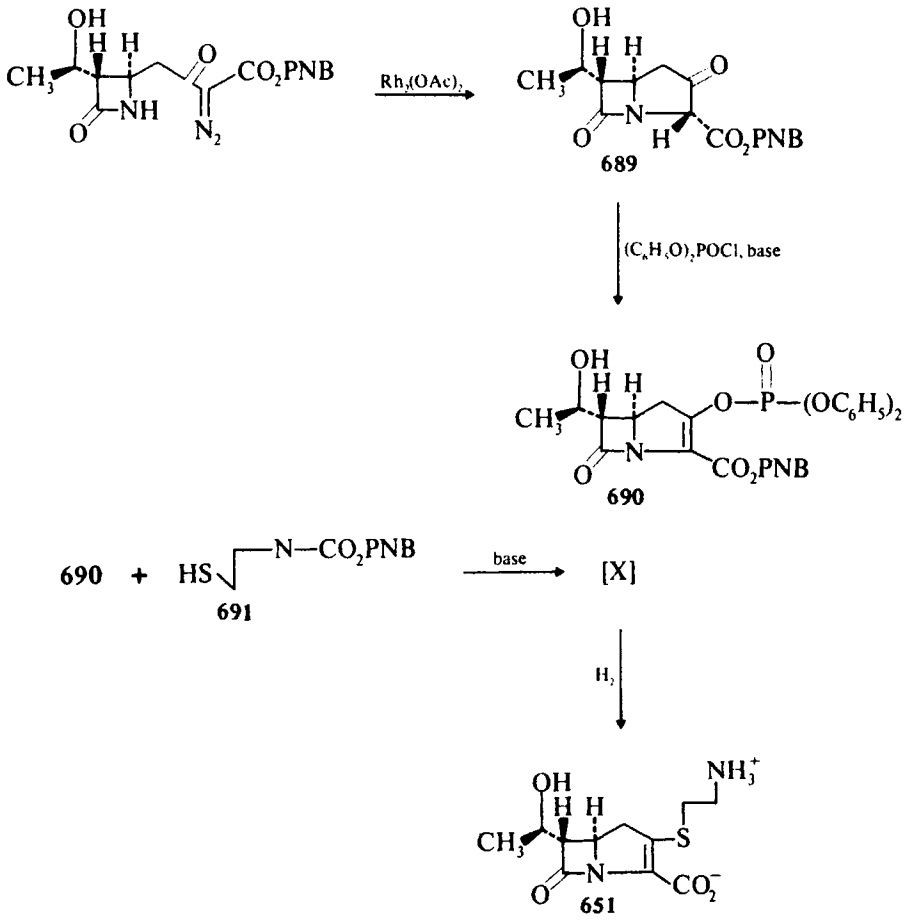


Figure 110

with imine **711** to give **712** in 50% yield. Similarly, oxazolone **713** underwent consecutive C_3–C_4 and N–C_2 bond formation with imine **711** to afford azetidinone **714** in 40% yield.[190] These transformations are presented in Figure 114. A proposed pathway for the formation of azetidinones from oxazolones and imines is shown in Figure 115.

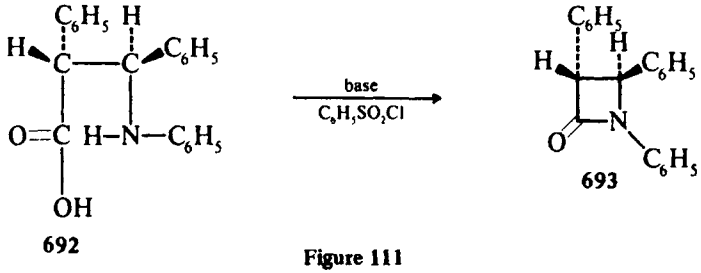
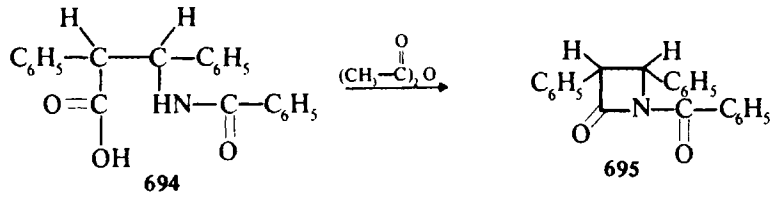


Figure 111



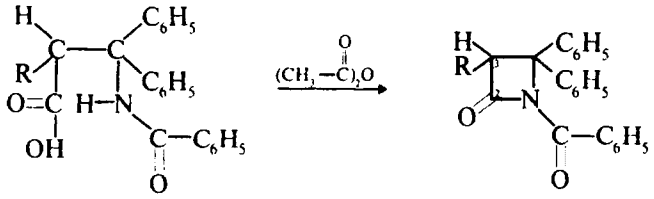
694 695

Figure 112

An interesting variant of oxazolone activation in the construction of β-lactams was reported by Raude and Hoppe.[191] They found that 4-methyl-2-methylthio-Δ^2-1,3-thiazolin-5-one **715** underwent pyridine-catalyzed condensation with *O*-ethyl-*N*-phenylformimidate **716** to give imine **717**, in 67% yield. Intermediate **717** was subsequently treated with sodium imidazolide to give the fused azetidinone **718** in 88% yield. These reactions are illustrated in Figure 116.

B. *Cyclization of β-Amino Esters: Grignard- and Aluminum-Catalyzed Condensations*

The first synthesis of an azetidinone from a β-amino ester and a Grignard reagent was reported by Breckpot in 1923.[192] For example, β-amino ester **719** reacted with ethylmagnesium bromide to afford a 24% yield of azetidinone **720**. Similarly **721**



β-Amidopropanoic acid Azetidinone

Azetidinone	R	Yield (%)
695	C_6H_5	98
696	3-$H_3CC_6H_4$	91
697	4-$H_3CC_6H_4$	92
698	2-ClC_6H_4	87
699	3-ClC_6H_4	92
700	4-ClC_6H_4	91
701	2-BrC_6H_4	86
702	4-BrC_6H_4	90
703	3-$CH_3OC_6H_4$	92
704	4-$CH_3OC_6H_4$	91
705	3,4-$(CH_3O)_2C_6H_3$	90
706	3,4-$CH_2O_2C_6H_3$	93
707	Naphthyl-1	94
708	Naphthyl-2	96

Figure 113

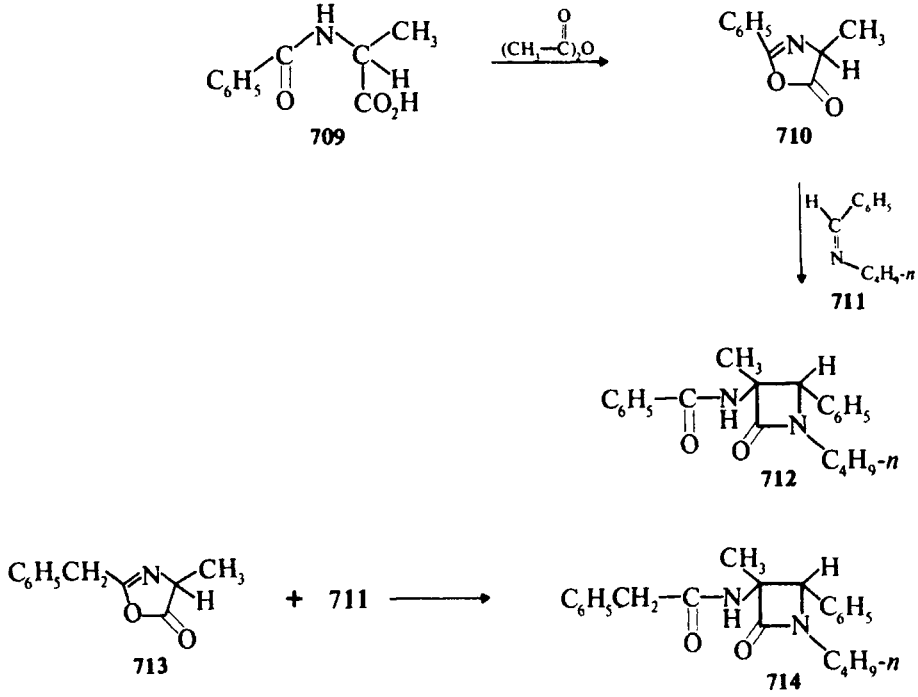


Figure 114

reacted with ethylmagnesium bromide to give a 35% yield of **722** (Figure 117). A significant improvement in the "Breckpot synthesis" was reported by Searles and Wann.[193] These investigators found that β-propriolactam **724**, previously synthesized from ethyl β-aminopropionate **723** and ethylmagnesium bromide in 0.76% yield,[192] could be prepared from **723** in 75% yield by substituting mesityl Grignard

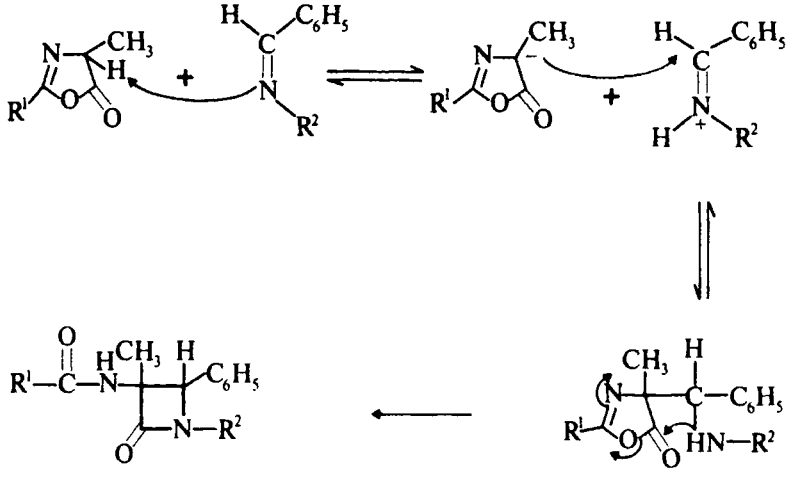


Figure 115

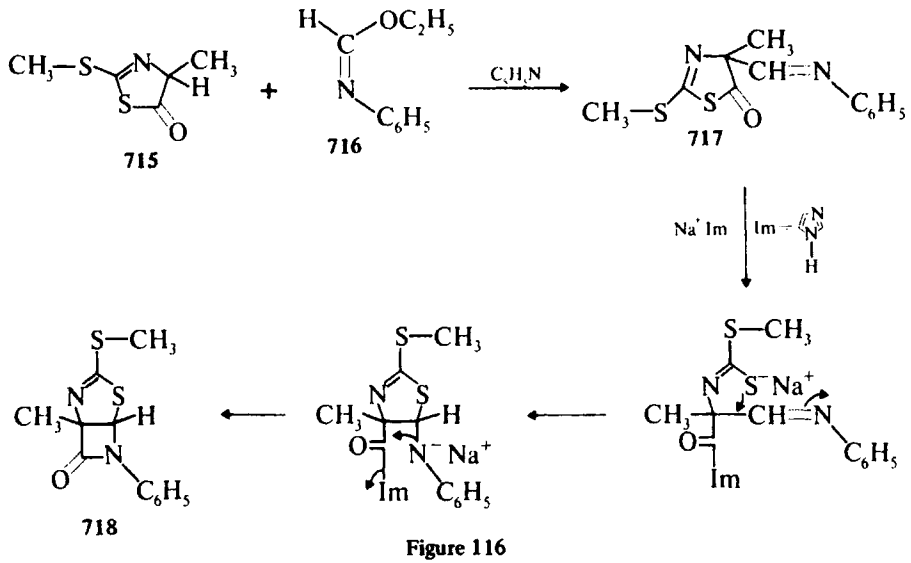


Figure 116

reagent for the ethyl Grignard reagent[193] (Figure 118). Cignarella and co-workers investigated the conversion of variously substituted β-aminoethyl esters with ethyl Grignard reagent to the corresponding azetidinones.[194] These are summarized in Figure 119.

An important extension of the Grignard catalyzed conversion of β-amino esters to the corresponding azetidinones was reported by Testa and Fontanella.[195] They discovered that ethyl α-phenyl-α-hydroxymethyl-β-aminopropionate (**729**) underwent ready cyclization with ethyl Grignard reagent to azetidinone **730** in 50% yield. Azetidinone **730** could be formed directly by an amine–ester carbonyl reaction (**729** → **730**). Alternately, a transient propiolactone **731** would rapidly be converted to **730** by amine–lactone carbonyl cyclization. These transformations are illustrated in Figure 120.

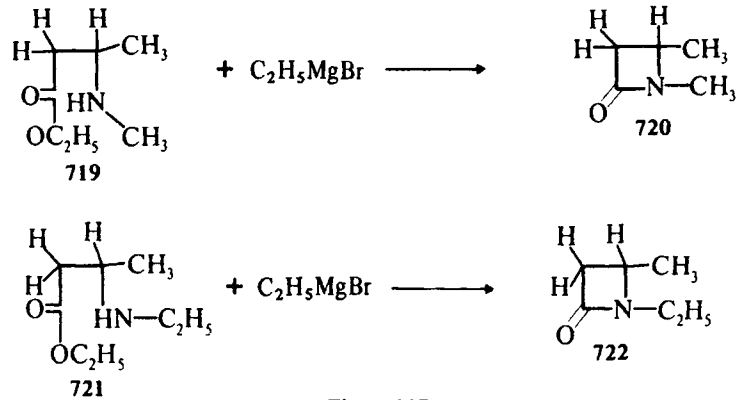


Figure 117

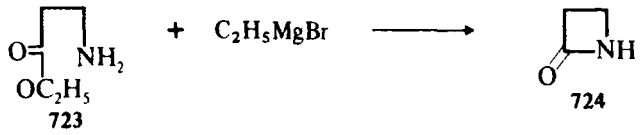
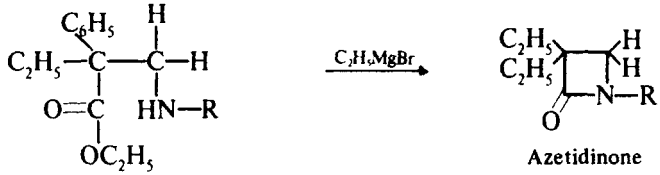


Figure 118

Earle, Hurst, and Viney reported that the Grignard-induced cyclization of β-amino esters could be utilized in the construction of fused β-lactams.[196] For example, ethyl α-(2-piperidyl)propionate 732 reacted with ethyl Grignard reagent



Azetidinone	R	Yield (%)
725	n-C_3H_7	23
726	i-C_3H_7	27
727	n-C_4H_9	60
728	$C_2H_5CH_2$	74

Figure 119

to give azetidinone 733 in 80% yield. Similarly, piperidyl propionate ester 734 underwent Grignard-induced cyclization to azetidinone 735 in 75% yield (Figure 121). Bellasio and co-workers[197] found that the threo-β-amino ester 736 underwent

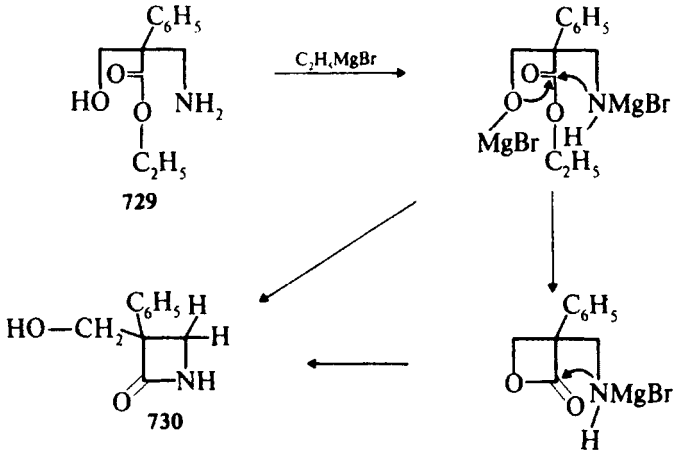


Figure 120

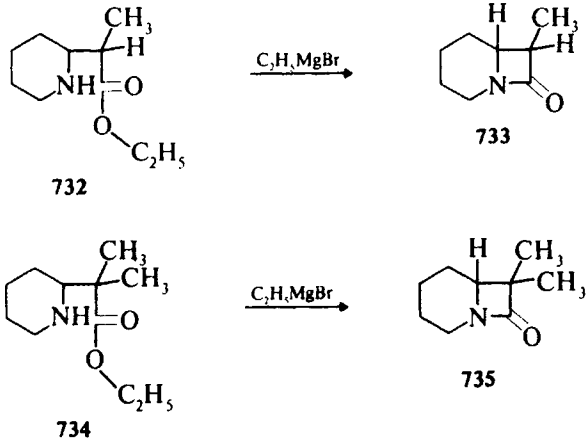


Figure 121

cyclization with methyl Grignard reagent to give *trans*-azetidinone **737** in 40% yield (Figure 122).

Birkofer and Schramm discovered that β-amino acids could be converted to azetidinones by conversion to the trimethylsilyl esters, which were treated with ethyl Grignard reagent to give, after hydrolysis, the corresponding azetidinone.[198] A mechanism for this transformation is illustrated in Figure 123, and a summary of azetidinones prepared by this method is presented in Figure 124.

Simova and co-workers reported that a variety of *t*-butyl esters condensed with Schiff base **17** in the presence of sodium amide in ether to give the corresponding azetidinones in good yield.[199] This reaction sequence is depicted in Figure 125 and a summary of azetidinones prepared by this method is shown in Figure 126.

Matsui and Motoi reported the synthesis of the strikingly unusual azetidinone **752**.[200] They discovered that the cyano ester **753** underwent cyclization with $AlCl_3$ in benzene to afford the azetidinone **752** in 38% yield. A pathway for its formation, suggested by Matsui and Motoi, is shown in Figure 127.

One of the most remarkable contributions to the field of β-lactam research was made by the late R. B. Woodward. During his Nobel lecture in 1964,[201] Woodward disclosed the first total synthesis of cephalosporin C (**4**), the construction of which was conceived and executed in a chirally specific manner. The synthetic sequence

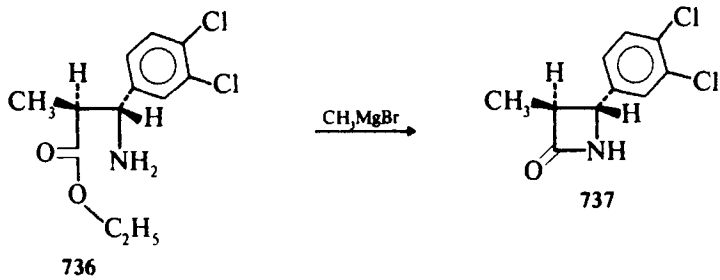


Figure 122

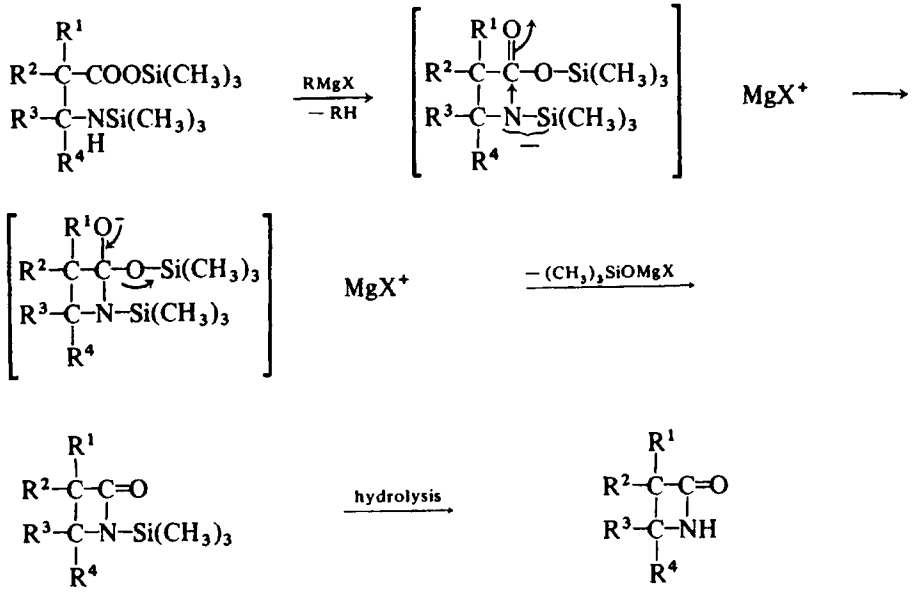
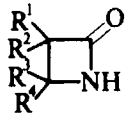


Figure 123

was initiated by converting L-cysteine **754** to its cyclic acetone adduct **755**. This was subsequently oxidized with dimethyl azodicarboxylate to give **756** in 88% yield. The azo adduct **756** was oxidized with lead tetraacetate in acetic acid to afford the *trans*-acetoxythiazolidine derivative **757** in 54% yield. A summary of the transformations leading to **757** and a plausible pathway for the synthesis of the formerly inaccessible and strategically important intermediates is presented in Figure 128. The *trans*-acetoxythiazolidine **757** was hydrolyzed to the *trans*-hydroxythiazolidine **758**, which was mesylated and converted to the *cis*-azido-



Compound	R^1	R^2	R^3	R^4	Yield (%)
738	H	H	H	H	23
739	CH_3	H	H	H	50
740	C_6H_5	H	H	H	59
741	H	H	CH_3	H	46
742	H	H	C_2H_5	H	62
743	H	H	n-C_3H_7	H	72
744	H	H	i-C_3H_7	H	78
745	H	H	C_6H_5	H	58
746	H	H	CH_3	CH_3	36
747	OH	H	H	H	48

Figure 124

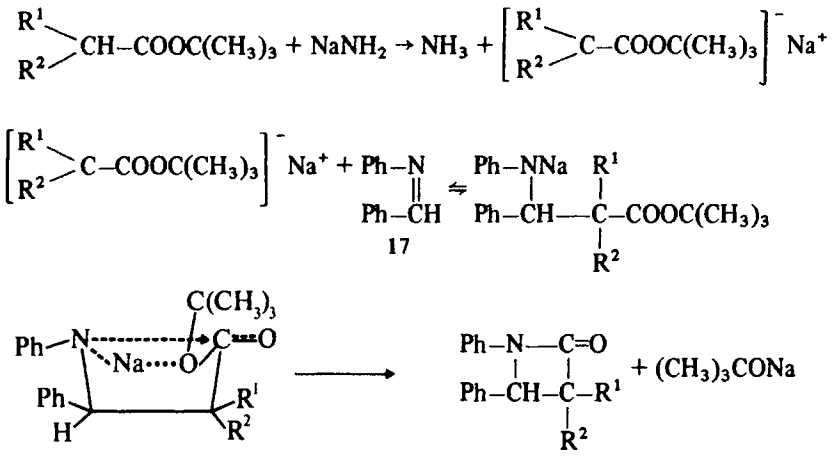
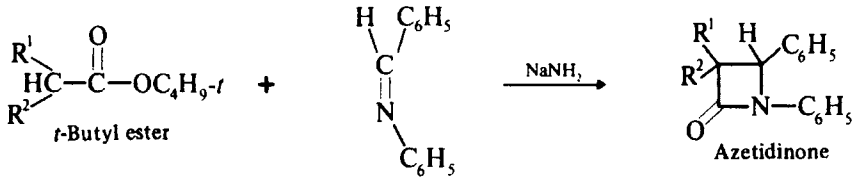


Figure 125



t-Butyl ester

Azetidinone

Azetidinone	R^1	R^2	Yield (%)
748	CH_3	CH_3	66
749	CH_3	C_6H_5	46
750	$CH_2(CH_2)_2CH_2$		35
751	$CH_2(CH_2)_3CH_2$		38

Figure 126

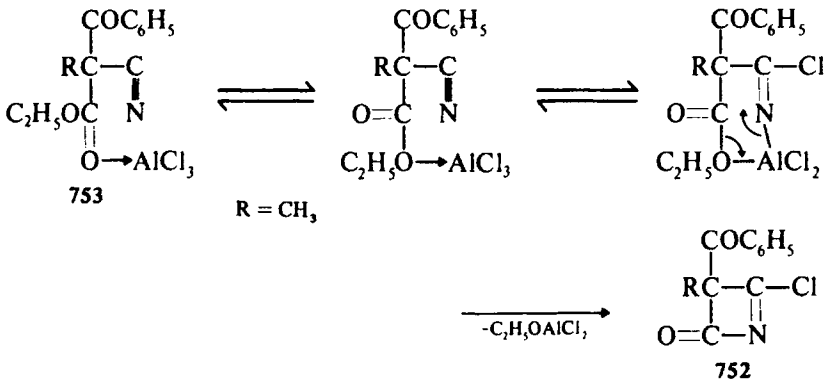
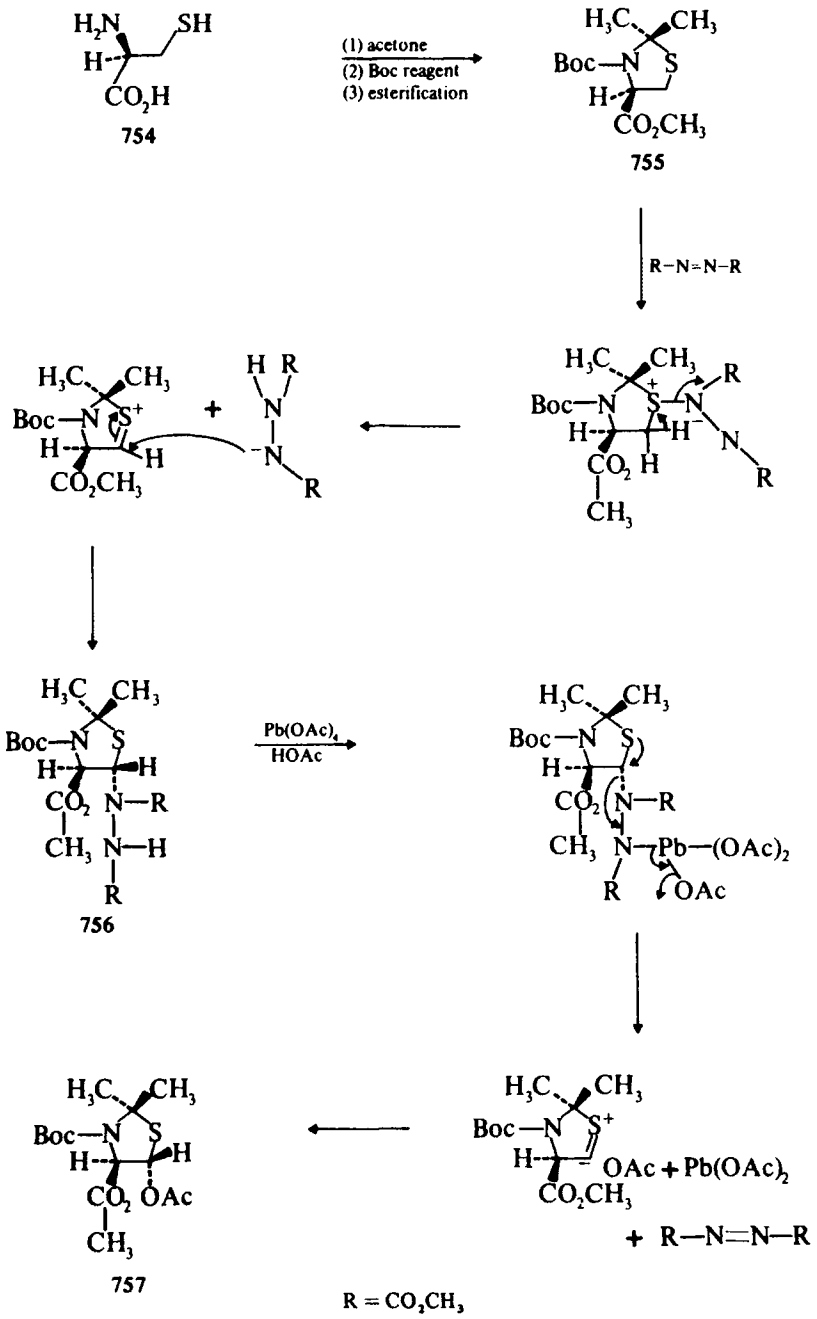


Figure 127



754 755 756 757

Figure 128

thiazolidine, **759**. This was reduced with stannous chloride dihydrate in 1 *N* sodium hydroxide to afford the *cis*-aminothiazolidine **760** in 63% yield. The crucial cycli-

zation of **760** was achieved with triethylaluminum in toluene, affording azetidinone **761** in 55% yield. This sequence is illustrated in Figure 129.

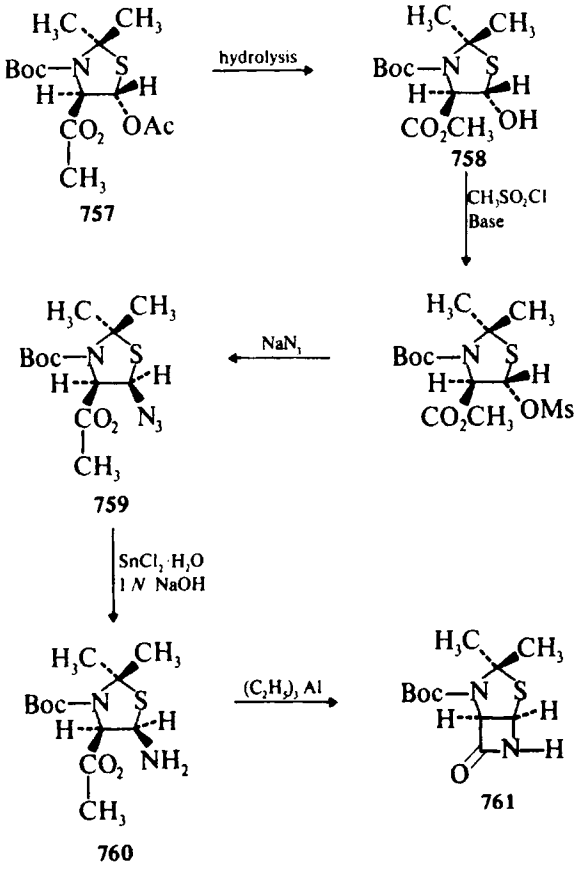


Figure 129

The stage was now set for the elaboration of the cephem nuclear structure. As will become apparent, the fate of chiral centers C_6 and C_7 had already been sealed with the construction of azetidinone **761** from L-cysteine. Azetidinone **761** was condensed with the malonaldehyde derivative **762** to afford the 1,4-conjugate addition product **763** in 44% yield. Azetidinone **763** was converted, in the presence of trifluoroacetic acid, to the Δ^2-cephem aldehyde **764** in 73% yield. This reaction sequence and the mechanism for the conversion of **763** to **764** are presented in Figure 130. The conversion of **764** to cephalosporin C was completed in the following sequence: Δ^2-cephem **764** was acylated with the protected D-aminoadipic acid **765**, giving amidocephem **766**. This in turn was reduced with diborane to give the 3′-hydroxymethylcephem derivative **767**, which was acetylated and equilibrated with pyridine to the Δ^3-cephem **768**. The completion of the synthesis of cephalosporin C (**4**) was achieved by removal of the carbamate protection with zinc and acetic acid. This final sequence is depicted in Figure 131.

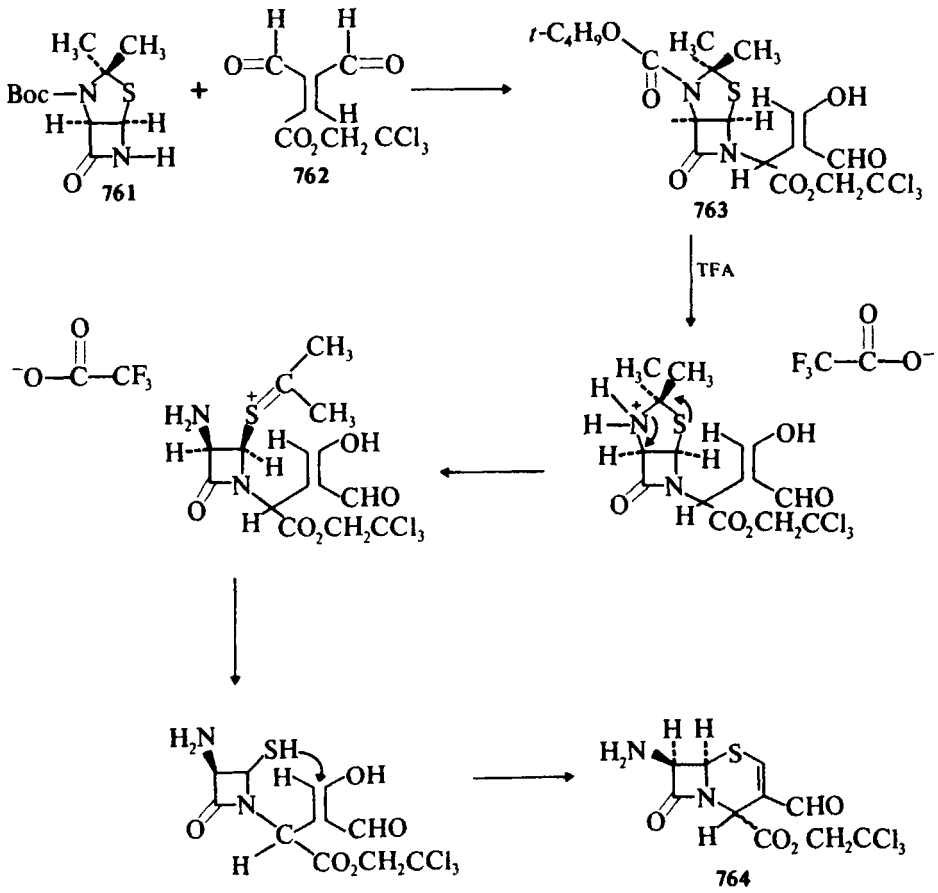


Figure 130

C. *Cyclization of β-Amino Esters: Reformatsky Reaction*

Girman and Speeter made the important discovery that Schiff base **10** reacted with ethyl α-bromoacetate **768** under Reformatsky conditions in the presence of zinc metal to afford azetidinone **771** in 56% yield.[202] Predictably, the zinc enolate **769** condensed with **10** to give the nitrogen-zinc intermediate **770**. Quite unexpectedly, **770** underwent cyclization to **771**. This is illustrated in Figure 132. The Reformatsky, zinc ion complex-mediated, cyclization supports the contention that "soft metal ions" (such as the Grignard MgX^+ ion) or a transition metal ion (such as ZnX^+) will effectively bind with the ester carbonyl in the transition state, facilitating the formation of the azetidinone.

Kagan and co-workers investigated the stereochemistry of azetidinones formed from the Reformatsky reaction.[203] They condensed **10** with various ethyl α-bromoesters in the presence of zinc metal in toluene to obtain the corresponding

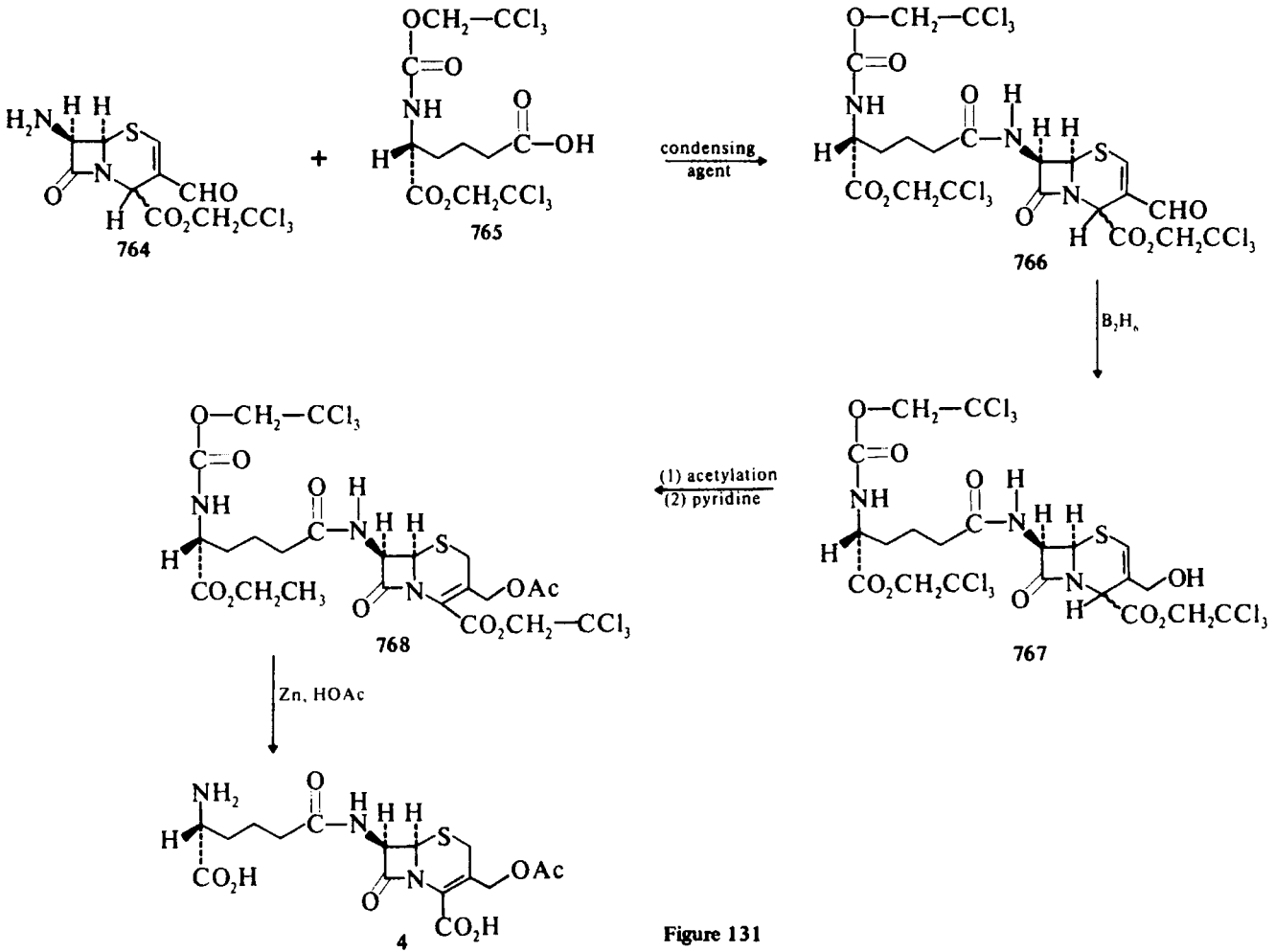

764
765
condensing agent
766
B_2H_6
767
(1) acetylation
(2) pyridine
768
Zn, HOAc
4

Figure 131

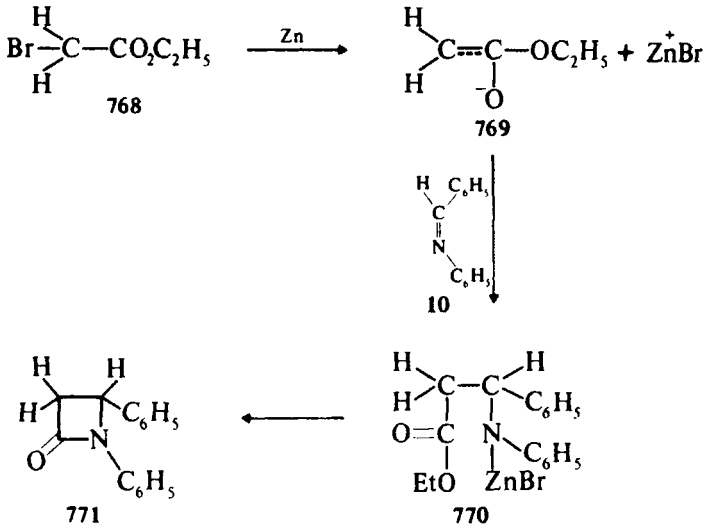


Figure 132

azetidinones in nearly quantitative yields. They found that when the steric requirements of the substituents at C_3 and C_4 of the developing azetidinone were small, the cis isomer predominated. For example the reaction of **10** with the Reformatsky enolate derived from ethyl α-bromopropionate **772** afforded azetidinone **773** as a mixture of cis and trans isomers at a ratio of 73:27. In contrast, when the steric requirements of the substituents at C_3 and C_4 of the developing azetidinone were quite large, the trans isomer was the predominant one. For example, **10** reacted with ethyl α-bromo-α-phenylacetate **774** to give azetidinone **775** as a mixture of cis and trans isomers at a ratio of 5:95. This sequence of reactions is presented in Figure 133. A summary of azetidinones prepared by this method is illustrated in Figure 134.

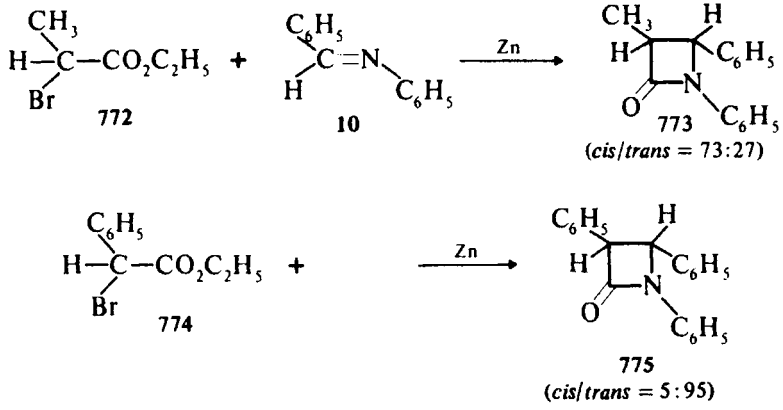
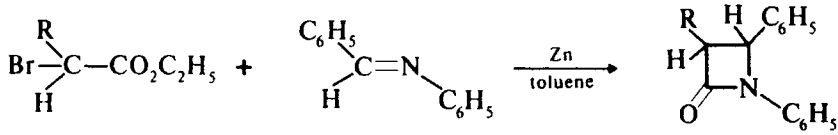


Figure 133



R	Stereochemistry *cis*	*trans*
CH_3	73	27
C_2H_5	64	36
i-C_3H_7	55	45
t-C_4H_9	25	75
C_6H_5	5	95

Figure 134

Luche and Kagan[204] investigated the effect of both ester and solvent variation on the C_3–C_4 stereochemistry of azetidinones formed in the Reformatsky reaction. Large ester groups (i.e., menthyl) promoted the formation of the *trans* isomer, and polar solvents (such as THF) promoted the formation of the *cis* isomer (Figures 135 and 136). A series of azetidinones prepared by the Reformatsky reaction is illustrated in Figure 137.

$$\phi CH{=}N\phi + R^1CHBrCO_2R^2 + Zn \xrightarrow{\phi CH_3} \textit{cis}\text{- + }\textit{trans}\text{-Azetidinone}$$

R^2	R^1 (% *cis*/*trans*) CH_3	*i*-C_3H_7	*t*-C_4H_9
CH_3	73/27	55/45	25/75
i-C_3H_7	66/34	34/66	2/98
(−)-Menthyl	38/62	10/90	

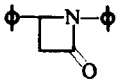
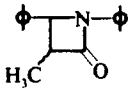
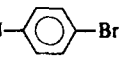
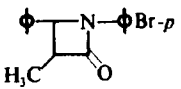
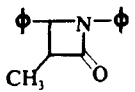
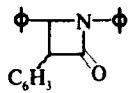
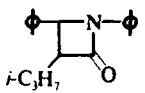
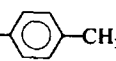
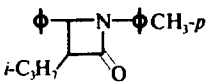
Figure 135

$$\phi CH{=}N\phi + RCHBrCO_2Me + Zn \xrightarrow{\text{solvent}} \textit{cis}\text{- + }\textit{trans}\text{-Azetidinone}$$

Solvent	R (% *cis*/*trans*) CH_3	C_2H_5	*i*-C_3H_7	C_6H_{11}	*t*-C_4H_9	ϕ
ϕCH_3	73/27	64/36	55/45	45/55	25/75	0/100
$Et_2O/\phi H$ (1 : 1)		63/37	80/20	76/25		
THF	80/20	74/36	100/0	100/0	100/0	0/100

Figure 136

A plausible mechanism for these results is as follows. When the R group is small (e.g., R = CH_3), one can envision the reaction proceeding through the erythro intermediate **776**, which undergoes a bond rotation of 180° to produce the critical intermediate **777**. As long as the steric requirements for R are small, this is the preferred transition state. The *cis*-azetidinone **778** is formed from **777** in the

Schiff Base	Ester Bromide	Yield (%)	β-Lactam	Solvent
ϕCH=Nϕ	CH_3BrCO_2–Menthyl	82		C_6H_6
ϕCH=Nϕ	$CH_3CHBrCO_2Me$	75		C_6H_6
ϕCH=Nϕ	$CH_3CHBrCO_2Me$	94	"	THF
ϕCH=N	$CH_3CHBrCO_2Me$	85	"	C_6H_6
ϕCH=N–  –Br	$CH_3CHBrCO_2Me$	90		THF
	$CH_3CHBrCO_2$–Menthyl	80		$C_6H_5CH_3$
ϕCH=Nϕ	$C_4H_5CHBrCO_2Me$	94		$C_4H_5CH_3$
"	"	96	"	THF
"	"	72	"	Et_2O–C_6H_5
ϕCH=Nϕ	i-$C_3H_7CHBrCO_2Me$	98		$C_6H_5CH_3$
"	"	92	"	THF
"	"	98	"	Et_2O–C_6H_5
ϕCH=Nϕ	i-$C_3H_7CHBrCO_2$–i-C_3H_7	93	"	$C_6H_5CH_3$
"	i-$C_3H_7CHBrCO_2$–Menthyl	90	"	$C_6H_5CH_3$
ϕCH=N–  –CH_3	i-$C_3H_7CHBrCO_2CH_3$	97		THF

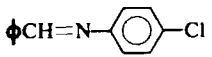
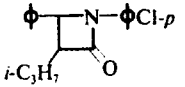
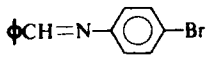
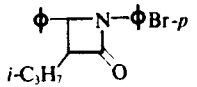
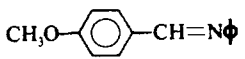
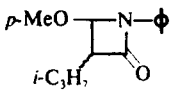
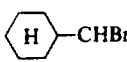
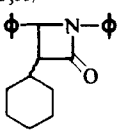
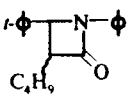
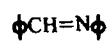
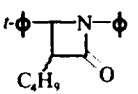
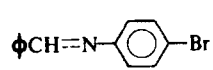
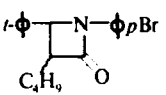
Schiff Base	Ester Bromide	Yield (%)	β-Lactam	Solvent
	"	98		THF
	"	95		$C_6H_5CH_3$
"	"	98	"	THF
	"	70		$C_6H_5CH_3$
		92		$C_6H_5CH_3$
	"	96	"	THF
"	"	98	"	Et_2O–C_6H_5
"	t-$C_4H_9CHBrCO_2CH_3$	71		$C_6H_5CH_3$
"	"	96	"	THF
	t-$C_4H_9CHBrCO_2$-i-C_3H_7	95		$C_6H_5CH_3$
	t-$C_4H_9CHBrCO_2Me$	98		$C_6H_5CH_3$
"	"	98	"	THF

Figure 137

rate-determining k_3 step. As the steric requirements for R are increased (e.g., R = C_6H_5), the energy of the transition state **777** becomes greater than that of the threo intermediate **779**; this is converted to the *trans*-azetidinone **780** in the rate-determining k_5 step. As one changes the solvent from the nonpolar toluene to the more polar THF, the erythro pathway (i.e., **776**) becomes preferred by virtue of the enhanced solvation of the zinc–nitrogen complex. The erythro and threo pathways for the formation of *cis*- and *trans*-azetidinone **778** and **780**, respectively, are shown in Figure 138.

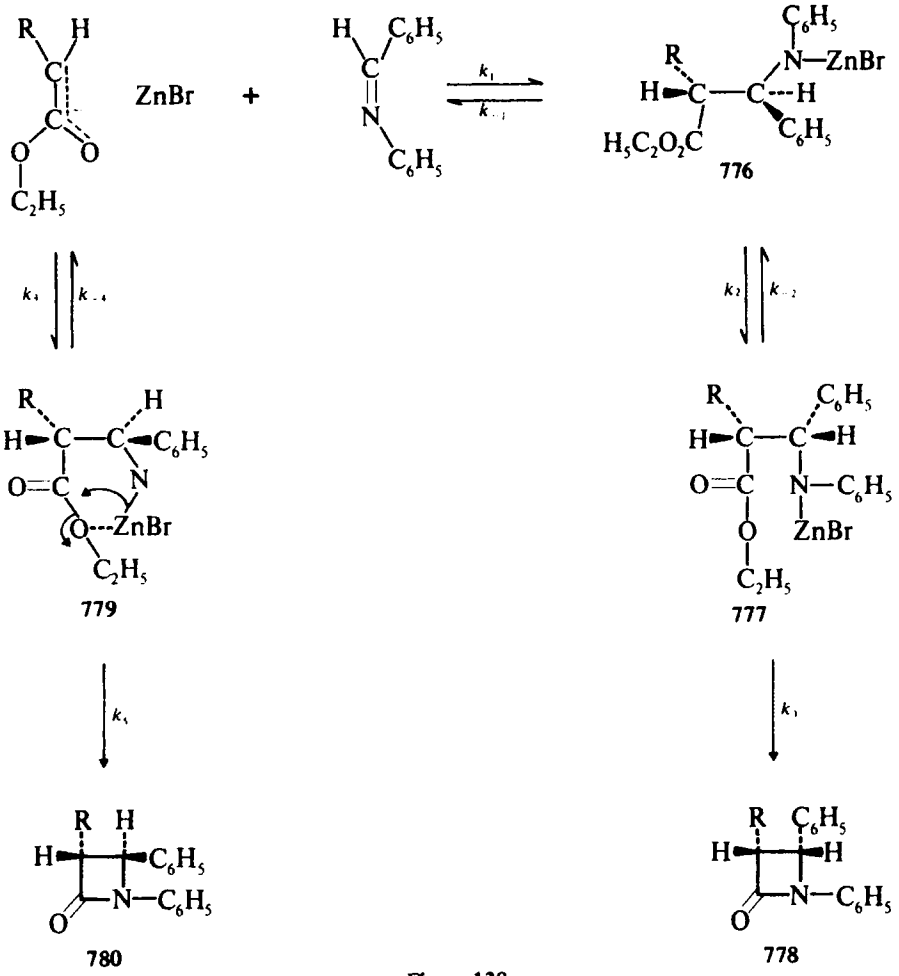


Figure 138

Dardoize and co-workers found that azetidinone synthesis by the Reformatsky reaction could be intercepted at the β-amino ester stage and that subsequent reaction of either the erythro- or threo-β-amino ester with ethyl Grignard reagent afforded either the *cis*- or the *trans*-azetidinone, respectively.[205] This series of transformations is outlined in Figure 139.

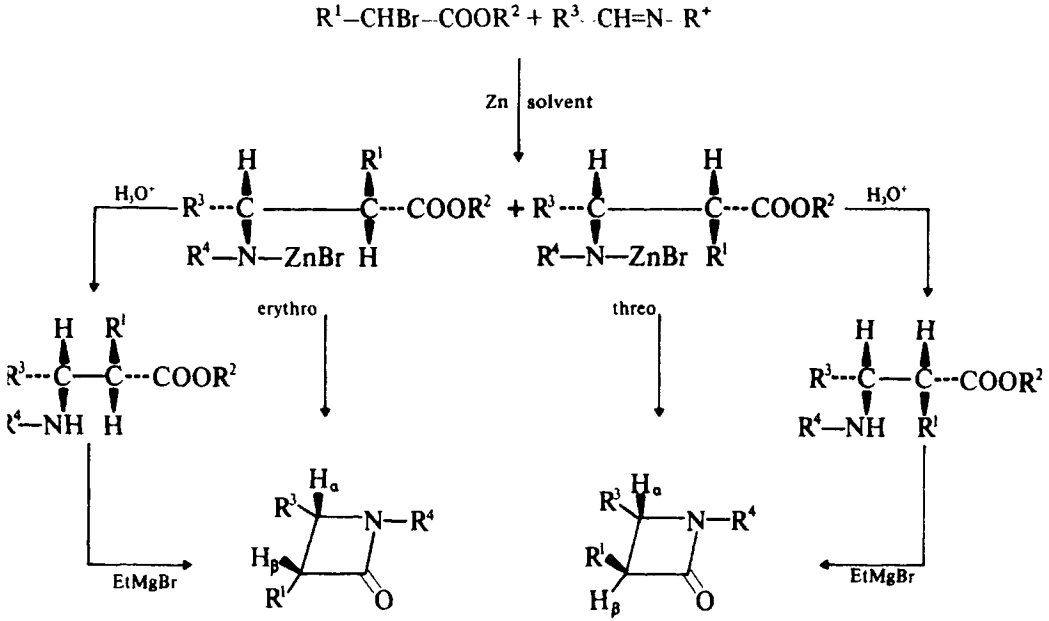


Figure 139

An interesting variant of the Reformatsky azetidinone synthesis was reported by Kagan and co-workers.[206] They found that benzonitrile **781** condensed with the zinc ester enolate **782** to give the imine–zinc complex **783**, which acylated a second equivalent of **782** to afford azetidinone **784**. This is illustrated in Figure 140. Deshpande and co-workers[207] reported that the ethylbromomalonate **785**

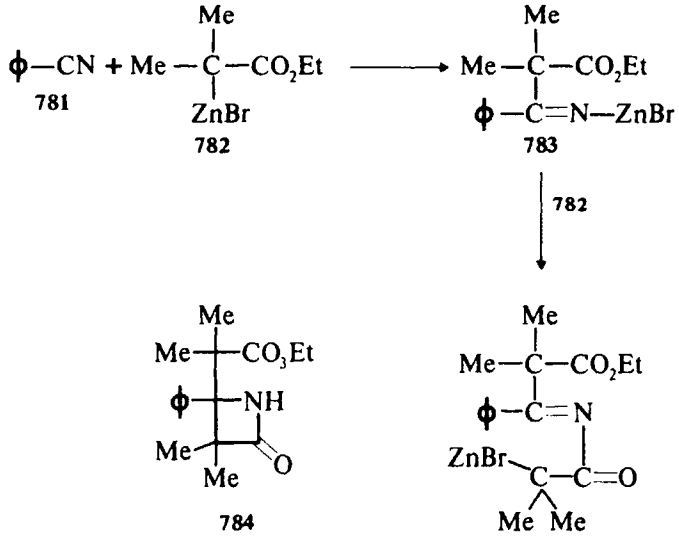


Figure 140

underwent the Reformatsky cyclization with **10** to afford azetidinone **786**, as depicted in Figure 141.

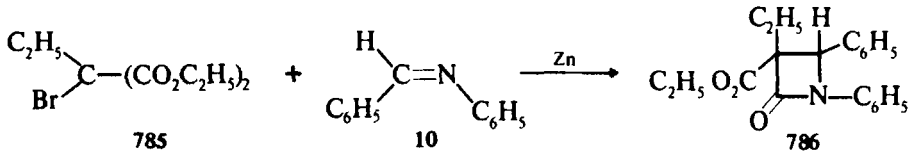
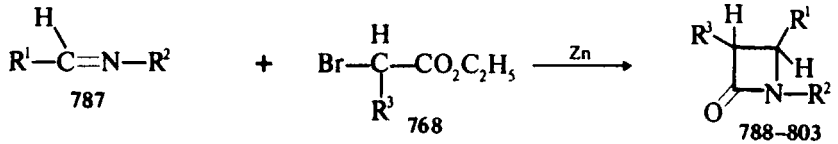


Figure 141

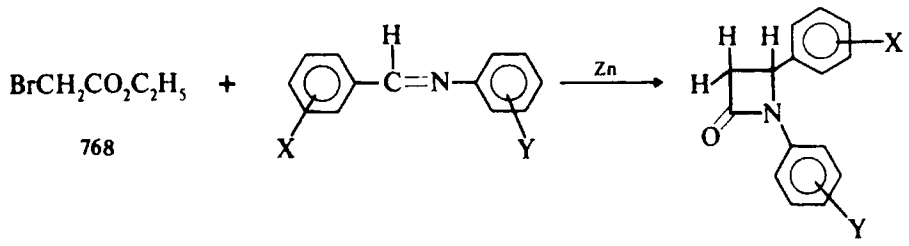
Cuingnet and co-workers extended the Reformatsky azetidinone synthesis to the ferrocene and manganese organometallic series.[208] For example, imine **787** reacted with **768** and zinc in THF to afford azetidinone **788** in 57% yield. A summary of organometallic azetidinones prepared by this method is presented in Figure 142.

Mohan and co-workers investigated the Reformatsky azetidinone synthesis with respect to the substituent effects of aryl imines. For example, benzylidine *p*-nitroaniline and *p*-nitrobenzylidine aryl amines gave no detectable β-lactams when they reacted with ethyl α-bromoacetate **768** and zinc.[209] A series of aryl azetidinones prepared by the Reformatsky reaction is illustrated in Figure 143.[209] Dardoize and co-workers reported that Schiff base, **813**, underwent a Reformatsky reaction with **768** and zinc to give a 67% yield of azetidinone **814**, as shown in Figure 144.[210]



Azetidinone	R^1	R^2	R^3	Yield (%)
788	$C_6H_5FeC_6H_4$	C_6H_5	H	57
789	$C_6H_5FeC_6H_4$	C_6H_5	CH_3	60
790	$C_6H_5FeC_6H_4$	*p*-$CH_3OC_6H_4$	H	28
791	$C_6H_5FeC_6H_4$	*p*-$CH_3OC_6H_4$	CH_3	36
792	$C_6H_5FeC_6H_4$	*p*-$C_2H_5OC_6H_4$	H	43
793	$C_6H_5FeC_6H_4$	*p*-$C_2H_5OC_6H_4$	CH_3	34
794	$C_6H_5FeC_6H_4$	*p*-ClC_6H_4	H	5
795	$C_6H_5FeC_6H_4$	*p*-ClC_6H_4	CH_3	31
796	$C_6H_5FeC_6H_4$	*p*-$CH_3C_6H_4$	CH_3	53
797	$C_6H_5FeC_6H_4$	*m*-$CH_3C_6H_4$	H	30
798	$C_6H_5FeC_6H_4$	*m*-$CH_3C_6H_4$	CH_3	33
799	$C_6H_5FeC_6H_4$	$C_6H_5FeC_6H_4$	H	62
800	C_6H_5	$C_6H_5FeC_5H_4$	H	66
801	*p*-$CH_3OC_6H_4$	$C_6H_5FeC_5H_4$	H	
802	$(CO)_3MnC_5H_4$	$C_6H_5FeC_5H_4$	H	62
803	$(CO)_3MnC_5H_4$	C_6H_5	H	35

Figure 142



Azetidinone	X	Y	Solvent of Crystallization	Yield (%)
804	H	H	Methanol	58
805	H	*p*-Cl	Benzene	54
806	H	*p*-Br	Benzene	59
807	H	*p*-OCH_3	Benzene	60
808	*p*-Cl	H	Methanol	64
809	*p*-Cl	*p*-Br	Methanol	57
810	*p*-Cl	*p*-Cl	Methanol	63
811	*o*-Cl	*p*-Br	Benzene	68
812	*p*-Cl	*p*-Cl	Methanol	70

Figure 143

D. *Cyclization of β-Amino Carbonyl Derivatives: Utilization of Titanium Tetrachloride and Transition Metal Complexes in the Construction of β-Lactams*

Ojima and co-workers reported that appropriately substituted Schiff bases underwent condensation with ketene silyl acetals in the presence of titanium tetrachloride to produce the corresponding azetidinones in one step.[211] For example, the reaction of imine **815** with ketene silyl acetal **816** and titanium tetrachloride in methylene chloride at room temperature afforded a 72% yield of azetidinone **817**. In contrast, the reaction of the aniline Schiff base **17** with **816** under the conditions described above produced a 92% yield of β-amino ester **818**. The ester was subsequently treated with lithium diisopropylamide (LDA) in THF to effect cyclication to azetidinone **819** in 91% yield. This sequence of reactions is represented in Figure 145. A summary of β-amino esters and the corresponding azetidinones constructed by this method is illustrated in Figure 146.

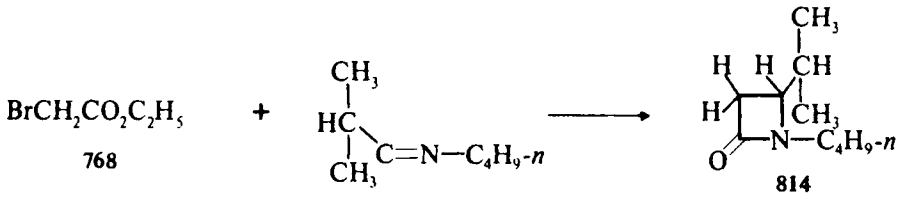


Figure 144

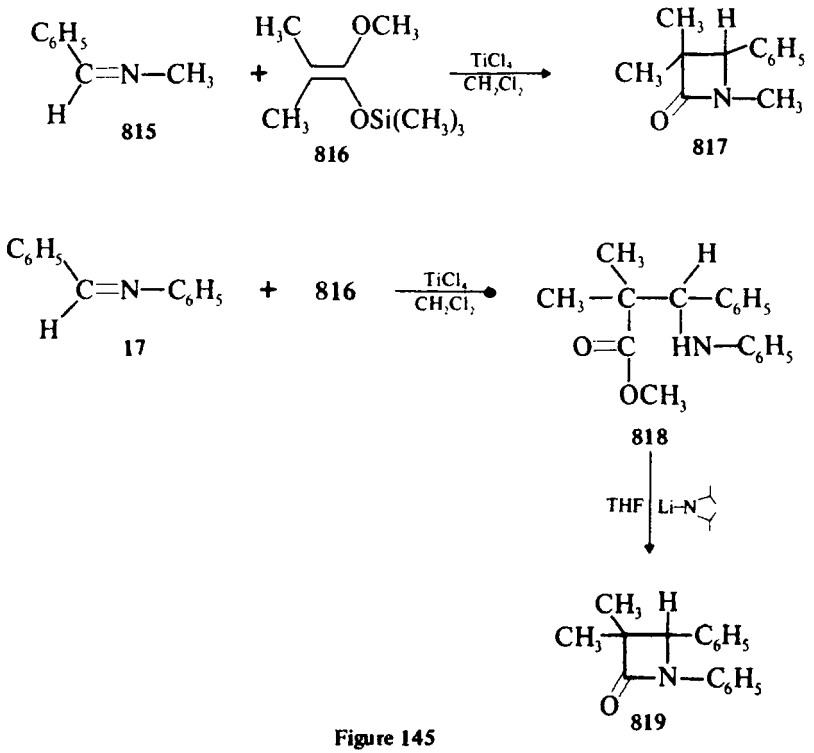
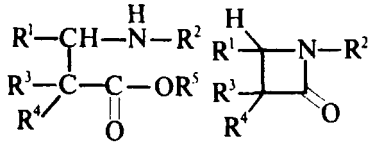


Figure 145

An extremely interesting rearrangement was discovered by these investigators with the β-amino ester **820**. The reaction of **820** with LDA in THF afforded the pyrrolidone **821**. If, however, the sequence was repeated with potassium *t*-butoxide in place of LDA, one obtained a 77% yield of azetidinone **822**. This series of reactions and a proposed mechanism to account for the synthesis of pyrrolidone **821** are illustrated in Figure 147.



R^1	R^2	R^3	R^4	R^5	Yield (%)	Yield (%)
Ph	Ph	Me	Me	Me	85	95
Ph	Ph	Me	H	Me	83	90
Ph	Ph	$(CH_2)_5$		Me	70	91
Ph	$PhCH_2$	Me	Me	Me	92	77
Ph	Me	Me	Me	Me		72
Pr	$PhCH_2$	Me	Me	Me		43
Et	PhMeCH	Me	Me	Me		54

Figure 146. **β-Amino esters and β-lactams obtained by the reaction of ketene silyl acetals with Schiff bases in the presence of titanium tetrachloride.**

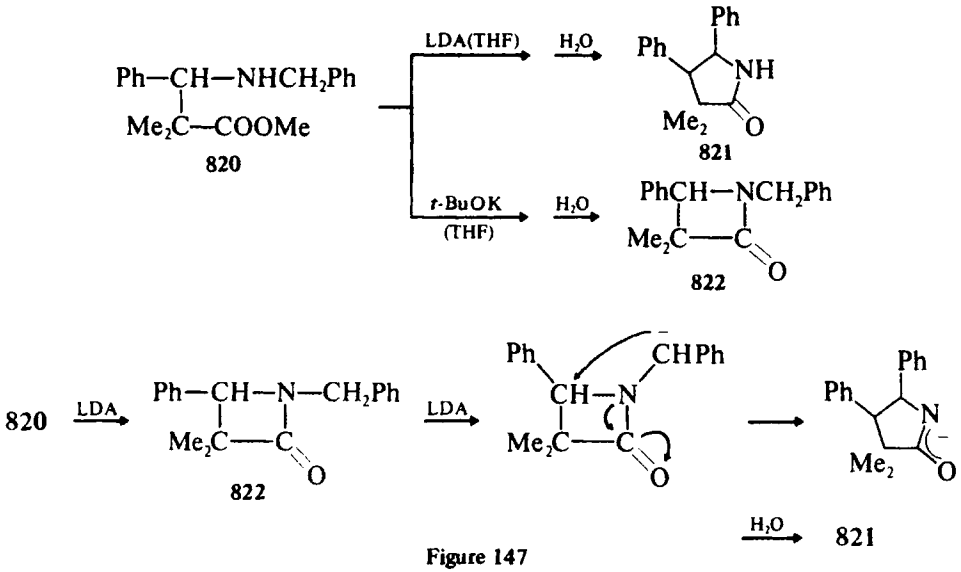


Figure 147

Ojima and Inaba elegantly extended the ketene silyl acetal-imine annelation to the construction of chiral azetidinones.[212] They found that **816** reacted with the chiral Schiff base (*S*)-isopentylidene (1-phenylethyl)amine **823** and titanium tetrachloride[211] to produce azetidinone **824** in 71% yield with 78% asymmetric induction. This transformation is illustrated in Figure 148. A summary of azetidinones with their corresponding percentages of asymmetric induction is presented in Figure 149. A "titanium-incorporated transition state" which could, in theory, justify the chiral selectivity found in this annelation has been proposed by Ojima et al. and is depicted in Figure 150.[212] According to Ojima et al.,[211] transition state A appears to be more favorable than B.

Ojima and Inaba investigated the ketene silyl acetal-imine annelation that culminated in the classical "chiral titanium template hypothesis". A virtually complete asymmetric induction in the synthesis of β-lactams from chiral Schiff bases derived from α-amino esters was produced.[213] Ojima suggested that the

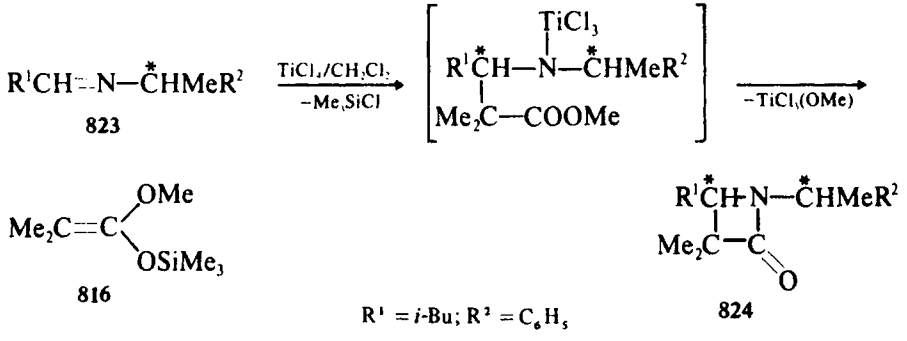


Figure 148

Compound	R^1	R^2	Yield (%)	Asymmetric Induction (%)
825	Et	Ph	66	54
826	*n*-Pr	Ph	72	66
827	*i*-Pr	Ph	26	44
828	*n*-Bu	Ph	73	66
824	*i*-Bu	Ph	71	78
829	Et	1-Naphthyl	69	56
830	*n*-Pr	1-Naphthyl	70	62
831	*i*-Pr	1-Naphthyl	10	52
832	*n*-Bu	1-Naphthyl	69	62
833	*i*-Bu	1-Naphthyl	72	70

Figure 149. Chiral β-lactams 824 obtained by the reaction of dimethylketene methyltrimethylsilyl acetals with (*S*)-alkylidene(1-arylethyl)amines in the presence of titanium tetrachlorides.

complete chiral selectivity is the result of the preferred transition state **834**, in contrast to **835**, which has a less favorable R^1-methyl interaction.[213] This is illustrated in Figure 151. A summary of chiral azetidinones synthesized by this method is presented in Figure 152.

Rosenblum and co-workers reported the synthesis of monocyclic and fused bicyclic β-lactams utilizing an iron–olefin complex with attendant insertion of a carbonyl into the carbon framework and oxidation.[214] For example **845**, derived from the reaction of the iron–ethylene complex **844** with benzylamine at −25°C, underwent rearrangement at 70°C and subsequent oxidation with silver oxide to give azetidinone **846** in 59% yield.[214] Similarly, **847** underwent rearrangement at 70°C to **848**, which was oxidized with Ag_2O to afford an 82% yield of azetidinone **849**. The sequence was successfully applied to the synthesis of the fused azetidinone **851**. Thus initial olefin exchange of Fp(isobutene)tetrafluoroborate with 1-hexenylammonium tetrafluoroborate gave **850**, which was subsequently deprotonated, rearranged at 65°C, and oxidized to the azetidinone **851** in 30% yield. These transformations are illustrated in Figure 153.

Mori and co-workers reported that various 2-bromo-3-aminopropenes underwent palladium-catalyzed rearrangements to the corresponding azetidinones.[215] For example, benzylamino olefin **852** reacted with *n*-Bu_3N in hexamethylphosporamide (HMPA) at 100°C under CO (1 atm.) with a catalytic amount of $Pd(OAc)_2$ and

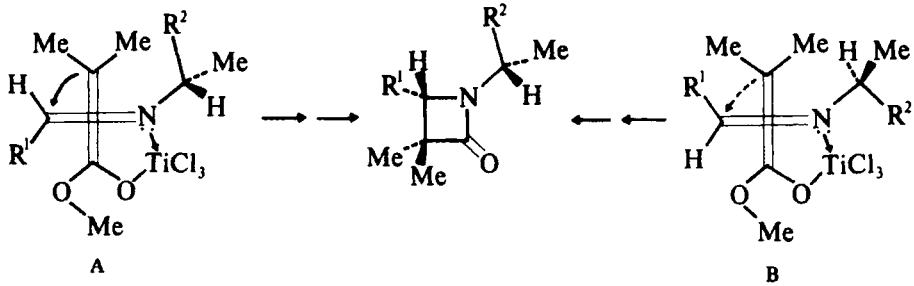


Figure 150

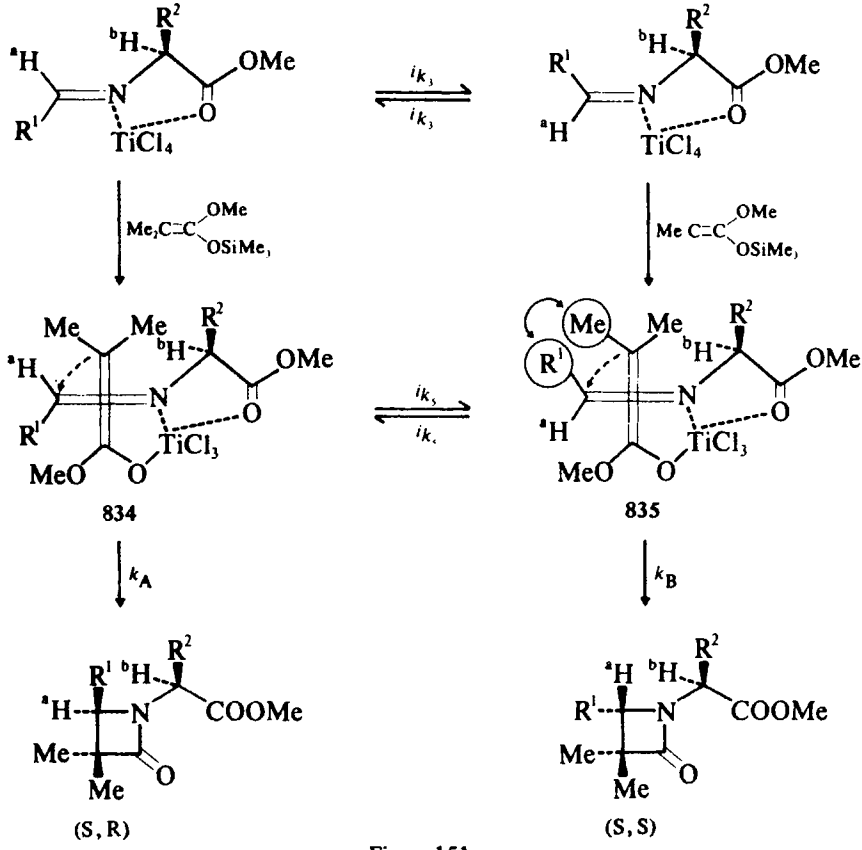


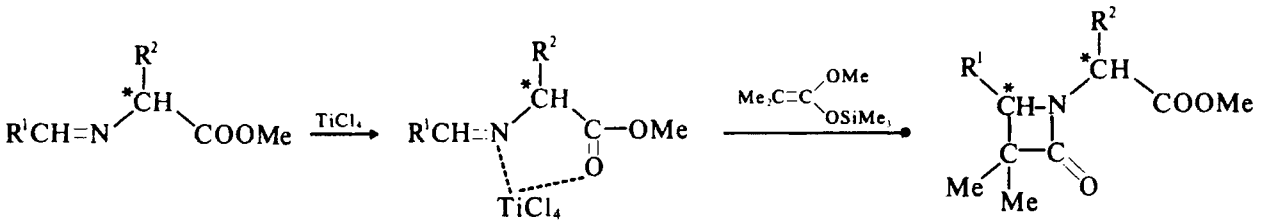
Figure 151

$P(C_6H_5)_3$ to afford a 67% yield of azetidinone **853**. This transformation and a mechanism for the azetidinone formation are illustrated in Figure 154. A summary of monocyclic β-lactam synthesized from the corresponding haloolefins is presented in Figure 155.

2. Formation of N–C_4 Bond (VII → VI)

A. *Cyclization of 3-Halopropionamides*

The construction of azetidinones from 3-halopropionamides was reported by Knunyants et al. and by Sarel and Shoshan, as reviewed by Mukerjee and Srivastava.[261-221] These investigators found that halopropionamide **863** could be cyclized to azetidinone **864** with sodium amide. A significant side reaction of the N–C_4 base-catalyzed cyclization of substituted amides is the competitive dehydrohalogenation affording **865**. Such dehydrohalogenation had discouraged many investigators from constructing biologically active β-lactams from these readily



Compound	R^1	R^2	Yield (%)	(Nmr δ ppm (relative yield %) (S, R)	(S, S)	Asymmetric Induction (%)
836	Et	*i*-Pr	73	3.78 (97)	3.88 (3)	94
837	*n*-Pr	*i*-Pr	74	3.78 (95)	3.89 (5)	90
838	*n*-Bu	*i*-Pr	77	3.79 (95)	3.90 (5)	90
839	*i*-Bu	*i*-Pr	81	3.76 (> 99)	3.89 (< 1)	> 98
840	Et	Me	28	4.23 (73)	4.43 (27)	46
841	Et	CH_2COOMe	53	4.44 (57)	4.34 (43)	14
842	Et	*i*-Bu	49	4.12 (70)	4.34 (30)	40
843	Et	CH_2Ph	45	4.27 (79)	4.88 (21)	58

Figure 152

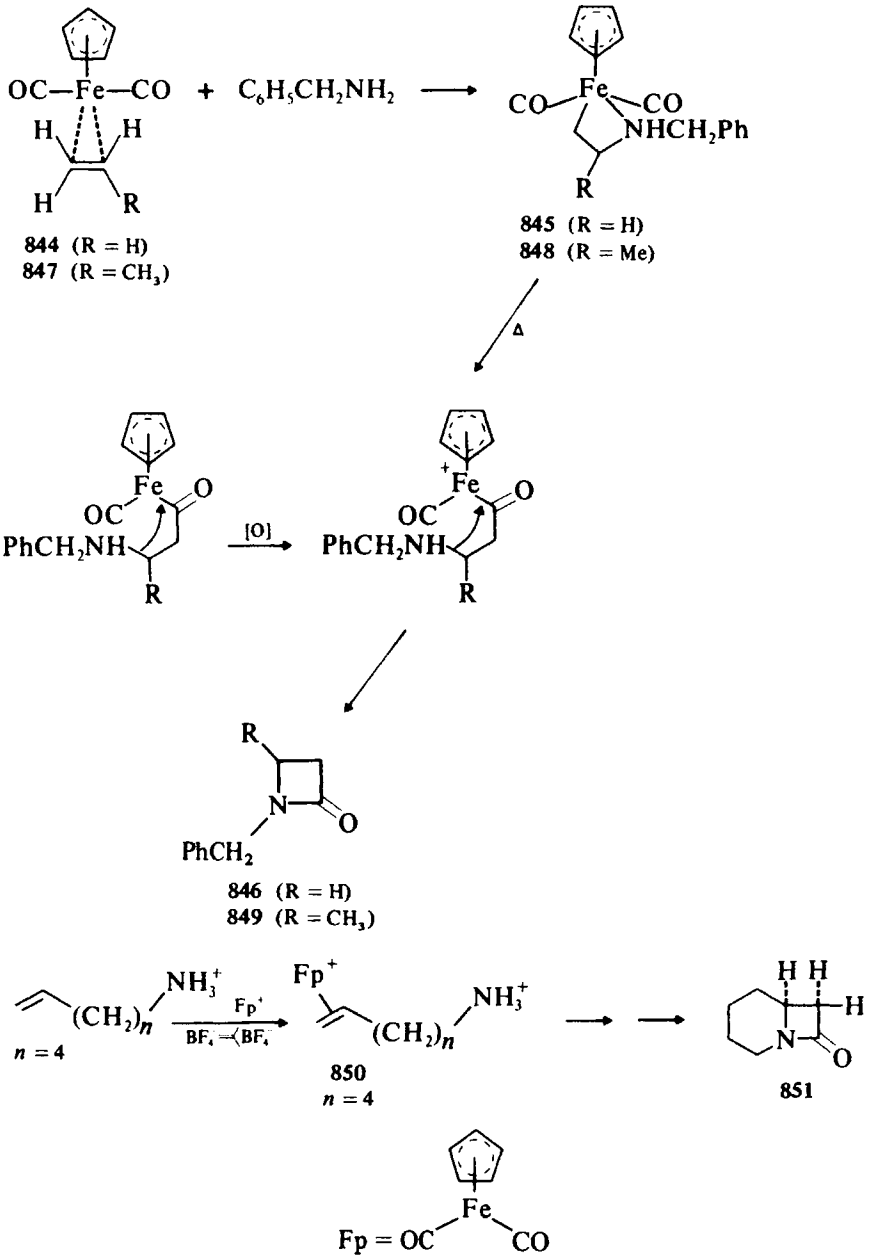


Figure 153

available precursors. Solutions to this problem will be presented in the next section. The steroid amide **866**, which cannot undergo dehydrohalogenation, was smoothly converted to azetidinone **867** with potassium *t*-butoxide.[222] These transformations are presented in Figure 156.

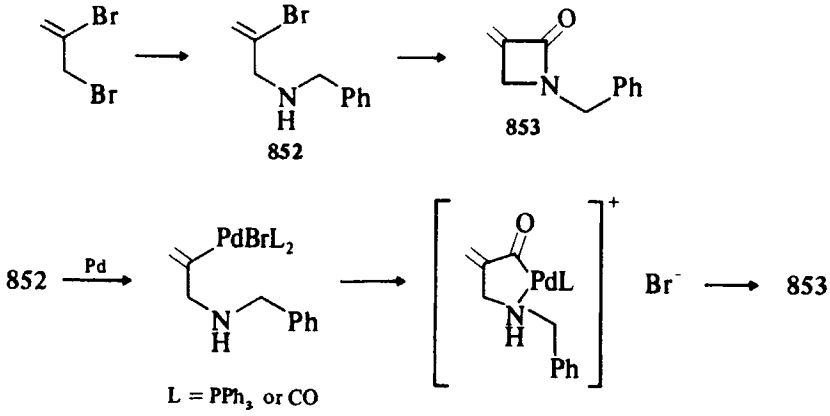


Figure 154

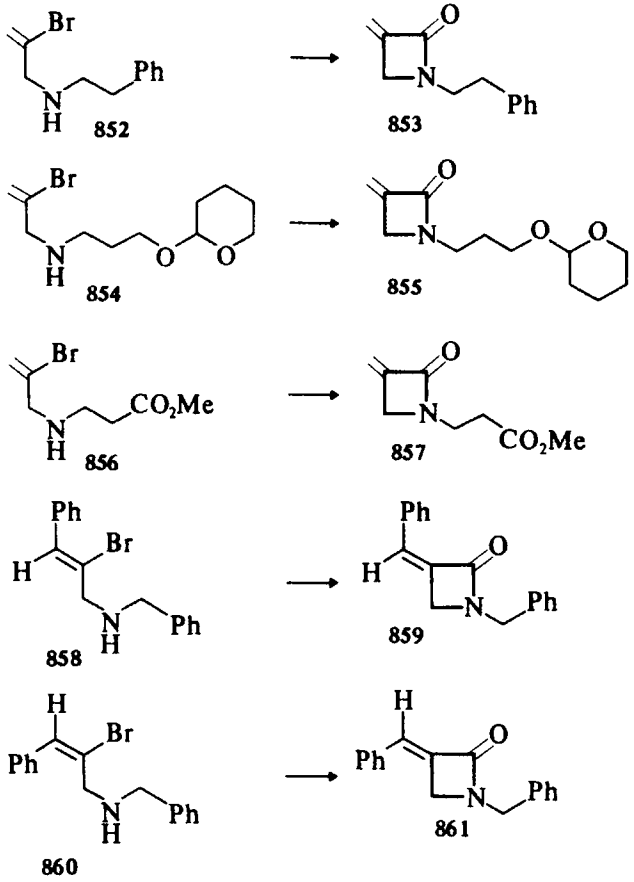


Figure 155

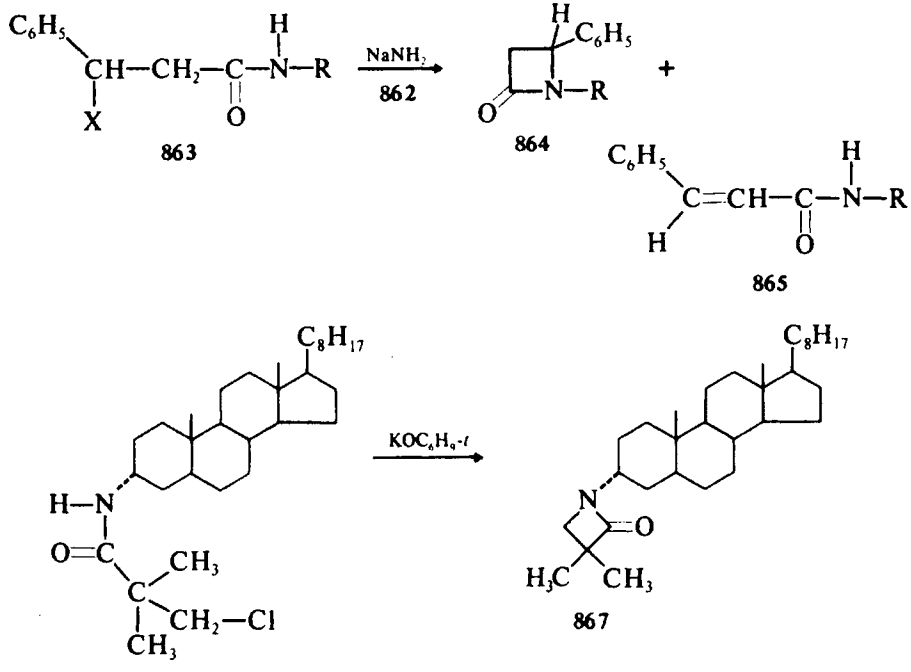


Figure 156

Nicolaus and co-workers investigated the synthesis of anilinoazetidinones.[223] They found that acid chloride **868** reacted with the aniline derivative **869** in ether to afford a 72% yield of **870**. Amide **870** was treated with sodium amide in liquid ammonia to produce azetidinone **871** in 77% yield. This sequence of reactions is illustrated in Figure 157.

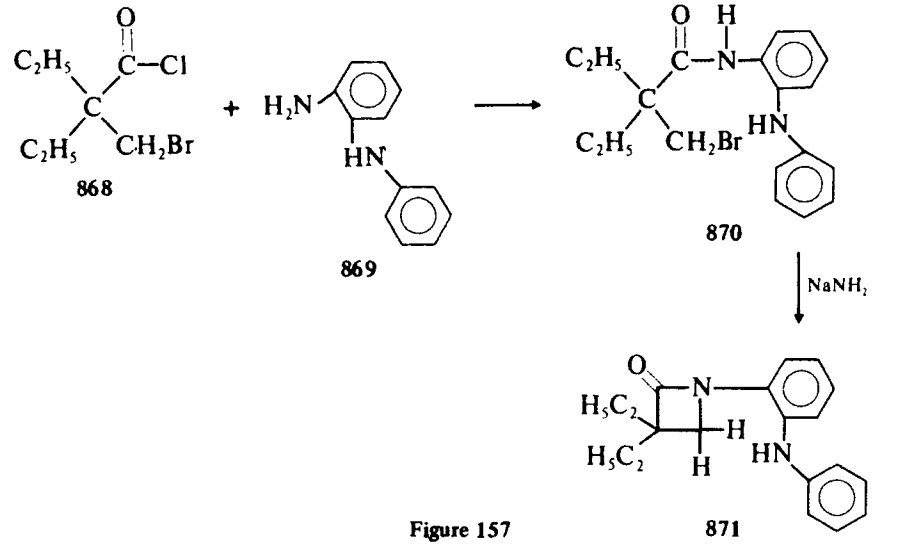
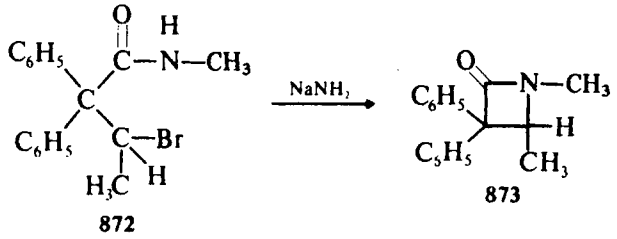
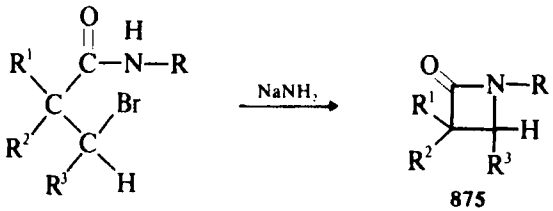


Figure 157

Bellasio and co-workers reported that the 3-bromopropionamide derivative **872**, upon conversion to its amide anion with sodium amide in liquid ammonia, underwent cyclization to azetidinone **873** in 65% yield.[224] Bellasio et al.[225] found that a variety of 3-bromopropionamide derivatives **874** could be converted to the corresponding azetidinones **875** with sodium amide in liquid ammonia.[225] This sequence of reactions is presented in Figure 158. A summary of azetidinones synthesized by this method is presented in Figure 159.

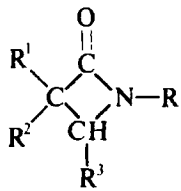


872 **873**



874 **875**

Figure 158



Compound	R	R^1	R^2	R^3	Yield (%)
876	H	n-C_3H_7	n-C_3H_7	CH_3	24
877	H	n-C_3H_7	n-C_3H_7	n-C_3H_7	42
878	H	C_2H_5	C_6H_5	CH_3	20
879	CH_3	n-C_3H_7	n-C_3H_7	CH_3	57
880	CH_3	n-C_3H_7	n-C_3H_7	n-C_3H_7	69
881	CH_3	C_2H_5	C_6H_5	CH_3	83

Figure 159

Manhas and Jen reported that a variety of bases could be used to cyclize β-halocarboxylic acid anilides to their corresponding azetidinones.[247] For example, **1061** was treated with sodium amide in liquid ammonia (method A) to afford a 68% yield of azetidinone **1062**. When **1061** was reacted with dimsyl anion, derived from sodium hydride in dimethyl sulfoxide (method B), a 96% yield of **1062**

was obtained. Finally, the reaction of **1061** with potassium *t*-butoxide in DMSO (method C) afforded a 70% yield of azetidinone **1062**. This series of reactions is illustrated in Figure 159a. A summary of azetidinones prepared by methods A, B, and C is presented in Figure 159b. Merger reported that *N*-methylbromopivaloylamide **882** reacted with lithium carbonate in paraffin oil at 200°C to afford a

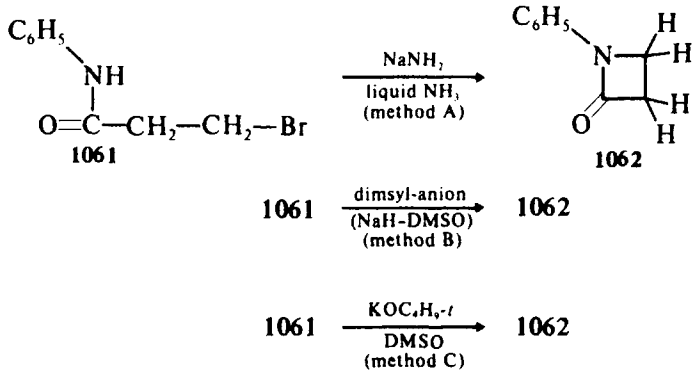


Figure 159a

Compound	Yield (%)	Method
1-Phenyl-2-azetidinone	68	A
	95.6	B
	70.3	C
1-*o*-Bromophenyl-2-azetidinone	71	B
1-*o*-Fluorophenyl-2-azetidinone	90.4	B
1-*p*-Bromophenyl-2-azetidinone	58	A
1-*p*-Bromophenyl-3,3-dimethyl-2-azetidinone	55	A
1-*p*-Chlorophenyl-2-azetidinone	73	B
1-*p*-Iodophenyl-2-azetidinone	80.6	B
1-*p*-Methoxyphenyl-2-azetidinone	50	A

Figure 159b

55% yield of azetidinone **883**.[226] This is represented in Figure 160. It is important to note that, with few exceptions, the successful conversions of 3-halopropionamides to the corresponding azetidinones involved precursor substrates in which the dehydrohalogenation pathway **884** → **885** was inhibited by α-alkyl disubsti-

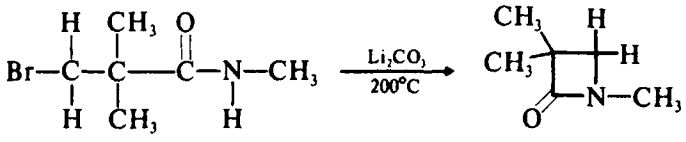


Figure 160

tution. Thus charge dissipation in the derived amide anion **886** could be achieved solely through N–C_4 bond formation to give **887**, as illustrated in Figure 161.

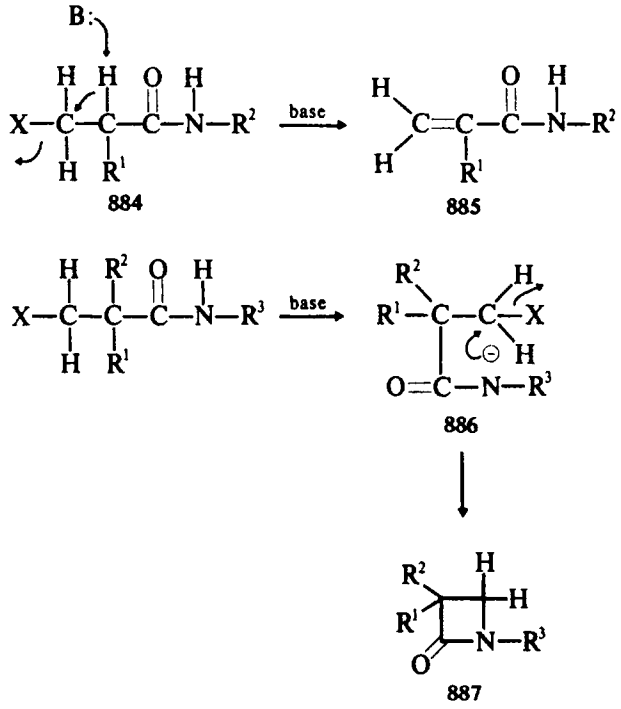
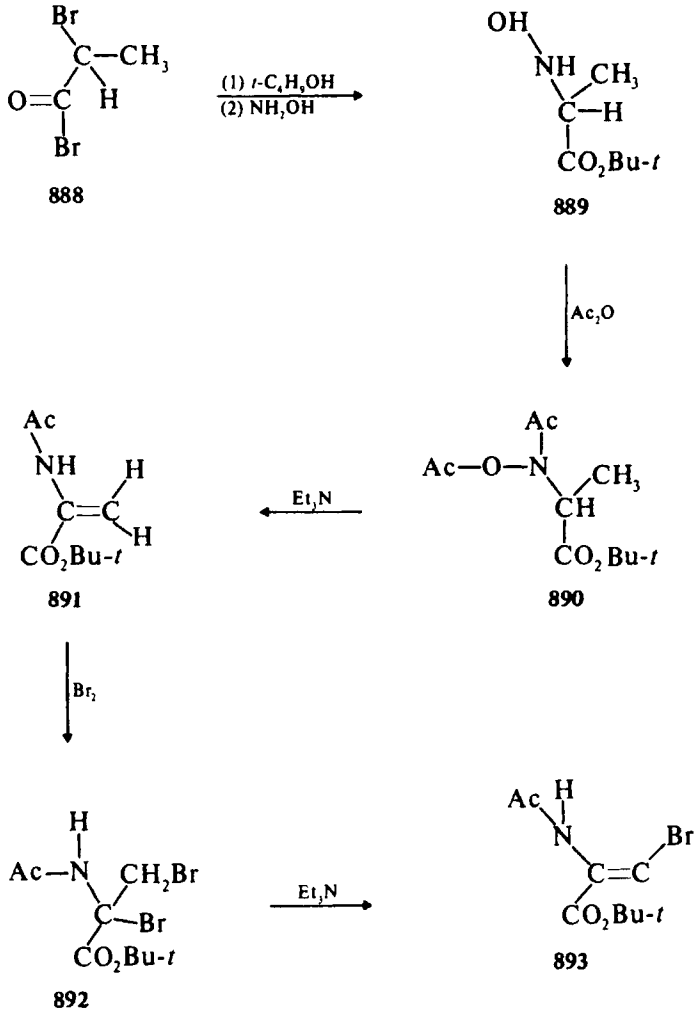


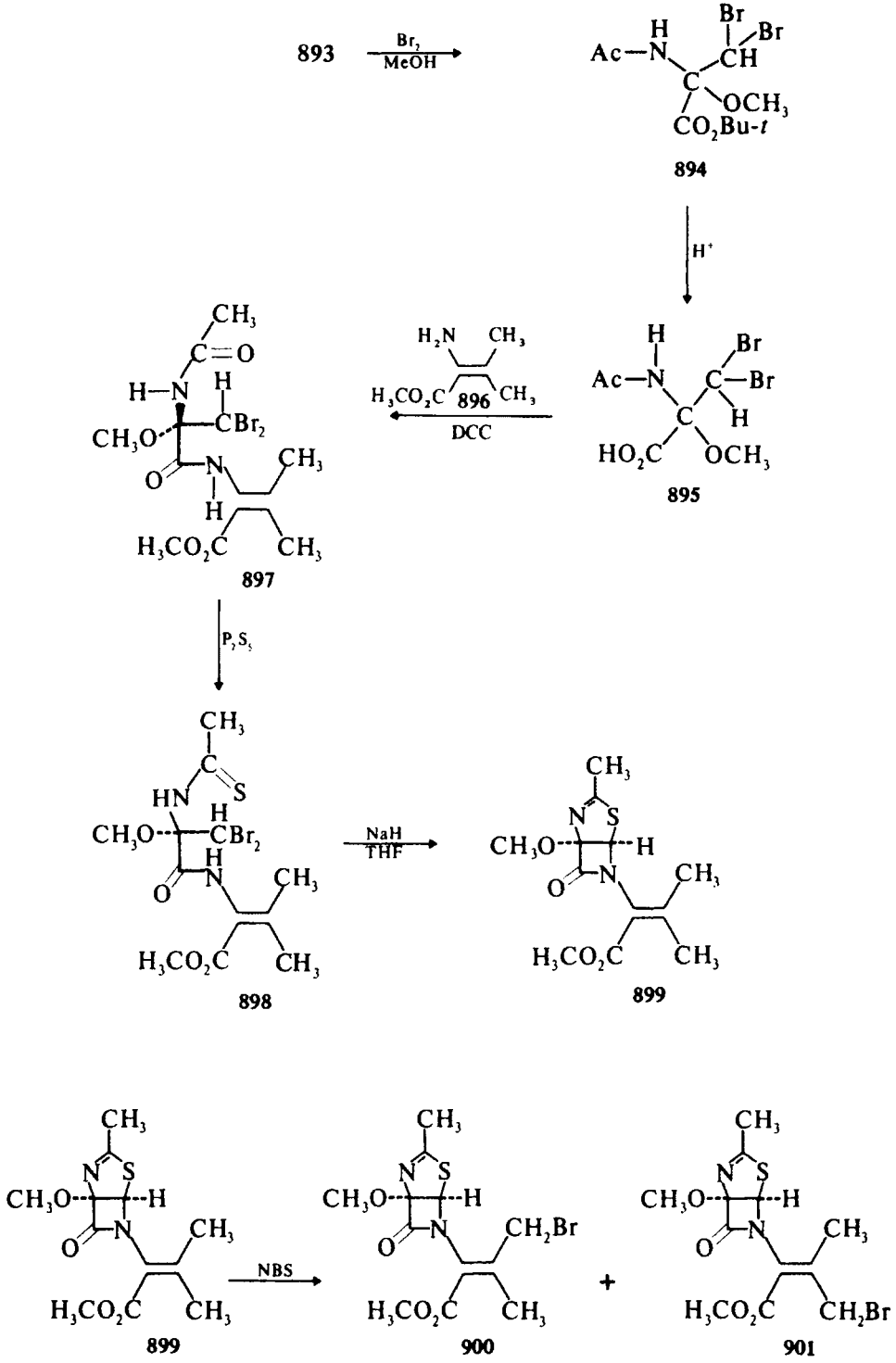
Figure 161

B. *Cyclization of 3-Halocysteinylamides*

Nature has presented the scientific community with a startling array of β-lactam antibiotics, a few of which have been isolated and identified. Because of its complex organization and stereochemistry, the 7-α-methoxycephem **904** has been a very attractive target for total synthesis. Y. Kishi, one of the most remarkable contemporary organic chemists, tried a new approach to the synthesis of β-lactams with the hope of achieving the total synthesis of **904**. Kishi and co-workers found that 2-bromopropionyl bromide **888** reacted with *t*-butanol–pyridine, followed by hydroxylamine, to afford **889**.[227] This was treated with acetic anhydride at 100°C to give **890**, which was converted with triethylamine to **891** in 72% overall yield. Compound **891** was brominated to give **892**. This in turn was dehydrohalogenated with triethylamine to afford the bromodehydroalanine **893** in 90% overall yield (from **891**). The bromo adduct **893** was treated with bromine in methylene chloride–methanol to afford the methoxy derivative **894** in 82% yield. At this stage of this synthesis, the *t*-butyl ester protecting group was removed under acidic conditions to give the free acid **895**, which was coupled with dehydrovaline

ester **896** (utilizing DCC) to give the amide **897**. The latter was converted to the thioamide **898** by reaction with phosphorus pentasulfide in THF at 50°C for 2 hours. The thiazoline β-lactam **899** was obtained in a double cyclization sequence with sodium hydride in THF. β-Lactam **899** was brominated with *N*-bromosuccinimide (NBS) to give bromides **900** and **901** in 70% yield. These were treated with zinc–acetic acid to afford the deconjugated esters **902** and **903**, as well as the conjugated ester **899**, in 90% yield. The isomer **902**, bearing the natural configuration at C_3, was treated with *m*-chloroperbenzoic acid (MCPBA) in benzene with a catalytic amount of trifluoroacetic acid (TFA), followed by reduction with phosphorus trichloride, to give the 7-α-methoxycephem **904** and 6-α-methoxypenicillin **905**.[227] These reaction sequences are illustrated in Figure 162.




893
Br2
MeOH
Ac—N
H
Br
Br
CH
C
OCH3
CO2Bu-t
894
H+
H2N CH3
H3CO2C 896 CH3
DCC
Ac—N
H
Br
C—Br
C
H
HO2C
OCH3
895
CH3
C=O
H—N
H
CH3O
CBr2
O
N
CH3
H
H3CO2C
CH3
897
P2S5
CH3
C
S
HN
H
CH3O
CBr2
H
O
N
CH3
H3CO2C
CH3
898
NaH
THF
CH3
N
S
CH3O
H
O
N
CH3
H3CO2C
CH3
899
CH3
N
S
CH3O
H
O
N
CH3
H3CO2C
CH3
899
NBS
CH3
N
S
CH3O
H
O
N
CH2Br
H3CO2C
CH3
900
+
CH3
N
S
CH3O
H
O
N
CH3
H3CO2C
CH2Br
901

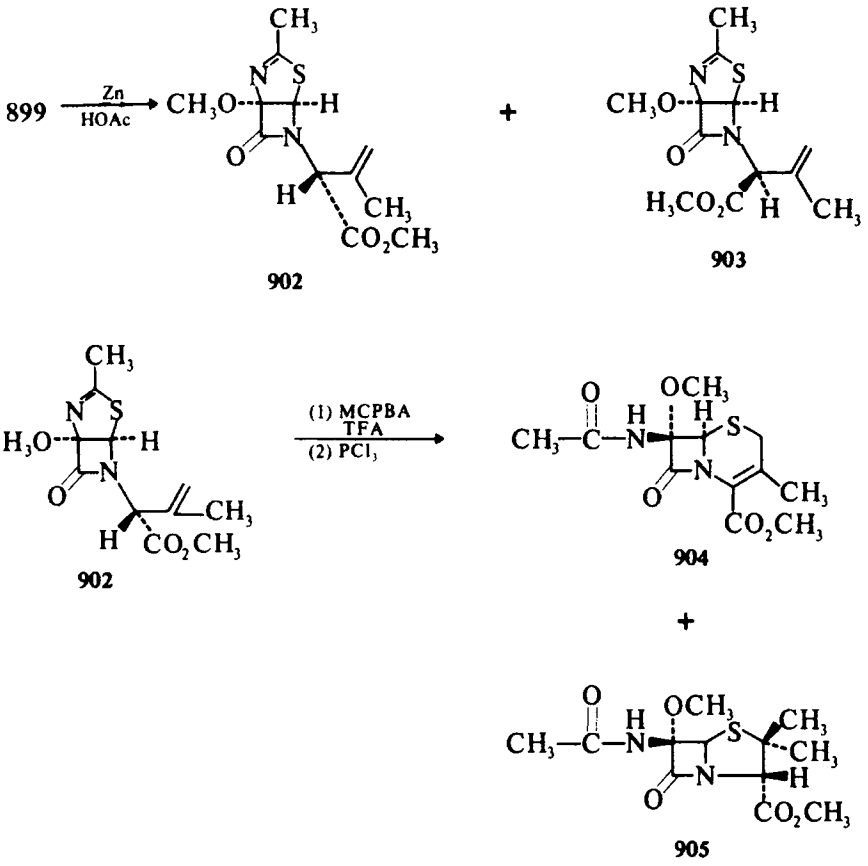


Figure 162

An alternate synthesis of **904** was reported by Kishi and co-workers.[227] They found that in an evaporated solution of methylene chloride, bromide **900** closed spontaneously to **904** in 40% yield.[227] This transformation is represented in Figure 163.

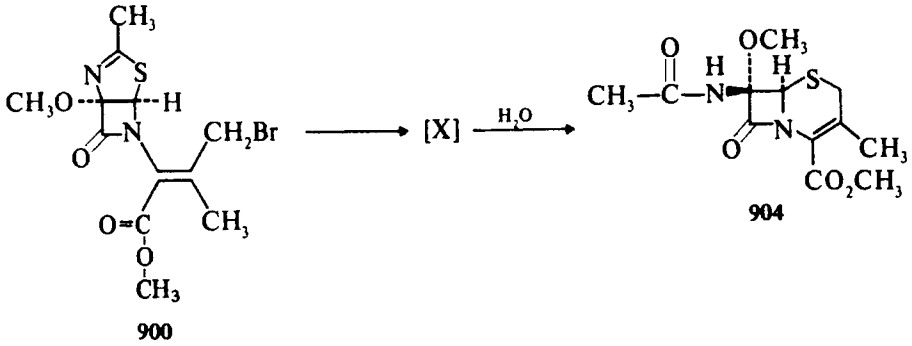
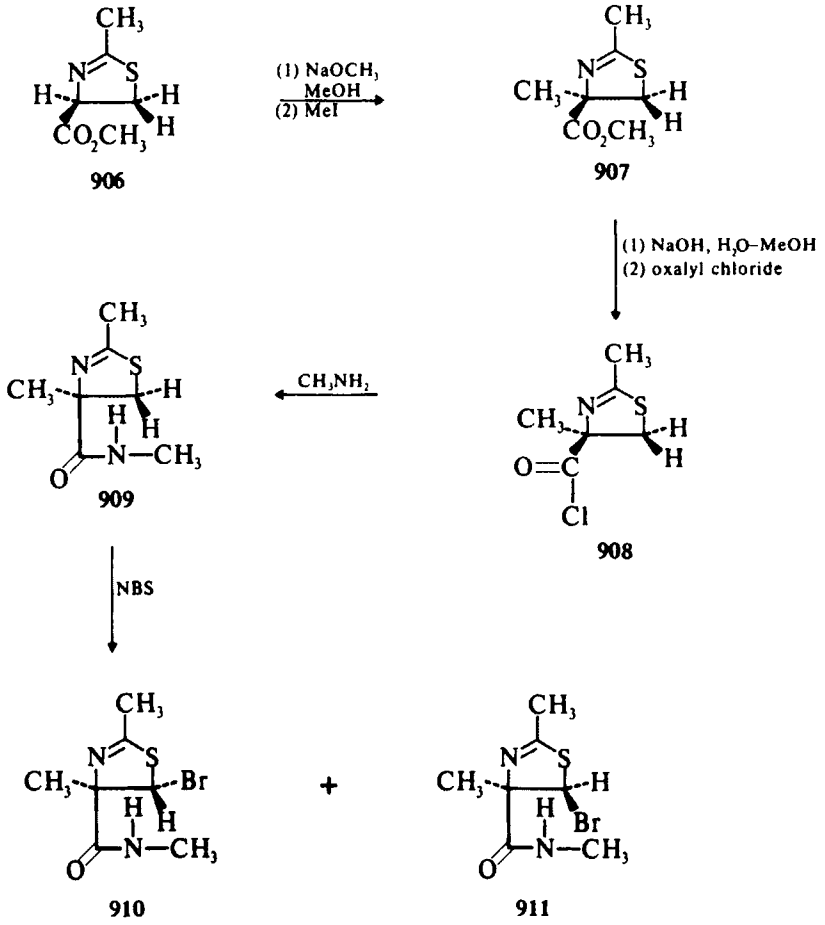


Figure 163

Kishi and co-workers[228] continued their investigation into the construction of cysteinyl β-lactams from cysteinyl precursors. For example, thiazoline **906** was treated with sodium methoxide and methyl iodide to afford a 74% yield of **907**. This was hydrolyzed with sodium hydroxide, converted to the acid chloride **908** with oxalyl chloride, and treated with methylamine to afford the amide **909** in 85% overall yield from **906**. The thiazoline amide **909** was treated with NBS to afford a 1 : 1 isomeric mixture of bromides **910** and **911**, which were separable by chromatography. The reaction of **910** with potassium hydride afforded β-lactam **912** in high yield. In contrast, when **911** was treated with potassium hydride, only starting material was obtained. These data support the contention that the cyclization proceeds through an S_N2 process. Isomer **911** could be converted to **912** by reaction with potassium hydride and lithium bromide–lithium perchlorate in THF. These transformations are illustrated in Figure 164.

Having demonstrated that the thiazoline amide **909** could be converted to the thiazoline β-lactam **912**, Kishi and co-workers applied this to the synthesis of the



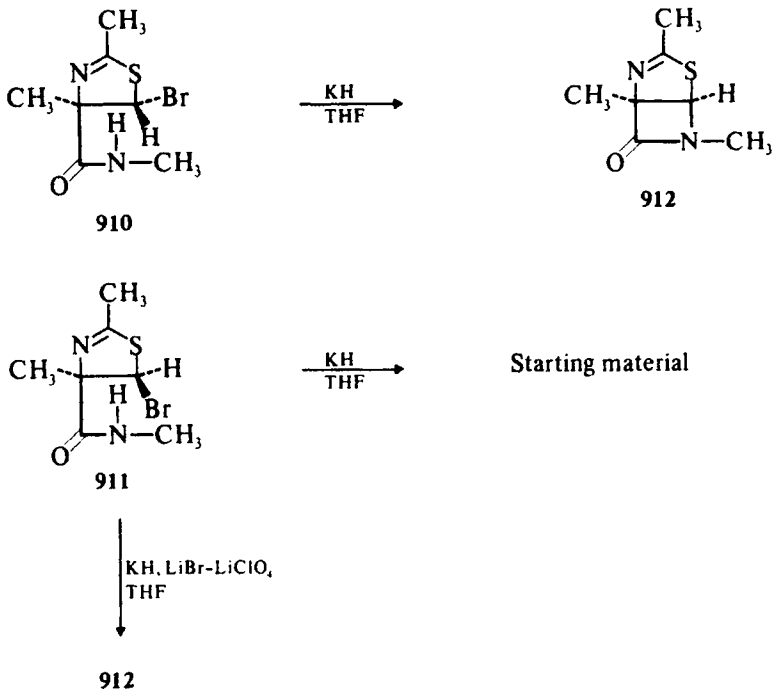
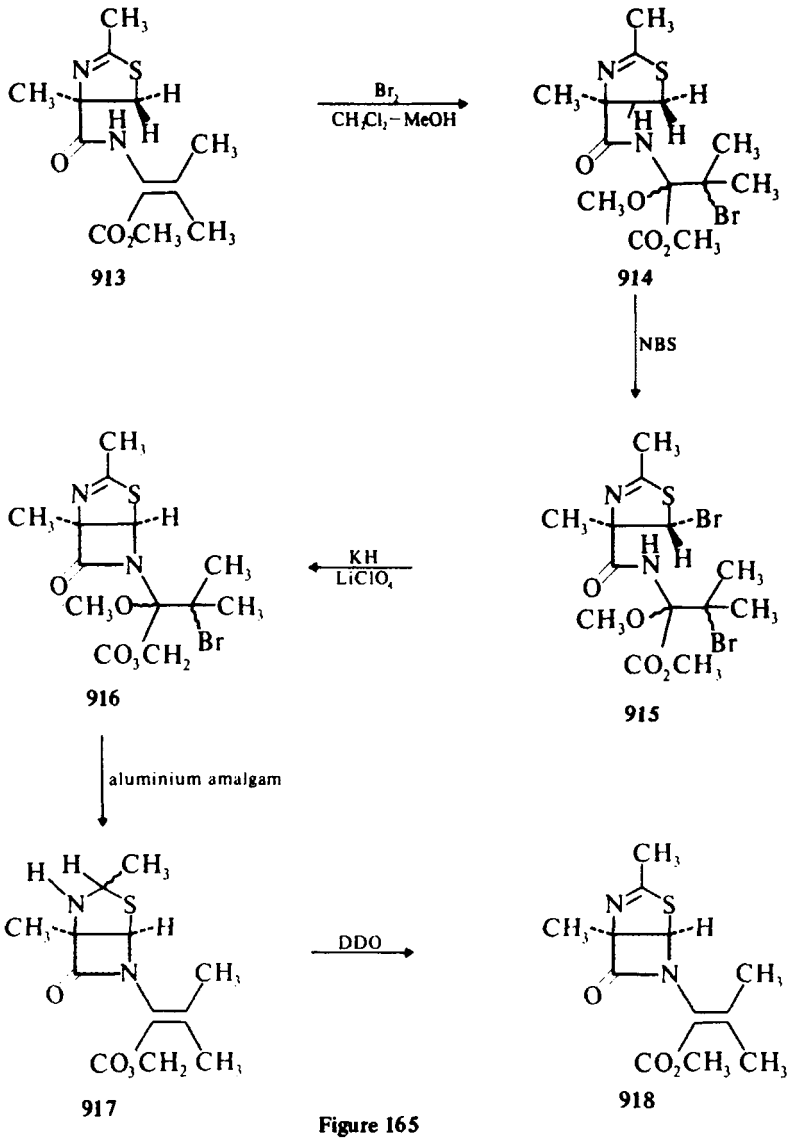


Figure 164

dehydrovaline thiazoline β-lactam **918**.[228] The thiazoline dehydrovaline amide **913** underwent smooth bromination (bromine in methylene chloride–methanol) to the bromomethoxyamide **914** (as a diastereomeric mixture) in 93% yield. The amide **914** was brominated with NBS to afford the bromothiazoline **915**, which was cyclized to the **916** with potassium hydride–lithium perchlorate in THF.[228] The β-lactam **916** was reduced with aluminum amalgam to the thiazoline **917**, which was oxidized with dichlorodicyanoquinone (DDQ) to afford the thiazoline β-lactam **918**. This synthesis is presented in Figure 165.

Kishi and co-workers extended their investigation to the synthesis of the C_3-hydrogen in β-lactams such as **924**.[228] They found that thiazoline **919** could be smoothly converted to **920** in 80% yield. The benzamide **920**, in the presence of MCPBA, was converted to sulfoxide **921** in 95% yield. This was treated with acetic anhydride–acetic acid (1 : 1) at 110°C to give a 40% yield of **922**. The conversion to the β-lactam **924** was achieved by reacting **922** with HCl gas to give **923**, which was treated with potassium hydride to give **924**. This sequence is illustrated in Figure 166.

Baldwin and co-workers investigated the use of thiazolidine amides **925** in the construction of β-lactams.[229] For example **926** reacted with benzoylperoxide in benzene to afford the benzoate **927** in 58% yield. This was subsequently treated with HCl gas to produce the chlorothiazolidine **928** in 95% yield. The closure of **928** to the thiazolidine β-lactam **929** was achieved (in 81% yield) with sodium hydride in methylene chloride containing tetra-*N*-butylammonium iodide (0.1



913 914 915 916 917 918

Figure 165

equivalent). In a similar manner, thiazolidine amide **930** was oxidized with benzoyl peroxide, treated with HCl gas, and cyclized with sodium hydride in methylene chloride–dimethyl formamide (4:1) to give β-lactam **931**. These transformations are summarized in Figure 167.

Baldwin and co-workers utilized this novel construction of thiazolidine β-lactams in an elegant, stereospecific synthesis of penicillin methyl ester **942**.[230] Thiazolidine amide **932** was treated with benzoyl peroxide in benzene to afford the benzoate **933** in 40% yield. This in turn was treated with HCl gas to give the chlorothiazolidine amide **934**, which was cyclized with sodium hydride in methylene chloride–DMF

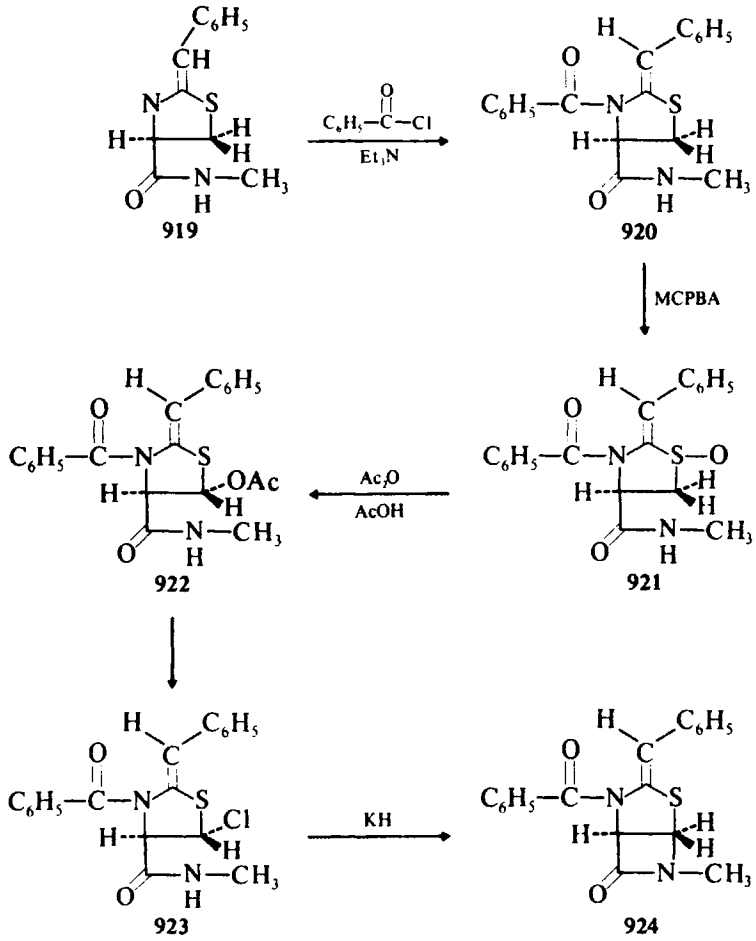


Figure 166

(4:1) at 0°C to produce the thiazolidine β-lactam **935** in 82% yield. At this stage, the thiazolidine function was modified to set the stage for the architectural development of the "penamsulfenic acid equivalent". To this end, **935** was oxidized with *m*-chloroperbenzoic acid (MCPBA) to afford the sulfoxide **936** in 67% yield. The sulfoxide underwent ring opening in benzene–dimethylacetamide (DMAC) with concentrated sulfuric acid (400 mole%) at 105°C to give the ketosulfide **937** in 41% yield. This was reacted with diazomethane in methanol–ether to give the epimeric epoxides **938** in 53% yield. The epoxide epimers were rearranged to the aldehyde epimers (**939**) by reaction with $BF_3 \cdot Et_2O$ in THF at −30°C. Finally, oxidation of **939** with MCPBA afforded the diastereomeric sulfoxides **940**, which were smoothly converted to penicillin sulfoxide **941** in 21% overall yield from **938**. The penicillin sulfoxide was reduced with phosphorous tribromide in DMF at 0°C to afford penicillin methyl ester **942** in 61% yield. This sequence of reactions is presented in Figure 168.

925
926
927
928
929
HCl (gas)
NaH

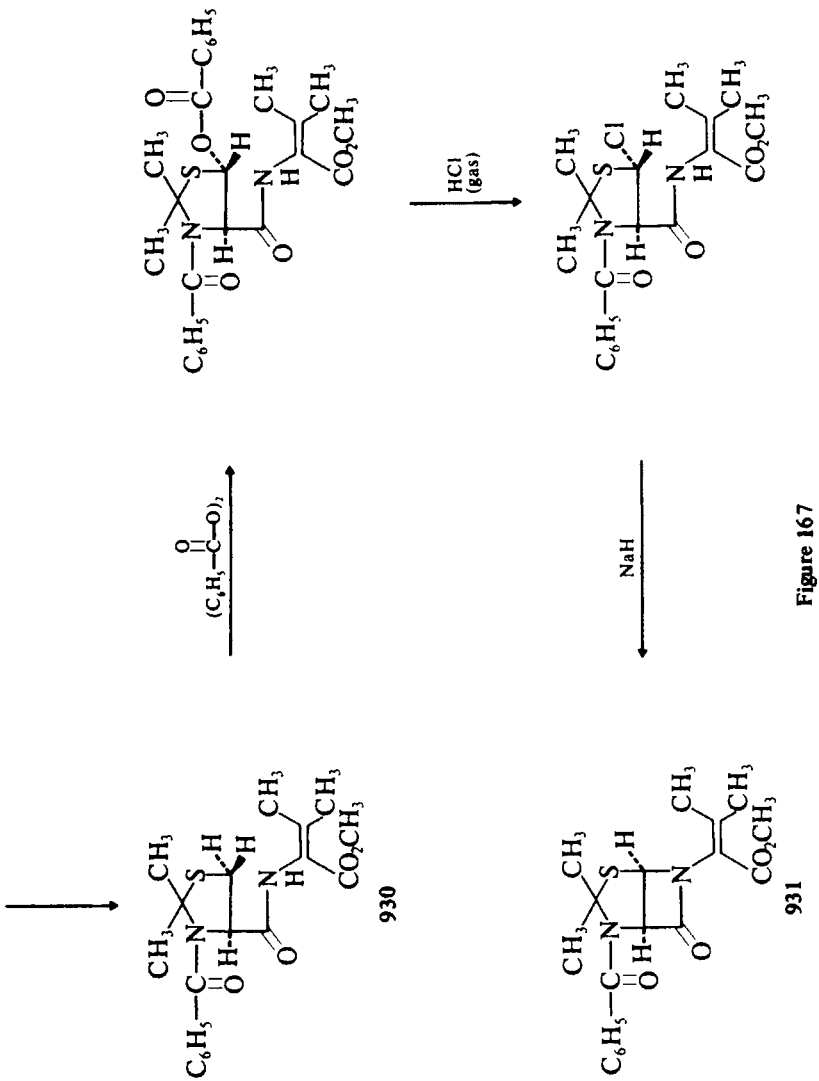
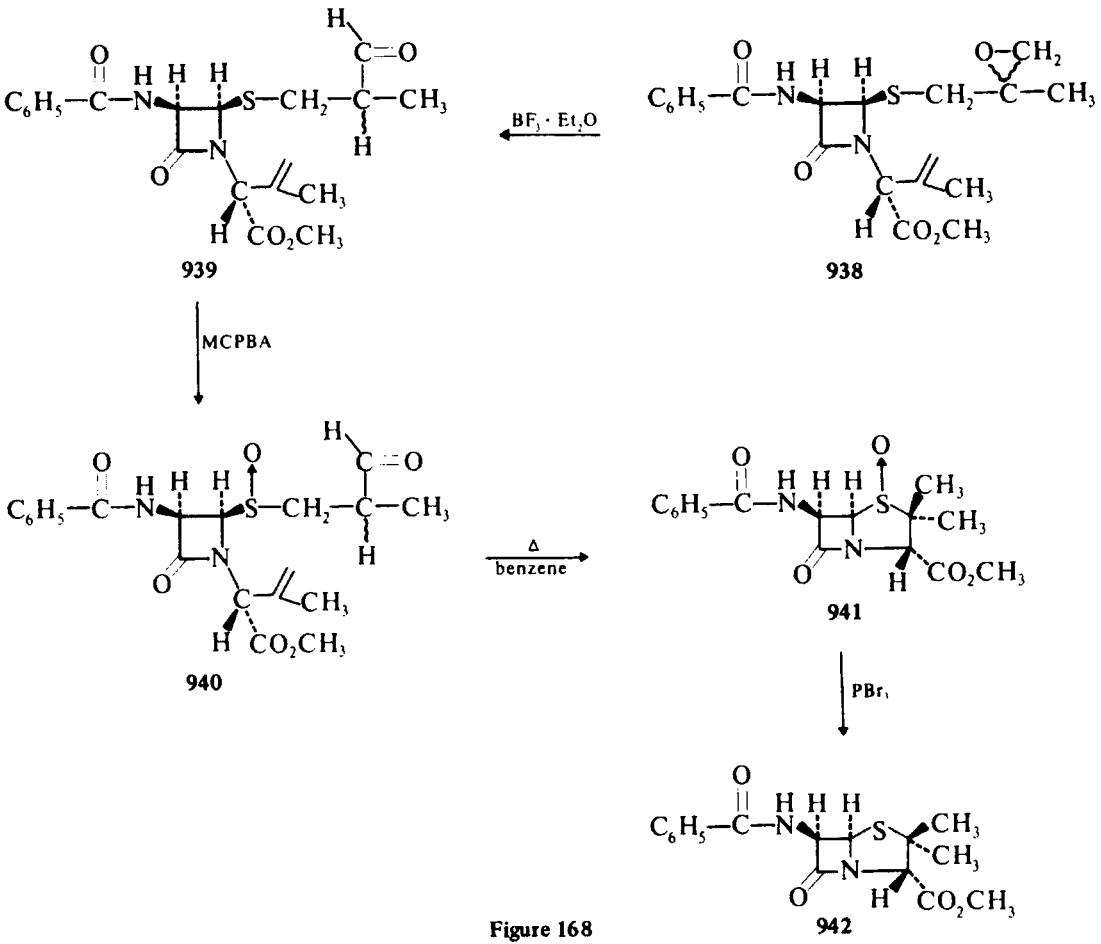


Figure 167

(C6H5—C—O)2
NaH
benzene
DMAC, H+
CH2N2
MCPBA
932
933
934
935
936
937

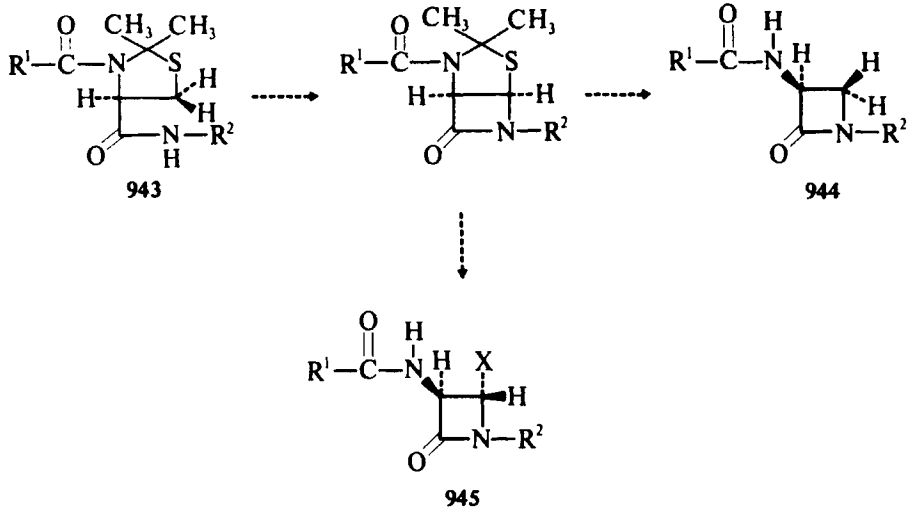


939 938 940 941 942

Figure 168

The thiazolidine amide construction of β-lactams described by Baldwin et al.[229] was effectively applied to the chirally specific total synthesis of nocardicin A **504**, as reported by Koppel and co-workers.[231] These investigators had envisioned utilizing the thiazolidine amide **943** for the synthesis of the β-lactam function because of the versatility of the C_4-sulfur bond, which could lend itself to the synthesis of the natural nocardicin system (**943** → **944**) and the potentially active derivatives of noncardicin A substituted at C^4 (**943** → **945**). For this purpose, Koppel et al. began to assemble the requisite chiral precursors. They reacted L-cysteine **946** with acetone and benzoyl chloride and obtained the thiazolidine acid **947** in very high yield. The D-*p*-hydroxphenylglycine **948** utilized in the nocardicin construction was modified with functional protecting groups as follows: **948**, was treated with *t*-butoxycarbonyl azide to afford **949**; this was reacted with two equivalents of potassium *t*-butoxide in DMAC, followed by two equivalents of benzyl bromide, to give the dibenzyl derivative **950**; this in turn was treated with HCl gas in methylene chloride–ether at 0°C to give the hydrochloride salt **951** in 85% yield from **948**. The thiazolidine acid **947** was coupled to the free amine **952** with DCC in methylene chloride, producing the thiazolidine amide **953** in 90% yield. This sequence is illustrated in Figure 169.

Having thus obtained the requisite functional groups and configuration of the nocardicin A nucleus, the research group directed its effort toward cyclizing dipeptide **953** to the thiazolidine β-lactam **956** in a stereospecific manner. The reaction of **953** with benzoyl peroxide in refluxing benzene afforded **954** in 45–55% yield. The benzoate **954** was converted to the chloro derivative **955** in quantitative yield with HCl gas. The cyclization of **955** with sodium hydride in CH_2Cl_2–DMF (4:1) at 0°C afforded in 85% yield a 3:1 ratio of β-lactams **956** and **957** (which were epimeric at C_3), respectively. The major isomer **956** was fractionally crystallized from ethyl acetate; the minor isomer **957** was crystallized from petroleum ether–ethyl acetate. The temporary loss of stereochemical control at C_3 (i.e.,



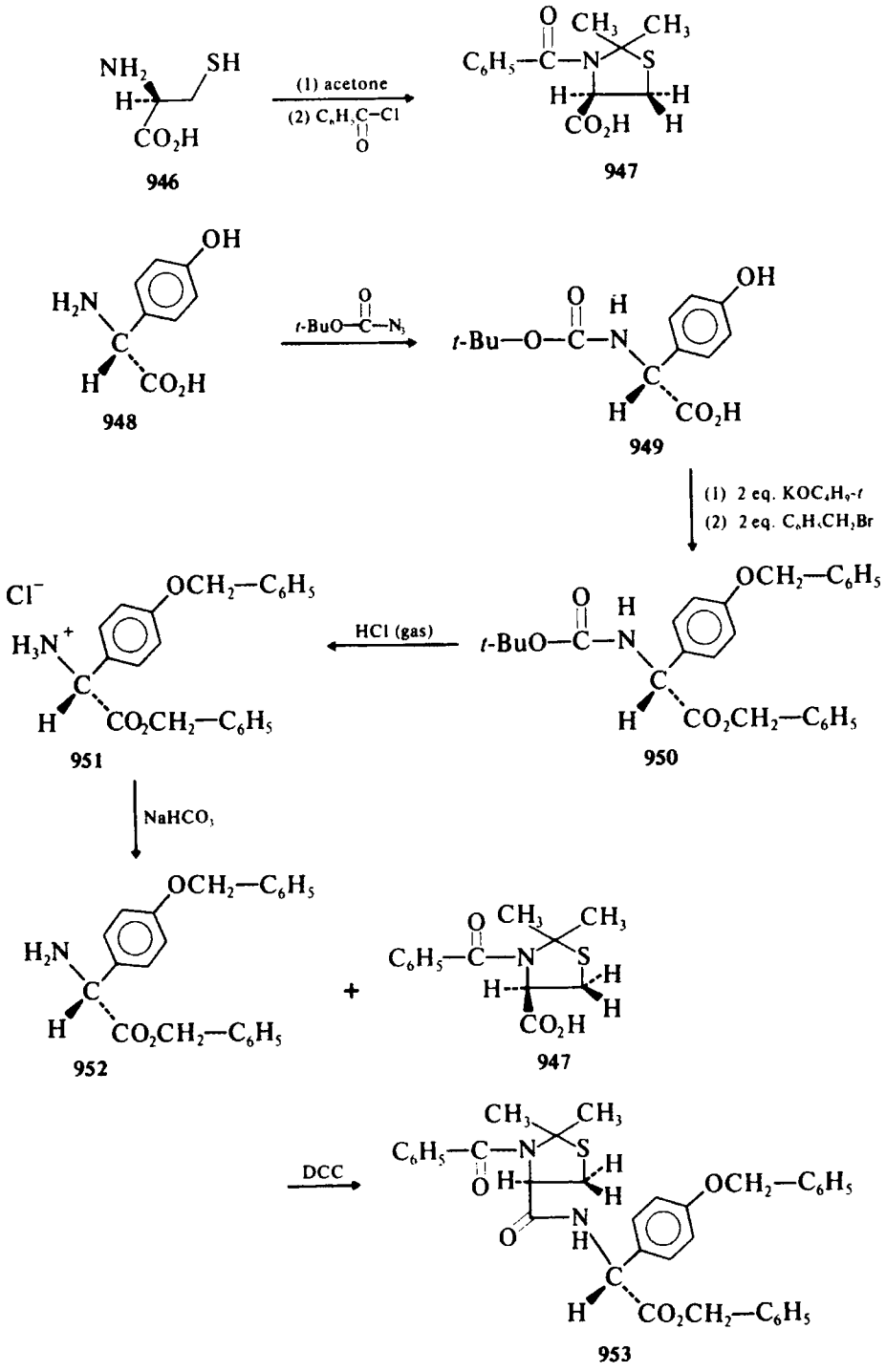

946
(1) acetone
(2) C6H5C(=O)Cl
947
948
t-BuO-C(=O)-N3
949
(1) 2 eq. KOC4H9-t
(2) 2 eq. C6H5CH2Br
950
HCl (gas)
951
NaHCO3
952
947
DCC
953

Figure 169

955 → **957**) was regained in an elegant epimerization–fractional crystallization sequence discovered by L. McShane of the Lilly Research Laboratories. McShane found that the reaction of **957** with pyridine–water afforded a quantitative yield of the correct epimer **956**, thus achieving a stereospecific synthesis of **956** in 85% yield. These transformations are illustrated in Figure 170.

The stage was now set for the unmasking of thiazolidine β-lactam **956** and its subsequent conversion to the nocardicin nucleus **962**. For this purpose, **956** was treated with mercuric acetate in aqueous THF to afford oxazoline **958** in high yield. The oxazoline was cleaved with PCl_5 in methylene chloride and pyridine to afford a quantititive yield of the crystalline chloroimino chloride **959**, which was reduced with tributyltin hydride to yield the Schiff base **960**. The direct treatment of crude **960** with *p*-TsOH · H_2O in ethyl acetate afforded the 3-ANA salt **961** in an overall yield of 34% from **955**. The 3-ANA salt was converted with sodium bicarbonate to the 3-ANA nucleus, which was hydrogenated to the nucleus **962** and converted to nocardicin A, as described by Kamiya et al.,[107] Koppel et al.,[231] and Cooper et al.[232] This sequence of reactions is illustrated in Figure 171.

As mentioned earlier, these investigators had envisioned utilizing an intermediate that would lend itself to the chirally specific synthesis of the potentially active derivatives of nocardicin substituted at C_4 (i.e., **943** → **945**). The immediate synthetic objective was the construction of the 4α-acetoxynocardicin **966**.[233] Koppel and Cooper[233] found that **956** underwent a smooth transformation to **963** with mercuric acetate in acetic acid. Intermediate **963** was hydrolyzed with mercuric acetate in THF–water to afford **964**. The first sign of synthetic difficulty associated with the construction of the 4α-acetoxynocardicin nucleus became apparent after **964** was cleaved with PCl_5 and pyridine to afford the ester nucleus **965**, for the hydrogenation of **965** to **966** was accompanied by extensive decomposition of **966**. These transformations are presented in Figure 172.

It was apparent from this result that a new series of protecting groups for both the side chain and the nucleus of nocardicin would have to be incorporated into the synthesis. To achieve this goal, thiazolidine β-lactam **956** was debenzylated, under hydrogenation conditions, to the acid **967**, which was reesterified with diphenyldiazomethane to give **968** in high yield. The β-lactam **968** was treated with mercuric acetate in acetic acid to afford **969**, which was hydrolyzed with mercuric acetate in THF–water to give **970**. The free phenolic hydroxyl of **970** was protected by conversion to its ethyl vinyl ether acetal **971** with ethyl vinyl ether and *p*-TsOH · H_2O in THF. Cleavage of **971** with PCl_5 in pyridine–CH_2Cl_2 followed by methanol and aqueous hydrolysis afforded the dimethyl phosphate **972**. In an attempt to avert the formation of the phosphate in the PCl_5 cleavage reaction, a more stable phenolic protecting group was utilized. Thus **970** was treated with dihydropyran and *p*-TsOH · H_2O in THF to give ketal **973** in good yield. The reaction of **973** with PCl_5 in pyridine–CH_2Cl_2, followed by methanol and aqueous hydrolysis, afforded the free 4α-acetoxynocardicin nucleus as its benzyhydryl ester **974**. This sequence of reactions is summarized in Figure 173.

Having completed the construction of the suitably protected 4α-acetoxynocardicin nucleus **974**, Koppel and Cooper[233] turned their attention to the task of protecting the nocardicin side chain function. Thus D-*t*-BOC methionine **975** was

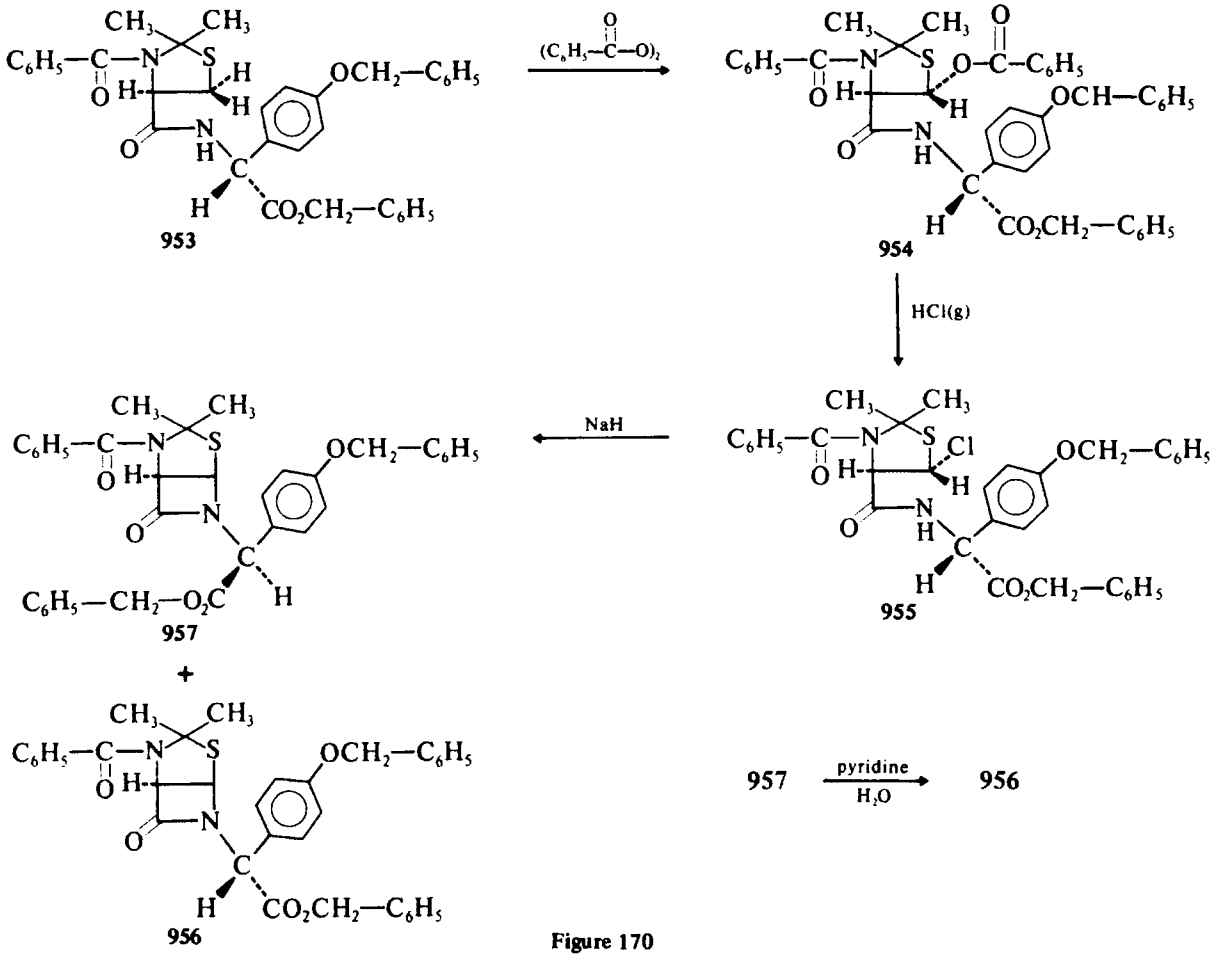


Figure 170

Hg(OAc)2
PCl5
pyridine
Bu3SnH
p-TsOH·H2O
956
958
959
960
961

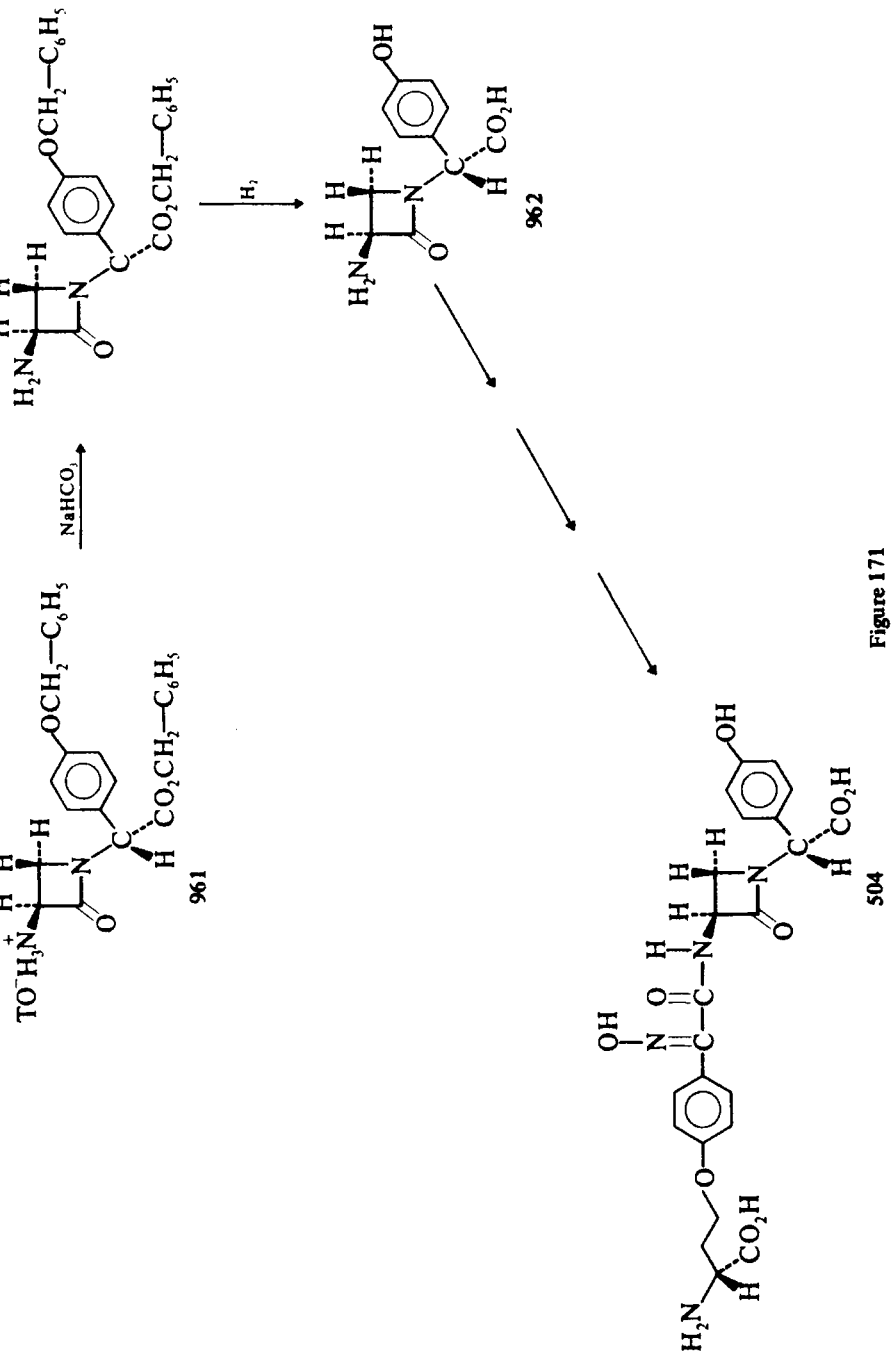
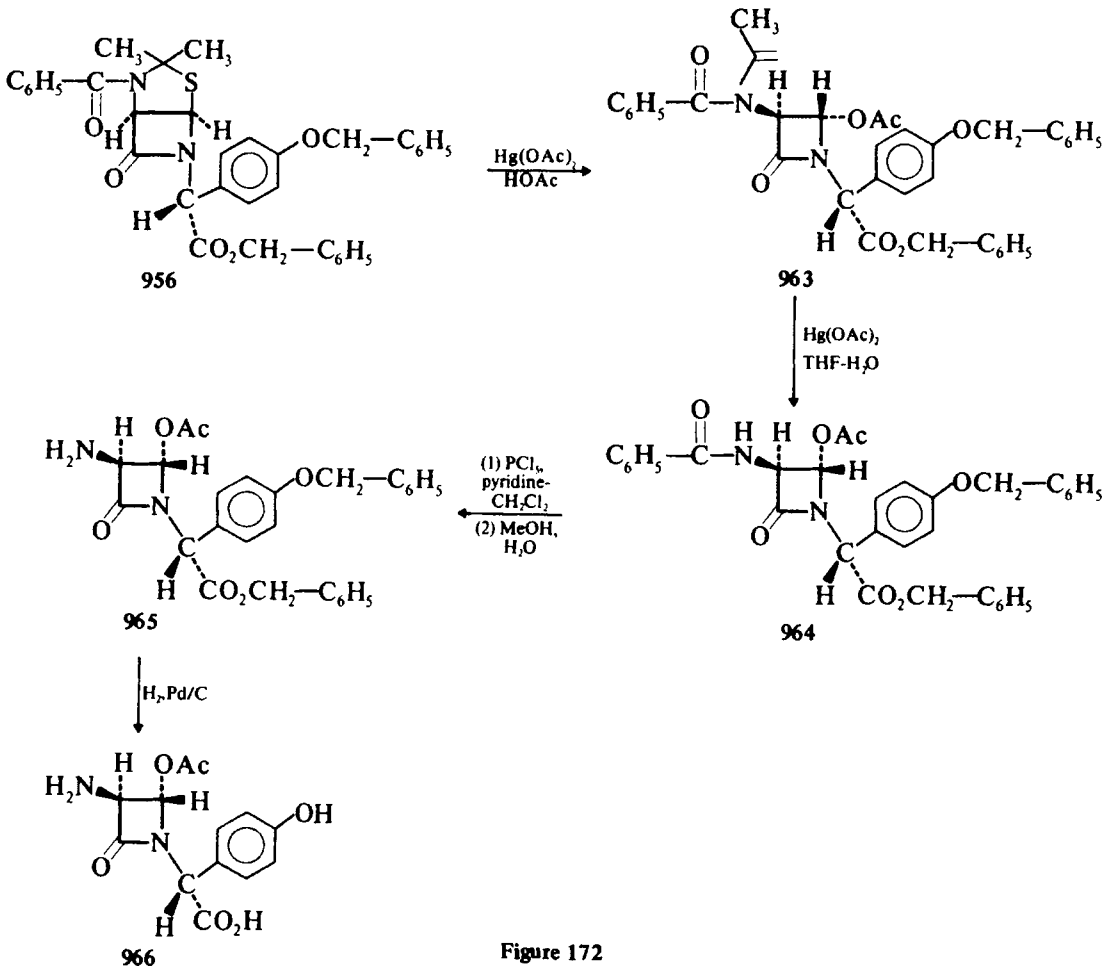


Figure 171



956 963 964 965 966

Figure 172

treated with trimethylsilyl chloride (TMSCl) in acetonitrile, followed by *S*-alkylation with methyl iodide, to afford the sulfonium salt **976**, which was treated with potassium *t*-butoxide in THF to give D-homoserine lactone **977** in 70% yield.[233] Hydrolysis of the lactone with one equivalent of KOH in aqueous dioxane afforded the potassium salt **978**, which was alkylated with benzhydryl bromide to give the homoserine ester **979** in 70% overall yield.[153] The unreactive keto group of *p*-hydroxyphenylglyoxalate ester **980** was converted to the *syn*-oxime **981** in 90% yield by reaction with hydroxylamine hydrochloride in bistrimethylsilyltrifluoroacetamide (Regisil) at 126°C for 12 hours. This was converted to the *p*-methoxybenzyloxime **982** in 60% yield by reaction with one equivalent of potassium *t*-butoxide and one equivalent of *p*-methoxybenzyl (PMB) bromide in dimethylacetamide at 0°C. The *p*-hydroxyphenylglyoxalate oxime **982** was joined to D-homoserine **979** by reaction with triphenylphosphine and dimethyl azodicarboxylate in THF to afford **983** in 68% yield. These transformations are illustrated in Figure 174.

Having protected the side chain and the 4α-acetoxynocardicin nucleus with groups that, in theory, could be removed efficiently by acid catalysis, these investigators turned their efforts to the coupling of the side chain to the nucleus. The *p*-nitrobenzyl (PNB) group of **983** was removed by electrolytic reduction by Dr. David Hall of the Lilly Research Laboratories to give the free acid **984**. The free acid was coupled with **974** in methylene chloride and DCC to afford **985** in 60% yield. The critical deblocking of **985** was achieved with trifluoroactic acid and anisole, producing **986** in quantitative yield. This sequence of reactions is illustrated in Figure 175.

Scott and co-workers utilized cysteinyl dipeptides in the construction of β-lactams by developing the C_4-anion and creating an electrophilic nitrogen.[234] To this end, these investigators reacted thiazoline **987** with base and methyl iodide, affording **988**, which was converted to its acid chloride **989** and finally to its hydroxamic acid derivative **990** in 55% overall yield. The hydroxamic acid **990** was transformed to the sulfonate adduct **991** and oxidized to the sulphone **992** with two equivalents of *m*-chloroperbenzoic acid. Finally, the reaction of **992** with potassium *t*-butoxide in THF afforded β-lactam **993** in 50% yield.[234] This series of reactions is presented in Figure 176.

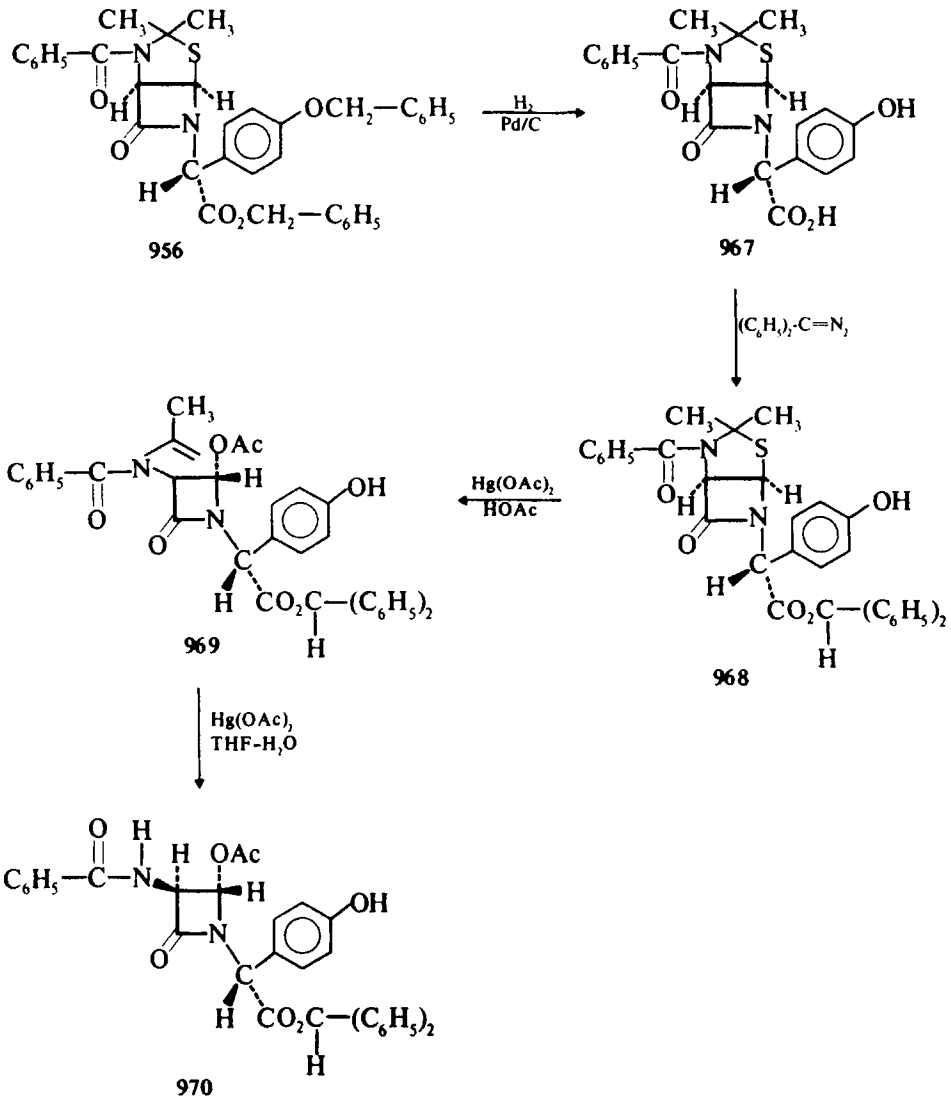
C. *Cyclization of Hydroxamic Acids*

Mattingly and co-workers made the important discovery that the dehydrohalogenation of 3-halopropionamides during base-promoted cyclization to the corresponding β-lactam could be prevented by utilizing the hydroxamic acid derivative.[235] Thus the reaction of **994** with sodium hydride in DMF afforded azetidinone **995** in 94% yield. Interestingly, cyclization of **996** to the corresponding azetidinone **997** could be achieved in 76% yield by using the weak base lithium carbonate in DMF. The advantage of this new synthetic method was demonstrated in the synthesis of chiral β-lactams from serine precursors. These investigators found that **998** underwent smooth cyclization to β-lactam **999** in 86% yield when treated

with sodium hydride in DMF–CH_2Cl_2. Similarly, **1000** cyclized to **1001** in 88% yield. Finally, the serine hydroxamic acid derivative **1002** was cyclized directly to **1001** in 90% yield by treatment with triphenylphosphine and diethyl azodicarboxylate in THF.[235] These reactions are shown in Figure 177.

D. *Miscellaneous N–C_4 Cyclizations*

Wasserman and co-workers made an important synthetic contribution in the construction of azetidinones from 3-halopropionamide precursors.[236] These investi-



956 967 968 969 970

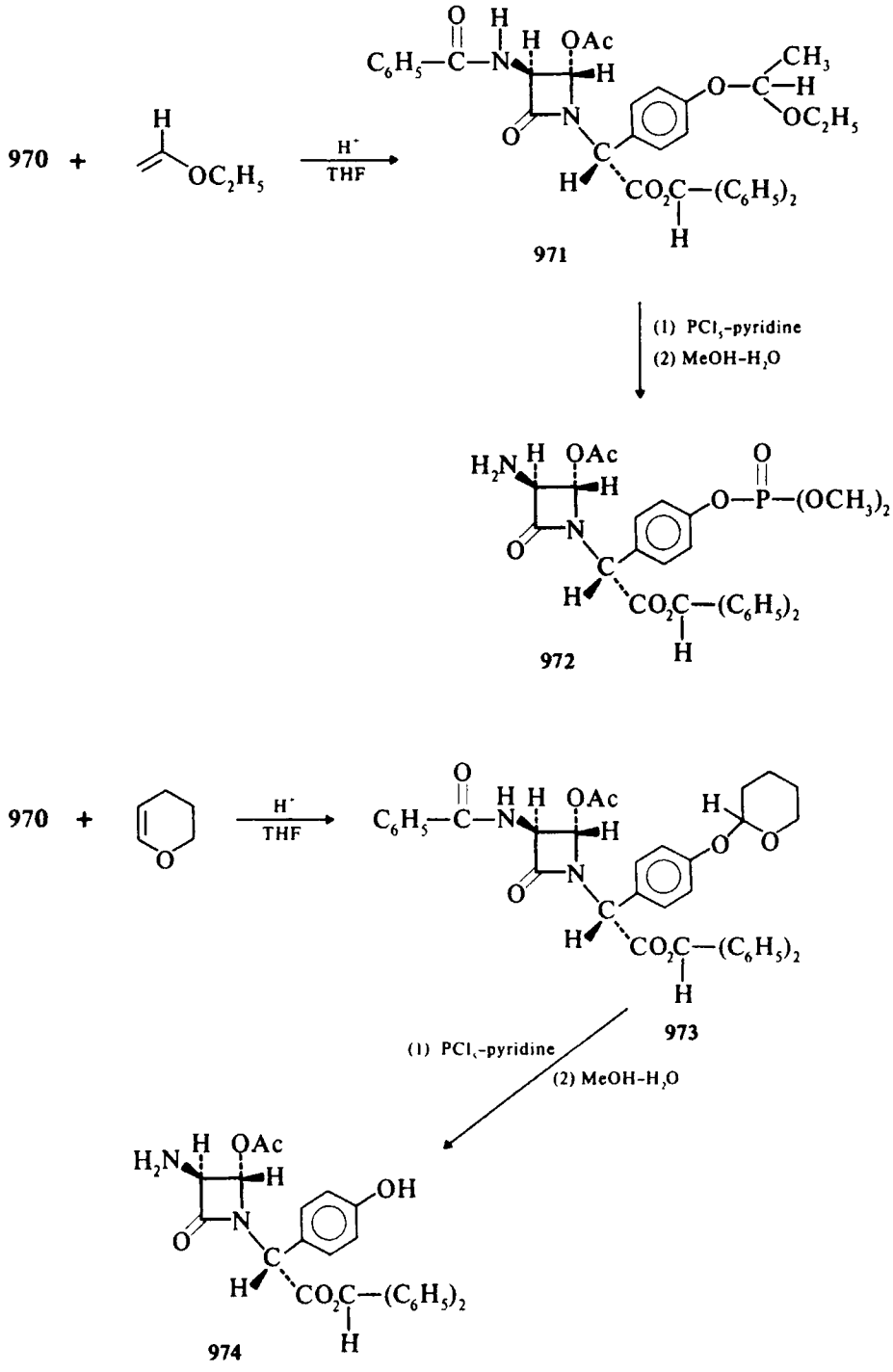

970 +
H⁺
THF
971
(1) PCl₅-pyridine
(2) MeOH-H₂O
972
970 +
H⁺
THF
973
(1) PCl₅-pyridine
(2) MeOH-H₂O
974

Figure 173

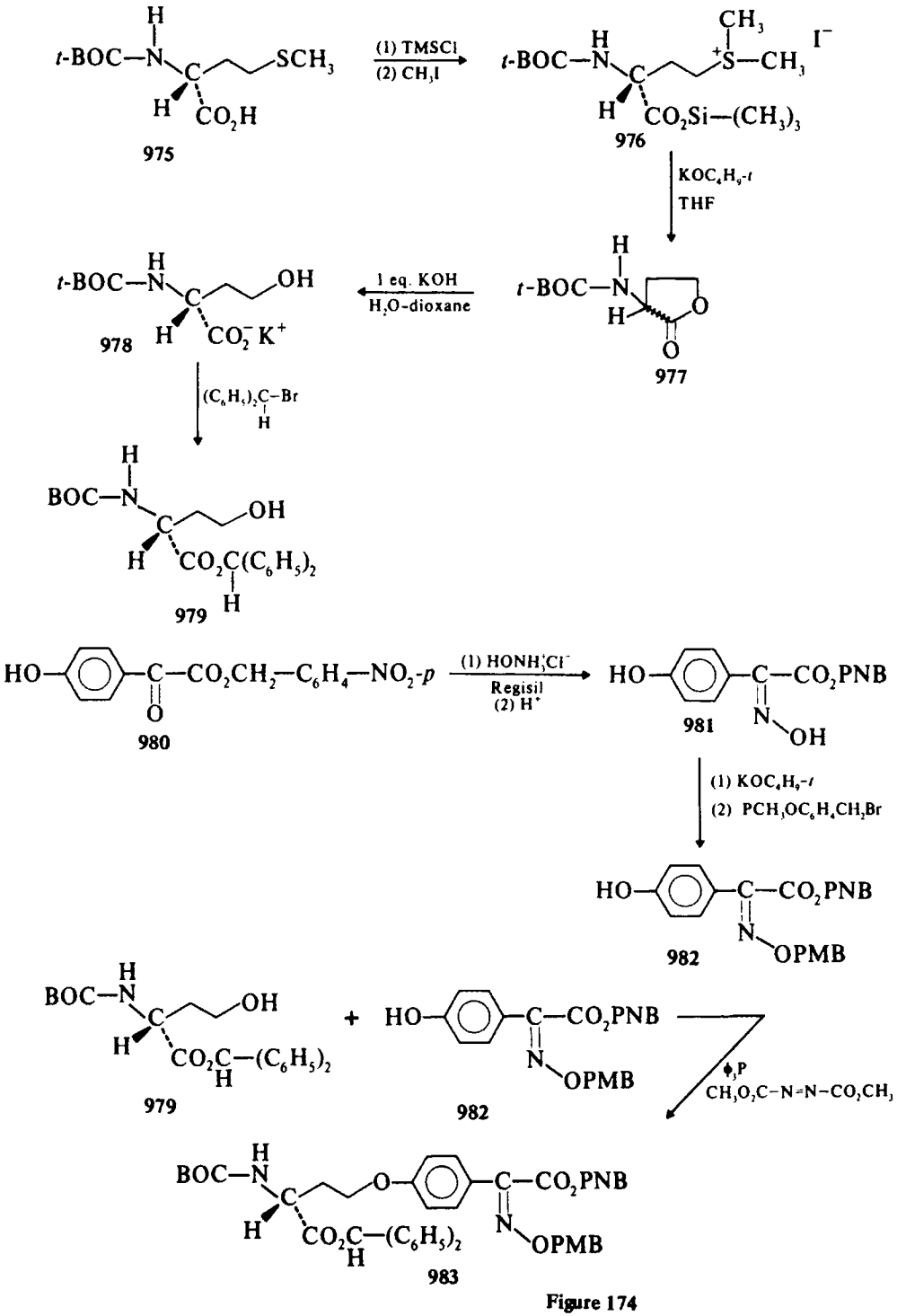

t-BOC—N—C—SCH3
H
CO2H
975
(1) TMSCl
(2) CH3I
t-BOC—N—C—S+—CH3 I−
CH3
CO2Si—(CH3)3
976
KOC4H9-t
THF
t-BOC—N
O
977
1 eq. KOH
H2O-dioxane
t-BOC—N—C—OH
CO2− K+
978
(C6H5)2C—Br
H
BOC—N—C—OH
CO2C(C6H5)2
H
979
HO—C—CO2CH2—C6H4—NO2-p
O
980
(1) HONH3Cl−
Regisil
(2) H+
HO—C—CO2PNB
N
OH
981
(1) KOC4H9-t
(2) PCH3OC6H4CH2Br
HO—C—CO2PNB
N
OPMB
982
BOC—N—C—OH
CO2C—(C6H5)2
H
979
+
HO—C—CO2PNB
N
OPMB
982
Φ3P
CH3O2C—N=N—CO2CH3
BOC—N—C—O—C—CO2PNB
CO2C—(C6H5)2
H
N
OPMB
983

Figure 174

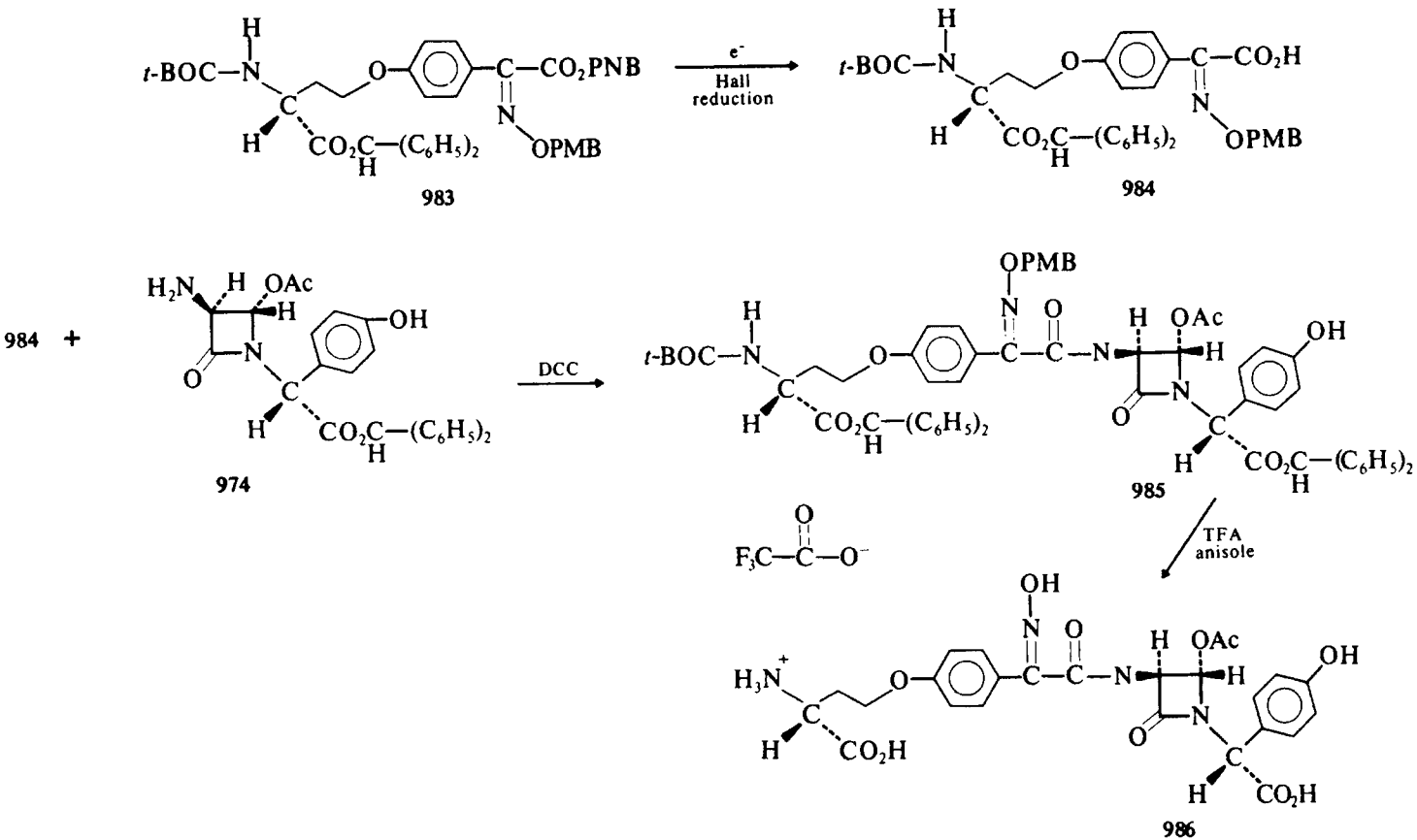
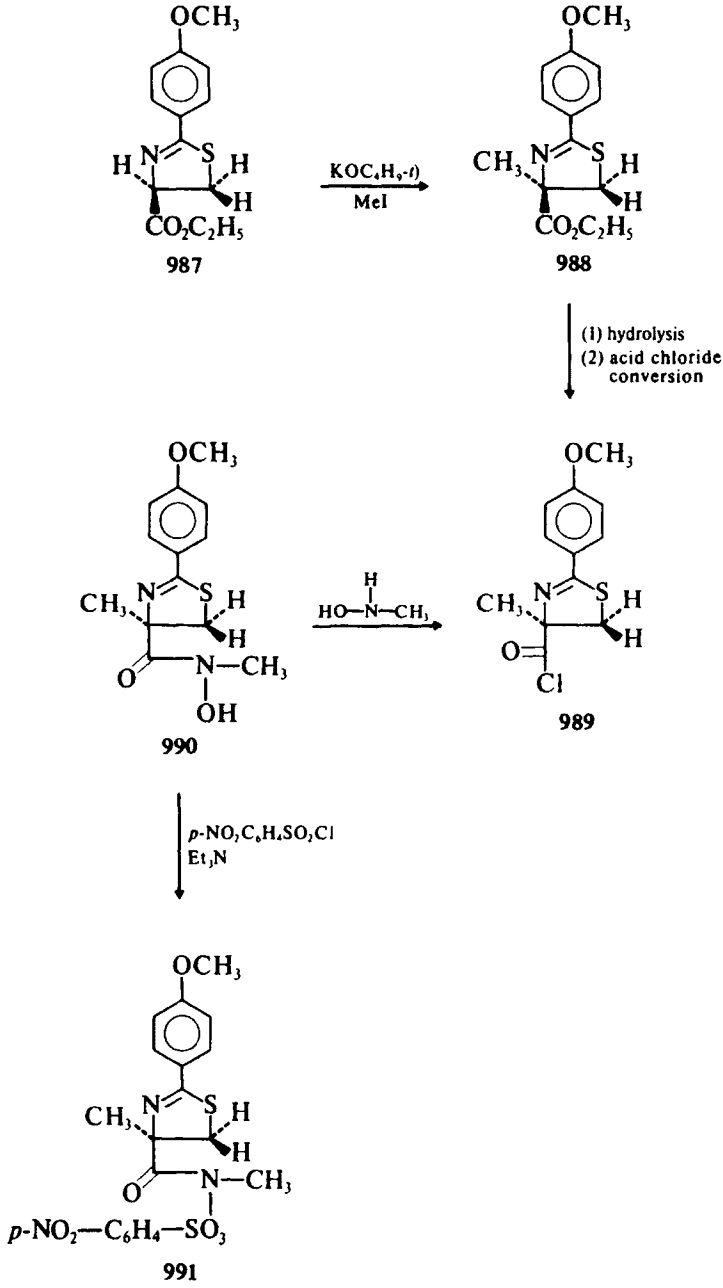

t-BOC—N
O
C—CO2PNB
N
OPMB
CO2C—(C6H5)2
H
e⁻
Hall reduction
CO2H
983
984
984 +
H2N
OAc
OH
974
DCC
OPMB
985
TFA
anisole
F3C—C—O⁻
H3N⁺
CO2H
986

Figure 175

gators discovered that 3-bromopropionamide **1002** reacted with 0.1 *M* sodium hydride in DMF–CH_2Cl_2 (1:4) to afford a 70% yield of the acrylamide **1003**. However, when the reaction was carried out in 0.05 *M* NaH, a 50% yield of azetidinone **1004** was obtained. The reactions of various 3-halopropionamides



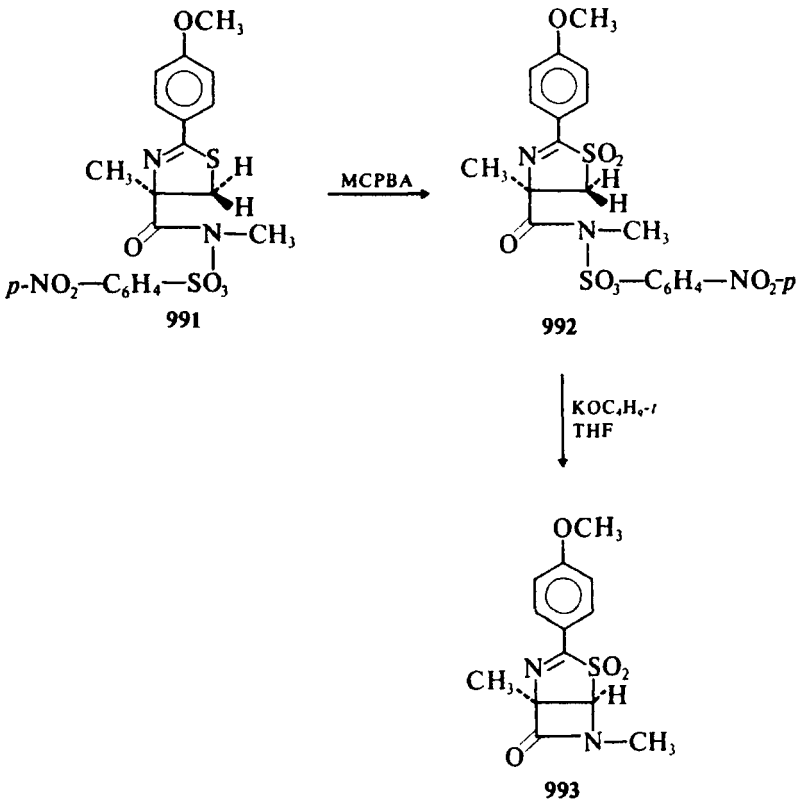


Figure 176

with 0.1 and 0.05*M* NaH are presented in Figure 178. A summary of additional azetidinones derived from their respective 3-halopropionamides is given in Figure 179.

Hirai and Iwano reported an elegant synthesis of azetidinones utilizing the dianion derived from phenylthioacetamide.[237] They reacted **1011** with two equivalents of sodium hydride and DMF to give **1011a**, which was alkylated with methylene iodide, affording **1012** in 54% yield. In a similar manner, **1013** underwent alkylation with methylene iodide to give **1014** in 38% yield. Finally, the reaction of **1015** with methylene iodide gave **1016** in 27% yield. These reactions are illustrated in Figure 180.

Chapman and Adams investigated the reactions of cinnamides under photolysis conditions.[238,239] For example, the irradiation of **1017** in 0.01 *M* benzene with a Hanovia type A 550-W lamp for 23 hours afforded a mixture of *cis*-azetidinone **1018** in 37% yield, *trans*-azetidinone **1019** in 2.3% yield, and lactam **1020** in 5% yield. Under similar conditions, *cis*-α-phenylcinnamide **1021** was converted to a mixture of *cis*-azetidinone **1022** in 13% yield, *trans*-azetidinone **1023** in 3% yield, and *trans*-stilbene **1024** in 2.5% yield.[238,239] This series of reaction is presented in Figure 181.

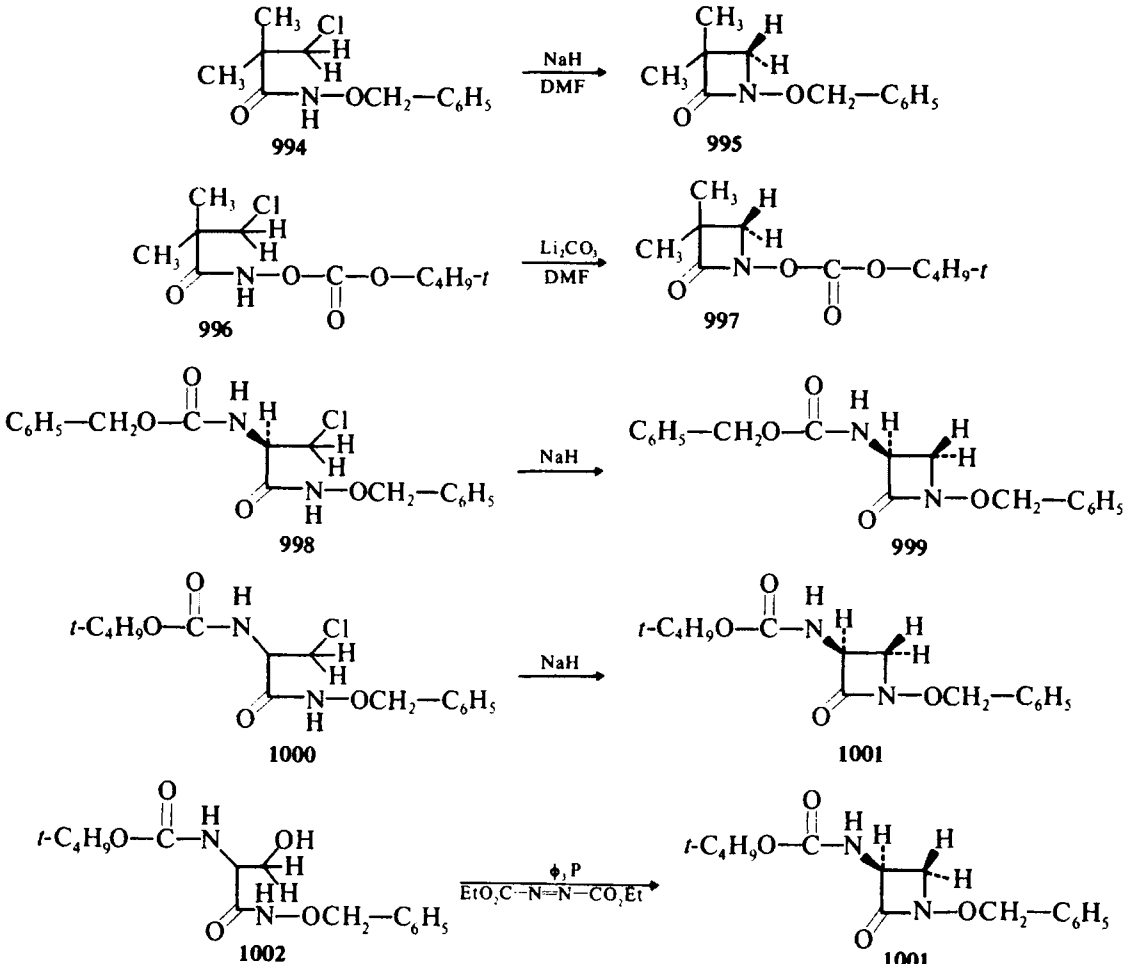
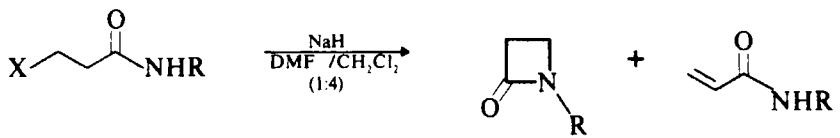

NaH
DMF
994
995
Li2CO3
DMF
996
997
NaH
998
999
NaH
1000
1001
ϕ3P
EtO2C–N=N–CO2Et
1002
1001

Figure 177



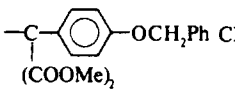
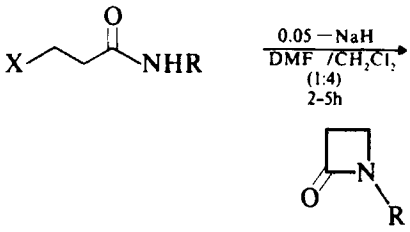
Halopropionamide	R	X	Azetidinone	Yield (%) 0.1 *M* NaH	Yield (%) 0.05 *M* NaH	Acrylamide	Yield (%) 0.1 *M* NaH	Yield (%) 0.05 *M* NaH
1002	$-CH_2CH_2Ph$	Br	**1004**	0	50	**1003**	70	0
1005	$-C(CH_3)_2COOEt$	Cl	**1006**	0	86	**1007**	74	0
1008		Cl	**1009**	32	76	**1010**	20	0

Figure 178



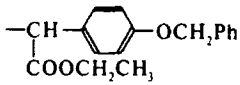
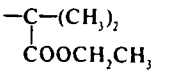
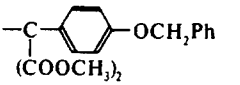
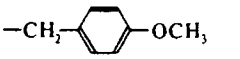
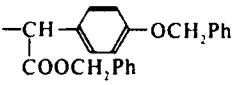
R	X	Yield (%)	
	Br	41	32
	^{18}I	56	13
$-CH_2CH_2Ph$	Cl	22	61
	Br	50	0
	Cl	26	50
	Br	60	6
	Br	80	0
	Cl	14	20
	Br	46	0
	Cl	86	0
	Br	65	0
	Cl	76	0
	Br	64	0

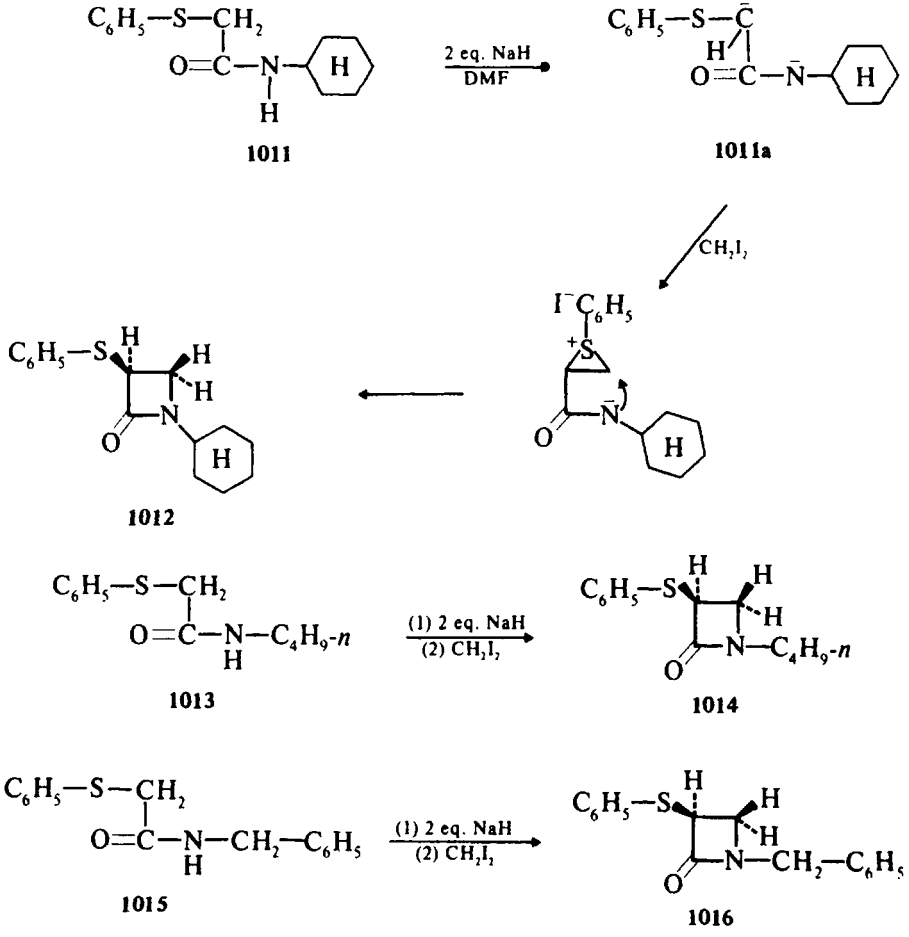
Figure 179

3. Formation of the C_3–C_4 Bond (VIII → VI)

A. *Cyclization of α-Halocarboxylic Amides*

Sheehan and Bose first demonstrated that azetidinones could be constructed through the formation of the C_3–C_4 bond.[240,241] For example, α-chloroacetanilidomalonate **1025** cyclized smoothly in triethylamine to azetidinone **1026**. Azetidinone **1026** could be hydrolyzed to the azetidinone acid **1027** without concomitant rupture of the β-lactam. These reactions are illustrated in Figure 182.

Okawara and Harada utilized the Sheehan–Bose azetidinone construction in the synthesis of chiral aspartic acid.[242] Thus D-(+)-α-ethylbenzylamine **1028** reacted with chloroacetonitrile **1029** to afford **1030**. This in turn was acylated with chloroacetic anhydride to afford amide **1031**. The cyclization of **1031** to azetidinone **1032** was achieved with sodium hydride in dioxane. The azetidinone **1032** was hydrolyzed with acid to give **1033**, which was hydrogenolyzed with palladium, affording L-aspartic acid **1034**. This sequence is presented in Figure 183.



1011 1011a 1012 1013 1014 1015 1016

Figure 180

Bose and co-workers reported a modification of these cyclization reactions.[243] They found that the acylation of the aminomalonate and the cyclization to the corresponding azetidinone could be combined into one step. Thus diethylanilinomalonate **1035** was acylated with α-chlorophenylacetyl chloride and triethylamine in benzene to afford, after 3 days, a 74% yield of azetidinone **1036**. This reaction sequence and a summary of azetidinones prepared by this one-step procedure are presented in Figure 184.

Chatterjee, Moza, and Roy discovered that α-haloacetanilidomalonates could be cyclized to the corresponding azetidinones and hydrolyzed to the monoacids in one step.[244] For example, if **1025** was treated with one equivalent of potassium hydroxide in ethanol, an 88% yield of azetidinone **1026** was obtained. If the sequence was repeated with two equivalents of potassium hydroxide in ethanol, a 79% yield of **1027** was obtained.[244] These results and a list of azetidinones prepared by this method are summarized in Figure 185.

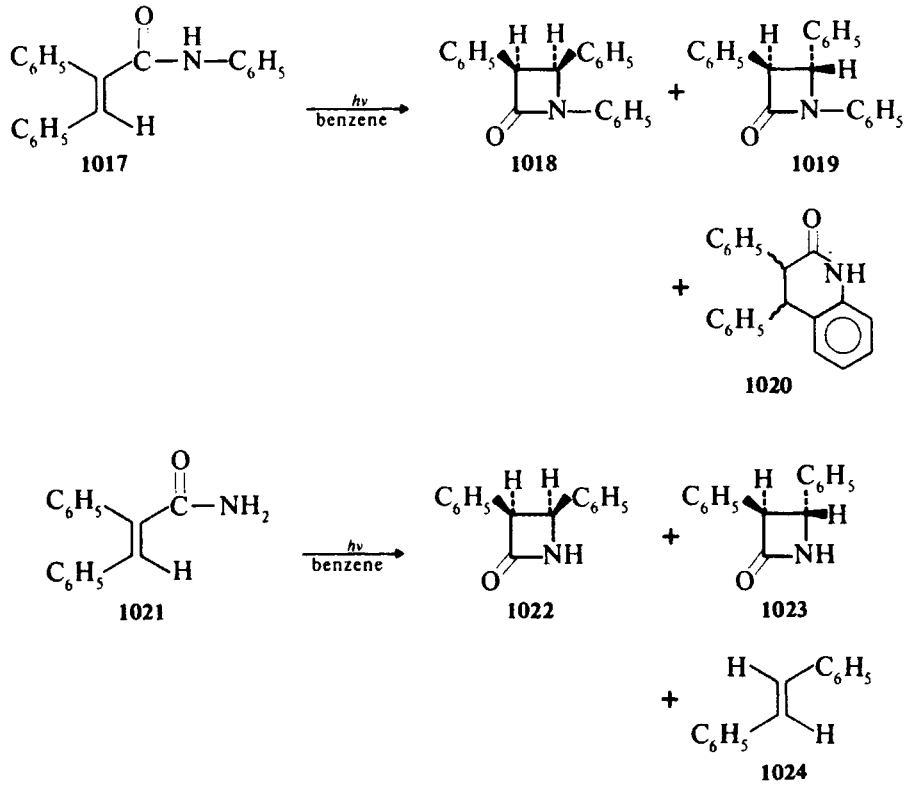


Figure 181

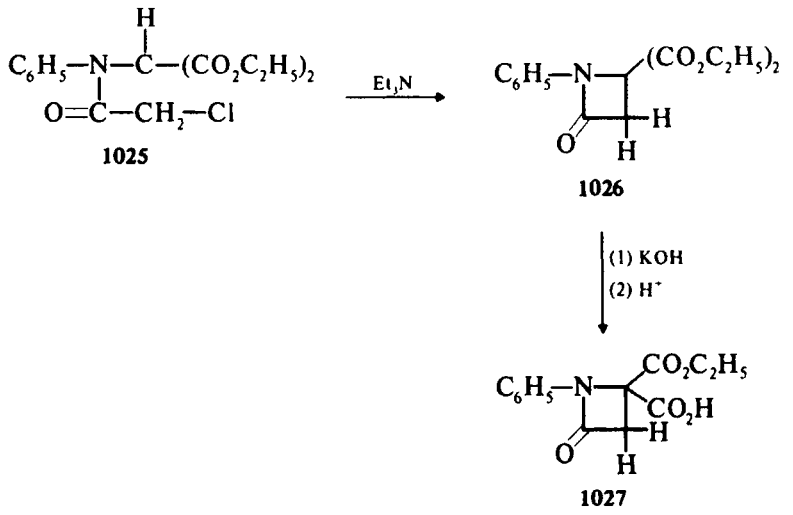


Figure 182

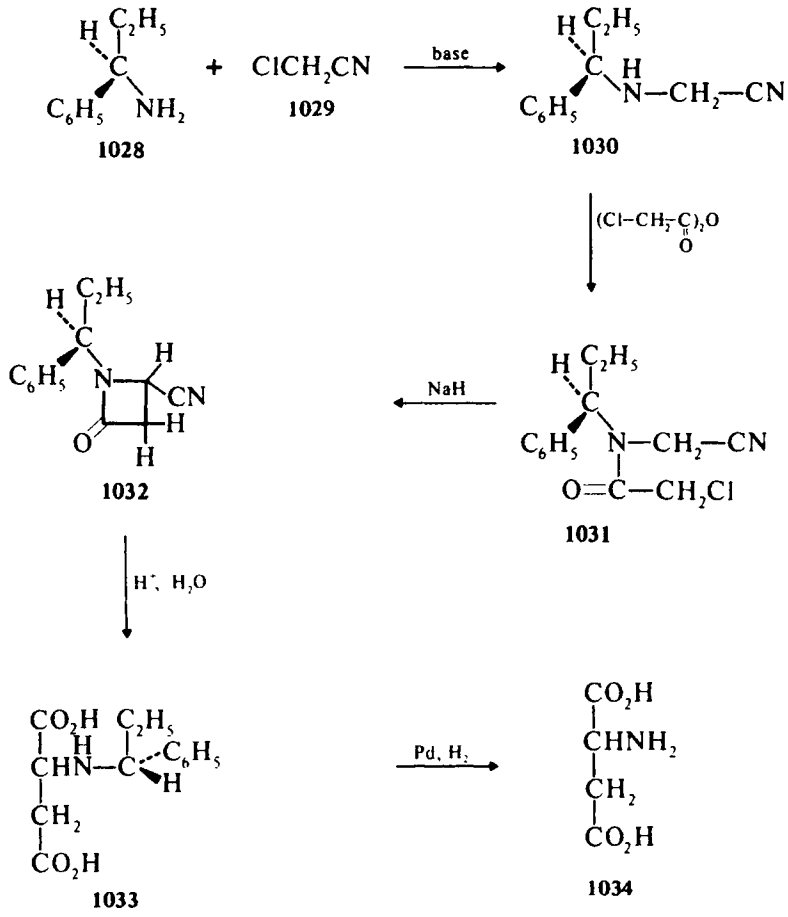
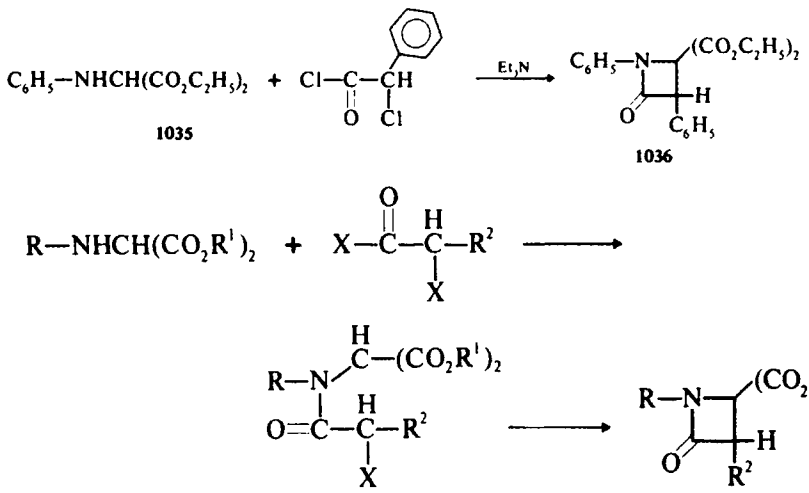


Figure 183

Chatterjee and co-workers discovered that *N*-substituted diethyl chloroacetamidomalonates and ethyl α-chloroacetamidophenylacetates underwent cyclization to the corresponding azetidinones in high yield when the quaternary ammonium hydroxide anion-exchange resin Amberlite IRA-400 (OH^-) was used as a catalyst.[254] For example, the reaction of **1037** with Amberlite IRA-400 (OH^-) in ethanol for 2 hours at room temperature afforded a 95% yield of azetidinone **1038**. Similarly, **1025** reacted with Amberlite IRA-400 (OH^-) in ethanol to give azetidinone **1026** in 90% yield. This sequence of reactions is presented in Figure 186, and a summary of azetidinones synthesized by this method is illustrated in Figure 187.

Chatterjee and Moza modified the cyclization of *N*-substituted diethyl haloacetamidomalonates to construct novel and biologically active azetidinones.[246] Thus the aniline derivative **1047** was alkylated with diethyl bromomalonate (**1048**) to produce the anilinomalonate **1049**. This in turn was acylated with chloroacetic acid to give **1050**, which was cyclized with triethylamine to afford azetidinone



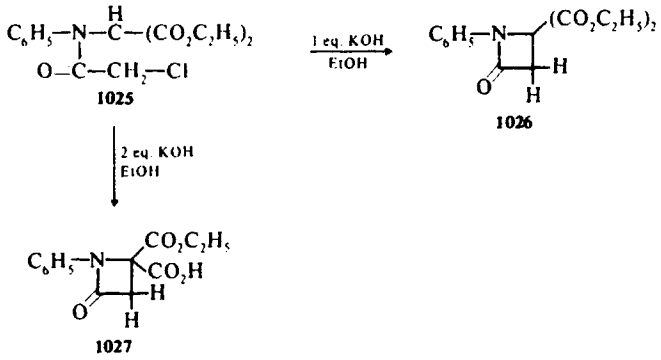
α-Halo Acid Halide	R	R^1	R^2	Yield (%)
$ClCH_2COCl$	C_6H_5	C_2H_5	H	72
$BrCH_2COBr$	C_6H_5	C_2H_5	H	75
$ClCH_2COCl$	p-$CH_3C_6H_4$	C_2H_5	H	83
$ClCH_2COCl$	$C_{10}H_7$	C_2H_5	H	79
$C_6H_5CHClCOCl$	C_6H_5	C_2H_5	C_6H_5	74

Figure 184

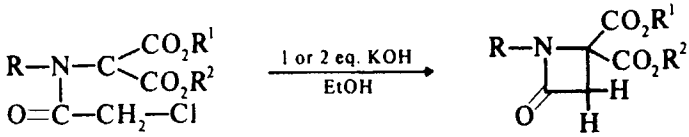
1051. Azetidinone **1051** was hydrolyzed and decarboxylated to give the ester **1052**. Azetidinone **1052** was converted to its acid chloride, reacted with diazomethane, and treated with hydrobromic acid to produce the versatile intermediate **1053**. Conversion to the thiazolyl azetidinone **1054** was completed by reacting **1053** with thiourea. This sequence of reactions is shown in Figure 188. A summary of azetidinones constructed by this procedure is presented in Figure 189.

Chatterjee and Rao investigated the cyclization of *N*-substituted α-chloroacetamide substrates to the corresponding azetidinones with potassium hydroxide in ethanol.[248] For example, **1063a** reacted with potassium hydroxide in ethanol to afford a 90% yield of **1064a**. In addition, **1063b** was smoothly converted to its corresponding azetidinone **1064b** in 80% yield under these conditions. This reaction sequence and the azetidinones prepared by this method are illustrated in Figure 190. Chatterjee and co-workers found that amides **1066** and **1067** could be cyclized with potassium hydroxide in ethanol to the corresponding azetidinones **1068** and **1069**, respectively.[248] In contrast, the reaction of **1066** and **1067** with triethylamine did not effect cyclization to the corresponding azetidinones.[248] These reactions are illustrated in Figure 191.

Kabbe and Joop reported that 2,3-bisalkyliminooxetanes reacted with α-halocarboxylic acids in the presence of base to give the corresponding azetidinones.[249] For example, 2,3-bis-*tert*-butylimino-4-methyloxetane **1070** reacted with bromoacetic acid **1071** to produce azetidinone **1072** in 80% yield.[249] Similarly, **1073**,

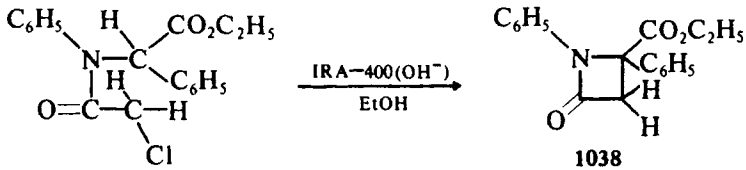


1025 1026 1027

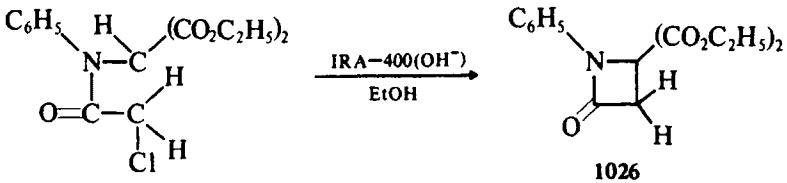


R	R^1	R^2	Yield (%)
C_6H_5	C_2H_5	C_2H_5	88
C_6H_5	C_2H_5	H	79
p-ClC_6H_4	C_2H_5	C_2H_5	88
p-ClC_6H_4	C_2H_5	H	80
p-BrC_6H_4	C_2H_5	C_2H_5	84
p-BrC_6H_4	C_2H_5	H	77
p-$CH_2C_6H_4$	C_2H_5	C_2H_5	85
p-$CH_2C_6H_4$	C_2H_5	H	76
$C_{10}H_7$	C_2H_5	C_2H_5	90
$C_{10}H_7$	C_2H_5	H	88

Figure 185

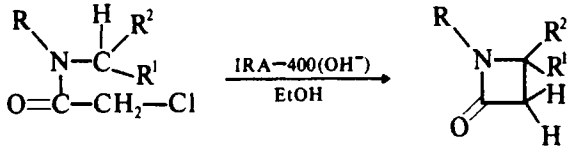


1037 1038



1025 1026

Figure 186



Compound	R	R^1	R^2	Yield (%)
1038	C_6H_5	C_6H_5	$COOC_2H_5$	95
1039	p-ClC_6H_4	C_6H_5	$COOC_2H_5$	89
1040	p-$CH_3C_6H_4$	C_6H_5	$COOC_2H_5$	90
1041	p-BrC_6H_4	C_6H_5	$COOC_2H_5$	91
1026	C_6H_5	$COOC_2H_5$	$COOC_2H_5$	90
1042	p-ClC_6H_4	$COOC_2H_5$	$COOC_2H_5$	83
1043	p-$CH_3C_6H_4$	$COOC_2H_5$	$COOC_2H_5$	92
1044	p-BrC_6H_4	$COOC_2H_5$	$COOC_2H_5$	95
1045	β-$C_{10}H_7$	$COOC_2H_5$	$COOC_2H_5$	92
1046	p-BrC_6H_4	$COOCH_3$	$COOCH_3$	–

Figure 187

reacted with **1071** and triethylamine to produce azetidinone **1074**, in high yield. These transformations are shown in Figure 192.

Chatterjee, Lahiri, and Abdulla investigated the cyclization of *N*-aryl-*N*-chloroacetylphenacyl amines.[250] For example, the reaction of **1075** with potassium hydroxide in ethanol afforded the 1,4-oxazine **1076** exclusively. If this sequence was repeated with **1077**, which has a weak electron-withdrawing group on the nitrogen, the cyclization produced 1,4-oxazine **1078** and β-lactam **1079**. Finally, the reaction of **1080** (which carries a strong electron-withdrawing group on the nitrogen) with potassium hydroxide in ethanol produced only the β-lactam **1081**.[250] These reactions are illustrated in Figure 193.

Chatterjee and Nyss found that, under competitive conditions, the β-lactam formed in preference to the γ-lactam.[251] For example, **1082** reacted with triethylamine in benzene to produce the β-lactam **1083** in 90% yield. This is illustrated in Figure 194.

Choudhury reported the construction of 3-haloazetidinones by the base-catalyzed cyclization of *N*-substituted trihaloacetamides.[252] The reaction of **1084** with potassium *tert*-butoxide in DMSO gave azetidinone **1085** in 66% yield. This is shown in Figure 195.

Kuntz and Kristinsson investigated the cyclization of various *N*-acylmethyl-*N*-chloroacetyl-2,6-dimethylanilines.[253] For example, **1086** reacted with sodium methoxide in methanol to give oxazine **1087** in 82% yield. In contrast, **1088** gave azetidinone **1089** in 76% yield. Compound **1090** gave butyrolactam **1091** in 82% yield. These transformations are illustrated in Figure 196.

Prassad and Petrizilka reported the synthesis of azetidinones utilizing an oxazolone reagent.[254] Thus the reaction of oxazolone **1092** with Schiff base **1093** in refluxing benzene afforded a 50% yield of azetidinone **1094**. This reaction sequence is illustrated in Figure 197.

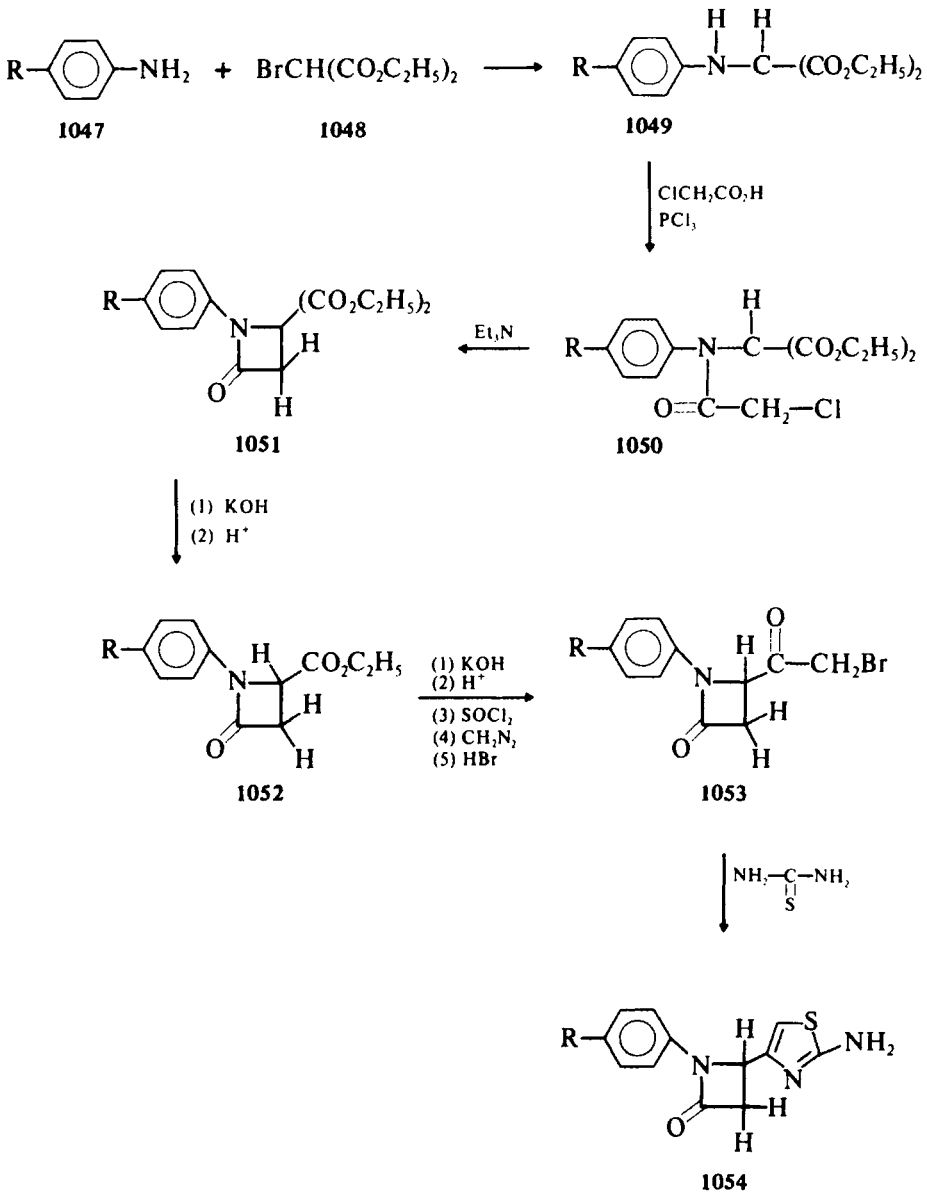
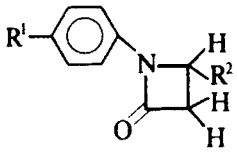


Figure 188

B. *Azetidinone Formation via Photochemical Cyclizations*

Lowe and Parker first reported the successful photocyclization of a diazolactam to the corresponding β-lactam.[255] For example, the photolysis of **1095** in carbon tetrachloride with a medium pressure mercury lamp in a pyrex vessel for 2 hours



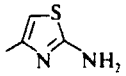
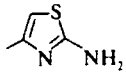
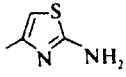
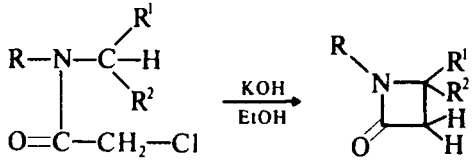
Compound	R^1	R^2	Yield (%)
1055	H	$COCH_2Br$	50
1056	Cl	$COCH_2Br$	53
1057	Br	$COCH_2Br$	51
1058	H		90
1059	Cl		77
1060	Br		77

Figure 189

at room temperature gave a mixture of **1096** and **1097** (in a *cis–trans* ratio of 1 : 2) in 80% yield. Similarly, photolysis of **1098** afforded a 15% yield of **1099** and a 40% yield of **1100**. In contrast to the piperidine system, photolysis of the pyrrolidine derivative **1101** gave only the β-lactone **1102**. These investigators predicted that the thiazolidine **1103** would undergo facile insertion at the C_2 position. Indeed, photolysis of **1103** afforded the fused β-lactam **1104** in 50% yield, along with the γ-lactone **1105** in low yield. This series of transformations is illustrated in Figure 198. Lowe and co-workers[256] reported the photocyclization of **1106** to **1107** and **1108** in 8 and 11% yields, respectively. This sequence is represented in Figure 199.

Johansson and co-workers reported the photocyclization of 2-oxoamides to the corresponding β-lactams.[257] For example, oxoamide **1109** was irradiated in benzene



1063 **1064**

1064	R	R^1	R^2	Yield (%)
a	C_6H_5	C_6H_5	$CO_2C_2H_5$	90
b	p-ClC_6H_4	C_6H_5	$CO_2C_2H_5$	80
c	p-BrC_6H_4	C_6H_5	$CO_2C_2H_5$	80
d	p-$CH_2C_6H_4$	C_6H_5	$CO_2C_2H_5$	89

Figure 190

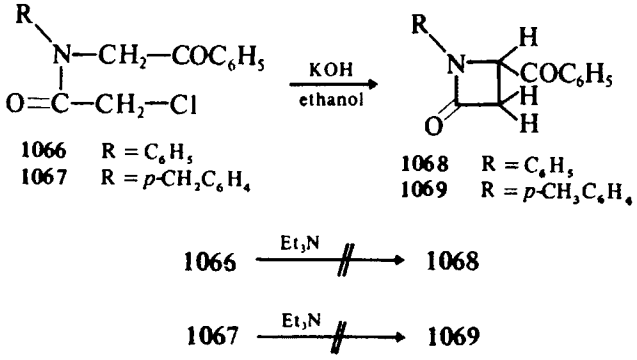


Figure 191

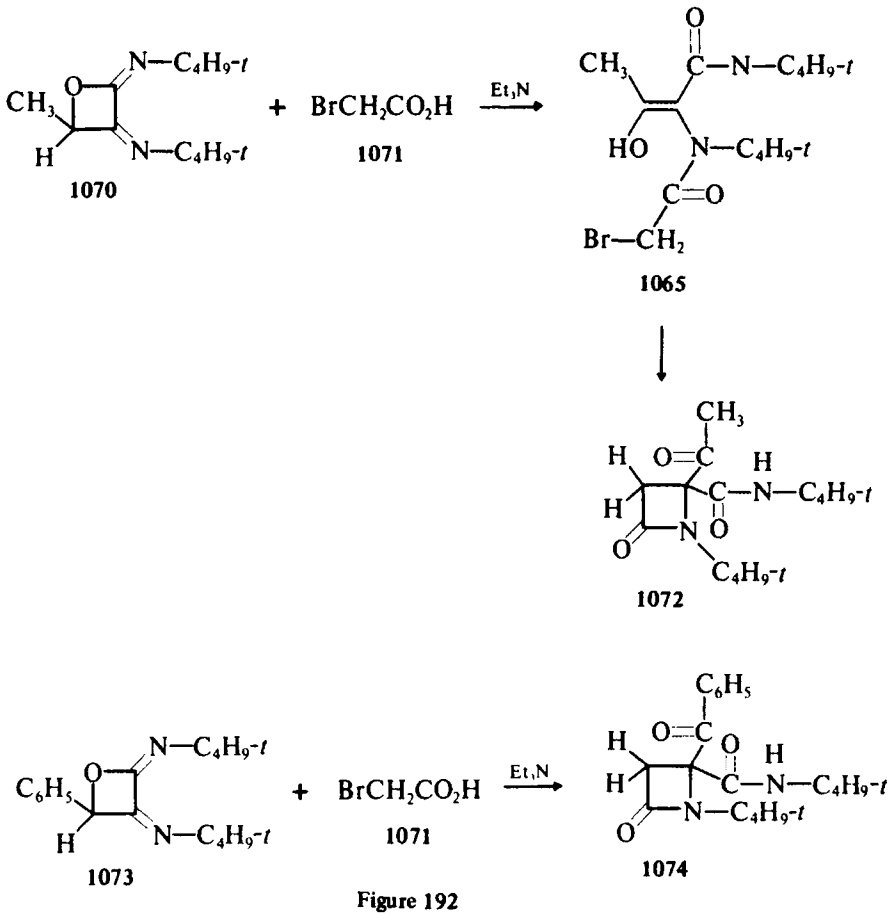
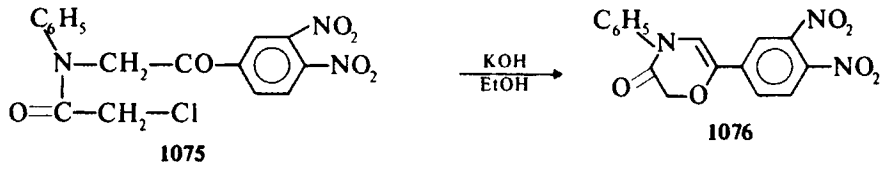
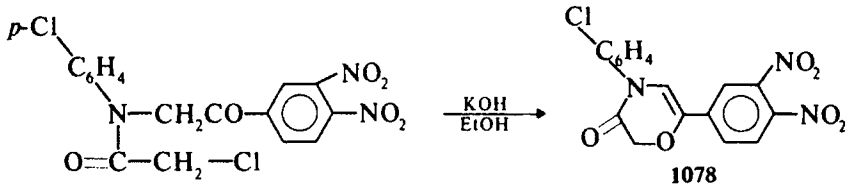


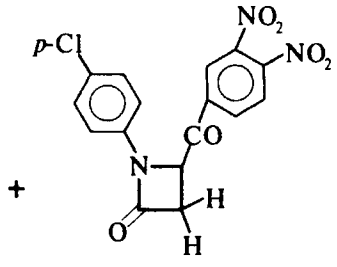
Figure 192



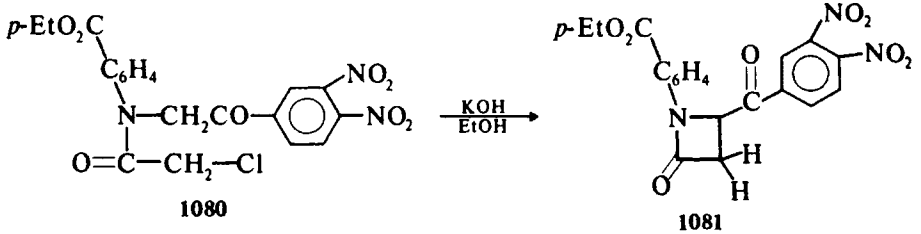
1075 1076



1077 1078

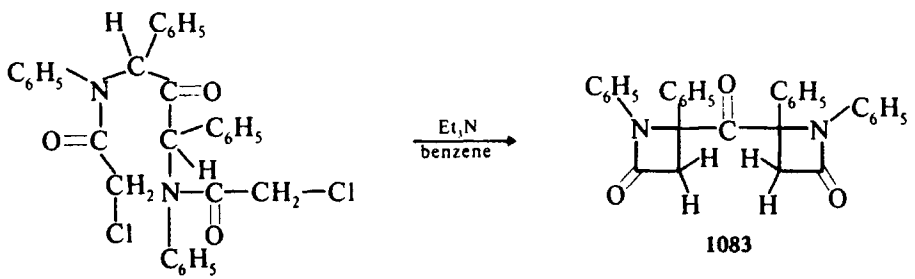


1079



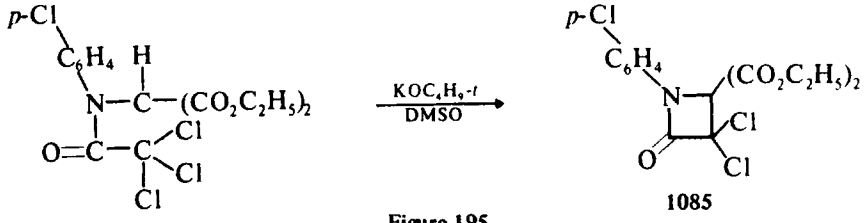
1080 1081

Figure 193



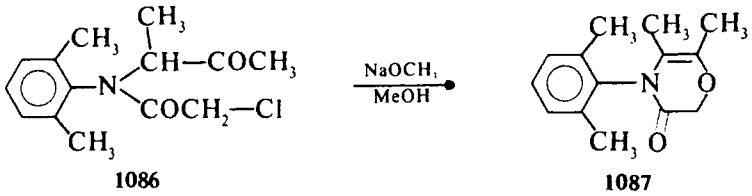
1082 1083

Figure 194

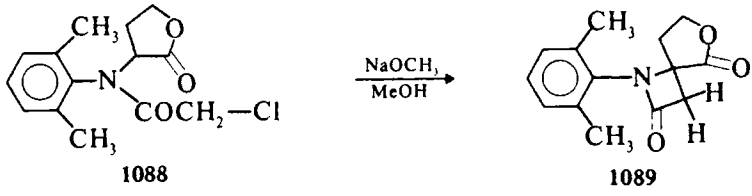


1084 1085

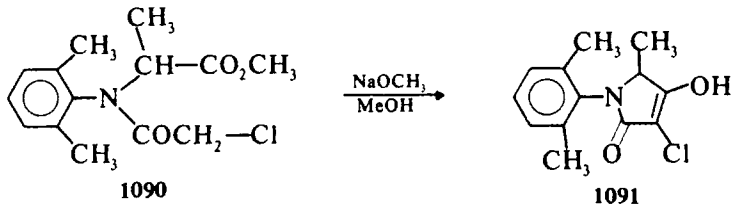
Figure 195



1086 1087

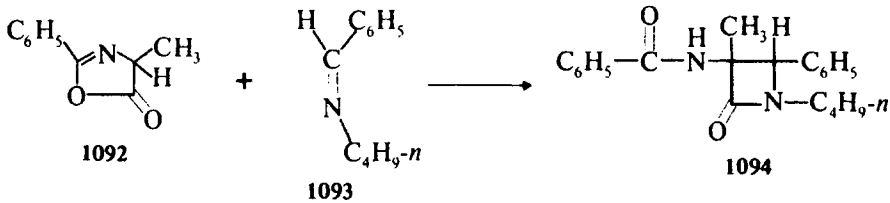


1088 1089



1090 1091

Figure 196



1092 1093 1094

Figure 197

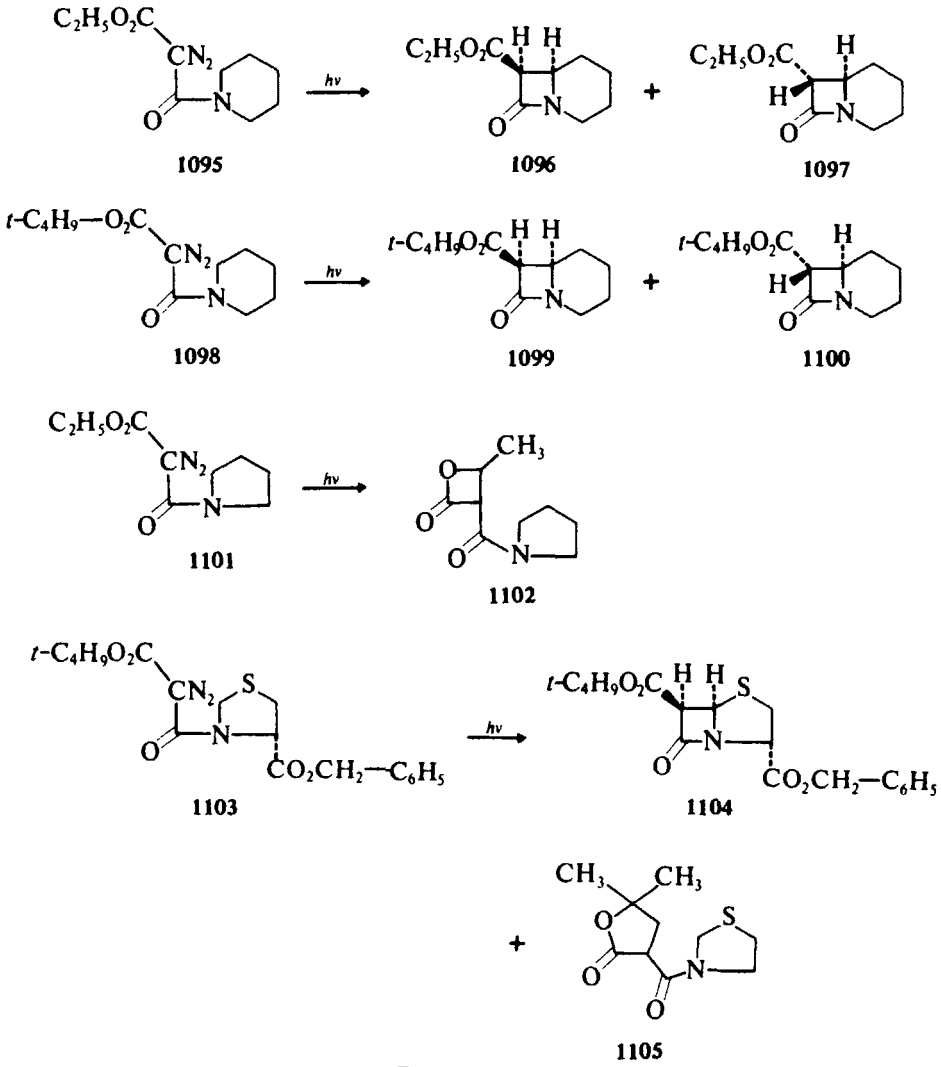
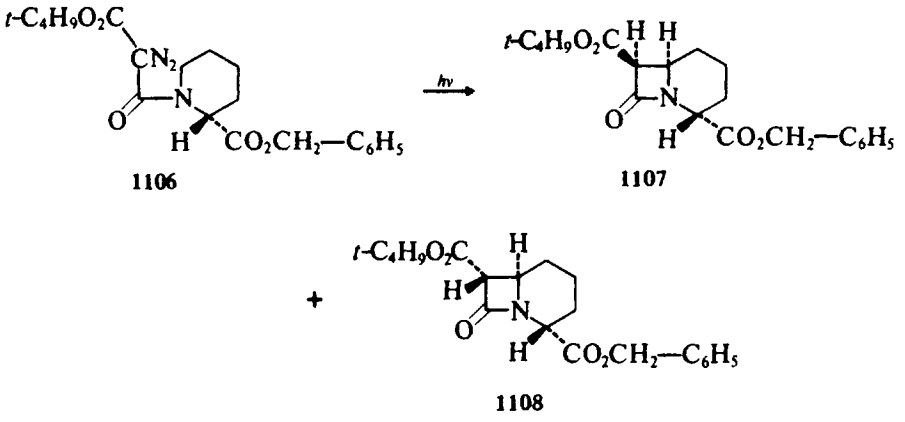


Figure 198

at 3500 Å for 40 hours to give azetidinone **1110** in 8% yield. This reaction is illustrated in Figure 200.

Aoyama and co-workers investigated the photochemical cyclization of *N,N*-dibenzyl and *N,N*-diisoropyl α,β-unsaturated amides.[258] They found that irradiation of **1111** with a low pressure mercury lamp under nitrogen gave azetidinone **1112** in 70% yield. Similarly, **1113** underwent photocyclization to afford **1114** in 84% yield. In contrast, compound 1115 was converted to the acyclic amide **1116** in 30% yield.[258] The latter transformation is also illustrated in Figure 201.

Aoyama and co-workers continued their investigation of the photocyclization of the dibenzylamide **1113**.[259] The formation of **1117** could proceed by direct



1106 1107 1108

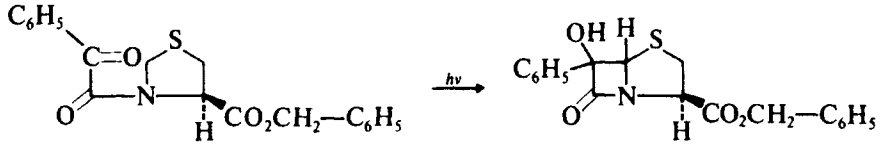
Figure 199

cyclization of diradical **1119** to the azetidinone **1114** (path A), or alternatively by the retro cleavage of **1119** to dimethylketene and the Schiff base, which could undergo a concerted [2+2] addition to give **1114** (path B). To determine which mechanism was operative, these investigators carried out the photolysis of **1113** in the presence of phenethylamine and obtained only isobutyramide **1121** in high yield, with no detectable amount of azetidinone **1114**, thus supporting path B (Figure 202).

Sen, Veal, and Young reported that dehydrovaline acrylamide **1122** underwent a [2+2] photocyclization (Hanovia 125-W medium pressure lamp and a pyrex filter) in dioxane to give azetidinone **1123** in 6% yield.[260] This reaction is presented in Figure 203.

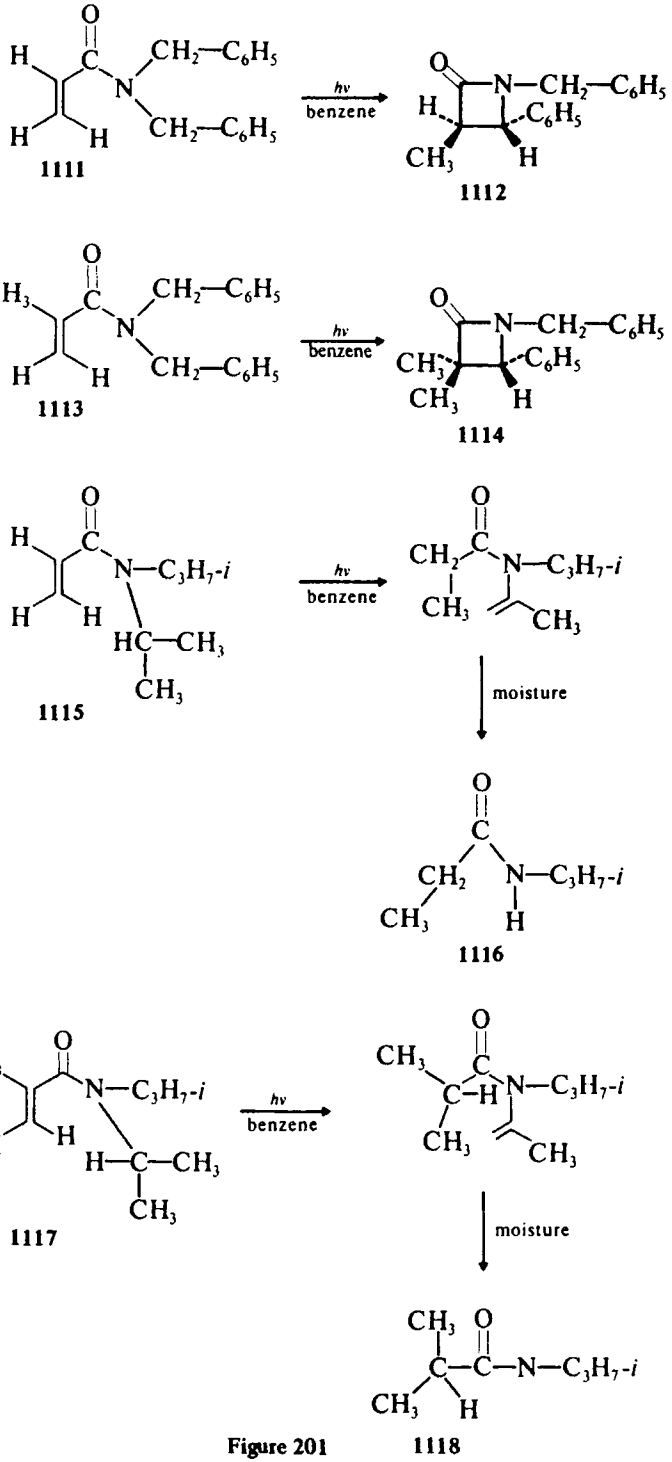
C. *Azetidinone Formation via Transition Metal Carbenes*

Johansson and Akermark investigated the reaction of dihaloacetamides with phenylmercury chloride **1125**.[261] For example, the reaction of **1124** and **1125** in benzene with potassium *tert*-butoxide at 5°C afforded a 50% yield of **1126**. The thermal decomposition of **1126** in refluxing bromobenzene afforded the *cis*-bromoazetidinone **1127** in 14% yield and the *trans*-bromoazetidinone **1128** in



1109 1110

Figure 200



1111 1112 1113 1114 1115 1116 1117 1118

Figure 201

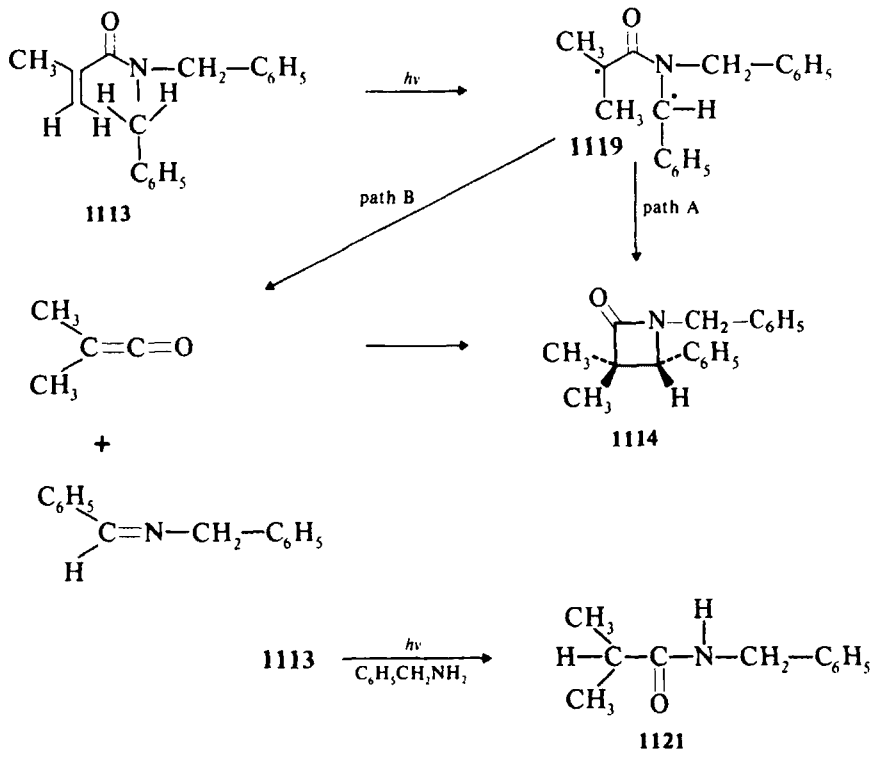


Figure 202

47% yield (Figure 204). Johansson[262] found that reacting **1124** and **1125** in THF with uncomplexed potassium *tert*-butoxide (made with equimolar amounts of potassium and *tert*-butanol) at −30°C afforded **1126** in 80% yield. Similarly **1129** reacted with **1125** to give **1130** in 60% yield. In contrast to the thermal decomposition of **1126**, which was complete in 1.7 hours, intermediate **1130** required 22 hours in refluxing bromobenzene to afford *cis*-chloroazetidinone **1131** in 8% yield and *trans*-chloroazetidinone **1132** in 45% yield (Figure 205).

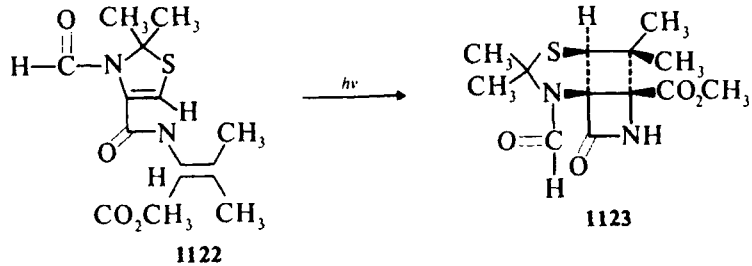


Figure 203

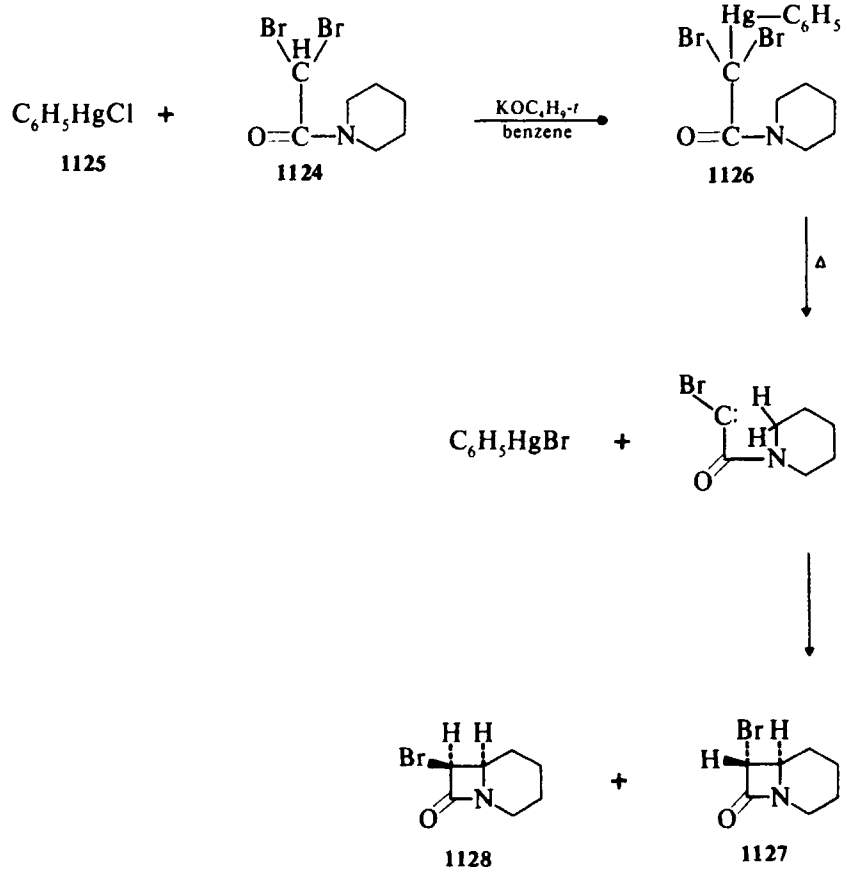


Figure 204

Akermark and co-workers investigated the reaction of the bromochloroacetamide **1133** with **1125**.[263] They found that **1125** reacted with **1133** in THF with potassium *tert*-butoxide at $-75^{\circ}C$ to give **1134** in 50% yield. Substrate **1134** was thermally decomposed in refluxing bromobenzene for 2.3 hours to afford (exclusively) the *trans*-chloroazetidinone **1132** in 54% yield. This sequence of reactions is described in Figure 206.

Akermark et al. reported the utilization of diethylthallium *tert*-butoxide **1135** in the conversion of dihaloacetamides to their corresponding azetidinones.[264] These investigators found that **1135** reacted with **1124** in THF at room temperature to give **1136**, which was thermally decomposed in bromobenzene to afford a 5:1 ratio of the trans and cis isomers **1128** and **1127**, respectively. Most importantly, these researchers discovered that **1135** reacted with **1137** to give intermediate **1138**, which was thermally decomposed in bromobenzene for 30 minutes to afford the cephalosporin analog **1139** in 5% yield.[264] This series of reactions is presented in Figure 207.

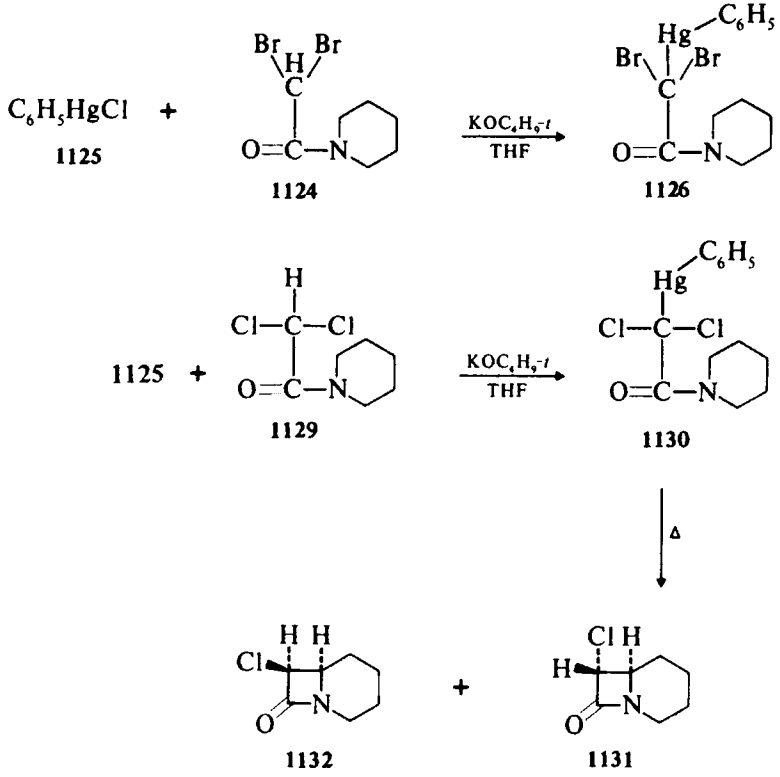


Figure 205

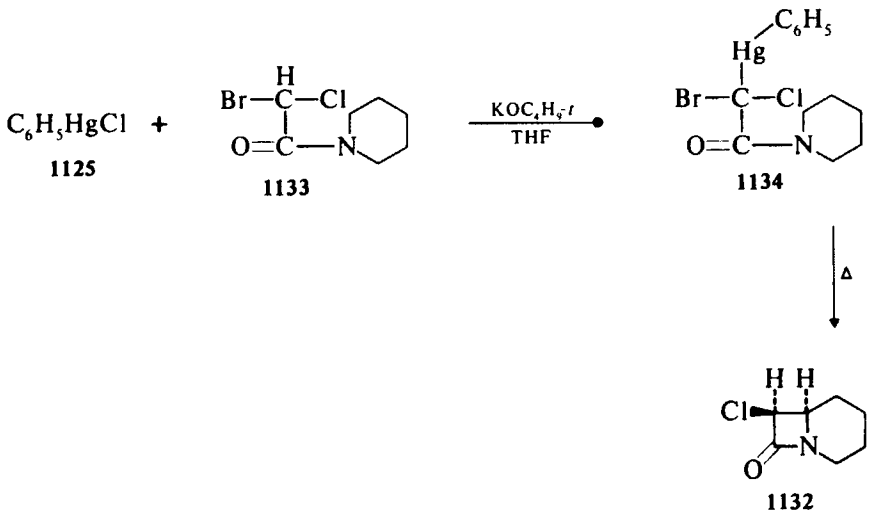


Figure 206

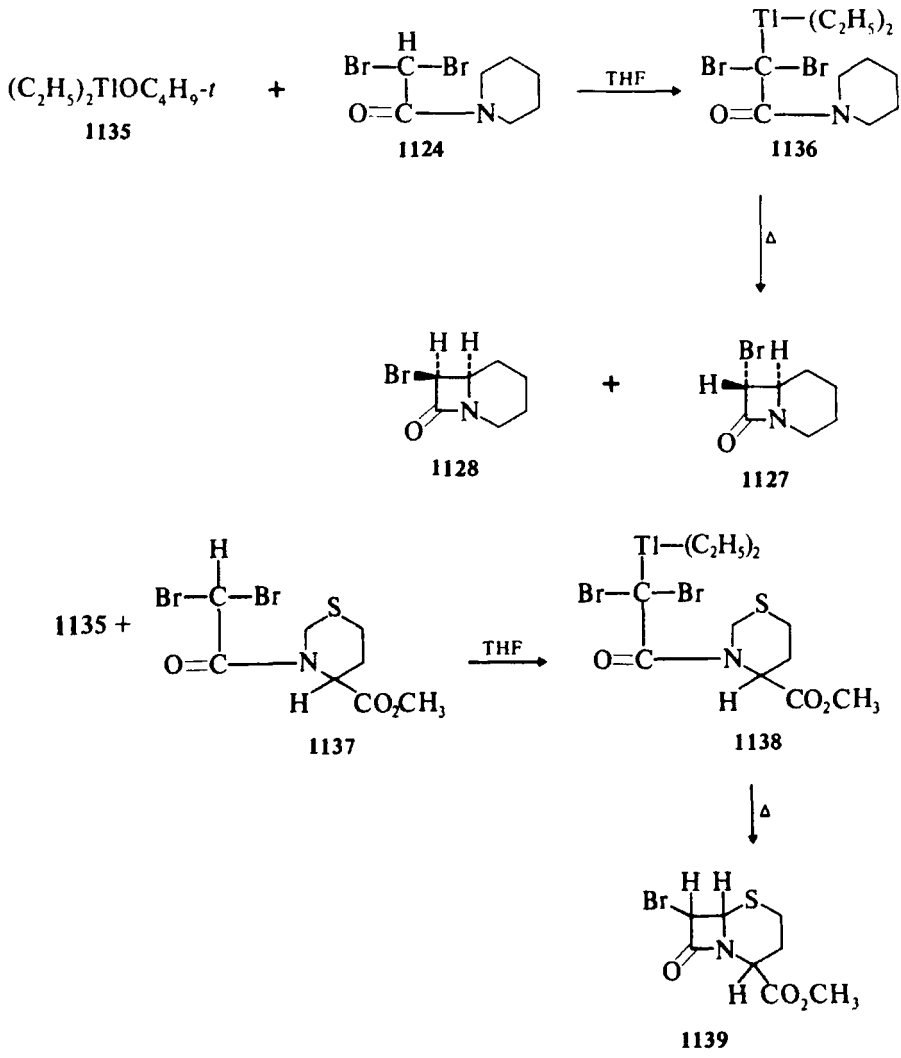


Figure 207

III. RING-EXPANSION REACTIONS (X → XI)

Sheehan and Izzo first reported that aryl isocyanates underwent initial cycloaddition with diazomethane to afford the α-lactam, which subsequently reacted with a second mole of diazomethane to produce the ring-expanded azetidinone.[265] For example, phenyl isocyanate **1140** reacted with an excess of diazomethane to afford azetidinone **1141**. Similarly, **1142** reacted with diazomethane to produce azetidinone **1143**. These reactions are presented in Figure 208.

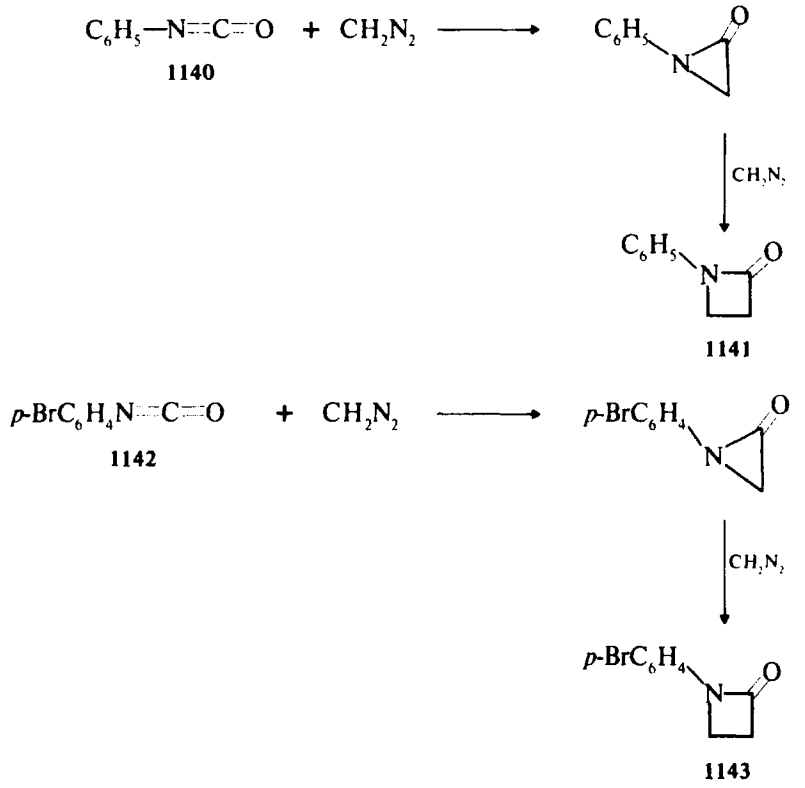


Figure 208

Toda and co-workers reported that diphenylcyclopropenone **1144** reacted with ammonia at −78°C to afford α-phenyl-β-amino-*trans*-cinnamaldehyde **1145**.[266] If, however, this sequence was repeated at room temperature, one obtained *cis*-azetidinone **1146** and *trans*-azetidinone **1147**, both in 30% yield.[266] These reactions are illustrated in Figure 209.

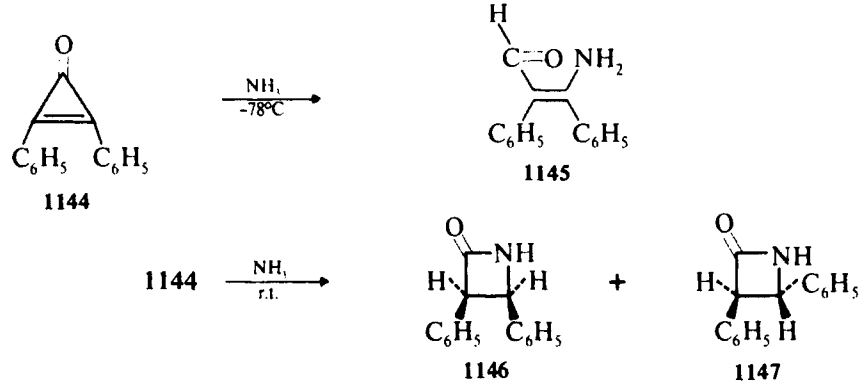


Figure 209

Deyrup and Clough reported an elegant ring expansion of aziridines to azetidinones.[267,268] They found that **1148** reacted with thionyl chloride to give azetidinone, **1149** (stereospecifically) in 79% yield. Similarly, **1150** reacted with thionyl chloride to afford azetidinone **1151** in 63% yield (Figure 210). A mechanism describing the stereospecific conversion of aziridine carboxylates to the corresponding azetidinones is depicted in Figure 210.

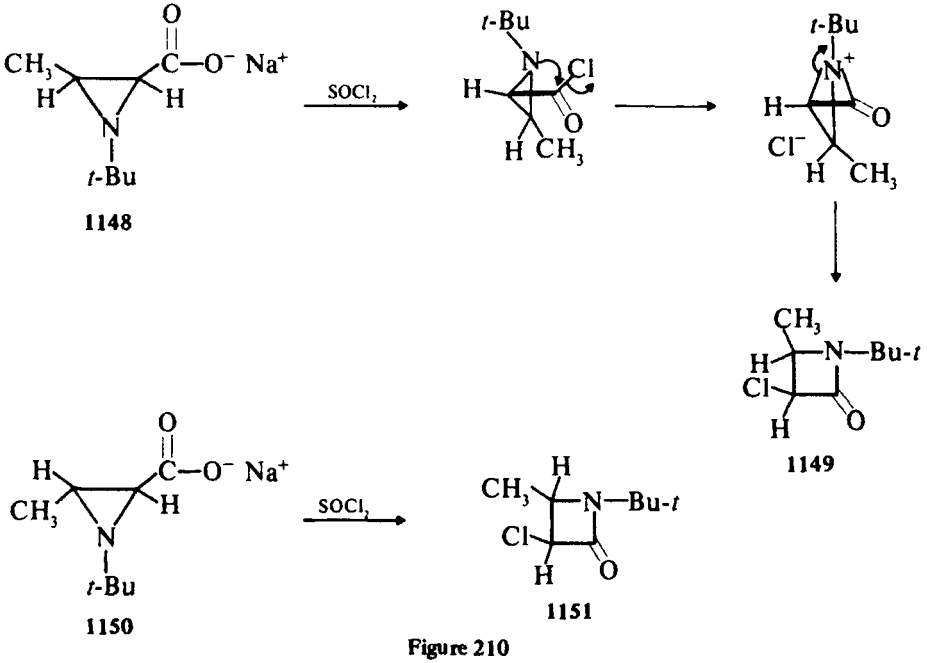


Figure 210

Wasserman and Baird[269] found that **1152** reacted with sodium azide in refluxing acetone to afford the fused β-lactams **1153** in 95% yield (Figure 211). Wasserman

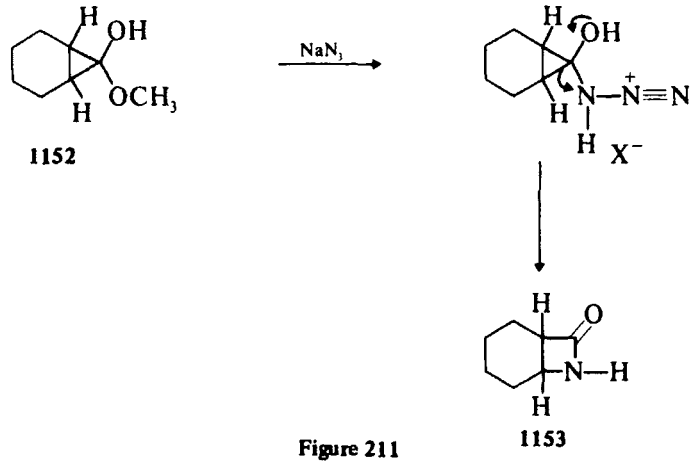


Figure 211

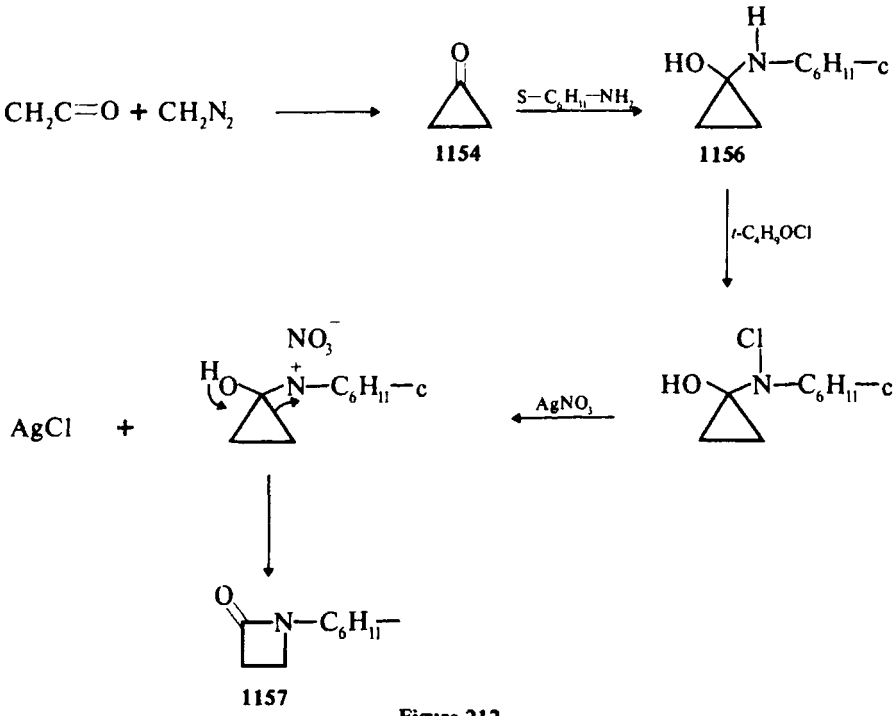
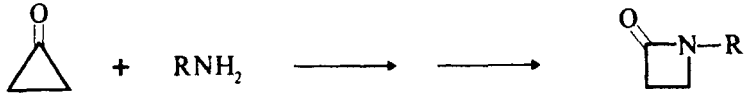


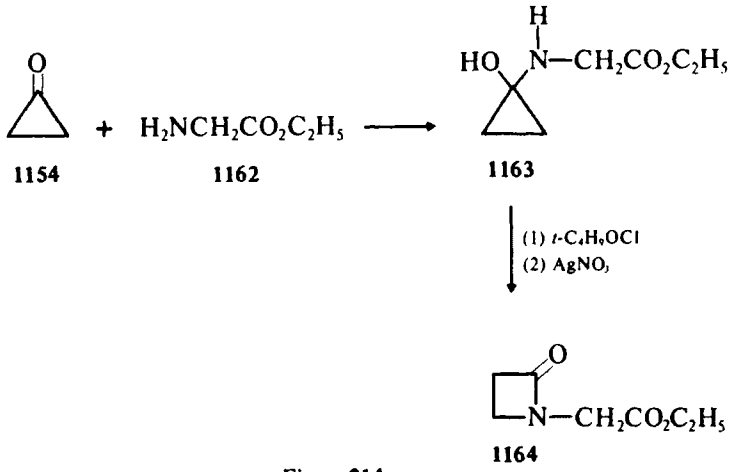
Figure 212

and co-workers reported the conversion of cyclopropanones to azetidinones in an oxidative ring-expansion sequence.[270] For example, ketene was treated with diazomethane in ether at $-78°C$ to give cyclopropanone **1154**, which was subsequently reacted with cyclohexylamine **1155** to afford carbanolamine **1156**. Intermediate **1156** was not isolated but reacted directly with one equivalent of *tert*-butyl hypochlorite in acetonitrile at 0°C for 1 hour, followed by treatment with silver nitrate, to afford a 61% yield of azetidinone **1157**.[270] This reaction sequence is presented in Figure 212. A summary of azetidinones prepared by this method is given in Figure 213.



β-Lactam	R	Yield (%)
1157	S-C_6H_{11}	61
1158	*n*-C_4H_9	43
1159	CH_3CH_2CH	38
1160	$(CH_3)_3C$	52
1161	$CH_3CH(CO_2C_2H_5)$	65

Figure 213

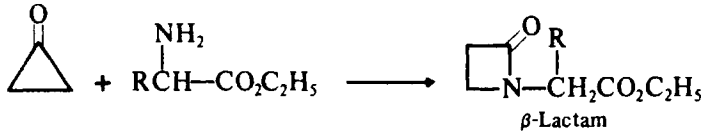


1154 **1162** **1163** **1164**

Figure 214

Wasserman and Glazer extended the oxidative cyclopropanone → azetidinone rearrangement to the construction of azetidinone derivatives of amino acids.[271] For example, the reaction of ethyl 2-aminoacetate **1162** with cyclopropanone **1154** at −80°C produced the carbinolamine **1163**, which was treated with one equivalent of *tert*-butyl hypochlorite at −10°C, followed by silver nitrate, to afford azetidinone **1164** in 33% yield.[271] This reaction sequence is presented in Figure 214. A series of azetidinones synthesized by this procedure is shown in Figure 215.

Wasserman and Glazer avoided the cumbersome procedure of carbinolamine halogenation by utilizing hydroxylamine derivatives.[272] For example, *N*-(α-cyano) butylhydroxylamine **1170**, prepared by treating butyraldehyde oxime with HCN, reacted with 1-acetoxycyclopropanol **1169** to afford **1171** in high yield. The carbinol amine **1171** was treated with one equivalent of *p*-toluenesulfonyl chloride in DMSO at 50°C to afford azetidinone **1172** in 45% yield.[272] This reaction sequence is presented in Figure 216. A summary of azetidinones prepared by this procedure is given in Figure 217.



β-Lactam

β-Lactam	R	Yield (%)
1164	H	33
1165	CH_3	47
1166	$(CH_3)_2CH$	65
1167	$(CH_3)_2CHCH_2$	65
1168	$C_6H_5CH_2$	70

Figure 215

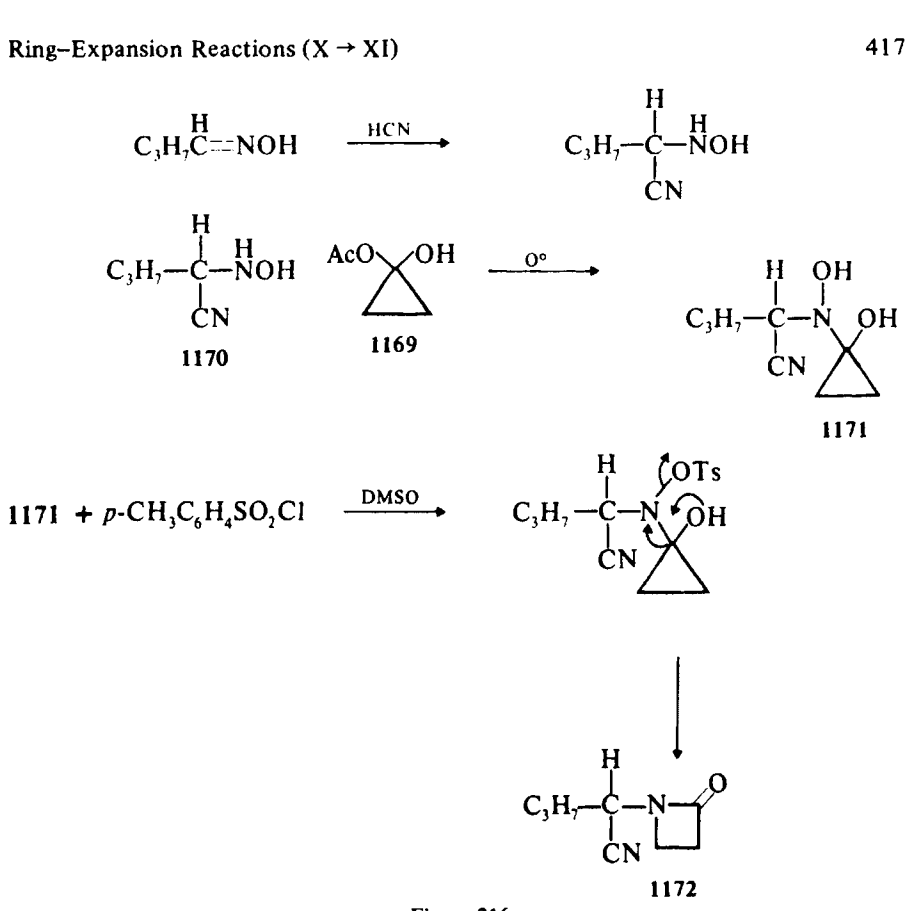
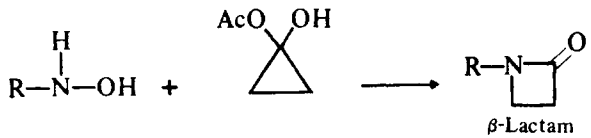


Figure 216



β-Lactam	R	Yield (%)
1172	$CH_3(CH_2)_2CH(CN)$	45
1173	$(CH_3)_2CHCH(CN)$	41
1174	$CH_3(CH_2)_3CH(CN)$	40
1175	$(CH_3)_2CHCH_2CH(CN)$	45
1176	C_6H_5	43

Figure 217

Greene and co-workers[273] reported that the reaction of tosylhydrazide **1177** with cyclopropanone **1178** afforded the 1 : 1 adduct **1179**. This was subsequently oxidized with manganese dioxide to give azetidinone **1180** in 25% yield. This transformation is presented in Figure 218.

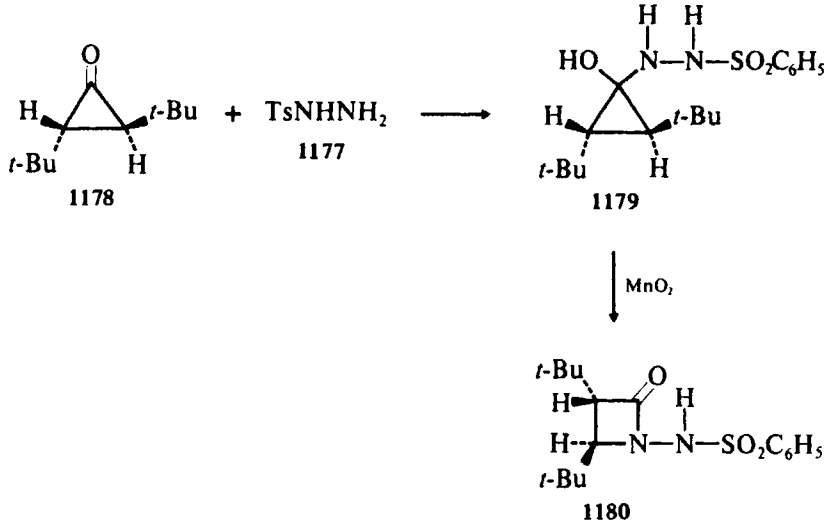


Figure 218

Talaty and co-workers reported the pyrolytic conversion of an α-lactam to the corresponding β-lactam.[274] They found that α-lactam **1181** underwent pyrolysis in a sealed tube at 115–160°C to give azetidinone **1182**. This sequence is represented in Figure 219. An interesting recently reported[275] ring expansion of an azirine to a β-lactam is depicted in Figure 219a.

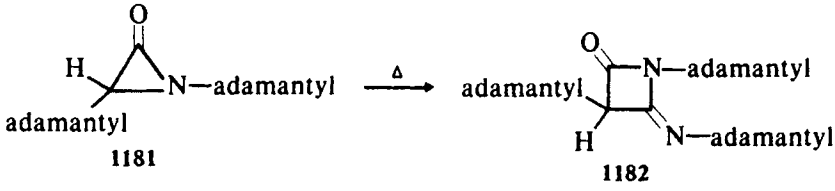


Figure 219

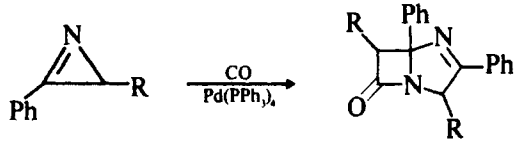


Figure 219a

IV. RING-CONTRACTION REACTIONS (XIII → XIV) AND (XV → XVI)

Chasle and co-workers first reported the ring contraction of a butyrolactam to the corresponding β-lactam.[276] For example, dichlorobutyrolactam **1183** reacted with sodium methoxide in methanol to afford, exclusively, the azetidinone **1184**. In contrast, **1185** produced a mixture of azetidinone **1186** and amide **1187**, comprising 20 and 80% of the reaction products, respectively. This series of transformations is illustrated in Figure 220. A summary of azetidinones constructed by this procedure is presented in Figure 221.

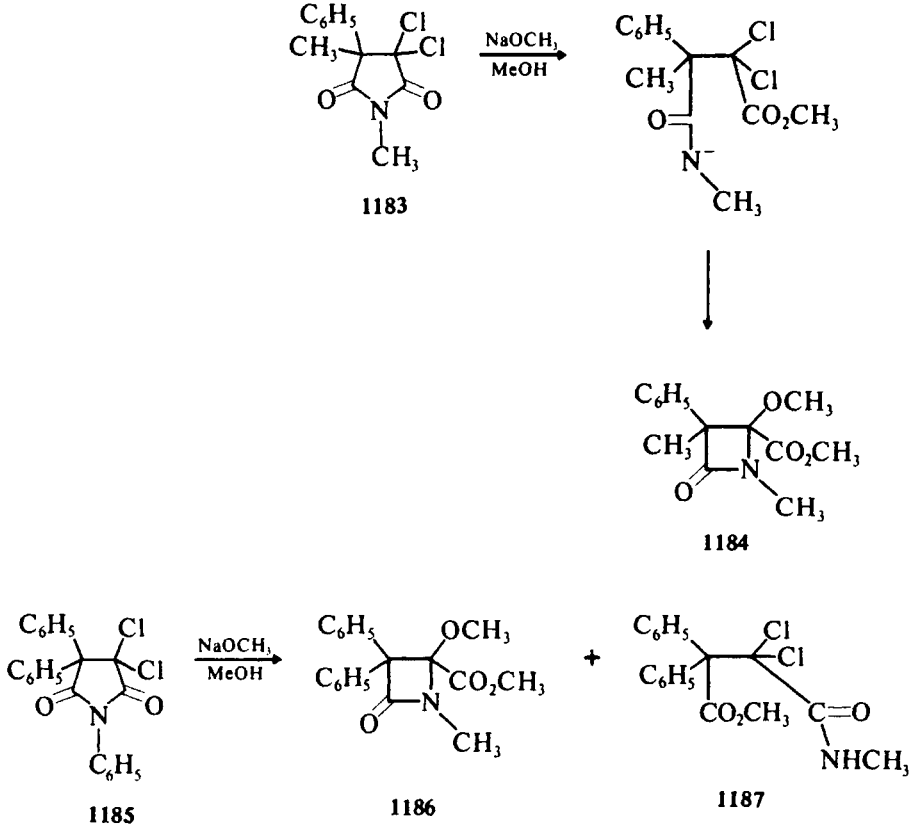
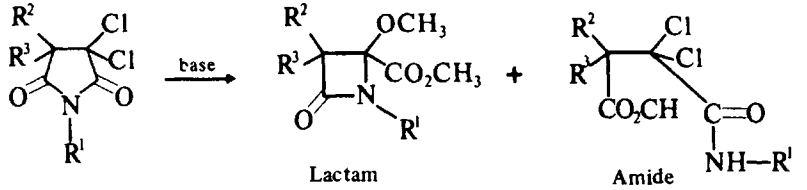


Figure 220

Lowe and Ridley reported that the Wolff rearrangement of diazopyrrolidinediones produced the corresponding β-lactams.[277] These investigators found that 3-diazo-5-methylpyrrolidine-2,4-dione **1188** underwent photolytic rearrangement (medium pressure mercury lamp in a pyrex vessel) in benzene in the presence of *t*-butyl carbazate (**1189**) at room temperature to give the *cis*-β-lactam **1190** and the *trans*-β-



R^1	R^2	R^3	Solvent	% Lactam	% Amide
CH_3	C_6H_5	CH_3	MeOH	100	0
C_6H_5	C_6H_5	C_6H_5	MeOH	20	80
CH_3	C_6H_5	C_6H_5	DMOS or methanol	0	100
CH_3	C_6H_5	C_6H_5	MeOH–DME (1 : 1)	10	90
CH_3	C_6H_5	C_6H_5	MeOH–dioxane (1 : 1)	25	75
CH_3	C_6H_5	C_6H_5	MeOH–*t*-BuOH (1 : 1)	25	75
C_6H_5	$(CH_2)_5$		MeOH	100	0
C_6H_5	$(CH_2)_5$		MeOH–DMSO (1 : 1)	90	

Figure 221

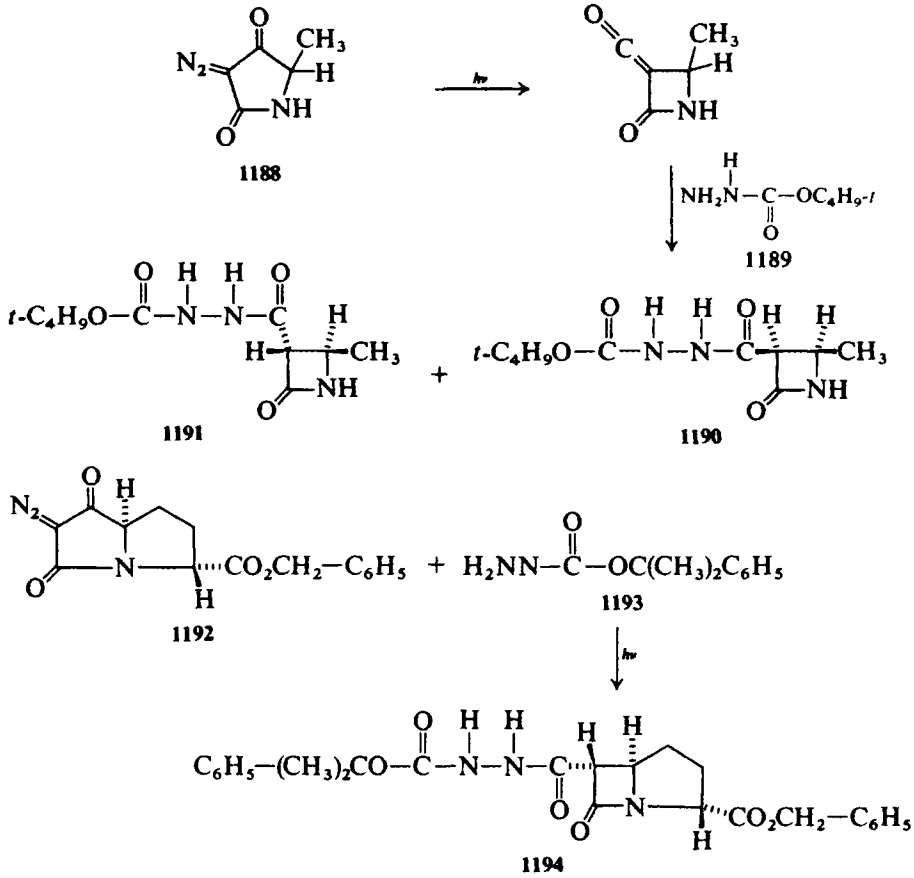


Figure 222

lactam **1191** in 36 and 55% yields, respectively. In addition, **1192** underwent a photolytically induced Wolff rearrangement in ether at −70°C in the presence of α,α-dimethylbenzyl carbazate **1193** to give the fused β-lactam, **1194**[277] (Figure 222). Surprisingly, the photolysis of **1195** in benzene in the presence of **1189** effected the conversion to the *trans*-azetidinone **1196**, but with concomitant isomerization of the double bond[278] (Figure 223).

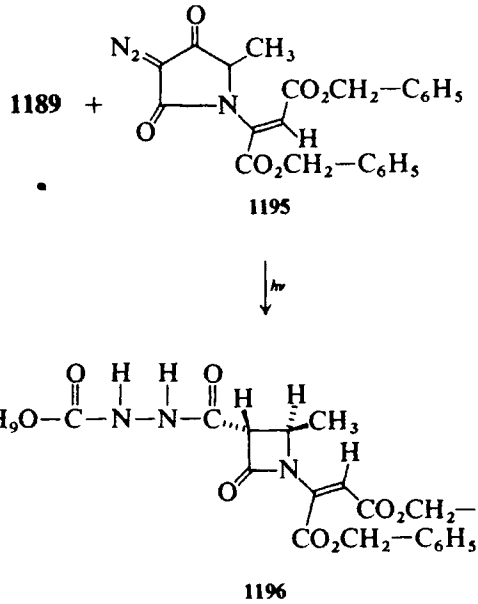


Figure 223

Lowe and Yeung extended the Wolff rearrangement to the synthesis of the biologically relevant 3-amidoazetidinones.[279] Compound **1197** underwent a photolitically induced Wolff rearrangement to give azetidinone **1198**. Azetidinone **1198** was converted to the hydrazide **1199**, which was treated with sodium nitrite and acid to afford the acyl azide **1200**. This in turn was refluxed in dry benzene, followed by the addition of *t*-butyl alcohol, to afford the urethane **1201**. This series of transformations is illustrated in Figure 224.

Stork and Szajewski[280] independently reported the successful conversion of 3-diazopyrrolidine-2,4-diones to the corresponding azetidinones utilizing the photochemical Wolff rearrangement. Stork conceived the Wolff rearrangement to azetidinones with the hope that (1) a new route to heretofore inaccessible β-lactams would be developed and that (2) there would be complete stereochemical control at all asymmetric centers. A fundamental question raised by Stork was whether the photochemical reaction of **1202** would afford the azetidin-2-one or the isomeric azetidin-3-one. *A priori*, one could not rule out the possibility that the nitrogen would stabilize the carbenoid intermediate more effectively. However, as pointed

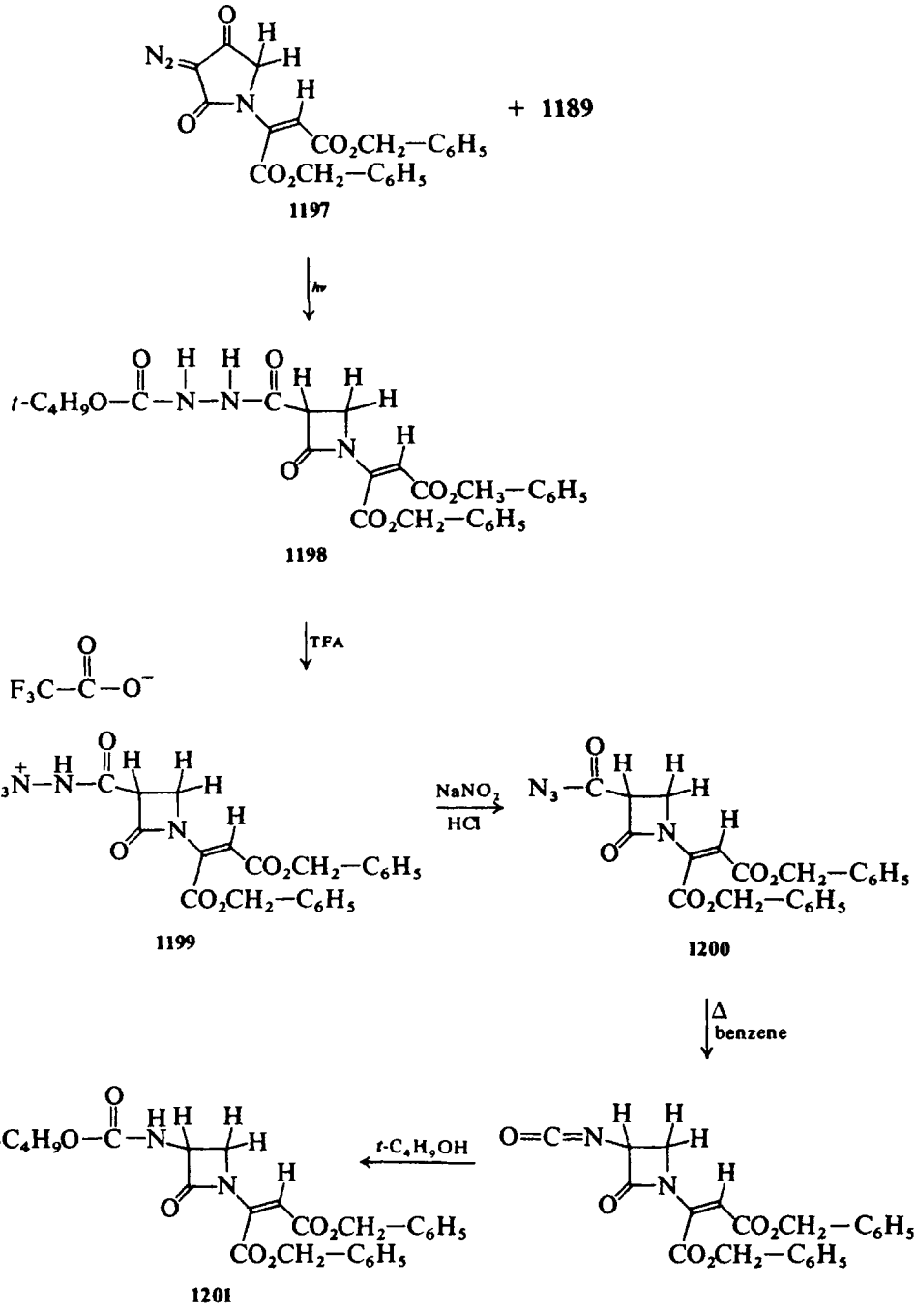

+ 1189
1197
hν
1198
TFA
1199
NaNO2
HCl
1200
Δ
benzene
t-C4H9OH
1201

Figure 224

out by Stork, participitation of nitrogen in the transition state would be discouraged by its active involvement in amide resonance. Indeed, this was demonstrated by the successful ring contraction of **1205** to azetidin-2-one **1206** in 95% yield. The photolysis (using a medium pressure mercury lamp and a pyrex filter) was carried out in ether at 0°C in the presence of methanol (Figure 225).

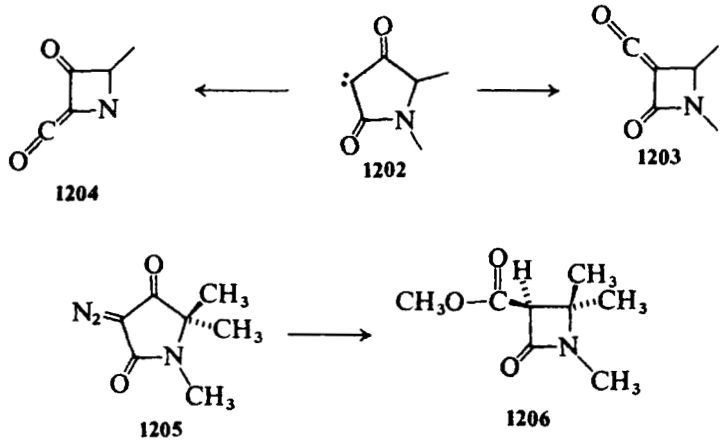


Figure 225

Having successfully converted the 3-diazopyrrolidine-2,4-dione to the azetidin-2-one, Stork and Szajewski[280] turned their attention to the question of stereochemical control at the C_3-position. Stork postulated that kinetic protonation from the more accessible α-face of the fused azetidinone intermediate **1208** would afford the thermodynamically less stable but biologically active C_3-β-substituted β-lactam **1209**. The photolysis of **1210** afforded a 2:5 mixture of azetidinones **1211** and **1212**, respectively, in 65% yield (Figure 226). These results suggest that protonation

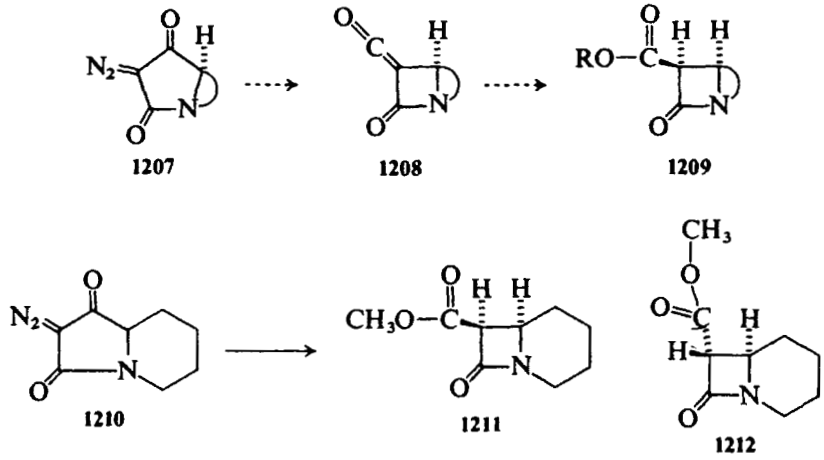
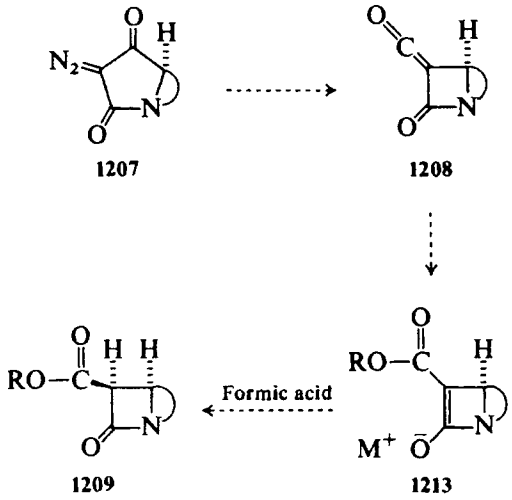


Figure 226

under these conditions (i.e., alcohol protonation) is not sufficiently sensitive to kinetically trap **1208**. An interesting possibility is raised by Stork's "kinetic protonation hypothesis." If one were to generate the ketene intermediate **1208** and react it with one equivalent of a metal alkoxide at low temperature, the resulting enolate **1213** could, in theory, be kinetically protonated with formic acid from the α-face to give **1209** stereoselectively (Figure 227).



1207 **1208** **1209** **1213**

Figure 227

Rapoport and co-workers reported the oxidative ring contraction of 2,3-pyrrolidinediones.[281,282] For example, the reaction of 1-methyl-2,3-pyrrolidinedione **1214** with sodium periodate at pH 7.0 afforded a 30% yield of β-lactam **1215**. Similarly, **1216** was oxidized with periodate to give azetidinone **1217** in 70% yield. Finally, **1218** was oxidized to afford azetidinone **1219** in 40% yield. This series of reactions is presented in Figure 228. A proposed mechanism for the oxidative ring contraction is illustrated in Figure 229.[283,284]

Ege reported his investigation of the photolysis of pyrazoldin-3-ones.[285] For example, **1220** underwent photolysis in methanol in a pyrex tube to afford 1-anilino-4-methylazetidin-2-one (**1221**) in 30% yield. Similarly, **1222** and **1223** were converted to azetidinones **1224** and **1225**, respectively.[286] These data are presented in Figure 230.

Hatch and Johnson[286] investigated the photolysis of 2-phenylacetyl-5,5-dimethylpyrazolidin-3-one **1226**. They found that **1226** underwent irradiation through a nondegassed solution in *t*-butyl alcohol to produce β-lactam **1227** in 40–50% yield. In a similar manner, irradiation of a 1% methanolic solution of **1228** with a Hanovia 450-W immersion lamp gave a 40–50% yield of fused β-lactam **1229**[287] (Figure 231). Johnson and Hatch[288] found that **1230** underwent ring contraction to the spiro azetidinone **1231** in 50% yield.[288] In addition, **1232** and **1233** were converted to azetidinones **1234** and **1235**, respectively[288] (Figure 232). Quite surprisingly, 1-acetylpyrazolidin-3-one **1236** was converted

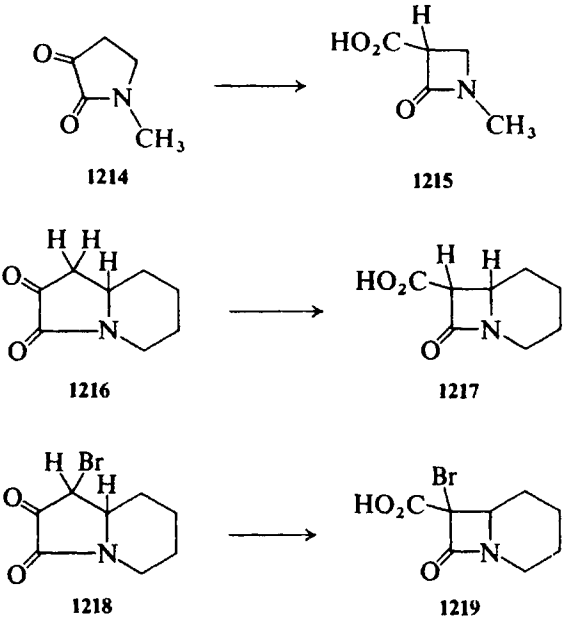


Figure 228

to azetidinone **1234** under photolytic conditions.[289,290] A mechanism for this transformation is illustrated in Figure 233.

Barton and co-workers reported their results of the photolysis of thiazolium hydroxide derivatives.[291] For example, photolysis of **1237** in methanol, followed by work-up with triphenylphosphine, afforded a 19% yield of azetidinone **1238**. Similarly, photolysis of **1239**, followed by work-up with triphenylphosphine, gave azetidinone **1240** in 9% yield.[291] These transformations, including a plausible mechanism, are illustrated in Figure 234.

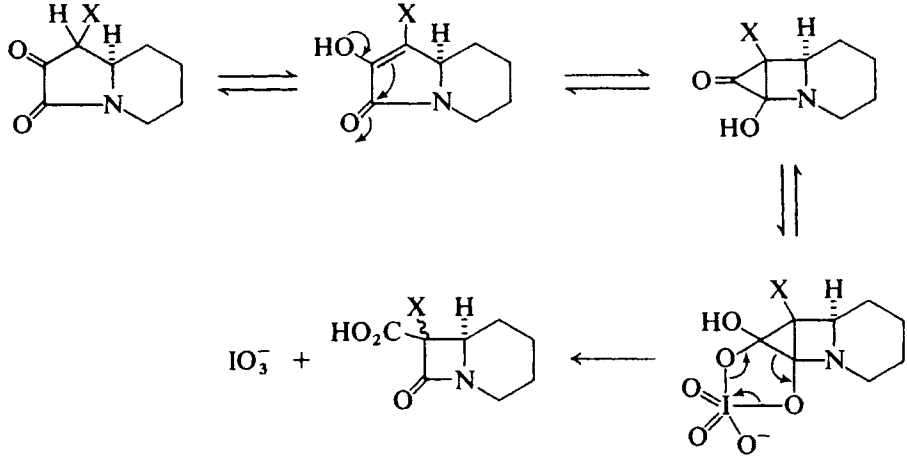
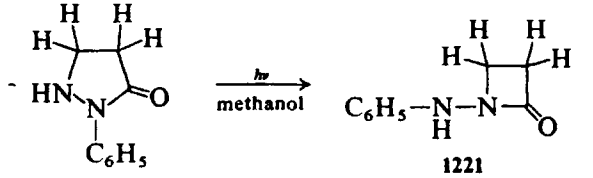
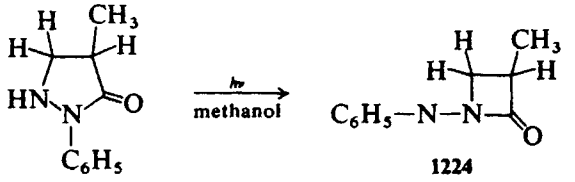


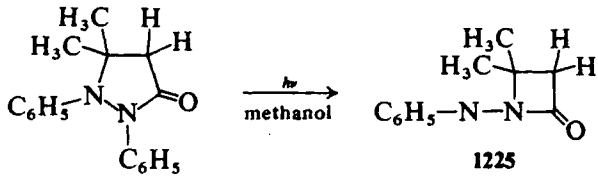
Figure 229



1220 1221



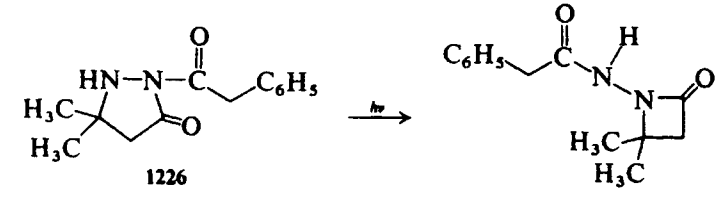
1222 1224



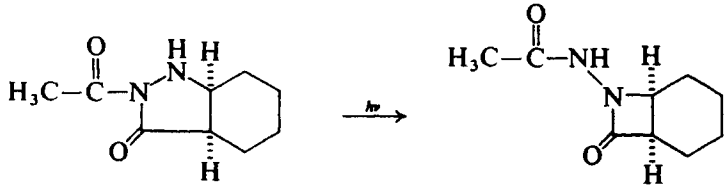
1223 1225

Figure 230

Sheradsky and Zbaida reported the Raney nickel–promoted ring contraction of thiazolium hydroxides to the corresponding azetidinones.[292,293] Anhydro-4-hydroxy-2,3,5-triphenylthiazolium hydroxide **1241** reacted with Raney nickel in methanol at room temperature for a few minutes to afford (stereospecifically) an 85% yield of azetidinone **1242**. This transformation is presented in Figure 235. A summary of azetidinones constructed by this ring-contraction reaction is given in Figure 236.



1226 1227



1228 1229

Figure 231

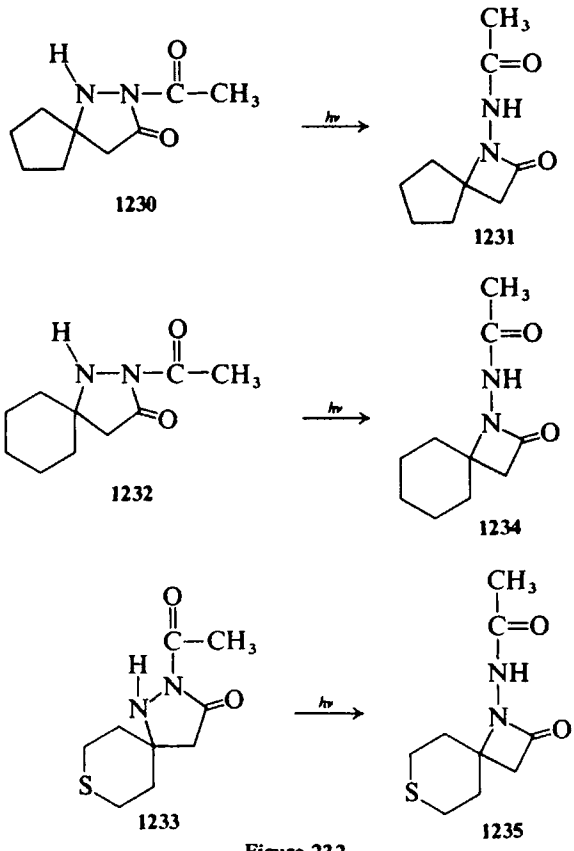


Figure 232

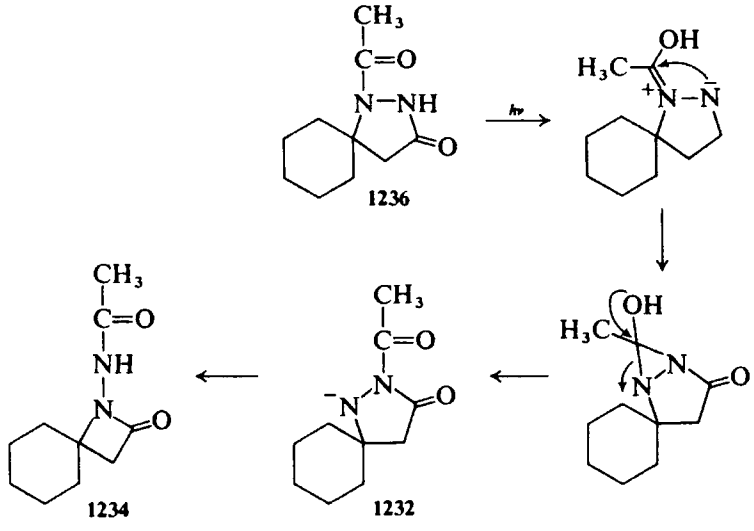
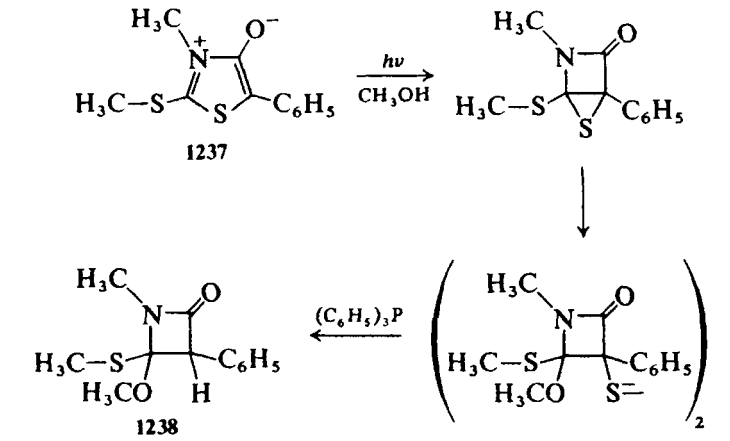
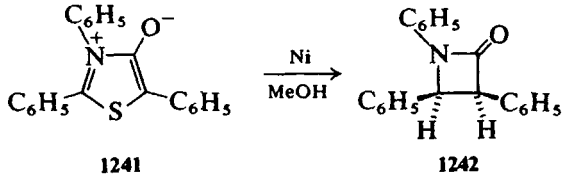


Figure 233



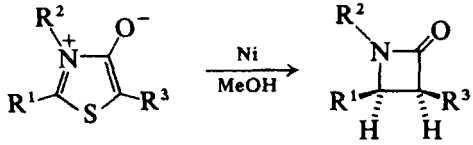
1237 1238 1239 1240

Figure 234



1241 1242

Figure 235



β-Lactam

β-Lactam	R^1	R^2	R^3	Yield (%)
1242	C_6H_5	C_6H_5	C_6H_5	85
1243	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	80
1244	C_6H_5	o-$CH_3C_6H_4$	C_6H_5	18
1245	C_6H_5	p-ClC_6H_4	C_6H_5	78
1246	C_6H_5	$C_6H_5CH_2$	C_6H_5	80

Figure 236

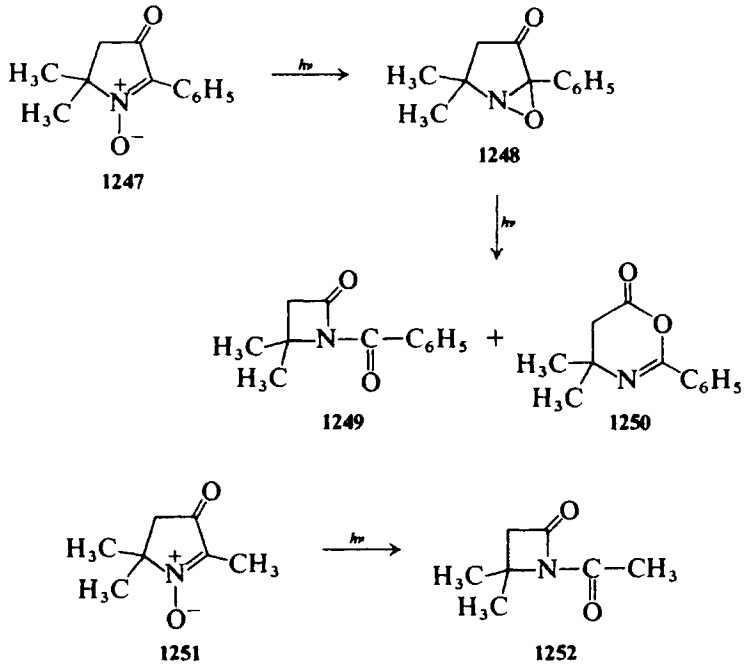


Figure 237

Black and Boscacci reported the successful conversion of 3-oxo-1-pyrroline-1-oxides to the isomeric azetidinones under photolytic conditions.[294] Thus irradiation of **1247** for 5 hours afforded the starting material and the oxaziridine **1248**.

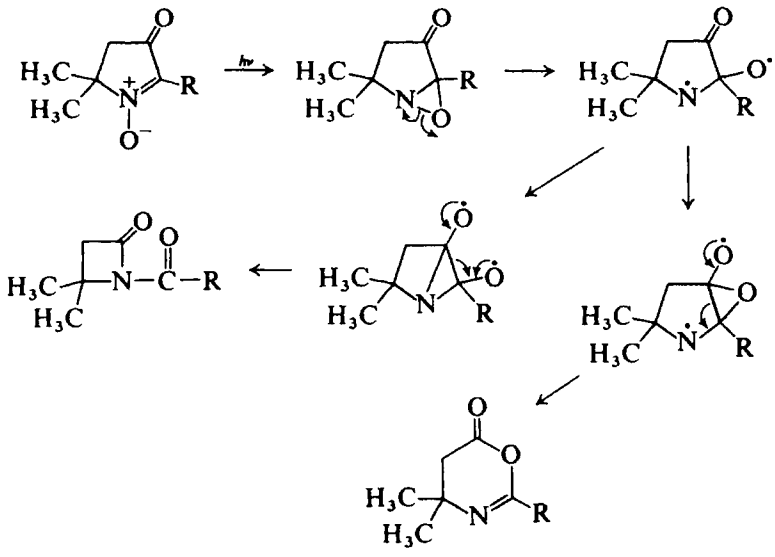


Figure 238

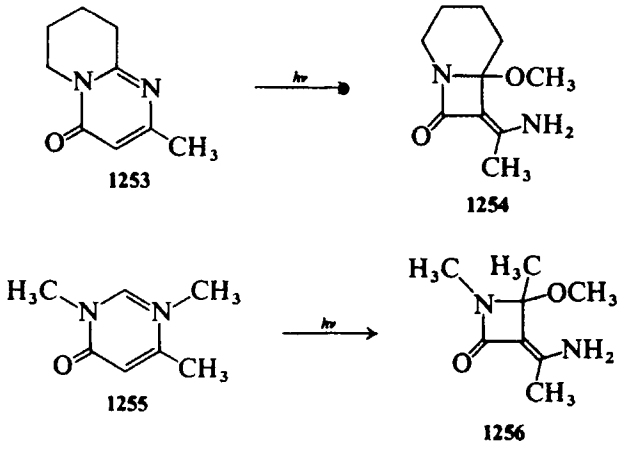


Figure 239

Additional irradiation for 18 hours produced the azetidinone **1249** in 42% yield, along with oxazinone **1250**. In addition, photolysis of **1251** afforded azetidinone **1252** in 50% yield. This series of reactions is presented in Figure 237. A mechanism for these reactions is illustrated in Figure 238.

Yamazaki and co-workers found that 4-pyrimidones could be photolyzed to azetidinones in alcohol solution.[295,296] For example, irradiation of **1253** in methanol afforded azetidinone **1254** in 6% yield. Similarly, **1252** was photolyzed in methanol to give **1256** in 57% yield. This sequence of reactions is presented in Figure 239, and a mechanism is illustrated in Figure 240.

Maruyama and co-workers investigated the photolysis of succinimides.[297] For example, irradiation of **1257** in acetonitrile with a 120-W low pressure mercury lamp for 7 hours afforded a 43% yield of **1258**. Similarly, **1259** was irradiated to give **1260** in 51% yield. These reactions are presented in Figure 241.

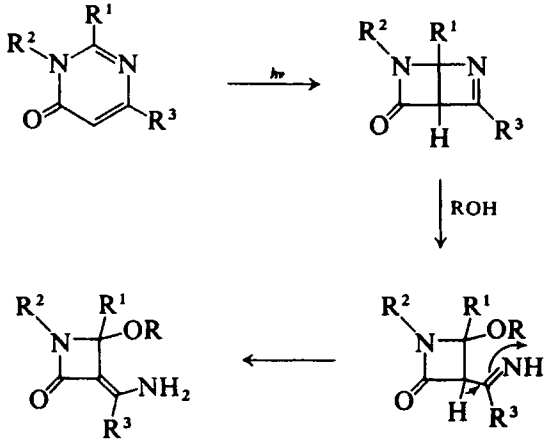


Figure 240

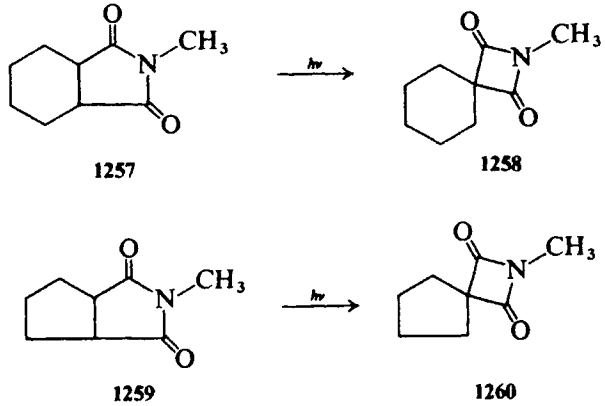


Figure 241

V. The Oxidation of Azetidines (XVII → VI)

Wasserman and Lipshutz reported that the anion **1261a**, derived from the reaction of **1261** with two equivalents of lithium diisopropylamide (LDA), could be trapped with oxygen to afford the hydroperoxy acid dilithium salt **1262**. This was acidified with *p*-toluenesulfonic acid to give the azetidinone **1263** in 50–61% yield.[298,229] This reaction sequence is presented in Figure 242.

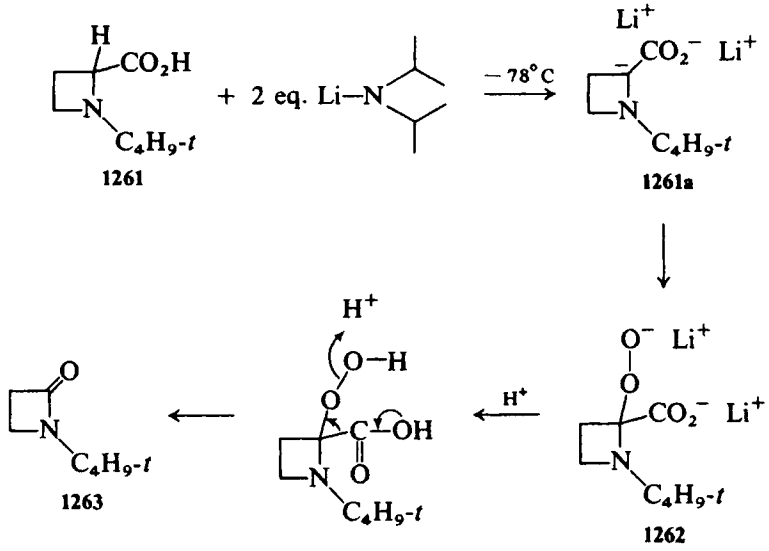


Figure 242

Wasserman and co-workers reported a modification of the azetidinone anion oxygenation.[300] For example, the reaction of **1264** with LDA and *t*-butyldimethyl-

chlorosilane afforded the enaminoketene acetal intermediate **1265**, which was oxygenated and treated with aqueous ammonium chloride to give azetidinone **1266** in 56% yield. This transformation is illustrated in Figure 243.

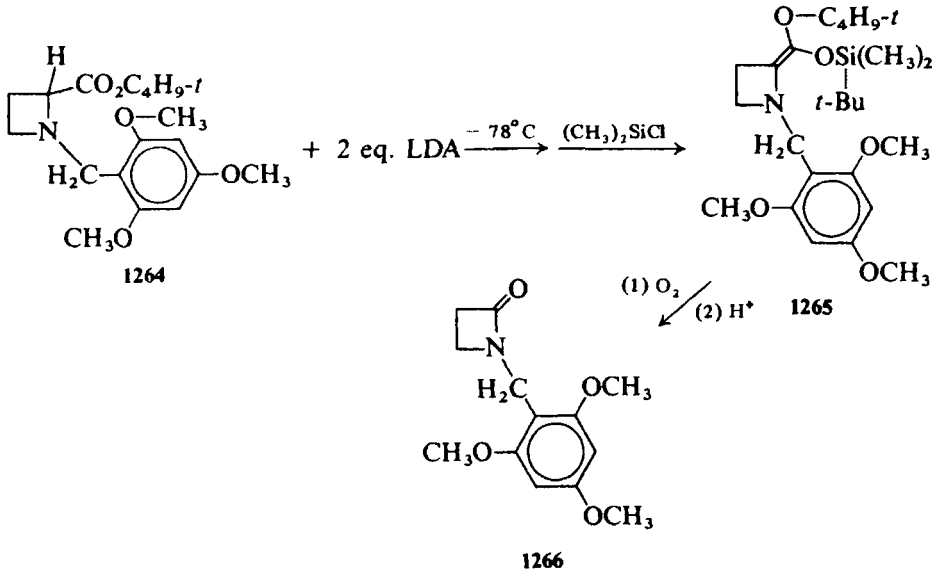


Figure 243

Wasserman and Tremper[301] found that **1267** reacted with an excess of oxalyl chloride and 70% perchloric acid to afford the azetidinium perchlorate **1268**. The intermediate **1268** was treated with *m*-chloroperbenzoic acid (MCPA), followed by pyridine, to give azetidinone **1269** in 70% yield. This reaction is presented in Figure 244.

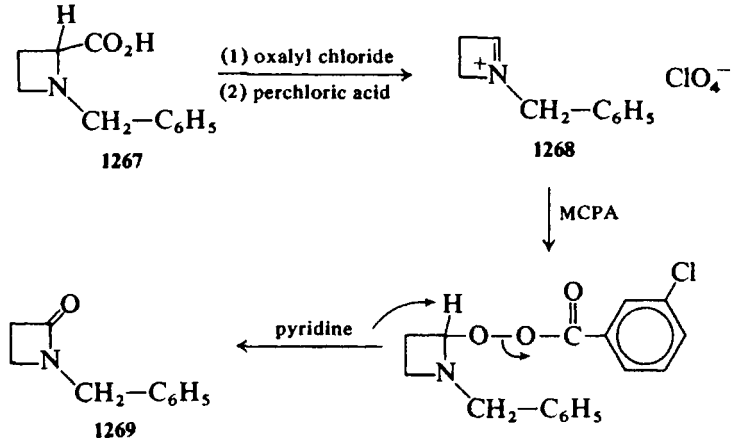


Figure 244

The azetidine oxidation was also applied to the construction of the nocardicin nucleus **1272**.[302] For example, **1270** reacted with oxalyl chloride and perchloric acid, followed by MCPA, to afford azetidinone **1271** in 53% yield. Azetidinone **1271** was then converted to the nocardicin nucleus **1272** (Figure 245).

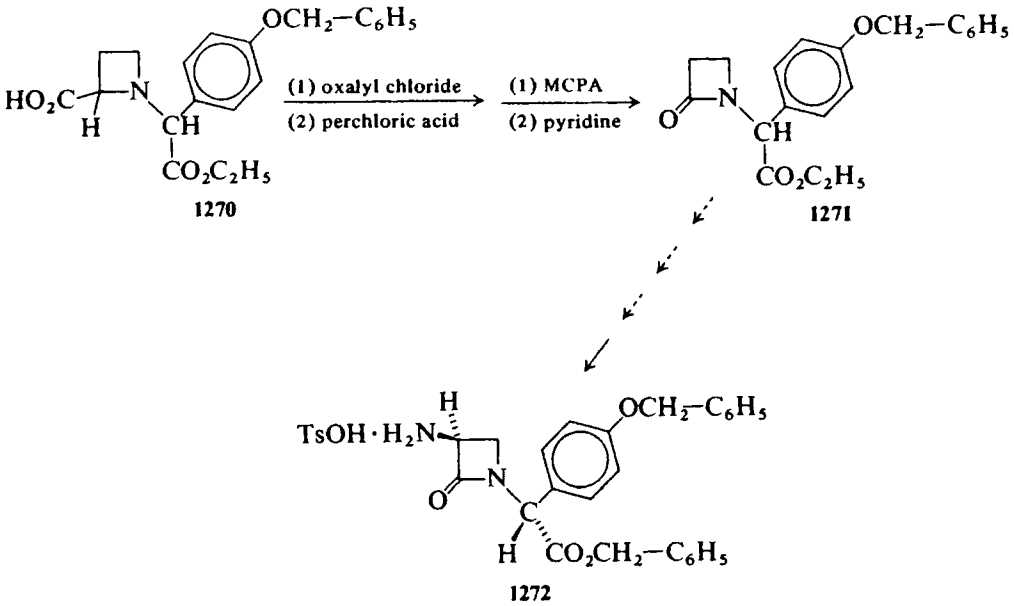


Figure 245

Acknowledgement: The author wishes to express his appreciation to Ms. Susan Lanham for the preparation of this manuscript.

VI. REFERENCES

1. A. Fleming, *Brit. J. Exp. Pathol.*, **10**, 226 (1929).
2. H. W. Florey, E. B. Chain, N. G. Heatley, M. A. Jennings, A. G. Sanders, E. P. Abraham, and M. E. Florey, *Antibiotics*, Vol. 2, Oxford University Press, London and New York, 1949.
3. (a) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, 79, 377 (1961); (b) D. C. Hodgkin and E. N. Maslen, *Biochem. J.*, 79, 393 (1961).
4. (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark and J. G. Whitney, *J. Am. Chem. Soc.*, 93, 2308 (1971); (b) E. O. Stapley, D. Hendlin, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, H. B. Woodruff, T. W. Miller, G. Albers-Schonberg, B. H. Arison and J. L. Smith, 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abs. No. 8 (1971).
5. J. S. Kahan, F. M. Kahan, E. O. Stapley, R. T. Coegelman, and S. Hernandez, U.S. Patent 3950357.
6. A. G. Brown, D. Butterworth, M. Cole, G. Hanscomb, J. D. Hood, and C. Reading, *J. Antibiotics*, **24**, 668 (1976).

7. H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosoda, Y. Kubochi, E. Iguchi, and H. Imanaka, *J. Antibiotics*, **24**, 492 (1976).
8. H. Staudinger, *Liebigs Ann. Chem.*, **356**, 51 (1907).
9. H. Staudinger and H. W. Klever, *Ber. Itsch. Chem. Ges.*, **39**, 968 (1906).
10. H. Staudinger, H. W. Klever, and P. Kober, *Liebigs Ann. Chem.*, **374**, 1 (1910).
11. A. Rachman, M. Sami Khan, and M. C. Cabaleiro, *Chem. Ind.*, 1423 (1962).
12. E. Ziegler and G. Kleinberg, *Monatsch. Chem.*, **96**, 1296 (1965).
13. H. Staudinger and S. Jelagin, *Chem. Ber.*, **44**, 365 (1911).
14. G. Kresze and A. Trede, *Tetrahedron*, **19**, 133 (1963).
15. J. C. Sheehan and E. J. Corey, "The Synthesis of β-Lactams," in R. Adams, Ed., *Organic Reactions*, Vol. 9, Wiley, New York, 1957, p. 388.
16. J. A. Moore, "Trimethyleneimines," in A. Weissberger, Ed., *Heterocyclic Compounds with Three and Four Membered Rings*, Part II, Wiley, New York, 1964, p. 885.
17. W. Brady and E. F. Hull, Jr., *J. Am. Chem. Soc.*, **92**, 6256 (1968).
18. R. Hull, *J. Chem. Soc. (C)*, 1154 (1967).
19. R. H. Holly and A. D. Holly, *J. Am. Chem. Soc.*, **73**, 3172 (1951).
20. H. T. Clarke, J. R. Robinson, and R. Robinson, *The Chemistry of Penicillin*, Princeton University Press, 1949.
21. A. K. Bose and I. Kugajevsky, *Tetrahedron*, **23**, 957 (1967).
22. (a) C. Metzger and J. Kurz, *Chem. Ber.*, **104**, 50 (1971); (b) W. T. Brady, E. D. Dorsey, and E. H. Parry III, *J. Org. Chem.*, **34**, 2846 (1969).
23. F. Duran and L. Ghosez, *Tetrahedron Lett.*, 245 (1970).
24. A. K. Bose, C. S. Narayanan, and M. S. Manhas, *Chem. Commun.*, 975 (1970).
25. D. A. Nelson, *Tetrahedron Lett.*, 2543 (1971).
26. W. T. Brady and R. A. Owens, *Tetrahedron Lett.*, 1553 (1976).
27. L. Birkofer and J. Schramm, *Liebigs Ann. Chem.*, 760 (1977).
28. I. Hoppe and V. Schollkopf, *Chem. Ber.*, **109**, 482 (1976).
29. D. F. Sullivan, D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.*, **41**, 112 (1976).
30. H. W. Moore, L. Hernandez, and A. Sing, *J. Am. Chem. Soc.*, **98**, 3728 (1976).
31. D. Kunert, R. Chambers, F. Mercer, L. Hernandez, Jr., and H. W. Moore, *Tetrahedron Lett.*, 929 (1978).
32. W. Weyler, W. Duncan, and H. W. Moore, *J. Am. Chem. Soc.*, **97**, 6187 (1975).
33. R. Chambers, D. Kunert, L. Hernandez, Jr., F. Mercer, and H. W. Moore, *Tetrahedron Lett.*, 933 (1978).
34. H. W. Moore, L. Hernandez, Jr., and R. Chambers, *J. Am. Chem. Soc.*, **100**, 2245 (1978).
35. Z. Lysenko, M. M. Joullie, I. Miura, and R. Rodebaugh, *Tetrahedron Lett.*, 1705 (1977).
36. E. Schaumann and H. Mrotzek, *Chem. Ber.*, **111**, 661 (1978).
37. (a) V. Georgian, S. K. Boyer, and B. Edwards, *Heterocycles*, **7**, 1003 (1977); (b) V. Georgian, S. K. Boyer, and B. Edwards, *J. Org. Chem.*, **45**, 1686 (1980).
38. J. L. Luche and H. B. Kagan, *Bull. Soc. Chim. France*, **6**, 2450 (1968).
39. J. L. Luche, H. B. Kagan, G. Tsoucaris, C. DeRango, and C. Zelwer, *Tetrahedron*, **24**, 1275 (1968).
40. J. L. Luche and H. B. Kagan, *Tetrahedron Lett.*, 3661 (1970).
41. J. L. Luche and H. B. Kagan, *Tetrahedron Lett.*, 3665 (1970).

42. A. M. VanLeusen, and J. F. Arens, *Rec. Trav. Chim. Pays. Bas*, **78**, 551 (1959).
43. T. Kametani, K. Kigosawa, M. Hiiragi, K. Wakisaka, H. Sugi, and K. Tanigawa, *Heterocycles*, **12**, 735 (1979).
44. H. G. Viehe, B. LeClef, and A. Elgavi, *Angew. Chem.*, **89**, 189 (1977).
45. A. Colens and L. Ghosez, *Nouv. J. Chim.*, **1**, 371 (1977).
46. R. A. Olofson, R. K. VanderMeer, and S. Stournas, *J. Am. Chem. Soc.*, **93**, 1544 (1971).
47. E. J. Corey and J. Streith, *J. Am. Chem. Soc.*, **86**, 950 (1964).
48. G. Kretscher and R. Warrener, *Tetrahedron Lett.*, 1335 (1975).
49. A. O. Fitton, J. R. Frost, P. G. Houghton, and H. Suschitzky, *J. Chem. Soc. Perkin*, **I**, 1450 (1977).
50. M. Rai, K. Krishan, and A. Singh, *Ind. J. Chem.*, **16B**, 832 (1978).
51. D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.*, **42**, 376 (1977).
52. M. D. Bachi and M. Rothfield, *J. Chem. Soc. Perkin 2*, 2326 (1972).
53. J. J. Barr and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 788 (1975).
54. R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem. Int. Ed.*, **7**, 826 (1968).
55. M. Kinugasa and S. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 466 (1972).
56. L. K. Ding and W. J. Irwin, *J. Chem. Soc. Perkin 1*, 2382 (1976).
57. C. Belzecki and Z. Krawczyk, *J. Chem. Soc., Chem. Commun.*, 302 (1977).
58. Z. Krawczyk and C. Belzecki, *Polish J. Chem.*, **53**, 643 (1979).
59. J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, **73**, 1204 (1951).
60. J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, **73**, 4367 (1951).
61. J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach, and J. J. Ryan, *J. Am. Chem. Soc.*, **72**, 3828 (1950).
62. J. C. Sheehan and G. D. Laubach, *J. Am. Chem. Soc.*, **73**, 4376 (1951).
63. A. K. Bose, G. Spiegellman, and M. S. Manhas, *J. Am. Chem. Soc.*, **90**, 4506 (1968).
64. A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Chem. Soc. (C)*, 188, 1971.
65. A. K. Bose, J. L. Fahey, and M. S. Manhas, *J. Heterocyclic Chem.*, **10**, 791 (1973).
66. A. K. Bose, J. C. Kapur, and M. S. Manhas, *Synthesis*, 891 (1974).
67. (a) A. K. Bose, B. Ram, W. A. Hoffman III, A. J. Hutchison, and M. S. Manhas, *J. Heterocyclic Chem.*, **16**, 1313 (1979); (b) A. K. Bose, W. A. Hoffman III, and M. S. Manhas, *J. Chem. Soc. Perkin 1*, 2343 (1976).
68. A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla, and B. Dayal, *J. Org. Chem.*, **39**, 2877 (1974).
69. A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
70. A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Lett.*, 3167 (1971).
71. A. K. Bose, K. H. Chiang, and M. S. Manhas, *Tetrahedron Lett.*, 4091 (1972).
72. M. S. Manhas, J. S. Chib, Y. J. Chiang, and A. K. Bose, *Tetrahedron*, **25**, 4421 (1969).
73. A. K. Bose, S. D. Sharma, J. C. Kapur, and M. S. Manhas, *Synthesis*, 216 (1973).
74. A. K. Bose, J. C. Kapur, S. G. Amin, and M. S. Manhas, *Tetrahedron Lett.*, 1917 (1974).
75. A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 2319 (1973).
76. M. S. Manhas, B. Lal, S. G. Amin, and A. K. Bose, *Synth. Commun.* **6**, 435 (1976).
77. T. Kametani, S. Yokohama, Y. Shiratori, S. Aihara, and F. Fukomoto, *Heterocycles*, **12**, 405 (1979).
78. S. D. Sharma, G. Singh, and P. K. Gupta, *Ind. J. Chem.*, **16B**, 74 (1978).

79. E. Ziegler, T. Wimmer, and H. Mittelback, *Mh. Chem.*, **99**, 2128 (1968).
80. D. A. Nelson, *J. Org. Chem.*, **37**, 1447 (1972).
81. M. S. Manhas, S. G. Amin, B. Ram, and A. K. Bose, *Synthesis*, 689 (1976).
82. M. S. Manhas, H. P. S. Chawla, S. G. Amin, and A. K. Bose, *Synthesis*, 407 (1977).
83. S. G. Amin, R. D. Glazer, M. S. Manhas, *Synthesis*, 210 (1979).
84. A. K. Bose, H. P. S. Chawla, B. Dayal, and M. S, Manhas, *Tetrahedron Lett.*, 2503 (1973).
85. A. K. Bose, M. S. Manhas, H. P. S. Chawia, and B. Dayal, *J. Chem. Soc. Perkin 1*, 1880 (1975).
86. A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 3797 (1973).
87. A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *J. Org. Chem.*, **39**, 312 (1974).
88. S. D. Sharma and P. K. Gupta, *Tetrahedron Lett.*, 4587 (1978).
89. S. D. Sharma, Sunita, and P. K. Gupta, *Tetrahedron Lett.*, 1265 (1979).
90. N. J. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).
91. A. K. Bose, B. Ram, S. G. Amin, L. Mukkavill, J. E. Vincent, and M. S. Manhas, *Synthesis*, 543 (1979).
92. R. A. Firestone, N. S. Maciegewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).
93. R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645 (1973).
94. R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4649 (1973).
95. N. G. Steinberg, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron Lett.*, 3567 (1974).
96. R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4653 (1973).
97. L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974).
98. R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).
99. W. F. Huffman, K. G. Holden, T. F. Buckley III, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, **99**, 2352 (1977).
100. D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *J. Am. Chem. Soc.*, **99**, 2353 (1977).
101. (a) T. Doyle, B. Belleau, B. Y. Luh, C. F. Ferrari, and M. P. Cunningham, *Can. J. Chem.*, **55**, 468 (1977); (b) T. Doyle, B. Belleau, B. Y. Luhm, T. T. Oonway, M. Menard, J. L. Douglas, D. Chu, G. Lim, L. R. Morris, P. Rivest, and M. Casey, *Can. J. Chem.*, **55**, 484 (1977).
102. G. Just and R. Zamboni, *Can. J. Chem.*, **56**, 2720 (1978).
103. G. Just and R. Zamboni, *Can. J. Chem.*, **56**, 2725 (1978).
104. G. Just, A. Vgolini, and R. Zamboni, *Syn. Commun.*, **9**, 117 (1979).
105. M. D. Bachi and J. Vaya, *J. Org. Chem.*, **44**, 4393 (1979).
106. J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and J. H. Fried, *Tetrahedron Lett.*, 2031 (1974).
107. T. Kamiya, T. Oku, O. Nakaguchi, H. Takeno, and M. Hashimoto, *Tetrahedron Lett.*, 5119 (1978).
108. M. Sekiya and T. Morimoto, *Chem. Pharm. Bull.*, **23**, 2353 (1975).
109. R. Lattrell and G. Lohaus, *Liebigs Ann. Chem.*, 870 (1974).
110. D. A. Neson, *J. Org. Chem.*, **37**, 1447 (1972).
111. E. Ziegler, T. Wimmer, and H. Mittelbach, *Monatsh. Chem.*, **99**, 2128 (1968).
112. T. Morimoto and M. Sekiya, *Chem. Pharm. Bull.*, **24**, 1935 (1976).

113. R. L. Bentley and H. Suschitzky, *J. Chem. Soc. Perkin 1*, 1725 (1976).
114. W. T. Brady and R. A. Owens, *J. Heterocyclic Chem.*, **14**, 179 (1977).
115. T. Minami, M. Ishida, and T. Agawa, *J. Chem. Soc., Chem. Commun.*, 12 (1978).
116. K. H. M. Hassan and F. M. Atta, *Ind. J. Chem., Sec. B*, 1073 (1978).
117. M. A. Abbady, K. H. M. Hassan, and M. A. El-Maghraby, *Ind. J. Chem., Sec. B*, 499 (1978).
118. K. M. Hassan and M. A. Abbady, *Ind. J. Chem., Sec. B*, **18**, 44 (1979).
119. V. K. Burger, F. Hein, H. Schickaneder, and J. Firl, *Chemiker.*
120. A. K. Bose, B. Lal, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 2633 (1974).
121. A. K. Bose, M. Tsai, and J. C. Kapur, *Tetrahedron Lett.*, 3547 (1974).
122. A. K. Bose and J. C. Kapur, *Tetrahedron Lett.*, 1811 (1973).
123. A. K. Bose, M. Tsai, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 3851 (1973).
124. A. K. Bose, M. Tsai, J. C. Kapur, and M. S. Manhas, *Tetrahedron*, **29**, 2355 (1973).
125. K. M. Hassan, A. K. El-Shafei, and H. S. El-Kashef, *Z. Naturforsch (B)*, **33B**, 1515 (1978).
126. A. M. Osman, K. M. Hassan, M. A. El-Maghraby, H. S. El-Kasheff, and A. M. Abdel-Mawgoud, *J. Prakt. Chem.*, **320**, 482 (1978).
127. L. Paul and K. Zieloff, *Chem. Ber.*, 1431 (1966).
128. L. Paul, A. Draeger, and G. Hilgetag, *Chem. Ber.*, 1957 (1966).
129. M. D. Bachi and O. Goldberg, *J. Chem. Soc. Perkin 2*, 2332 (1972).
130. M. D. Bachi and O. Goldberg, *J. Chem. Soc. Perkin 1*, 1184 (1974).
131. M. D. Bachi and K. J. Ross-Petersen, *J. Chem. Soc., Chem. Commun.*, 12 (1974).
132. M. D. Bachi and O. Goldberg, *J. Chem. Soc., Chem. Commun.*, 319 (1972).
133. H. Bohme, S. Ebel, and K. Hartke, *Chem. Ber.*, **98**, 1463 (1965).
134. V. R. Lattrell, *Angew. Chem.*, **85**, 983 (1973).
135. D. Hoppe and M. Kloft, *Tetrahedron Lett.*, 2145 (1977).
136. M. Kloft and D. Hoppe, *Tetrahedron Lett.*, 2141 (1977).
137. A. K. Bose, B. Dayal, J. C. Kapur, B. Lal, and M. S. Manhas, *Tetrahedron Lett.*, 3135 (1974).
138. A. K. Bose and J. L. Fahey, *J. Org. Chem.*, **39**, 115 (1974).
139. A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Lett.*, 2823 (1972).
140. B. Paul, P. Polczynski, and G. Hilgetag, *Chem. Ber.*, 2761 (1967).
141. T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, K. Wakisaka, K. Tanigawa, and H. Sugi, *Heterocycles*, **12**, 741 (1979).
142. M. S. Manhas, S. G. Amin, H. P. S. Chawla, and A. K. Bose, *J. Heterocyclic Chem.*, **15**, 601 (1978).
143. M. S. Manhas, S. G. Amin, and R. D. Glazen, *J. Heterocyclic Chem.*, **16**, 283 (1979).
144. T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, H. Sugi, and K. Tanigawa, *Heterocycles*, **12**, 795 (1979).
145. M. Perelman and S. A. Mizsak, *J. Am. Chem. Soc.*, **84**, 4988 (1962).
146. G. Opitz and J. Koch, *Angew. Chem.*, **75**, 167 (1963).
147. R. F. Abdulla and K. H. Fuhr, *J. Med. Chem.*, **18**, 625 (1975).
148. (a) R. Graf, *Liebigs Ann. Chem.*, **661**, 111 (1963); (b) for a review see J. Rasmussen and A. Hassner, *Chem. Rev.*, **76**, 389 (1976).
149. F. Effenberger and R. Fleiter, *Angew. Chem.*, **75**, 450 (1963).
150. F. Effenberger and R. Fleiter, *Chem. Ber.*, **97**, 1576 (1964).

151. E. F. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966).
152. E. F. Moriconi and J. F. Kelly, *J. Am. Chem. Soc.*, **88**, 3657 (1966).
153. E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).
154. R. Hoffman and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).
155. E. J. Moriconi and C. C. Jalandoni, *J. Org. Chem.*, **35**, 2073 (1970).
156. T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).
157. H. Bestian, H. Biener, K. Clauss, and H. Heyn, *Ann. Chem.*, **718**, 94 (1968).
158. T. Haug, F. Lohse, K. Metzger, and H. Batzer, *Helv. Chem. Acta*, **51**, 2069 (1968).
159. P. Goebel and K. Clauss, *Ann. Chem.*, **722**, 122 (1969).
160. K. Clauss, *Ann. Chem.*, **722**, 110 (1969).
161. R. Lattrell, *Ann. Chem.*, **722**, 132 (1969).
162. F. Effenberger, P. Fischer, G. Prosell, and G. Keifer, *Chem. Ber.*, **104**, 1987 (1971).
163. F. Effenberger, G. Prossel, and P. Fischer, *Chem. Ber.*, **104**, 2002 (1971).
164. H. J. Friedrich, *Tetrahedron Lett.*, 2981 (1971).
165. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).
166. K. Clauss, *Tetrahedron Lett.*, 1271 (1974).
167. K. Clauss, D. Grimm, and G. Prossel, *Ann. Chem.*, 539 (1974).
168. K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.*, **21**, 1090 (1973).
169. K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.*, **21**, 1305 (1973).
170. G. T. Furst, M. A. Wachsman, J. Pieroni, J. G. White, and E. F. Moriconi, *Tetrahedron*, **29**, 1675 (1973).
171. T. J. Barton and R. J. Rogido, *J. Chem. Soc., Chem. Commun.*, 878 (1972).
172. T. J. Barton and R. J. Rogido, *Tetrahedron Lett.*, 3901 (1972).
173. J. C. Martin, P. L. Carter, and J. L. Chitwood, *J. Org. Chem.*, **36**, 2225 (1971).
174. P. H. Mazzocchi, T. Halchak, and H. J. Tamburin, *J. Org. Chem.*, **41**, 2808 (1976).
175. R. Lattrell, *Ann. Chem.*, **722**, 142 (1969).
176. J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris, and R. H. Meen, *J. Org. Chem.*, **36**, 2205 (1971).
177. T. Mukaiyama, R. Yoda, and I. Kuwajima, *Tetrahedron Letters*, 6247 (1966).
178. R. W. Hoffman, V. Bressel, J. Gehlhaus, and H. Hauser, *Chem. Ber.* **104**, 873 (1971).
179. N. Vd-Din, J. Riegl, and L. Skattebol, *J. Chem. Soc., Chem. Commun.*, **271** (1973).
180. H. Staudinger, H. W. Klever, and P. Kober, *Liebigs Ann. Chem.*, **374**, 1 (1910).
181. J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1262 (1957).
182. J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **81**, 3089 (1959).
183. J. E. Dolfini, J. Schwartz, and F. Weisenborn, *J. Org. Chem.*, **34**, 1582 (1969).
184. R. Heymes, G. Amiard, and G. Nomine, *C. R. Acad. Sci. Paris*, **263**, 170 (1966).
185. G. Nomine, *Chim. Therapeut.*, **6**, 53 (1971).
186. D. G. Melillo, I. Shinkai, T. Liv, K. Ryan, and M. Sletzinger, *Tetrahedron Lett.*, 2783 (1980).
187. E. Simova and B. Kurtev, *Monatsh. Chem.*, **96**, 722 (1965).
188. C. Ivanov and A. Dobrev, *Monatsh. Chem.*, **96**, 1746 (1965).
189. A. Dobrev and C. Ivanov, *Chem. Ber.*, **104**, 981 (1971).
190. K. K. Prasad and T. Petrizilka, *Helv. Chim. Acta*, **58**, 2504 (1975).
191. E. Raude and D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, **16**, 544 (1977).

192. R. Breckpot, *Bull. Soc. Chim. Belg.*, **32**, 412 (1923).
193. S. Searles, Jr. and R. E. Wann, *Chem. Ind.*, **51**, 2097 (1964).
194. G. Cignarella, G. F. Cristiani, and E. Testa, *Liebigs Ann. Chem.*, **661**, 181 (1963).
195. E. Testa and L. Fontanella, *Liebigs Ann. Chem.*, **661**, 187 (1963).
196. R. H. Earle, Jr., D. T. Hurst, and M. Viney, *J. Chem. Soc. (C)*, 2094 (1969).
197. E. Bellasio, A. Vigevani, and G. Cristiani, *Farm. Ed. Sci.*, 409 (1970).
198. L. Birkofer and J. Schramm, *Liebigs Ann. Chem.*, 2195 (1975).
199. E. Simova, M. Mladenova, B. Kurtev, *Izev. Khum. Nauki Bulgar. Akad. Nauk.*, **3**, 497 (1970).
200. K. Matsui and M. Motoi, *Bull. Chem. Soc. Japan*, **46**, 1755 (1973).
201. (a) R. B. Woodward, "Recent Advances in the Chemistry of Natural Products," Nobel Lecture, December 11, 1964, Stockholm, Sweden; (b) R. B. Woodward, *Science*, **153**, 487 (1966).
202. H. Girman and M. A. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).
203. H. B. Kagan, J. Basselier, and J. Luche, *Tetrahedron Lett.*, 941 (1964).
204. J. Luche and H. B. Kagan, *Bull. Soc. Chim. France*, 3500 (1969).
205. F. Dardoize, J. L. Moreau, and M. Gaudemar, *Bull. Soc. Chim. France*, 1668 (1973).
206. H. B. Kagan, A. Noreau, and M. Heng Suen, *Mem. Pres. Soc. Chim. France*, 1457 (1965).
207. S. M. Deshpande, A. K. Mukerjee, and P. M. Dey, *Ind. J. Chem.*, **6**, 238 (1968).
208. E. Cuingnet, D. Poulain, and M. Tarterat-Adalberon, *Bull. Soc. Chim. France*, 514 (1969).
209. S. Mohan, P. S. Sethi, and A. L. Kapoor, *J. Ind. Chem. Soc.*, **48**, 11 (1971).
210. M. M. Dardoize, J. L. Moreau, and M. Gaudeman, *C. R. Acad. Sci. Paris*, 268 (1969).
211. I. Ojima, S. Inaba, and K. Yoshida, *Tetrahedron Lett.*, 3643 (1977).
212. I. Ojima and S. Inaba, *Tetrahedron Lett.*, 2077 (1980).
213. I. Ojima and S. Inaba, *Tetrahedron Lett.*, 208 (1980).
214. P. K. Wong, M. Madhauarao, D. F. Marten, and M. Rosenblum, *J. Am. Chem. Soc.*, **99**, 2823 (1977).
215. M. Mori, K. Chiba, M. Okita, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 698 (1979).
216. A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 327 (1973).
217. I. L. Knunyants and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel Khim. Nauk*, 1037 (1955).
218. I. L. Knunyants and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel Khim. Nauk*, 834 (1957).
219. I. L. Knunyants, E. E. Rytslin, and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel Khim. Nauk*, 527 (1960).
220. I. L. Knunyants, E. E. Rytslin, and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel Khim. Nauk*, 83 (1961).
221. S. Sarel and R. Ben Shoshan, *Bull. Res. Council Israel (A)*, **6**, 298 (1957).
222. A. K. Bose, B. Anjaneyula, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
223. B. J. R. Nicolaus, E. Bellasio, G. Pagani, L. Mariani, and E. Testa, *Helv. Chim. Acta*, **48**, 1867 (1965).
224. E. Bellasio, G. Cristiani, and E. Testa, *Farm. Ed. Sci.* 3 (1970).
225. E. Bellasio, G. Cristiani, and E. Testa, *Ann. Chim.*, **59**, 1122 (1969).
226. F. Merger, U.S. Patent 3,711,469 (1973).

227. S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, **97**, 5008 (1975).
228. S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, **97**, 5010 (1975).
229. J. E. Baldwin, A. Au, M. Christie, S. B. Haber, and D. Hesson, *J. Am. Chem. Soc.*, **97**, 5957 (1975).
230. J. E. Baldwin, M. A. Christie, S. B. Haber, and L. I. Kruse, *J. Am. Chem. Soc.*, **98**, 3045 (1976).
231. G. A. Koppel, L. McShane, F. Jose, and R. D. G. Cooper, *J. Am. Chem. Soc.*, **100**, 3933 (1978).
232. R. D. G. Cooper, F. Jose, L. McShane, and G. A. Koppel, *Tetrahedron Lett.*, 2243 (1978).
233. G. A. Koppel and R. D. G. Cooper, U.S. Patent 4,203,896 (1980).
234. A. I. Scott, S. E. Yoo, S. K. Chung, and J. A. Lacadie, *Tetrahedron Lett.*, 1137 (1976).
235. P. C. Mattingly, J. F. Kerwsin, Jr., and M. J. Miller, *J. Am. Chem. Soc.*, **101**, 3983 (1979).
236. H. H. Wasserman, D. J. Hlasta, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, 2031 (1979).
237. K. Hirai and Y. Iwano, *Tetrahedron Lett.*, 2031 (1979).
238. O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, **89**, 4243 (1967).
239. O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, **90**, 2333 (1968).
240. J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).
241. J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **73**, 1761 (1951).
242. T. Okawara and K. Harada, *J. Org. Chem.*, **37**, 3286 (1972).
243. A. K. Bose, M. S. Manhas, and B. N. Ghosh-Mazumdar, *J. Org. Chem.*, **27**, 1458 (1962).
244. B. G. Chatterjee, P. N. Moza, and S. K. Roy, *J. Org. Chem.*, **28**, 1418 (1963).
245. B. G. Chatterjee, V. V. Rao, and B. N. G. Mazumdar, *J. Org. Chem.*, **30**, 4101 (1965).
246. B. G. Chatterjee and P. N. Moza, *J. Med. Chem.*, **9**, 259 (1966).
247. M. S. Manhas and S. J. Jen, *J. Org. Chem.*, **32**, 1246 (1967).
248. B. G. Chatterjee and V. V. Rao, *Tetrahedron*, **23**, 487 (1967).
249. H. J. Kabbe and N. Joop, *Liebigs Ann. Chem.*, **730**, 151 (1969).
250. B. G. Chatterjee, S. K. Lahiri, and R. F. Abdulla, *Z. Naturforsch.*, **25**, 675 (1970).
251. B. G. Chatterjee and N. L. Nyss, *Z. Naturforsch.*, **26**, 395 (1971).
252. R. Choudhury, *J. Ind. Chem. Soc.*, 405 (1974).
253. W. Kunz and H. Kristinsson, *Helv. Chim. Acta.*, **62**, 872 (1979).
254. K. K. Prassad and T. Petrizilka, *Helv. Chim. Acta*, **58**, 2504 (1975).
255. G. Lowe and J. Parker, *Chem. Commun.*, 577 (1971).
256. D. M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc. (C)*, 3757 (1971).
257. N. G. Johansson, B. Akermark, and B. Sjoberg, *Acta. Chem. Scand.*, **B30**, 383 (1976).
258. T. Hasegawa, M. Watabe, H. Aoyama, and Y. Omote, *Tetrahedron*, **33**, 485 (1977).
259. H. Aoyama, T. Hasegawa, M. Okazaki, and Y. Omote, *J. Chem. Soc. Perkin*, **I**, 263 (1979).
260. P. K. Sen, C. J. Veal, and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 678 (1977).
261. N. G. Johansson and B. Akermark, *Acta Chem. Scand.*, **26**, 1927 (1971).
262. N. G. Johansson, *Acta Chem. Scand.*, **27**, 1417 (1973).
263. B. Akermark, S. Bystrom, E. Florin, N. G. Johansson, and I. Lagerlund, *Acta Chem. Scand.*, **28**, 375 (1974).
264. B. Akermark, J. Chodowska-Palicka, and I. Lagerlund, *J. Organometal. Chem.*, **113**, C4 (1976).

265. J. C. Sheehan and P. I. Izzo, *J. Am. Chem. Soc.*, **71**, 4059 (1949).
266. F. Toda, T. Mitote, and K. Akagi, *Bull. Chem. Soc. Japan*, **42**, 1777 (1969).
267. J. A. Dreyrup and S. C. Clough, *J. Am. Chem. Soc.*, **91**, 4590 (1969).
268. J. A. Dreyrup and S. C. Clough, *J. Am. Chem. Soc.*, **96**, 902 (1974).
269. H. H. Wasserman and M. S. Baird, *Tetrahedron Lett.*, 3721 (1971).
270. H. H. Wasserman, H. W. Adickes, and O. E. deOchoa, *J. Am. Chem. Soc.*, **93**, 5586 (1971).
271. H. H. Wasserman and E. Glazer, *J. Org. Chem.*, **40**, 1505 (1975).
272. H. H. Wasserman and E. Glazer, *Tetrahedron Lett.*, 4855 (1973).
273. F. D. Greene, R. L. Camp, V. P. Abegg, and G. O. Pierson, *Tetrahedron Lett.*, 4091 (1973).
274. E. R. Talaty, A. E. Dupuy, C. M. Utermoehlen, and L. H. Stekoll, *J. Chem. Soc., Chem. Commun.*, 48 (1973).
275. H. Alper, C. P. Pererd, and F. R. Ahmed, *J. Am. Chem. Soc.*, **103**, 1289 (1981).
276. (a) M. F. Chasle, M. A. Feucaud, and M. H. Normant, *C. R. Acad. Sci. Paris*, 1945 (1970); (b) M. F. Chasle and A. Forcaud, *Bull. Soc. Chim. France*, 195 (1972).
277. G. Lowe and D. D. Ridley, *J. Chem. Soc., Chem. Commun.*, 328 (1973).
278. G. Lowe and D. D. Ridley, *J. Chem. Soc., Perkin Trans.*, **1**, 2024 (1973).
279. G. Lowe and H. W. Yeung, *J. Chem. Soc., Perkin Trans.*, **1**, 2907 (1973).
280. G. Stork and R. P. Szajewski, *J. Am. Chem. Soc.*, **96**, 5787 (1974).
281. D. R. Bender, L. F. Bjeldanes, D. R. Knapp, D. R. McKean, and H. Rapoport, *J. Org. Chem.*, **38**, 3439 (1973).
282. D. R. Bender, L. F. Bjeldanes, D. R. Knapp, and H. Rapoport, *J. Org. Chem.*, **40**, 1264 (1975).
283. D. Bender and H. Rapoport, *J. Org. Chem.*, **40**, 3208 (1975).
284. D. R. Bender, J. Brennan, and H. Rapoport, *J. Org. Chem.*, **43**, 3354 (1978).
285. S. N. Ege, *J. Chem. Soc. (C)*, 2624 (1969).
286. C. E. Hatch and P. Y. Johnson, *Tetrahedron Lett.*, 2719 (1974).
287. P. Y. Johnson, C. E. Hatch III, and N. R. Schmuff, *J. Chem. Soc., Chem. Commun.*, 725 (1975).
288. P. Y. Johnson and C. E. Hatch III, *J. Org. Chem.*, **40**, 3502 (1975).
289. P. Y. Johnson and C. E. Hatch III, *J. Org. Chem.*, **40**, 3510 (1975).
290. P. Y. Johnson, N. F. Schmuff, and C. E. Hatch III, *Tetrahedron Lett.*, 4089 (1975).
291. D. H. R. Barton, E. Buschmann, J. Hausler, C. W. Holzapfel, T. Shoradsky, and D. A. Taylor, *J. Chem. Soc. Perkin*, **I**, 1107 (1977).
292. T. Sheradsky and D. Zbaida, *Tetrahedron Lett.*, 2037 (1978).
293. T. Sheradsky and D. Zbaida, *J. Org. Chem.*, **45**, 2165 (1980).
294. D. S. C. Black and A. B. Boscacci, *Aust. J. Chem.*, **30**, 1109 (1977).
295. T. Yamazaki, M. Nagata, S. Hirokami, and Y. Hirai, *Heterocycles*, **9**, 505 (1978).
296. S. Hirokami, Y. Hirai, M. Nagata, T. Yamazaki, and T. Date, *J. Org. Chem.*, **45**, 2083 (1979).
297. K. Maruyama, T. Ishitoku, and Y. Kubo, *J. Am. Chem. Soc.*, **101**, 3670 (1979).
298. H. H. Wasserman and B. H. Lipschutz, *Tetrahedron Lett.*, 4611 (1975).
299. H. H. Wasserman and B. H. Lipschutz, *Tetrahedron Lett.*, 4613 (1976).
300. H. H. Wasserman, B. H. Lipschutz, and J. S. Wu, *Heterocycles*, **7**, 321 (1977).
301. H. H. Wasserman and A. W. Tremper, *Tetrahedron Lett.*, 1449 (1977).
302. H. H. Wasserman, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, 1089 (1979).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

CHAPTER III

Four-Membered Rings Containing Two Nitrogen Heteroatoms

Reinhard Richter and Henri Ulrich

The Upjohn Company, D. S. Gilmore Research Laboratories, North Haven, Connecticut

I. 1,2-Diazetines and 1,2-Diazetidines 444
1. Introduction 444
2. Methods of Preparation 445
A. Cycloaddition Reactions 445
a. [2+2] Cycloadditions 445
i. Alkenes and Azo Compounds 445
ii. Electron-Rich Alkenes and Azo Compounds 450
iii. Ketenes, Ketenimines, and Allenes 458
iv. Dimerization of Imines 470
v. Intramolecular [2+2] Cycloadditions 471
b. [3+1] Cycloadditions 476
c. Miscellaneous Cycloadditions 476
B. Ring-Closure Reactions Involving HX Abstraction 478
C. Ring Contractions 484
3. Reactions 489
A. Reactions with Retention of the Heterocycle 489
B. Ring-Opening Reactions 492
a. Thermal and Photochemical Fragmentation 492
b. Ring Opening by Chemical Agents 497
C. Molecular Rearrangements 503
4. Structure and Special Properties 506
5. References 512
II. 1,3-Diazetidines 517
1. Introduction 517
2. Methods of Preparation 520
A. Dimerization of Imines 520
B. Dimerization of Isocyanates 522
C. Cycloaddition of Isocyanates to Carbodiimides 526
D. Cycloaddition of Isocyanates to Imines 528
E. Ring-Closure Reactions 530
F. Miscellaneous Methods of Synthesis of 1,3-Diazetidines 532

3. Physical and Spectral Properties 534
4. Reactions 535
A. Fragmentation 535
B. Ring Expansion to Six-Membered-Ring Heterocycles 536
C. Nucleophylic Ring-Opening Reactions 538
5. References 542

I. 1,2-DIAZETINES AND 1,2-DIAZETIDINES

1. Introduction

Four-membered rings with two adjacent nitrogen atoms are named – following the extended Hantzsch–Widman system adopted by IUPAC – 1,2-diazetidines, 1,2-diazetines, and 1,2-diazetes, depending upon the degree of unsaturation. Replacement nomenclature (e.g., 1,2-diazacyclobutane for 1,2-diazetidine) will only be used in fused, multinuclear heterocyclic systems. Earlier names for 1,2-diazetes included aziethane and glyazine,[1] and for 1-2-diazetines the name 1,2-diazene[2] has been used.



1,2-Diazetidine



Δ^1-1,2-Diazetine



Δ^2-1,2-Diazetine



Δ^3-1,2-Diazetine



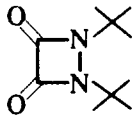
1,2-Diazete



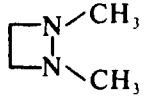
Attempts to synthesize members of this class of compounds date back over 100 years, but most of the earlier reports in the literature were later found to be wrong.[3] In 1912 Staudinger[4] described briefly the synthesis of 1,2,4,4-tetraphenyl-1,2-diazetidine-3-one from diphenylketene and azobenzene. Since then, a large number of these heterocycles has been synthesized. Up to about 1960 not more than 20–30 compounds with proven 1,2-diazetidine structure were known, but the renewed interest in these heterocycles in the last 20 years has led to a dramatic increase in the number of known compounds and to a better understanding of their chemistry and physical properties. Most of these compounds are derivatives of the fully hydrogenated heterocycle 1,2-diazetidine. Several of the unsaturated 1,2-diazetines have been synthesized in recent years. However, none of the cyclobutadiene analog (1,2-diazetes) are known to date.

By far the largest number of 1,2-diazetidine derivatives has been prepared by cycloaddition of compounds with C=C bonds (olefins, heterocumulenes, allenes) and azo compounds. Activation of both components by introducing electron-withdrawing or electron-releasing groups (reverse electron demand) adjacent to the double bond was used to facilitate the additions. Occasionally, such adducts were modified, most often with the intent of introducing double bonds into the heterocycle. Ring-closure reactions involving HX abstraction and ring contractions are other ways of synthesizing 1,2-diazetines and 1,2-diazetidines; both methods have been introduced in the last 10 years.

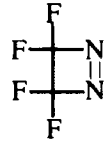
1,2-Diazetidines and 1,2-diazetines are predominantly solids, which often decompose or rearrange when heated. Several of the nonfused 1,2-diazetidines are liquids; tetrafluoro-Δ^1-1,2-diazetine is a gas at room temperature.



m.p. = 56–57°C[5]



b.p. = 70–72°C[6,7]



b.p. = Approx. −131°C[8]

Spectroscopic methods such as IR; UV; ^{1}H-, ^{13}C- and ^{19}F-nmr; esr; photoelectron (PE) and mass spectroscopy; and x-ray analysis have been used to characterize these heterocycles.

2. Methods of Preparation

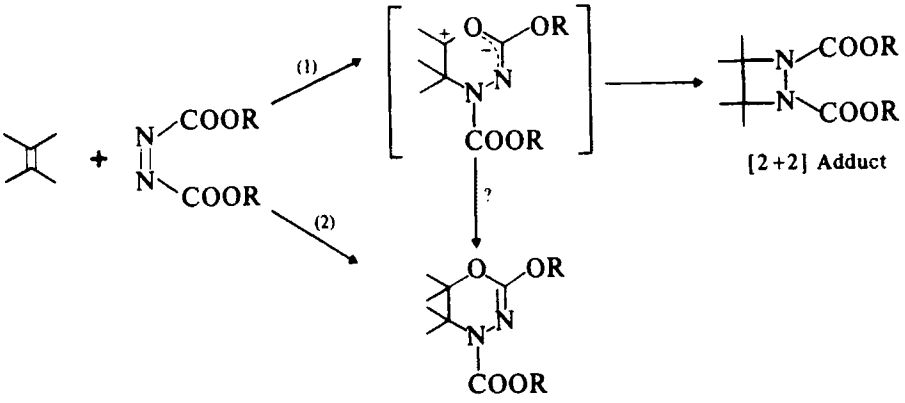
A. *Cycloaddition Reactions*

a. [2+2] CYCLOADDITIONS

i. ALKENES AND AZO COMPOUNDS. By far the largest number of 1,2-diazetidine derivatives has been prepared by [2+2] cycloaddition of olefinic components with azo compounds. These reactions require that at least one of the two components be activated by either electron-donating or electron-withdrawing groups. Typically, electron donors such as OR or NR_2 are introduced adjacent to the C=C bond (enol ethers, enamines, ketene acetals or ketene aminals), while electron-withdrawing substituents (COR, COOR, $CONR_2$, etc.) are attached to the azo group.

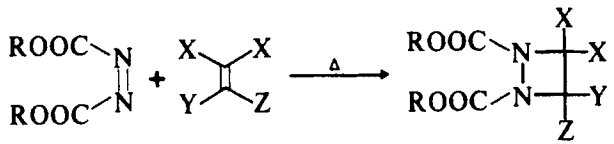
Mechanistic aspects of these reactions have been discussed in detail by E. Koerner von Gustorf et al.[9] It has been pointed out that thermally induced cycloadditions involving olefins and azodicarbonyl compounds, leading (in a $[_\pi 2_s + _\pi 2_s]$ electron process) to 1,2-diazetidines, must involve the formation of a dipolar or diradical intermediate, since a concerted process is forbidden by the Woodward–Hoffmann rules. Also possible are [2+4] cycloadditions leading to oxadiazine derivatives, in which the azodicarbonyl component reacts like a heterodiene. These Diels–Alder reactions with reverse electron demand, if carried out with an electron-rich

dienophile and an electron-poor heterodiene, are energetically favored over the [2+2] process. Experimental data support the hypothesis that a high degree of polarity and polarizability of the olefin, coupled with a high polarizing power of the dienophile, lowers the activation energy of 1,2-diazetidine formation via a dipolar intermediate. It is very likely, however, that even the [2+4] cycloaddition reactions proceed in a stepwise fashion via the same dipolar intermediate.[10]



In addition, side reactions can be expected from certain olefins, which may undergo substitution reactions with azo compounds.[11,12] The same is true for enamines or vinyl ethers with alkyl groups CH_2–R on the β-carbon, which have been found to react with CH insertion at the "indirect" allylic position, followed by shift of the double bond ("ene" reaction).[13]

A number of olefins that bear no activating groups, such as NR_2 or OR attached to the double bond, have also been used – with varying success – in cycloadditions involving azodicarbonyl compounds. A series of simple alkenes (ethylene, propene) and halogenated olefins was shown to react readily with azodicarboxylates at elevated temperatures (160–180°C) in a steel pressure reactor to yield liquid 1,2-diazetidine-1,2-dicarboxylates (**1**; see Table 1).[14–17]

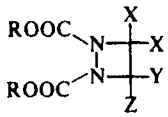


R = Alkyl
X = H, F
Y = H, Cl, F
Z = H, Cl, F, CH_3, CF_3

1

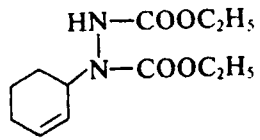
Some doubts have been cast on the validity of some of these reactions, especially those involving ethylene. Nunn and Warrener[18] reported about unsuccessful attempts to repeat the reaction of dimethyl azodicarboxylate with ethylene. No

TABLE 1. 1,2-DIAZETIDINE-1,2-DICARBOXYLATES FROM OLEFINS AND DIALKYL AZODICARBOXYLATES

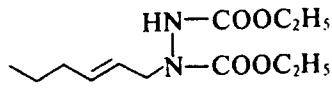


R	X	Y	Z	Yield, %	b.p., °C (mm Hg)	Ref.
CH_3	H	H	H	30.5	130–140 (4)	16
C_2H_5	H	H	H	40	153 (4)	16
$(CH_3)_2CH$	H	H	H	44.4	120 (3)	16
CH_3	H	H	Cl	26	128 (3)	16
C_2H_5	H	H	Cl	28.1	160 (3)	16
$(CH_3)_2CH$	H	H	Cl	34.1	155 (3)	16
CH_3	H	H	CH_3	41.5	98–100 (3)	16
C_2H_5	H	H	CH_3	51.7	123–125 (3)	16
$(CH_3)_2CH$	H	H	CH_3	56.5	126 (3)	16
CH_3	F	F	F	47	90 (28)	15
C_2H_5	F	F	F		66 (3)	14
$(CH_3)_2CH$	F	F	F	54	84 (3)	17
n-C_3H_7	F	F	F	41.5	120 (20)	17
$(CH_3)_2CHCH_2$	F	F	F	36	135 (10)	17
n-C_4H_9	F	F	F	40	145 (26)	17
C_2H_5	F	Cl	F	60	117 (19)	17
n-C_3H_7	F	Cl	F	28	110.5 (4)	17
$(CH_3)_2CH$	F	Cl	F	51.5	97.5 (3)	17
$(CH_3)_2CHCH_2$	F	Cl	F	21	106.5 (3)	17
n-C_4H_9	F	Cl	F	12	117.5 (3)	17
$(CH_3)_2CH$	F	H	F	44	54.5[a]	17
n-C_3H_7	F	H	F	19.7	122 (3)	17
$(CH_3)_2CHCH_2$	F	H	F	11	120 (2)	17
n-C_4H_9	F	H	F	9	130 (2)	17
$(CH_3)_2CH$	F	F	CF_3	45.5	85 (3)	17

[a] Melting point.



2

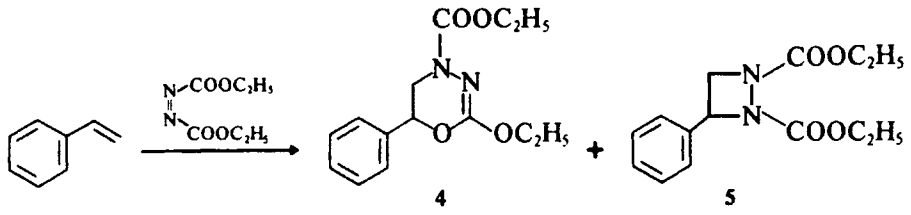


3

cycloadduct could be detected either by ^{1}H-nmr or mass spectroscopy. Cyclohexene and 1-hexene reacted with diethyl azodicarboxylate in a photochemically as well as thermally induced ene reaction, producing acyclic products **2** and **3**.[19]

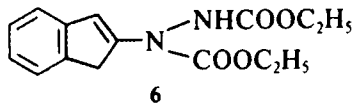
The photolysis of mixtures of styrene and diethyl azodicarboxylate gave 1,3,4-oxadiazine derivative **4** as the major product and traces of a second product, which could be the [2+2] adduct **5**.[19]

The reaction of indene with azodicarboxylate has been the subject of several investigations. A 1:1 adduct, for which structures **6** and **7** were proposed, was

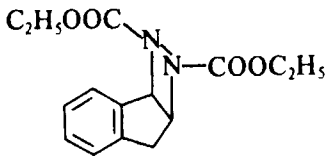


4 5

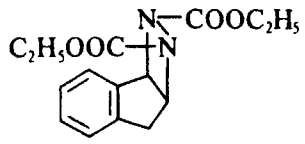
obtained with diethyl azodicarboxylate at room temperature in 80% yield after one month.[20]



6

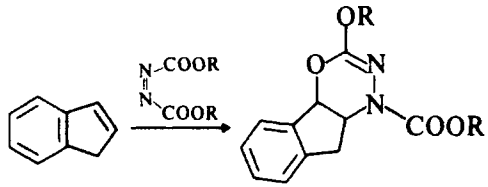


7a

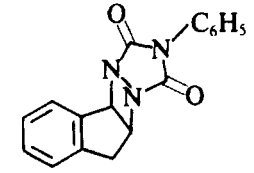


7b

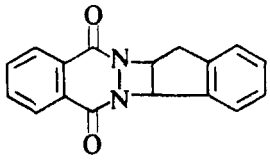
Since 2-indanone was obtained on alkaline hydrolysis of the adduct, Adler and Niklas[11] preferred structure **6**, but subsequent analysis of spectral data seemed to suggest that the adduct was **7**.[21,22] A more detailed chemical degradation led to a further revision of the structure of the adduct, which proved to be the [2+4] cycloadduct, as shown below.[9,10,23] On the other hand, indene reacts with the cis-locked azodicarbonyl compound 4-phenyl-1,2,4-triazoline-3,5-dione at room temperature to give in 34% yield the [2+2] cycloadduct **8**,[9a] yet the same triazoline dione was shown to produce a [3+2] adduct with vinyl azides.[9b] Similar adducts are obtained from two diazaquinones with styrene and indene: [2+2] cycloaddition of indene with phthalazine-1,4-dione (prepared *in situ* by lead tetraacetate oxidation of phthalhydrazide), which had been described earlier as being devoid of enophilic character,[24] produces **9** in 58% yield,[25] and pyridazine-3,6-dione (prepared *in situ* from maleic acid hydrazide and *t*-butyl hypochloride) reacts with styrene to give initially the [2+2] cycloadduct **10** in 45% yield. This product was not isolated in pure form because of its tendency to hydrolyze (with ring opening) to give **11**.[26]



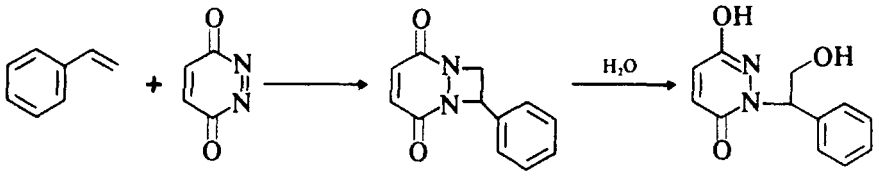
R = CH_3, C_2H_5



8
m.p. = 166–167.5°C

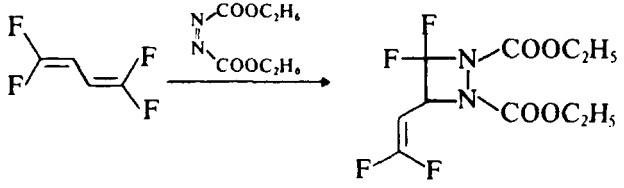


9



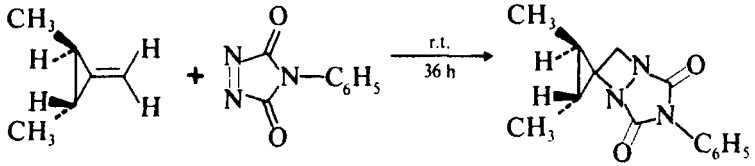
10 11

1,1,4,4-Tetrafluorobutadiene reacts with diethyl azodicarboxylate at 90°C (12 hours) at only one double bond to give the liquid [2+2] cycloadduct **12** in 12% yield.[27]



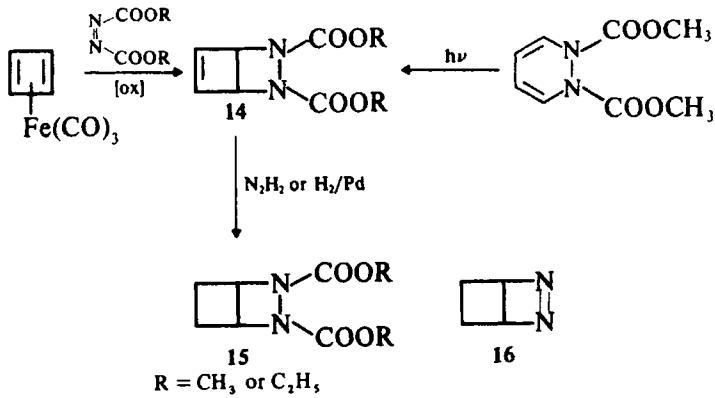
12
b.p. = 90°C

In a study involving several cycloaddition reactions of alkenylidenecyclopropanes, it was found that *trans*-2,3-dimethylmethylenecyclopropane gave a 1 : 1-adduct with 4-phenyl-1,2,4-triazoline-3,5-dione, for which structure **13** has been suggested based on spectroscopic evidence. Benzylidinecyclopropane and (4-phenylbutylidene)cyclopropane gave, with the same enophile under similar conditions, either structurally different cycloadducts or products of an "ene" reaction.[28]

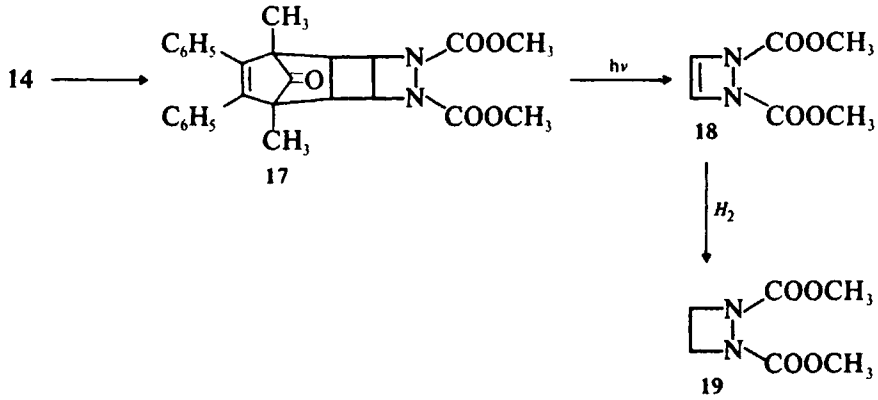


13

The reaction of cyclobutadieneironcarbonyl with dialkyl azodicarboxylates in the presence of oxidizing agents (lead tetraacetate–pyridine, ceric ammonium nitrate) has been described by two different research groups.[18,29] The products of these reactions were structurally identical with **14** (R = CH_3), derived from photochemi-

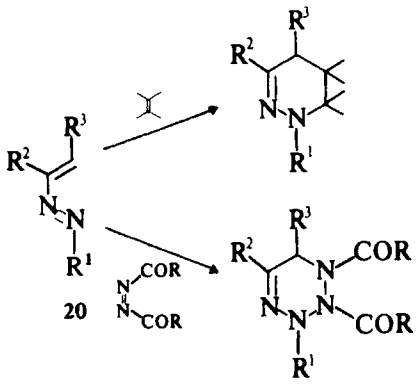


cally induced intramolecular [2+2] cycloaddition of dimethyl-1,2-dihydropyridazinedicarboxylate.[30] The cycloadduct **14** was used as the starting material for the synthesis of 2,3-diazabicyclo[2.2.0]hex-2-ene **16**, a strong-smelling liquid, via 2,3-diazabicyclo[2.2.0]hexane-2,3-dicarboxylate **15**.[30,29] Addition of 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone to **14** (R = CH_3) gave the 1 : 1 cycloadduct **17** which, on irradiation (medium pressure Hg lamp) at 0°C eliminated carbon monoxide and 1,4-dimethyl-2,3-diphenylbenzene to afford dimethyl-Δ^3-1,2-diazetine-1,2,-dicarboxylate **18** and, eventually, the tetrahydro derivative **19**.[18] All structure assignments are based on spectroscopic data; experimental details have not been published.



A number of 1,2-diazabutadienes with the general formula **20** were shown to react with alkenes at room temperature with formation of [2+4] cycloadducts (Diels–Adler adducts); the same azoalkenes (**20**) add to azodicarbonyl compounds with formation of tetrahydro-1,2,3,4-tetrazines.[31,32]

ii. ELECTRON-RICH ALKENES AND AZO COMPOUNDS. Activated alkenes with one or more electron-donating groups such as OR, SR or NR_2, attached to either one of the carbon atoms of the C=C bond, are much more susceptible to addition reactions with azo compounds than simple olefins. All that has been

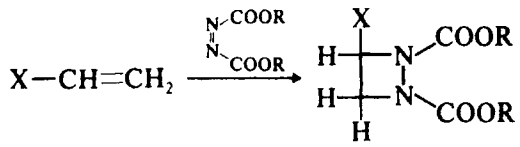


said in Section 2.i about the types of products that can be expected in reactions of olefins with azo compounds is valid here too. The formation of [2+2] and [2+4] cycloadducts, either alone or side by side, has been observed with azocarbonyl compounds; insertion into the CH bond of β-carbons of enol ethers and enamines may take place too. The cycloadditions leading to [2+4] adducts were shown to be regiospecific; i.e., the electron-deficient nitrogen of the azodicarbonyl component is always attached to the electron-rich β-carbon of the olefinic component.

In a comparison of reactions of enol ethers and enamines with bisacylazo compounds, two general trends were observed: (1) compounds with the general formula $XCH{=}CH_2$ (where X is an electron donor) tend to yield [2+2] cycloadducts; (2) α- or β-monosubstituted enol ethers and enamines ($XRC{=}CH_2$ or XCH=CHR) prefer to undergo CH insertion (substitution) on the β-carbon. A good example is the reaction between *trans*-β-piperidinostyrene and dimethyl azodicarboxylate, which yields a mixture of stereoisomeric β-substitution products instead of a [2+2] cycloadduct.[13] Enamines with two substituents on the β-carbon tend to give cycloadducts of the [2+2] type, but if the R substituent is proton carrying (e.g., R = CH_3 or CH_2R'), then "ene" reactions become possible.[13]

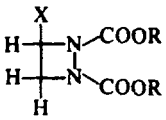
Reactions of several alkyl vinyl ethers with dialkylazodicarboxylate (neat or in solution) lead almost exclusively to the formation of [2+2] cycloadducts (**21**; see Table 2).[12,9,22] It was shown that *cis*-azodicarboxylates react much faster than the trans forms; an acceleration of addition was also observed on irradiating the reaction solutions.[9]

Vinyl acetate was also claimed to give a 1,2-diazetidine derivative with dimethyl azodicarboxylate, but subsequent experiments showed that a 1,3,4-oxadiazine derivative is formed instead.[9,10]



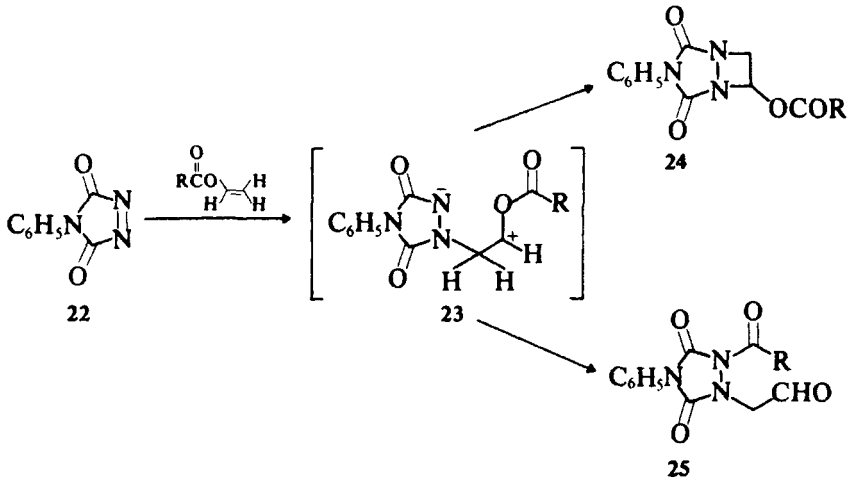
21
X = O-alkyl

TABLE 2. 1,2-DIAZETIDINE-1,2-DICARBOXYLATES (21) FROM ENOL ETHERS AND DIALKYL AZODICARBOXYLATES



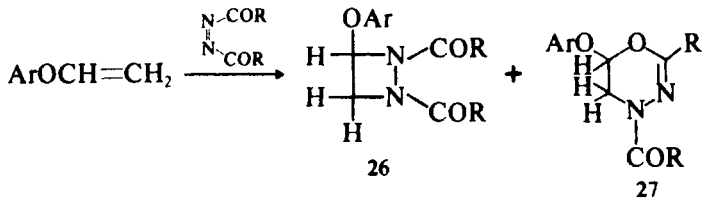
R	X	m.p. (b.p.), °C	Yield, %	Ref.
CH_3	OCH_3	(40–50/10^{-5} mm)	28	9
CH_3	OC_2H_5	(125–130/0.1 mm)	86	9, 12
CH_3	$OCH_2CH(CH_3)_2$	38	82	12
CH_3	$O(CH_2)_{17}CH_3$	90	78	12
C_2H_5	OC_2H_5	(130)	30	9

The very powerful cyclophile 4-phenyl-1,2,4-triazoline-3,5-dione (**22**) reacts with β-unsubstituted vinyl esters, such as vinyl isobutyrate, pivalate, and benzoate, to give 1,2-diazetidines **24** in low yield. The cycloadditions are accompanied by formation of 1-formylmethyl-2-acyl-4-phenyl-1,2,4-triazoline-3,5-diones **25**, which gives direct evidence for the involvement of 1,4-dipolar intermediates, such as **23**;[33] polymeric products are also formed.



R	(°C)	Yield (%)
C_6H_5		~ 7
$(CH_3)_2CH$	163–64	6.3
$(CH_3)_3C$	171–72	36%

The trend to form [2+2] cycloadducts exclusively or predominantly from β-unsubstituted alkyl vinyl ethers and azodicarboxylates or other bisacylated azo compounds is not maintained in reactions of arylvinyl ethers. Mixtures of 1,2-diazetidines **26** and 5,6-dihydro-1,3,4-oxadiazines **27** are obtained.[3,4,10] Yield determinations showed that enol ethers with increasing donor ability favored the formation of [2+2] adducts. The reactions with these enol ethers were also found to be faster than those with electron-withdrawing substituents.



26 27

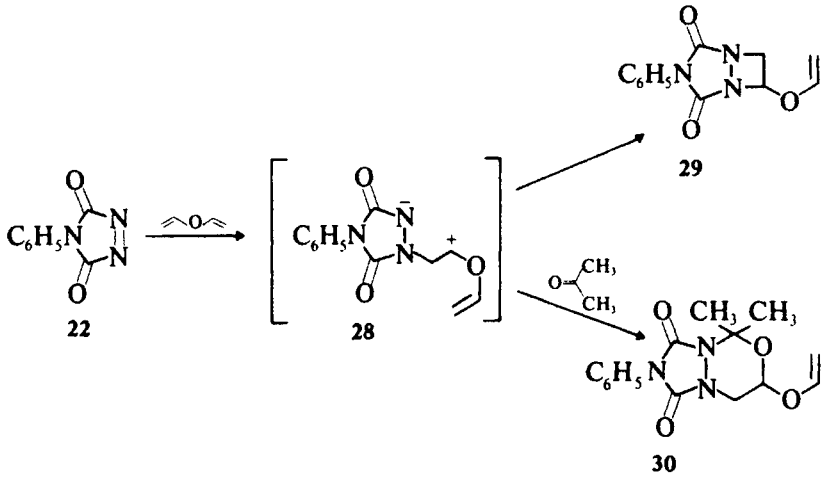
Ar	R	Total Yield (%)	(°C)	Yield (%)	m.p. (°C)	Yield (%)
C_6H_5	OCH_3	73[a]	Oil	77 ± 3	103	23 ± 3
C_6H_5	OC_2H_5	84[a]	54	65	101	35
C_6H_5	OCH_2CCl_3	85[a]	73	> 95	–	< 5 (nmr)
C_6H_5	C_6H_5	–[a]	–	< 5	112	> 95
p-$CH_3OC_6H_4$	OCH_3	82[c]	79	87 ± 3	–[b]	13 ± 3
p-$CH_3C_6H_4$	OCH_3	85[c]	–[b]	84	–[b]	16
p-ClC_6H_4	OCH_3	56[c]	–[b]	67	–	33
p-$O_2NC_6H_4$	OCH_3	40[c]	–	< 5	123	> 95

[a] Reactions carried out without solvent.
[b] Not obtained in pure form.
[c] Reactions carried out in solvent.

A pronounced effect of the solvent polarity on the nature of the product was also noted. Highly polar solvents favored (as was expected for reactions involving dipolar intermediates) the formation of [2+2] adducts and vice versa.

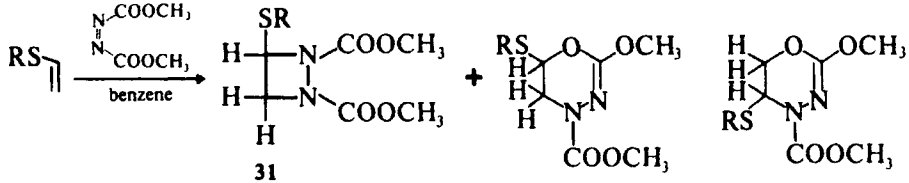
Most of the 1,2-diazetidine-1,2-dicarboxylates are moisture sensitive and hydrolyze readily, with ring opening. The identification of the degradation products often helps in assigning the structure to parent cycloadducts.

A unique case of solvent participation in a cycloaddition was found in the reaction of divinyl ether with 4-phenyl-1,2,4-diazoline-3,5-dione (**22**) in presence of acetone. The expected [2+2] adduct **29** was obtained along with the [2+4] cycloadduct **30**, which was obviously formed by interception of the 1,4-dipolar intermediate **28** by acetone.[35]

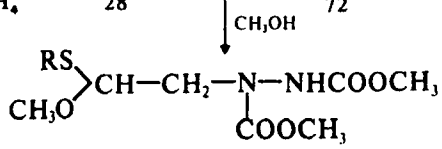


22 28 29 30

Vinyl thioethers have also been reacted with dialkyl azodicarboxylates. In all cases, mixtures of [2+2] and [2+4] cycloadducts **31** and **32** were obtained in combined yields of more than 80%.[36] Both adducts are readily solvolyzed in methanol, giving identical products. This implies that the formation of **32** is regiospecific, since the isomeric cycloadduct **33** would afford a different product.



R	Yield (%)	Yield (%)
C_2H_5	35 ± 3	65 ± 3
C_6H_5	34	66
4-ClC_6H_4	28	72

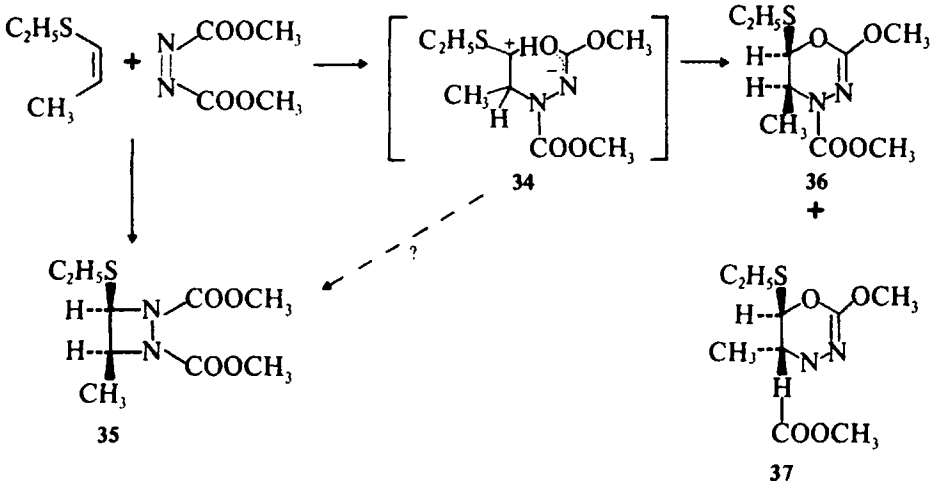


The reactions leading to **31** and **32** are kinetically controlled, since none of the cycloadducts can be interconverted under the conditions employed.

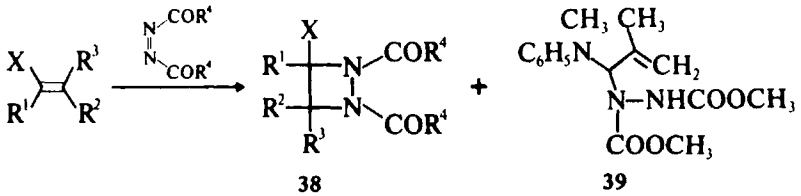
The reaction of *cis*-1-ethylthiopropene with dimethyl azodicarboxylate afforded a mixture of three 1 : 1 cycloadducts (**35**, **36**, and **37**). The vinyl thioether and the isomeric [2+4] cycloadducts **36** and **37** retained their stereochemistry when exposed to the reaction conditions, indicating that the formation of the 5,6-dihydro-1,3,4-oxadiazines is not a concerted $[_{\pi}2_s + _{\pi}4_s]$ process, but proceeds via a 1,4-dipolar intermediate (**34**). Interestingly, trapping experiments in protic solvents showed that formation of the [2+2] cycloadduct **35** might not involve such a 1,4-dipole.[36] Furthermore, it would be unlikely that an intermediate (**34**) should produce the stereochemically unfavored cis-adduct.

Enamines react readily with azobiscarbonyl compounds with formation of [2+2] cycloadducts or substitution products, occasionally side by side. With the limited amount of experimental material available, it is not always possible to predict the course and outcome of a reaction by looking only at the enamine component. Several β-unsubstituted enamines were shown to give cleanly [2+2] cycloadducts, while others with one or two substituents in the β-position yielded either [2+2] adducts and substitution products or only substitution products. It seems that the product type is determined to a large degree by the basicity of the enamine and the electrophilicity of the enophile in each particular combination.

Thus 1-vinylcarbazole and 1-vinylpyrrolidine-2-one react with azodicarboxylate at room temperature in ether to give the 1,2-diazetidines in high yields (see Table 3).[12] Likewise, several cyclohexanone enamines give [2+2] cycloadducts with bisaroylazo compounds (see Table 3).[37] In the reaction of 1-(*N*-methylanilino)-2-



methylpropene with dimethyl azodicarboxylate at room temperature, a mixture containing a [2+2] cycloadduct of type **38** (X = $CH_3NC_6H_5$; R^1 = H; R^2 = R^3 = CH_3; R^4 = OCH_3) and substitution product **39** (with shifted double bond) was obtained, while similarly built β-disubstituted enamines gave only [2+2] cycloadducts (see Table 3).[13]



X = Dialkylamino, arylalkylamino
R^1, R^2, R^3 = H, alkyl
R^4 = OCH_3, aryl, NC_6H_5

On the other hand, *trans*-β-(1-piperidino)styrene, an enamine with one β-substituent, gave only two stereoisomeric acyclic 1:1 adducts (**40**) in a 5:1 ratio with dimethyl azodicarboxylate.[13]

1,2-Diazetidines of type **38** are hydrolytically very unstable and react with water

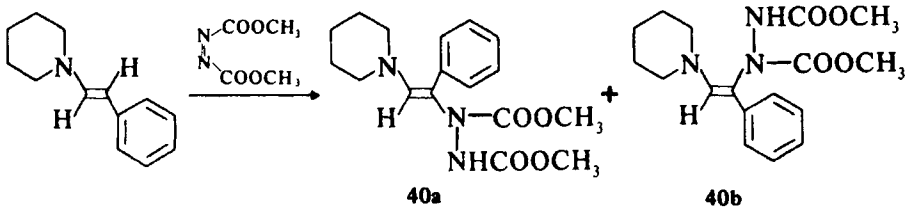
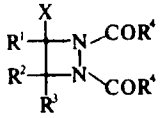
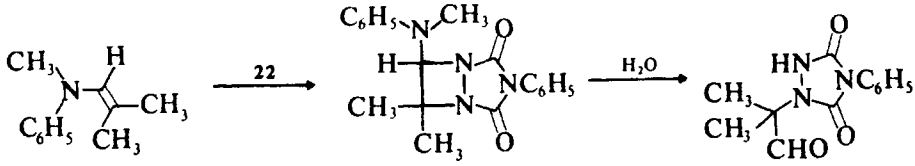


TABLE 3. 1,2-DIAZETIDINES (38) FROM ENAMINES AND AZODICARBONYL COMPOUNDS



X	R^1	R^2	R^3	R^4	m.p. (°C)	Ref.
	$-(CH_2)_4-$		H	C_6H_5	100	37
	$-(CH_2)_4-$		H	C_6H_5	156	37
	$-(CH_2)_4-$		H	C_6H_5	154	37
	$-(CH_2)_4-$		H	$4\text{-}CH_3C_6H_4$	149–151	37
$(CH_3)_2N-$	H	CH_3	CH_3	OCH_3	–	13
$C_6H_{11}NCH_3$	H	CH_3	CH_3	OCH_3	–	13
1-Carbazolyl	H	H	H	OCH_3	135 (84%)	12
1-Pyrrolidon-2-yl	H	H	H	OCH_3	137 (87%)	12
$CH_3NC_6H_5$	H	CH_3	CH_3	$>NC_6H_5$		38

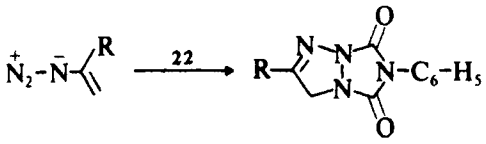
or alcoholic OH groups by ring opening. The cycloadduct **41**, formed from 1-(*N*-methylanilino)-2-methylpropene and 4-phenyl-1,2,4-triazoline-2,5-dione, was not isolable in pure form; exposure to atmospheric water caused rapid hydroysis with formation of 1(1-formyl-1-methylethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione **42**.[38]



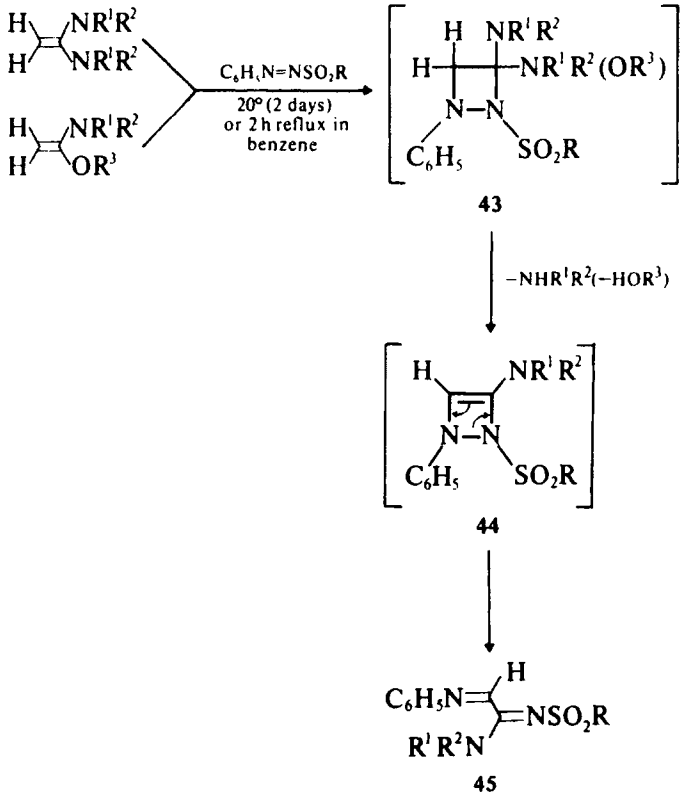
41 **42**

Azido olefins react with **22** to form fused five-membered 1,2,3-triazolines rather than diazetidines.[9b]

Olefins with two electron-donating substituents (RO, RS, or R_2N) attached to the same carbon atom of the double bond have also been shown to undergo cyclo-



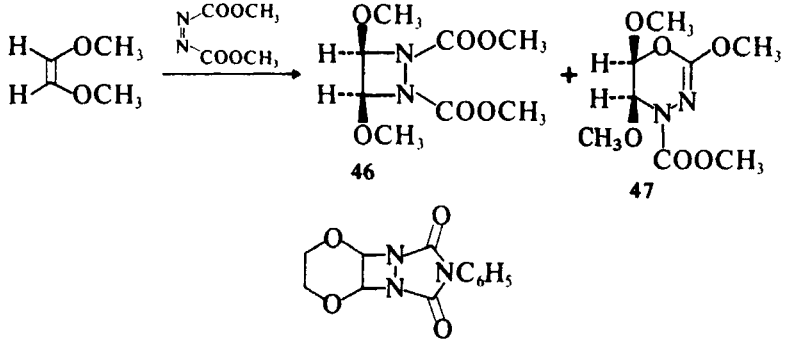
addition reactions with electrophilic azo compounds, although the reaction products were found to be unstable. Keten-*N,N*- and keten-*O,N*-acetals react rapidly with phenyl azosulfones in a multistep process to yield imino amidines (**45**).[39] It was originally believed that the products were Δ^3-1,2-diazetines (**44**),[40] formed by [2+2] cycloaddition and loss of dialkylamine or alcohol from the 1,2-diazetidine intermediates (**43**).



Later investigations revealed, however, that the Δ^3-1,2-diazetines (**44**) undergo further rearrangement with cleavage of the N–N bond and formation of glyoxylic acid derivatives (**45**). The cycloadduct formation in these cases is surprising, since it is known that other electrophilic reagents (such as isocyanates and isothiocyanates) react with β-unsubstituted keten-*N,N*- and *O,N*-acetals, generally with β-substitution.[41,42]

Subsequent attempts to prepare [2+2] cycloadducts from a large number of ketene acetals, thioacetals, and aminals (with one or no substituents on the β-carbon) and diethyl azodicarboxylate or ethyl benzoyl-azocarboxylate in solution at room temperature failed.[43,44] Acyclic products and/or [2+4] cycloadducts (in which the acylated azo compound reacts as 1,4-heterodiene) were obtained instead. 2,2-Disubstituted ketene acetals either failed to react or underwent the "ene" reaction when treated with azodicarboxylate.[43]

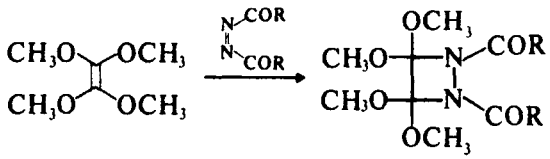
The behavior of olefins, substituted at the α- and β-carbon with electron-donating groups (OR), toward acylated azo compounds has also been studied. Dihydro-1,4-dioxine, vinylene carbonate, and *trans*-1,2-dimethoxyethylene each gave a 1:1 cycloadduct with dihydro-1,3,4-oxadiazine structure when reacted with dialkyl azodicarboxylates. *Cis*-1,2-dimethoxyethylene and dimethyl azodicarboxylate, however, gave an unseparable mixture of [2+2] and [2+4] cycloadducts **46** and **47** in a ratio of 1:4.[9] It is believed that the "cis effect" of the two methoxy groups helps to prevent the exclusive formation of a [2+4] cycloadduct in this case. 4-Phenyl-1,3,4-triazoline-3,5-dione and dihydro-1,4-dioxine gave for the same reason only a 1,2-diazetidine (**48**) when kept for several days in dioxane at −40 to −60°C.[9]



46 **47**

48
m.p. = 208–212°C (17%)

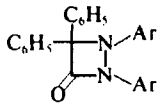
The high electron density as well as the high polarizability of the double bond in 1,1,2,2-tetramethoxyethylene are believed to be responsible for the exclusive formation of [2+2] cycloadducts **49** (by lowering the activation energy for 1,2-diazetidine formation via a 1,4-dipolar intermediate) with dialkyl azodicarboxylates and 4-phenyl-1,2,4-triazoline-3,5-dione.[46]



49a R = OC_2H_5; m.p. = 111°C (95%)
49b R = $OCH_2C_6H_5$; m.p. = 99–100° (86%)
49c R–R = NC_6H_5

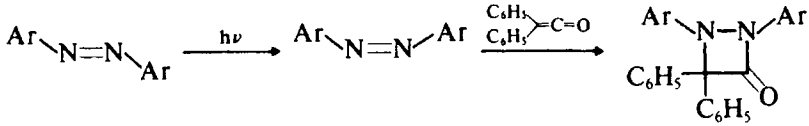
iii. KETENES, KETENIMINES, AND ALLENES. Ketenes and ketenimines have been widely used in 1,2-cycloaddition reactions with azo compounds. A comparatively large number of 1,2-diazetidinones and imino-1,2-diazetidines have been prepared by this method. A first report about this type of cycloaddition was published by Staudinger[4] in 1912, who described the thermal reaction between

TABLE 4. 1,2,3,3-TETRAARYL-1,2-DIAZETIDINONES (50) FROM DIPHENYLKETENE AND AZOBENZENES



Ar	Irradiation Time (h)	Yield (%)	m.p. (°C)	Ref.
H	1.5	71	175–176	48, 49
2-CH_3	4	91	170–170.3	49
3-CH_3	–	–	118	48
4-CH_3	–	–	172	48
3-Cl	7	55	166.5–167	49
4-Cl	16	17	154–155	49
2-NO_2	14	20	197–197.5	49
3-NO_2	7	37	171–172	49
3-Br	6	76	180–181	49
4-Br	5	14	185–186	49
2-OCH_3	1.5	19	158	48, 49
3-OCH_3	0.3	69	103–106	49
4-OCH_3	8	71	145	49
4-$COOCH_3$	1.7	33	143–145	49
2-Naphthyl	–	–	222	48

azobenzene and diphenylketene; this was reinvestigated several years later by Ingold and Weaver.[47] It was found later that *trans*-azobenzene in solution does not react with diphenylketene, while the cis isomer, generated by irradiation of the trans form, adds exothermally to give 1,2,3,3-tetraphenyl-1,2-diazetidinone.[48–50] Thus it became standard to irradiate solutions of the reactants in order to generate *cis*-azobenzene *in situ* from the predominating trans form. Occasionally, *cis*-azobenzenes have been prepared and isolated in pure form, especially for kinetic investigations.[50–52] Several of the [2+2] cycloadducts (**50**) prepared by this method are listed in Table 4.

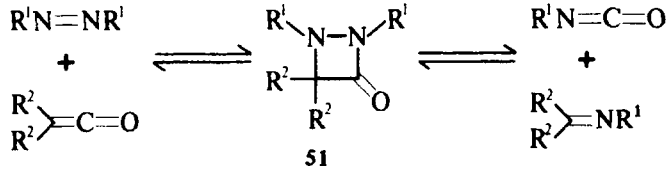


50

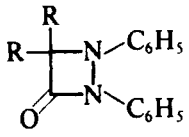
Di-*p*-nitroazobenzene does not add to diphenylketene under these conditions, probably because only very small amounts of the cis isomer are formed during irradiation. In a similar reaction with *p,p'*-bis(dimethylamino)azobenzene, only fragments of the [2+2] cycloadduct (*p*-dimethylaminophenyl isocyanate and benzophenone-*N*-[*p*-dimethylaminophenyl]imine could be identified.[49] This result is in line with similar observations during thermal degradation of cycloadducts of type **51**, which generally yield isocyanates and imines.[48, 53, 54]

Ketene itself and dimethylketene have also been shown to react with azobenzene upon irradiation[53] or with *cis*-azobenzene[55] to give the corresponding 1,2-diaryl-

1,2-diazetidinones (**52**). Reactions of ketene with asymmetrically substituted azobenzenes have also been described and will be discussed later.



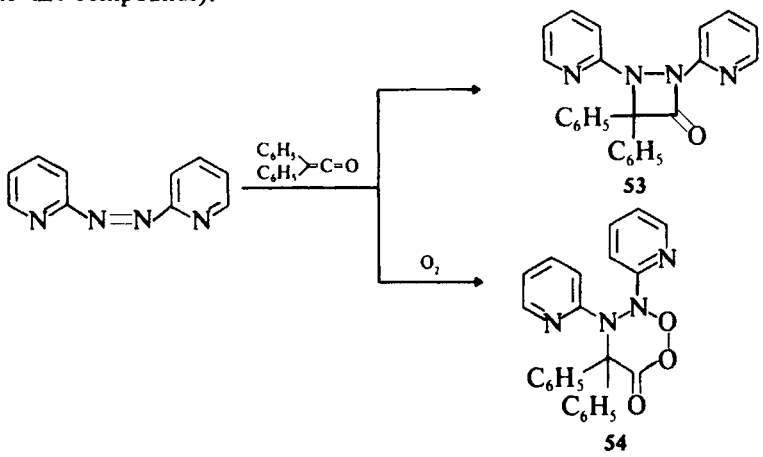
51



52

R = H (68%)
R = CH_3 (40%; m.p. = 74°C)

Several azo compounds bearing heteroaryl groups attached to the N=N group have also been found to undergo cycloaddition reactions with diphenylketene. Thus 2,2′-azopyridine and diphenylketene (generated *in situ* from azibenzil) give the expected 1,2-diazetidinone **53**. If the reaction is conducted in the presence of oxygen, a different product is obtained, for which structure **54** has been suggested.[56] Excess diphenylketene will lead, under the same conditions, to a 2:1 cycloadduct (ketene–azo compounds).



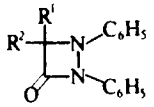
53

54

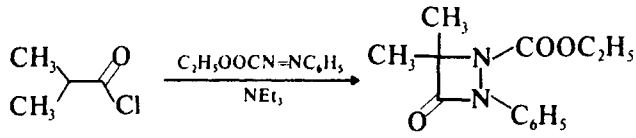
A cycloadduct similar to **53** has also been obtained from 2,2′-azoquinoline on heating with diphenylketene in benzene. Phenylazopyridine and phenylazoquinoline react analogously, giving cycloadducts with presumably similar structures, although no details about the regioselectivity of the reactions have been published.[56]

As the examples above show, it is not always necessary to work with the free ketene in these reactions. It is possible to generate the ketene component in the reaction solution. Thus generation of dimethylketene from isobutyryl chloride

TABLE 5. 1,2,3-TRIARYL-1,2-DIAZETIDINONES FROM DIAZOKETONES AND AZOBENZENES



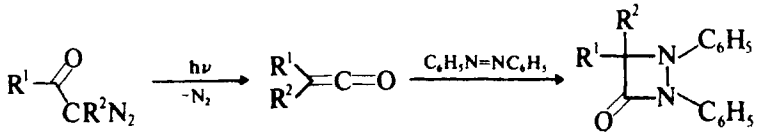
R^1	R^2	Yield (%)	m.p. (°C)	Ref.
C_6H_5	H	32	92	58
2-$NO_2C_6H_4$	H	5	142	59
3-$NO_2C_6H_4$	H	43	125	59
4-$NO_2C_6H_4$	H	47	125	59
2-ClC_6H_4	H	9	128	59
3-ClC_6H_4	H	13	96	59
4-ClC_6H_4	H	42	131	59
2-BrC_6H_4	H	20	129	59
4-BrC_6H_4	H	48	135	59
4-$CH_3C_6H_4$	H	42	106	59
3-$CH_3OC_6H_4$	H	57	142	59
4-$CH_3OC_6H_4$	H	53	116	59
C_6H_5	C_6H_5	61	173	58. 59
α-$C_{10}H_7$	H	30	147	59



55

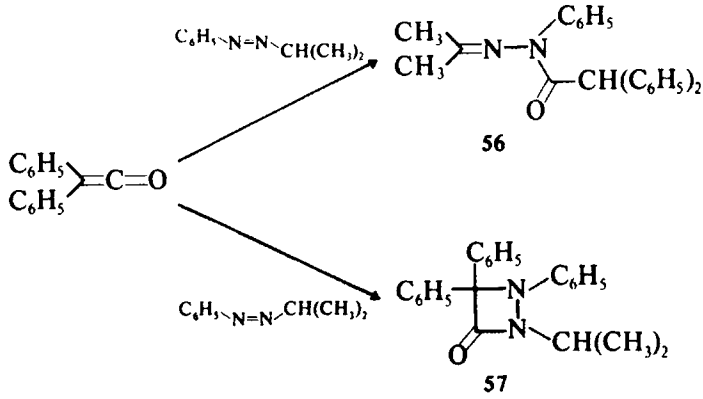
and triethylamine in the presence of ethyl phenylazocarboxylate produced ethyl 4,4-dimethyl-2-phenyl-3-oxo-1,2-diazetidine-1-carboxylate **55**.[57]

It is also possible to prepare ketene–azobenzene cycloadducts by irradiating solutions of diazoketones in the presence of azobenzene or azonaphthalene.[58,59] A large number of 1,2-diazetidines has been prepared this way (see Table 5).

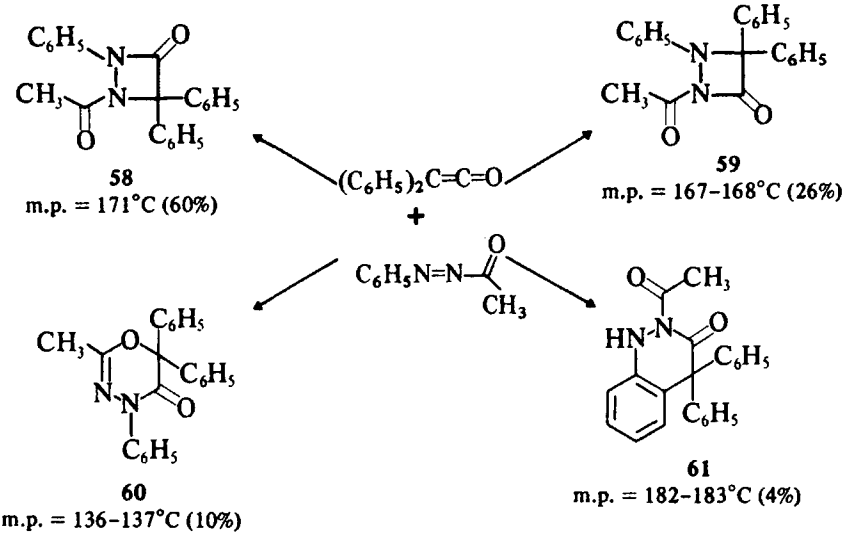


R^1 = Aryl
R^2 = H, aryl

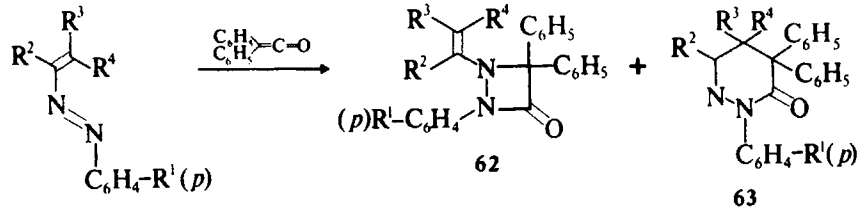
In several reactions of azo compounds with ketenes complications were encountered because groups adjacent to the nitrogen–nitrogen double bond participated in the cycloaddition or other reactions. Thus, on allowing *trans*-2-(phenylazo)propane to react with diphenylketene, acetone *N*-(diphenylacetyl)-*N*-phenylhydrazone **56** was obtained as the product of an "ene" reaction. Irradiation of the reaction solutions produces the *cis*-azo compound, which adds to diphenylketene with formation of the [2+2] cycloadduct **57** in 12% yield.[50]



A different type of neighbouring group participation has been observed in the attempted cycloaddition of arylazoalkenes and arylazocarbonyl compounds to ketenes. Here [2+4] cycloadducts may be formed aside from or instead of the desired [2+2] cycloadducts. While ethyl phenylazocarboxylate was found to give only 1,3,3-triphenyl-2-ethoxycarbonyl-1,2-diazetidin-4-one* with diphenylketene on heating[47,50] or on irradiation in hexane,[50] a mixture of products is obtained from acetylazobenzene and diphenylketene.[60] Both components react exothermally with formation of two regioisomeric [2+2] cycloadducts, **58** and **59**, as well as the [2+4] cycloadduct **60** (dihydro-1,3,4-oxadiazine) and a product (**61**) believed to arise from **60** by a subsequent 1,3-H shift.[60] Similarly, arylazoalkenes are capable of reacting as enes and heterodienes, giving [2+2] and [2+4] cycloadducts **62** and **63** with diphenylketenes.[61] The product ratio can be influenced by changing the polarity of the solvent. Polar solvents (CH_3CN instead of benzene) favor the for-



* The wrong structure was assigned to this adduct by C. K. Ingold and S. Weaver.[47]

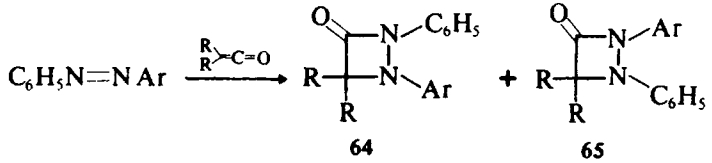


62 63

				62		63	
R^1	R^2	R^3	R^4	m.p. (°C)	Isolated Yield (%)	m.p. (°C)	Isolated Yield (%)
H	H	C_6H_5CO	H	148	86	205–206	
H	H	CH_3COO	H	80–81	85	168–169	
H	CH_3	CH_3COO	H	149–150	46	138–139	13
Cl	CH_3	CN	H	175–176	75	147	10
Cl	CH_3	H	CN	165–166	89		
H		$(CH_2)_4$	H			196–197	72
H	H		H			164–165	84

mation of the [2+2] cycloadducts, indicating that the 1,2-diazetidinones are formed via dipolar intermediates. It also becomes apparent from the product distribution that the [2+4] adduct formation is favored as the donor capacity of the substituents on the C=C double bond of the heterodiene increases.

Reactions of ketene or diphenylketene with asymmetrically substituted azobenzenes were found always to produce mixtures of the two possible regioisomeric [2+2] cycloadducts **64** and **65**.[50,62] Regioselectivity in these 1,2-diazetidinone formations was low. Kerber and co-workers[50] found in their studies that isomers **64** were predominant in all reaction mixtures regardless of whether the substituents on



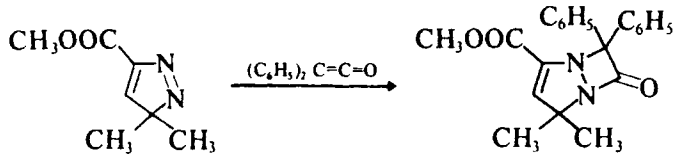
64 65

		64		65		
R	Ar	Yield (%)	m.p. (°C)	Yield (%)	m.p. (°C)	Ref.
H	$2\text{-}CH_3OC_6H_4$	81	80			62
H	$3\text{-}CH_3C_6H_4$	29	75	36	121	62
H	$4\text{-}CH_3C_6H_4$	50	85	7	113	62
C_6H_5	$4\text{-}CH_3OC_6H_4$[a]	64		36		50
C_6H_5	$4\text{-}CH_3C_6H_4$[a]	54		46	178–179	50
C_6H_5	$4\text{-}ClC_6H_4$[a]	59	164	44		50
C_6H_5	$4\text{-}NO_2C_6H_4$[a]	61	167–168	39		50
C_6H_5	$4\text{-}NCC_6H_4$[a]	64	188–190	36	219–221	50

[a] Prepared by irradiation of the components in benzene at 80°C; yields are ± 1–3%.

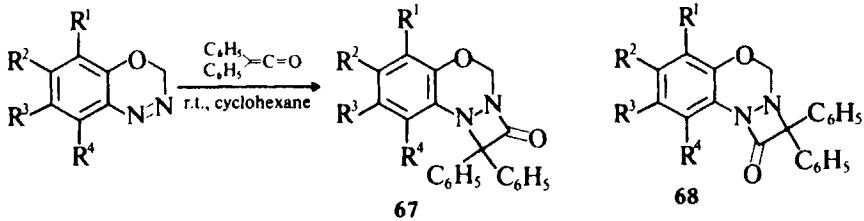
the aryl group were electron donating or withdrawing. These observations lead to the conclusion that the cycloadditions are practically concerted, although not entirely synchronous processes. Other findings, however, point toward a stepwise $[\pi 2_s + \pi 2_a]$ addition via dipolar intermediates in these cyclizations.[61]

Compounds that contain an azo group locked into a cis configuration in most cases react readily with ketenes, very often at room temperature. An exception is 2,3-diazabicyclo[2.2.1]hept-2-ene, which does not give [2+2] cycloadducts with ketene or dimethylketene, probably because of added ring strain in the adducts.[55] 3,3-Dimethyl-5-carbomethoxy-3H-pyrazole, however, reacts readily with diphenylketene at 20°C to give the bicyclic diazetidinopyrazole **66**.[63]



66

3H-4,1,2-Benzoxadiazines too undergo cycloadditions with diphenylketene at room temperature to yield 2-oxo-1,1-diphenyl-1,2-dihydro-4H-1,2-diazeto[1,2-a]-4,1,2-benzoxadiazines (**67**) in good to excellent yields.[64] The additions are regiospecific, since only one of the two isomers (**67** and **68**) is obtained. Structure assignment is based on IR spectral data (large R^4 substituents on **67** weaken the phenyl ring absorptions at position 1).

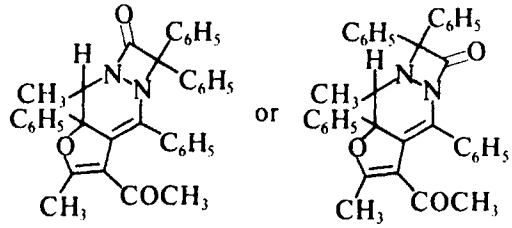


67 **68**

R^1	R^2	R^3	R^4	Yield (%)	m.p. (°C)
Cl	H	Cl	H	90	182–183
Cl	H	Cl	Cl	59	165–167
H	H	NO_2	H	33	174–175
$C(CH_3)_3$	H	$C(CH_3)_3$	H	51	100–102
H	H	Cl	H	92	159–160
Cl	Cl	Cl	Cl	76	190–191
H	NO_2	H	H	64	178–179
Br	H	Br	H	85	173–174

A related cycloaddition, leading to the tricyclic heterocycles **69** or **70**, takes place between 2,7-dimethyl-4,7a-diphenyl-3-acetyl-7,7a-dihydrofuro[2,3-d]pyridazine and diphenylketene in benzene at room temperature.[65]

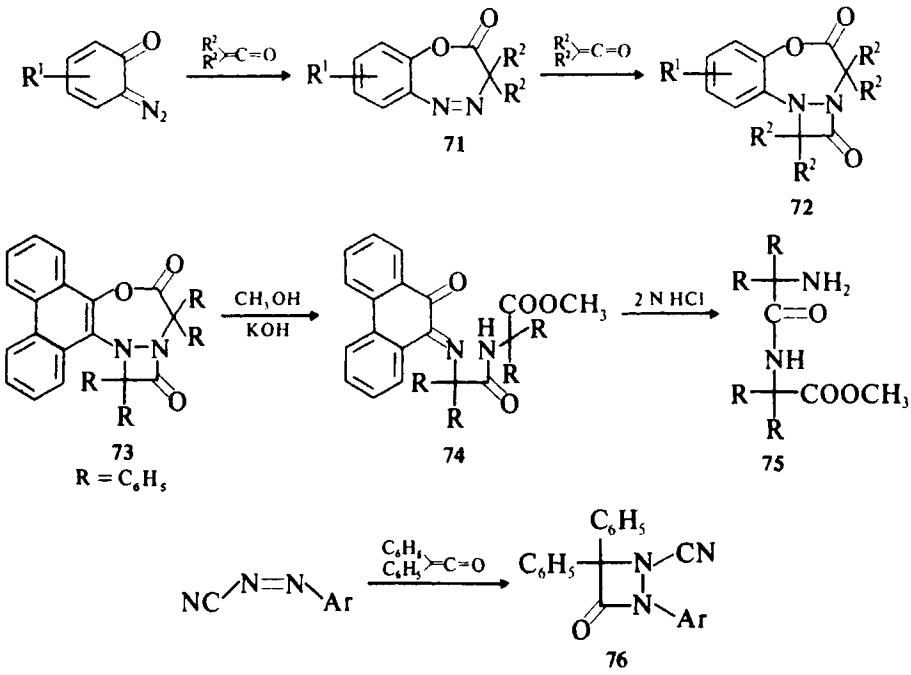
o-Diazo oxides react with dimethyl and diphenylketene in a double cycloaddition giving the bicyclic 1:2 adducts **72**. The first step is a 1,5-dipolar cyclo-



69 or 70

addition of the ketene to the diazo oxide giving, in case of (substituted) benzene-1,2-diazo oxide, 2-oxo-2,3-dihydrobenzo-1,4,5-oxadiazepines **71**. Subsequent addition of a second molecule of ketene to the *cis*-azo group yields 2,4-dioxo-1,2,2a,3,4,4a-hexahydrobenzo[b]diazet[1,2-d]-1,4,5-oxadiazepines **72**.[66,67] The general character of this type of reaction was established by using a variety of *o*-diazo oxides in these cycloadditions (see Table 6). Tetrachlorobenzene-1,2-diazo oxide failed to undergo the second cycloaddition; dimethylketene and this diazo oxide gave only the corresponding 1,4,5-benzoxadiazepine.[67] Stepwise chemical degradation of one diazetidino[1,2-d]-1,4,5-oxadiazepine **73** with potassium hydroxide–methanol and hydrochloric acid confirmed the direction of the ketene addition in the second step.

Several *cis*-arenediazocyanides add readily to diphenylketene to give regiospecifically the 1,2-diazetidine derivative **76** (Table 7). The direction of the ketene addition was confirmed by chemical degradation and partial independent synthesis.[68–70]



71 72 73 $R = C_6H_5$ 74 75 76

TABLE 6. 1,2-DIAZETIDINONES FROM *o*-DIAZO OXIDES AND KETENES[66,67]

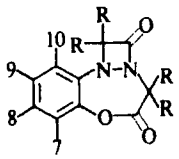
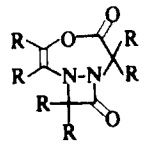
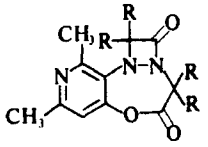
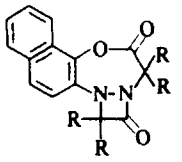
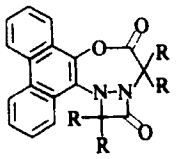
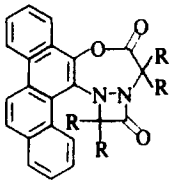
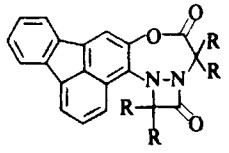
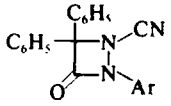
Compound	Substituent	R	m.p. (°C)	Yield (%)
	7,9-Di-*t*-butyl	C_6H_5	128	85
	9-Nitro	C_6H_5	143	51
	9-Chloro-8,10-dimethyl	C_6H_5	185	47
	7,9-Dichloro	C_6H_5	109	81
	7,8,9,10-Tetrachloro	C_6H_5	211	45
	7,9,Di-*t*-butyl	CH_3	131–132	52
	8-Chloro	CH_3	127.5–128.5	58
	9-Chloro	CH_3	122.5–123.5	60
	8-Bromo	CH_3	152–154	40
	9-Bromo	CH_3	100.5–101.5	40
		C_6H_5	140	41
		C_6H_5	180	38
		C_6H_5	193	75
		C_6H_5	175	70
		C_6H_5	156	56
		C_6H_5	154	31

TABLE 7. 1-ARYL-3,3-DIPHENYL-2-CYANO-1,2 DIAZETIDINONES (76) FROM ARENEDIAZOCYANIDES AND DIPHENYLKETENE



Ar	Yield (%)	m.p. (°C)	Ref.
2-ClC_6H_4	87	123	68
3-ClC_6H_4	80	105–108	68
4-FC_6H_4		104–106	69
4-BrC_6H_4	92	126–127	68
3-$NO_2C_6H_4$		127–129	69
4-$NO_2C_6H_4$	70	143–146	68
2,4-$Cl_2C_6H_3$	38	104–106	68
2,6-$Cl_2C_6H_3$[a]	55	140–142	68–70
2,5-$Cl_2C_6H_3$[b]		146	70
2,4-$Br_2C_6H_3$[b]		110	70
4-CNC_6H_4		133–134	69
4-$C_6H_5OC_6H_4$		125–127	69
3-$CF_3C_6H_4$		115–117	69

[a] Also prepared with ArN=^{15}NCN.
[b] Prepared with ArN=^{15}NCN.

Interestingly, the unsubstituted *cis*-benzene and α-naphthalene diazocyanides, as well as *p*-methoxybenzenediazocyanide, failed to undergo these cyclizations. This seems to imply that the arenediazocyanides are the electron acceptors in these additions, and not (as is usually the case) the electron donors. A special characteristic of the cyanosubstituted 1,2-diazetidines **76** is their ability to undergo thermally induced rearrangements giving imidazo[1,2-a]benzimidazoles; details about these reactions are found in section 3.C.

Ketenimines react with *cis*-azobenzenes to give imino-1,2-diazetidines in moderate to good yields. Irradiation of the reaction solutions (in order to convert the *trans*-azobenzenes into the reactive cis isomers) is necessary for the [2+2] cycloadditions to take place.[71] Azobenzene samples enriched with the cis isomer react with ketenimines even in the dark. Electron-donating substituents on the azobenzenes cause an increase of the reaction rate. No [2+2] cycloadduct could be isolated with *p,p'*-dihydroxyazobenzene, although the appearance of a carbodiimide band at 2150 cm^{-1} in the IR spectra of the reaction mixture indicated its formation and subsequent dissociation.[71] Other imino-1,2-diazetidines of type **77** (see Table 8)

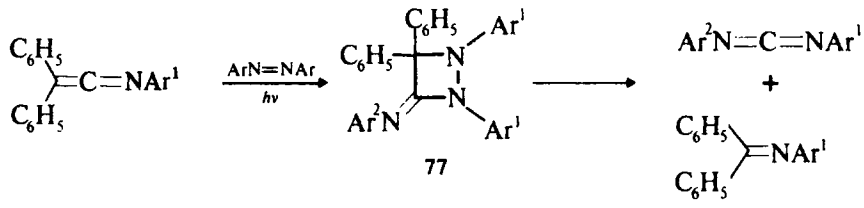
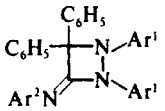


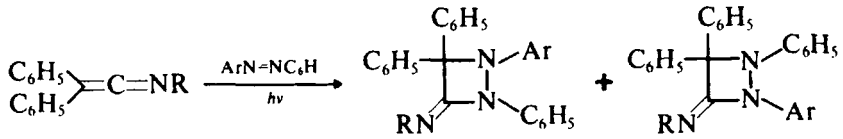
TABLE 8. 1,2,3,3-TETRAARYL-1,2-DIAZETIDIN-4-IMINES (77) FROM AZOBENZENES KETENIMINES



Ar^1	Ar^2	Yield (%)	m.p. (°C)	Ref.
C_6H_5	$4\text{-}CH_3C_6H_4$	83	175–176	71
$3\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	20.8	168–169	71
$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	37.6	158–159	71
$4\text{-}ClC_6H_4$	$4\text{-}CH_3C_6H_4$	30.6	183–185	71

dissociated on heating above 200°C, affording carbodiimides and benzophenone imines in high yield; no back dissociation into starting materials was observed.[71,72]

Asymmetrically substituted azobenzenes and ketenimines afford mostly mixtures of the two regioisomers **78** and **79**.[72] In cases where adduct mixtures were obtained (see examples below), separation into pure components was not possible because of their thermal instability. The isomer distribution in these cyclizations was influenced more by the size than by the electronic characteristics of the substituent on the asymmetric azobenzene $ArN{=}NC_6H_5$, with larger substituents favoring the formation of **78** over **79**. The reaction rates were only moderately influenced by solvents. On the basis of these data, it was concluded that the cyclizations do not proceed via dipolar intermediates.[71] This is in line with similar observations and deductions by Kerber et al.[50,51] on ketene–azobenzene cycloadditions, which were found to be concerted processes.



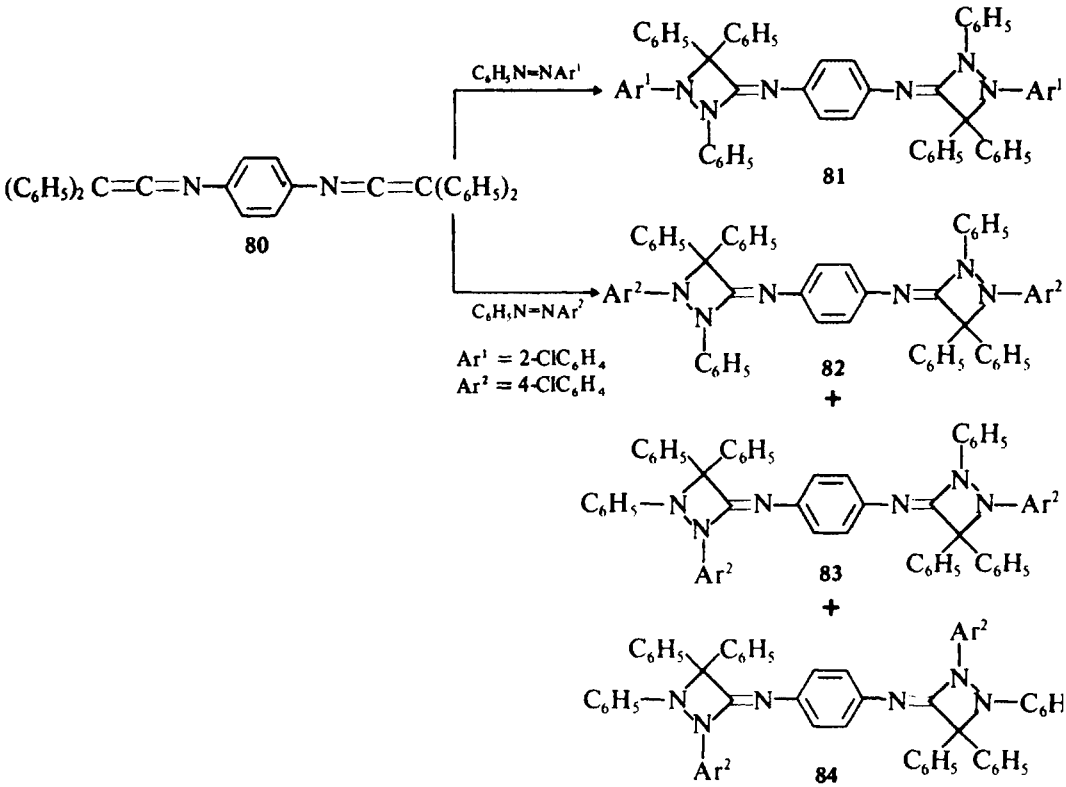
78 **79**

$R = C_6H_4CH_3\text{-}4$

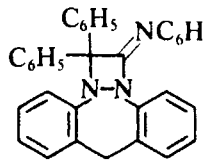
Ar	Yield, 78 (%)	m.p. (°C)	Yield, 79 (%)	Total yield (% crude)
$4\text{-}CH_3C_6H_4$	65		35	92
$3\text{-}CH_3C_6H_4$	72		28	49
$2\text{-}CH_3C_6H_4$	100	189	–	48
$4\text{-}ClC_6H_4$	71		29	88
$3\text{-}ClC_6H_4$	78		22	30
$2\text{-}ClC_6H_4$	100	207	–	36
$4\text{-}CNC_6H_4$	65		35	24
$2\text{-}CNC_6H_4$	100	207–208	–	21
$4\text{-}BrC_6H_4$	77		23	92
$4\text{-}(CH_3)_2NC_6H_4$	100	151	–	74
$4\text{-}(C_2H_5)_2NC_6H_4$	100	143	–	62
$4\text{-}CH_3OC_6H_4$	93		7	71
$3\text{-}NO_2C_6H_4$	85		15	15

Bisketenimines form similar cycloadducts with azobenzenes.[73] Thus, *N,N'*-bis(diphenylethenylidene)-1,4-benzenediamine (**80**) and azobenzene on irradiation for 48 hours, afford in 65% yield a 1 : 2 cycloadduct containing two 1,2-diazetidine rings; the structure of the product was confirmed by thermal degradation into benzophenone-*N*-phenylimine and a biscarbodiimide.

Asymmetrically substituted azobenzenes lead, as expected, to mixtures of isomers. A low degree of regioselectivity in the cycloaddition of **80** with 4-chloroazobenzene causes the formation of the isomeric imino-1,2-diazetidines **82–84**. Steric hindrance in 2-chloroazobenzene, in analogy to the monoketenimine reactions, leads only to one cycloadduct (**81**).[73]

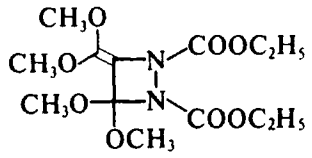


Dibenzo[c,f]diazepine, which contains an azo group locked in cis configuration, reacts in the dark with diphenyl-*N*-*p*-tolylketenimine to give 68% of the corresponding imino-1,2-diazetidine **85**.[72] Benzocinnoline, which also has a *cis*-azo group as part of the aromatic system, does not give a cycloadduct with the ketenimine.

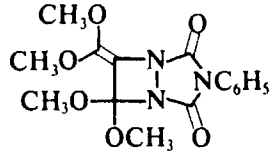


85

The electron-rich tetramethoxyallene reacts readily with diethyl azodicarboxylate to give 43% of the dimethoxymethylene-1,2-diazetidine **86** and with 4-phenyl-1,2,4-triazolin-3,5-dione to afford 69% of the corresponding adduct **87**. Nmr data and chemical degradation confirmed the structure of both adducts.[74]

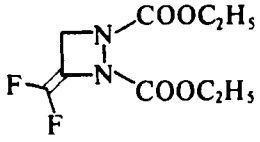


86
m.p. = 85°C



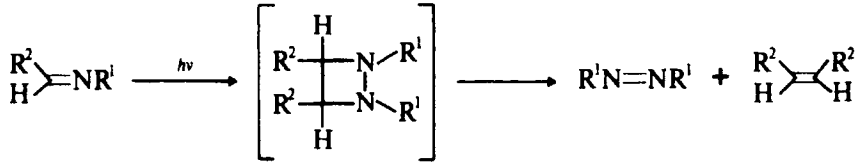
87
m.p. = 125–128°C

The addition of diethyl azodicarboxylate to 1,1-difluoroallene at elevated temperature affords 3-difluoromethylene-1,2-dicarboethoxy-1,2-diazetidine (**88**; b.p., 97°C/1.4 mm) in low yield.[75] The direction of the addition to this asymmetrically substituted allene was deduced from the ^{19}F-nmr spectra.



88

iv. DIMERIZATION OF IMINES. Thermally induced oligomerizations of aldimines (especially those derived from formaldehyde) produce cyclotrimers (1,3,5-triazine derivatives) and possibly cyclodimers (1,3-diazetidines) in which the heteroalkenes add in a head-to-tail fashion. The recently investigated photolysis of 4-*N*-dimethylaminobenzylideneaniline in ether shows, however, that a 1,2-diazetidine derivative (**89**) might be formed as an intermediate in a process that yields azobenzene and 4,4′-bis(dimethylamino)stilbene.[76]

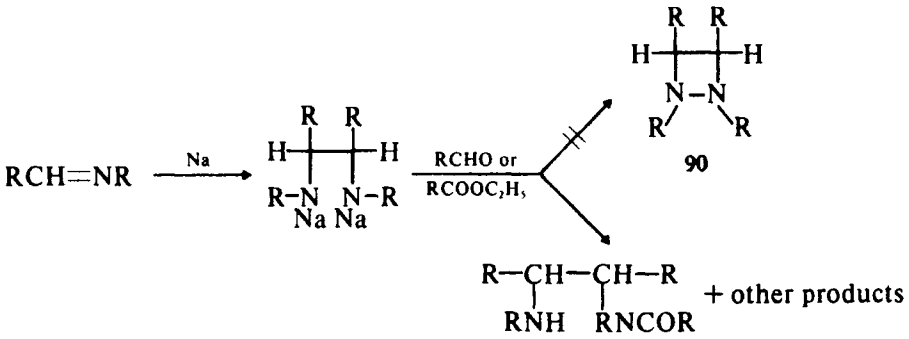


89
$R^1 = C_6H_5$
$R^2 = C_6H_4N(CH_3)_2$-*p*

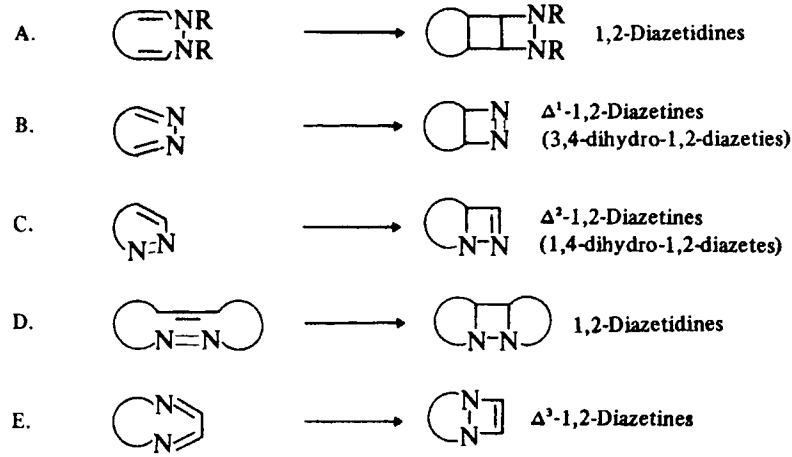
The reverse reaction (i.e., photolytic [2+2]-cyclo-reversion of a 1,2-diazetidine derivative into two molecules of imine) has been observed.[77]

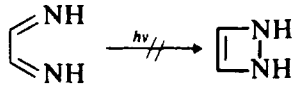
The photochemically induced dimerization of other *N*-alkylated benzaldemines, carried out in alcoholic solvents, gave *meso*-*N*,*N*′-dialkyl-1,2-diphenyl-1,2-diaminoethanes,[78–80] which are products of head-to-head reductive dimerizations of the imines.

A reexamination[81] of an earlier report about the head-to-head cyclodimerization of benzylideneaniline in the presence of sodium and either ethyl benzoate or benzaldehyde, which was claimed to give 1,2,3,4-tetraphenyl-1,2-diazetidine **90**,[82] revealed that a mixture of acyclic ethylenediamine derivatives (*d,d,l,l*-, and *meso*-*N*-benzoyl-*N,N'*-1,2-tetraphenylethylenediamine as well as *dd,ll*-*N,N'*-1,2-tetraphenylethylenediamine and *N*-benzoyl-*N,N'*-diphenylstilbene-α,α-diamine) is formed instead.



v. INTRAMOLECULAR [2+2] CYCLOADDITIONS. A number of compounds containing at least a pair of supplementary C=C, C=N, or N=N double bonds, either in conjugation or separated by (several) single bonds, have been shown to be capable of undergoing photolytically induced intramolecular [2+2] cycloadditions with formation of 1,2-diazetidine or 1,2-diazetine derivatives. Some of the products formed in these cycloadditions are thermolabile and revert back to the starting materials or undergo secondary reactions. Several of the possible cyclizations are shown below (reactions A–E). Examples for the synthesis of 1,2-diazetidine derivatives by reactions A–D have been described in the literature; cyclizations of diimines to yield Δ^3-1,2-diazetines (reaction E) are not known to date. Calculations of the potential energy surfaces of the ground state and lowest excited

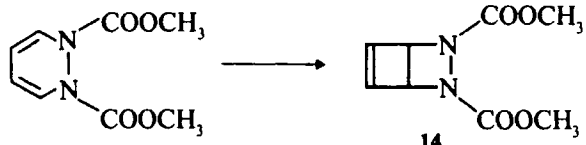




91

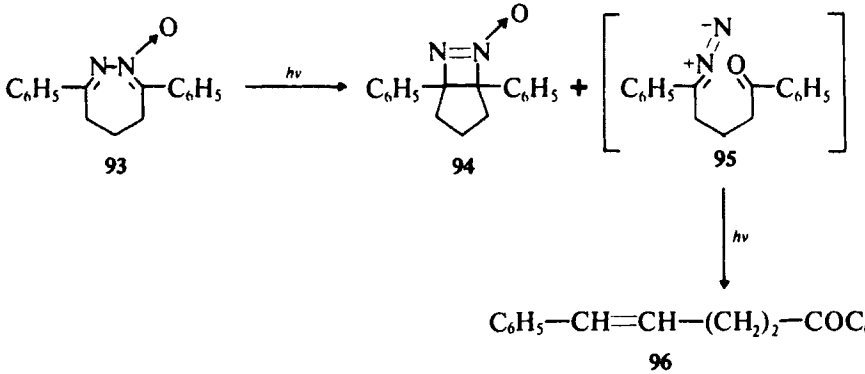
states (by an all-electron *ab initio* SCF–CI method) for the "linear" reaction path of a disrotatory cyclization of 1,4-diaza-1,3-butadiene to Δ^3-1,2-diazetine **91** lead to the conclusion that such a process is unlikely to occur.[83]

Dimethyl 1,2-hihydropyridazine-1,2-dicarboxylate (**92**) (obtained from dimethyl 1,2,3,6-tetrahydropyridazine dicarbonate via allylic bromination followed by dehydrohalogenation) can be transformed into the 2,3-diazabicyclo[2.2.0]hex-5-ene derivative **14** on irradiation with a high pressure mercury lamp in diethyl ether.[30] A similar intramolecular cycloaddition has been reported for 1,2-dihydropyridines.[84]



92 14

Irradiation of the azine oxide 3,7-diphenylhexahydro-1,2-diazepine-1-oxide (**93**) in methylene chloride solution with a medium pressure mercury lamp (pyrex filter) gave a mixture of products, of which one was identified as 1,4-diphenyl-2,3-diazabicyclo[3.2.0]hept-2-ene-2-oxide (**94**; 28% yield; m.p. = 135°C) on the basis of chemical and spectroscopic evidence.[85,86] The coproduct was found to be the ketone **96**, which is formed via the diazoketone **95** (its formation was indicated by a transient appearance of a red color in the reaction solution). It was further found that the yield of both end products, **94** and **96**, can be increased by adding the low energy triplet quencher piperylene to the reaction solution.

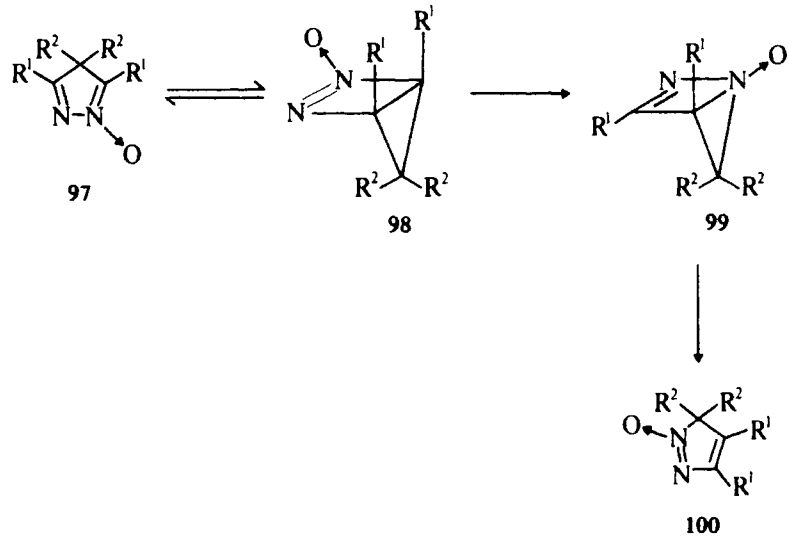


93 94 95

96

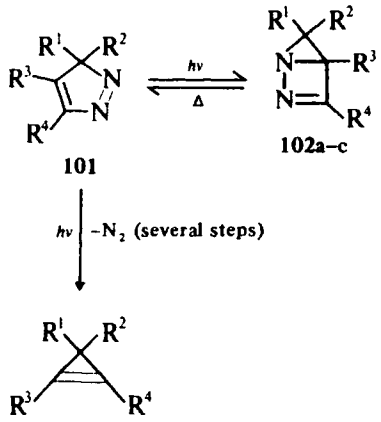
Irradiation of other cyclic and acyclic azine oxides gave no Δ^1-1,2-diazetine-1-oxides, although experimental evidence in one case points to the transient formation of such a heterocycle.[86] Thus photolysis of 3,4,5-persubstituted 4H-pyrazole-1-oxides (**97**) in ether or methylene chloride leads cleanly to bond

isomerization with formation of **100**. These reactions are best explained by assuming that Δ^1- and Δ^2-1,2-diazetidine-1-oxides of type **98** and **99** are produced as intermediates. H-Nmr spectroscopic evidence for the formation of an intermediate of type **98** was obtained during low temperature photolysis of **97** ($R^1 = CH_3$, $R^2 = C_2H_5$).



97 **98** **99** **100**

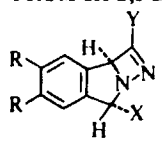
Fully substituted 3H-pyrazoles (**101**), which readily lose N_2 on irradiation with formation of cyclopropenes, have been shown to photoisomerize at low temperature in an allowed 4π-electron disrotatory ring closure to give 1,2-diazabicyclo [2.1.0] pent-2-enes (**102**).[87-89] The reactions, if carried out at -55 to -60°C, lead



101 **102a–c**

	R^1	R^2	R^3	R^4	Ref.
a.	CH_3	CH_3	CH_3	CH_3	88, 89
b.	CH_3	CH_3	$CH_2CH_2CH_2CH_2$		87, 88
c.	CH_3	CH_3	$CH_2(CH_2)_3CH_2$		87, 88

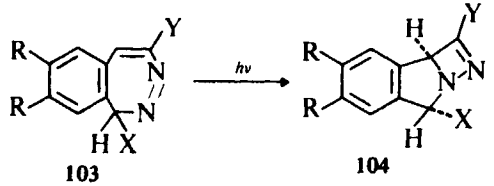
TABLE 9. 2a,7-DIHYDRO[1,2]DIAZETO[4.1-a]ISOINDOLES (104) FROM 1H-2,3-BENZODIAZEPINES (103)



Y	X	R	m.p. (°C)	Ref.
H	H	H	62–64	91
H	H	OCH_3	119–122	91
H	CH_3	OCH_3	116–119	91
H	CH_3	H	77–81	91
C_6H_5	CH_3	H	97–100	91
H	C_6H_5	H	94–97	91
C_6H_5	H	H	77–83	91
C_6H_5	$C_6H_5CH_2$	H	122–123	91

generally to mixtures of cyclopropenes and bicyclopentenes **102**, with less polar solvents favoring the formation of cyclopropenes. Methylene chloride or methanol as solvents suppress N_2 evolution completely. The strained bicyclic ring systems are very unstable and easily revert back to the starting materials on heating to room temperature; they can therefore not be isolated in substance, although they have been fully characterized spectroscopically (nmr, UV, IR).

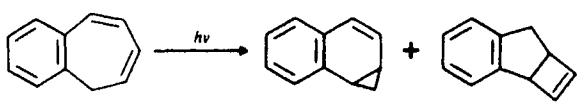
An analogous intramolecular cycloaddition takes place during irradiation of solutions of 1H-2,3-benzodiazepines (**103**), affording 2a,7-dihydro[1,2]diazeto[4,1-a]isoindoles (**104**) in virtually quantitative yields (Table 9). In contrast to the bi- and tricyclic diazetines **102**, the adducts **103** are stable at room temperature, although partial decomposition takes place in certain cases during purification.[90,91]



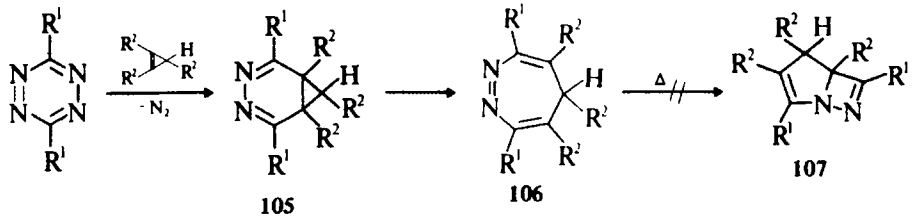
103 **104**

These valence isomerizations of 1H-2,3-benzodiazepines (leading to Δ^2-1,2-diazetines) are quite different from the carbocyclic analogs, which undergo a 1,7-hydrogen shift followed by ring contraction.[92] They also differ from 1,2-benzodiazepines, which were shown to extrude nitrogen on irradiation.[93]

Reports about the formation of diazabicyclo[3.2.0]heptadienes of type **107** during the thermally induced reaction of diphenyl-*s*-tetrazines with cyclopropenes,



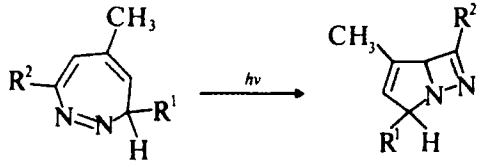
(0.5%)



105 106 107

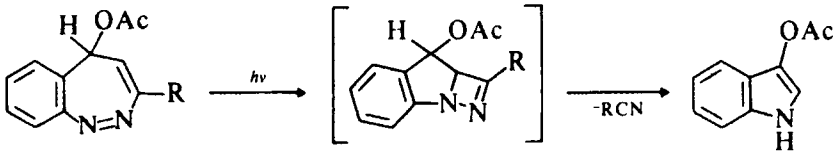
which proceeds with loss of nitrogen, proved to be wrong.[94] A reexamination of the original results and additional work verified that diazanorcaradienes (**105**) and diazacycloheptatrienes (**106**) are formed as the sole products.[95]

Substituted 3H-1,2-diazepines are claimed to isomerize upon irradiation to give [1,2]diazeto[4,1-a]pyrroles (**108**); no experimental details have been published for these reactions.[96]



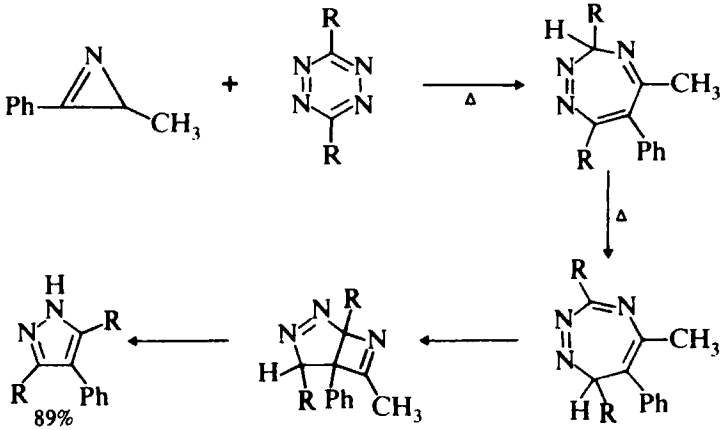
108

The photolysis of 5-acetoxy-5H-1,2-benzodiazepine yields 3-acetoxyindole and a nitrile (RCN) as the sole products. This reaction is likely to proceed via a tricyclic intermediate (**109**).[97]



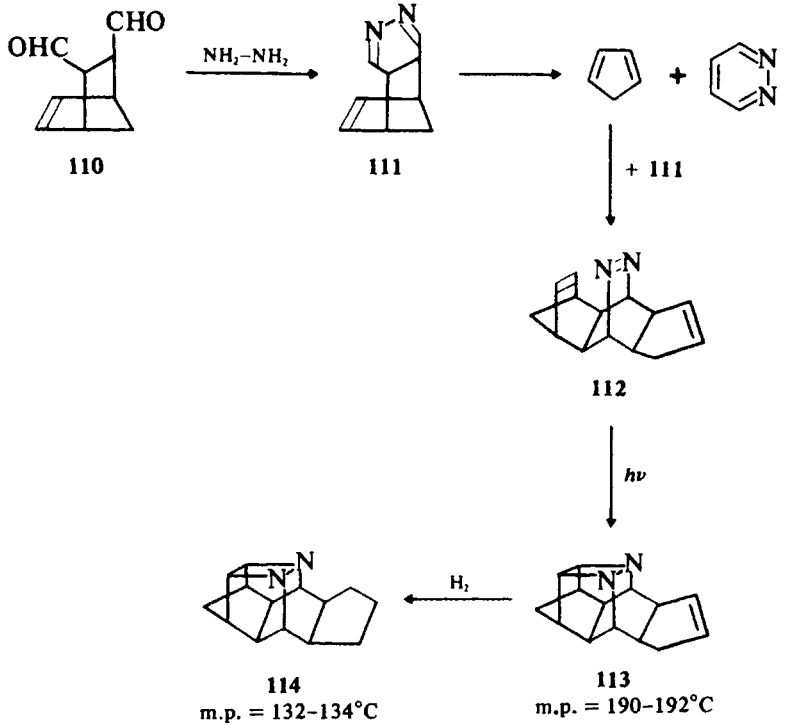
109

A similar extrusion of nitrile has been postulated[98] in the thermal conversion shown below:



R = 2-pyridyl

A rigid polycyclic compound, in which a N=N bond is situated parallel and in close proximity to a C=C bond, was prepared from the dialdehyde **110** and hydrazine in dilute acetic acid by the reaction path shown below. The initially formed azine **111**, formally a pyridazinecyclopentadiene cycloadduct, suffers cycloreversion to pyridazine and cyclopentadiene; the latter compound instantaneously reacts with unconverted **111** to give **112**. Irradiation of **112** in acetonitrile leads to the cage compound **113** in high yield.[99] Compound **113** can be further hydrogenated to **114**.[100]



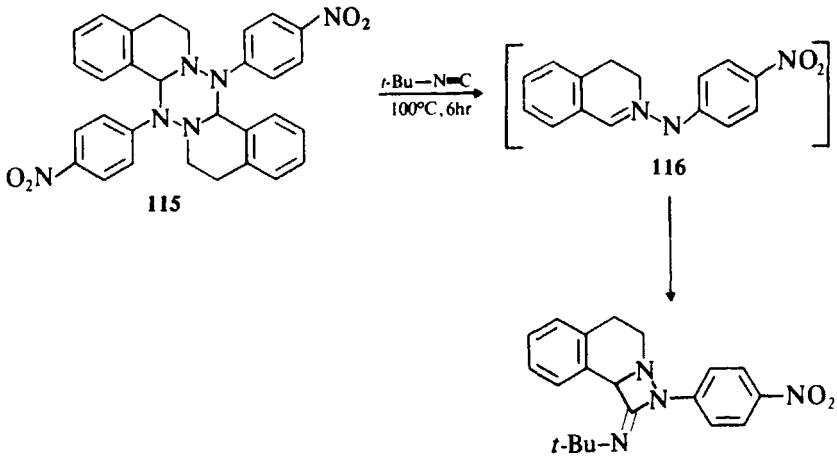
b. [3+1] CYCLOADDITIONS

Only one example of a [3+1] cycloaddition reaction affording a 1,2-diazetidine derivative is known to date. Excess *t*-butyl isonitrile reacts with the 1,3-dipolar azomethine imine **116**, generated *in situ* by heating the hexahydro-1,2,4,5-tetrazine precursor **115**, to give the imino-1,2-diazetidine **117** in 51% yield.[101]

c. MISCELLANEOUS CYCLOADDITIONS

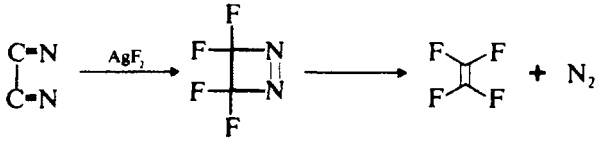
This category includes reactions leading to 1,2-diazetidine and 1,2-diazetine derivatives that proceed either by an unknown reaction mechanism or do not strictly fit the classification of [2+2] or [3+1] cycloadditions.

Tetrafluoro-Δ^1-1,2-diazetine **118** is obtained in excellent yield when a stream of cyanogen is directed over heated (105–110°C) argentic fluoride, supported on

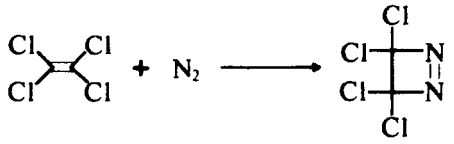


115 116 117

copper gauze;[8] slightly higher reaction temperatures will lead to different products.[102] Spectral data fully support the structure of the reaction product.[103,104] It seems likely that **118** is formed in a process involving several intermediates. Thermal decomposition of **118** leads to the formation of nitrogen, tetrafluoroethylene, and its cyclodimer, perfluorocyclobutane.[8] The reverse reaction, namely nitrogen fixation, was observed during irradiation of a mixture containing tetrachloroethylene and nitrogen with a ^{60}Co source at a rate of 280 rad/sec in a stainless steel reactor; this led to the formation of tetrachloro-Δ^1-1,2-diazetine **119**.[105] An increase in the N_2 fixation rate was observed with increasing N_2 pressure, higher temperature, and irradiation dose. IR and UV spectra support the structure of **119**.



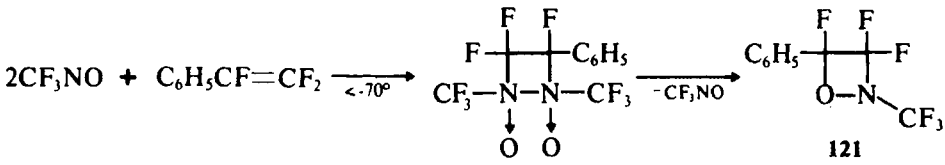
118



119

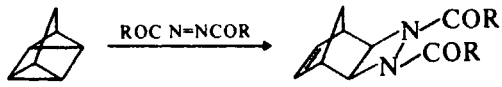
The reaction of trifluoronitrosomethane with α,β,β-trifluorostyrene at low temperature leads to a cycloadduct with a molar ratio of 2:1, which is believed to be 3,3,4-trifluoro-4-phenyl-1,2-bis(trifluoromethyl)-1,2-diazetidine-1,2-dioxide (**120**).[106] One can rationalize that the cyclization is preceded by a linear dimerization of trifluoronitrosomethane to azotrifluoromethane-*N*,*N*′-dioxide (in analogy to many other aliphatic nitroso compounds), although this seems unlikely since this nitroso compound shows no tendency to dimerize even in the liquid form.[107] The

cycloadduct **120** is thermolabile and loses one mole of trifluoronitrosomethane on heating above its melting point (76°C), producing the oxazetidine **121**. If styrene is treated with trifluoronitrosomethane, a 1:2 adduct is obtained; this adduct was identified as a 1,2,3-oxadiazolidine derivative.[106]



120 **121**

The nonolefinic hydrocarbon quadricyclane, with highly strained σ bonds, readily reacts with acylated azo compounds, such as azodicarboxylates[108] and diaroyldiazines,[109] to give (in a $[2\pi+2\sigma+2\sigma]$ process) regio- and stereospecific 1,2-diazetidine derivatives of type **122** (3,4-substituted 3,4-diazatricyclo[4.2.1.$0^{2,5}$] non-7-enes). Reaction rate measurements in the diarolydiazine additions showed an increase caused by electron-withdrawing groups (CF_3 vs. CH_3O) in the para position of the aryls and also by polar solvents (CH_3CN vs. CCl_4), indicating that polar intermediates are formed during the cyclization process.[109]



122

R	m.p. (°C)	Yield (%)	Ref.
OCH_3		74	108
OC_2H_5			108
C_6H_5	211–212	65[a]	109
$C_6H_4OCH_3(4)$	190–191	60[a]	109
$C_6H_4CF_4(4)$	220–221	90[a]	109

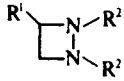
[a] Crude yields above 90%.

Diazomethane and diphenyldiazomethane have been claimed to react with 2,2′-azopyridine, 2,2′-azoquinoline, and ethyl 2-quinolineazocarboxylate with formation of diaziridines and 1,2-diazetidines,[110–112] but reinvestigations of these reactions by Katritzki and Musierowicz[113] and by Markert and Fahr[114] led to a revision of the structure assignments. The compounds obtained from 2,2′-azopyridine and diazomethanes, believed to be 1,2-diazetidines (**123**), were found to be *N*-formyl-2,2′-hydrazopyridines (**124**) and those believed to possess diaziridine structure turned out to be triazolines (**125**).

B. *Ring-Closure Reactions Involving HX Abstraction*

1,2-Dialkyl-1,2-diazetidines are conveniently prepared by heating 1,2-dialkylhydrazines with *vic*-dibromo alkanes in the presence of sodium carbonate as a

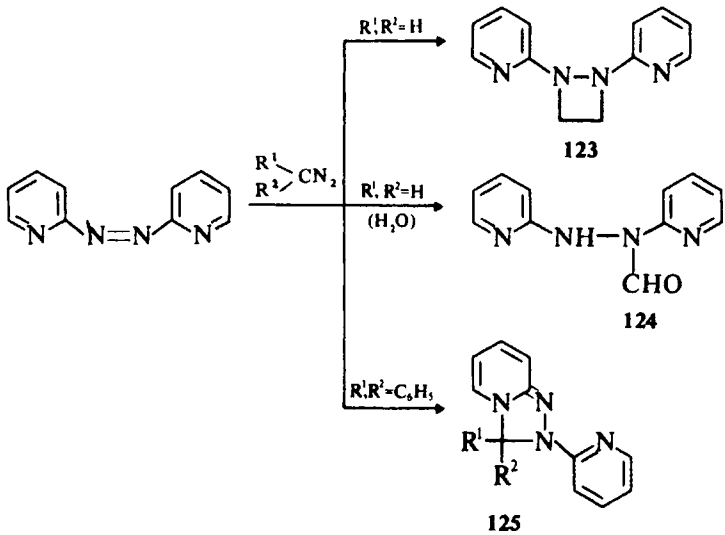
TABLE 10. 1,2-DIALKYL-1,2-DIAZETIDINES FROM 1,2-DIALKYLHYDRAZINES AND *vic*-DIBROMO ALKANES



R^1	R^2	b.p. (°C)	Yield (%)	Ref.
H	CH_3	70–72	32[a]	6, 7, 115
H	C_2H_5	119–120	28	7
H	$(CH_3)_2CH$	154–155	60	7, 115
H	$(CH_3)_3C$	30–31/4.7 mm	2.3[b]	7
CH_3	C_2H_5	25/9 mm	24	7
C_6H_5	$(CH_3)_2CH$	105/1 mm	2	7

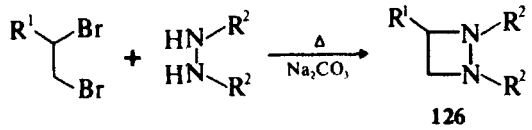
[a] Contaminated by an unidentified impurity.
[b] Obtained only once.

hydrogen bromide scavenger.[6,7,115] Best yields are obtained on adding a large excess of dibromide dropwise to the dilute hydrazine solution in xylene, which also contains the Na_2CO_3. The yields of 1,2-diazetidines obtained by this method vary widely (see Table 10); they tend to be significantly lower if bulky substituents are present on either the bromo or hydrazine component.[7]



The 1,2-diazetidines **126** are remarkably stable compounds; they are not easily cleaved on heating above 100°C, are chemically resistant to 98% sulfuric acid and concentrated hydrochloric acid, and the N–N bond is not cleaved on attempted catalytic hydrogenation over Pt–C.[7]

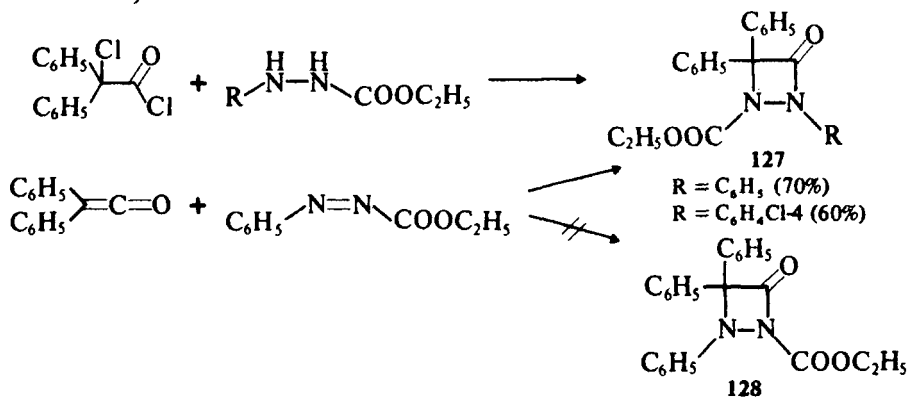
Ethyl phenylhydrazinecarboxylate reacts with diphenylchloroacetyl chloride on heating in benzene to give 1,2,4,4-tetrasubstituted 1,2-diazetidine-3-ones (**127**) in good yields.[68,116] This synthesis was helpful in elucidating the structures of [2+2]



126

R^1 = H, alkyl, aryl
R^2 = Alkyl

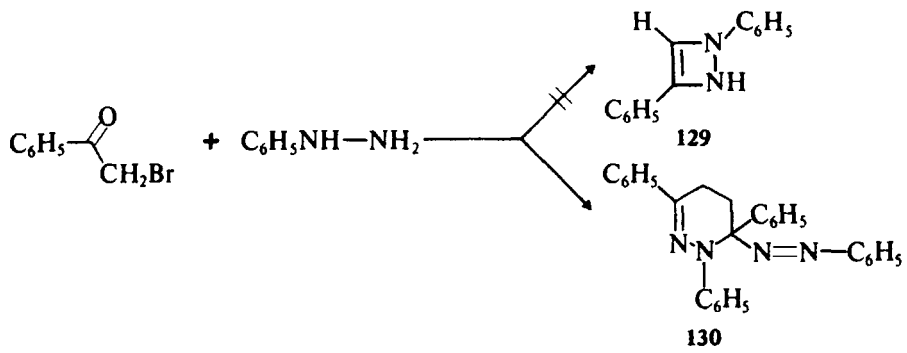
cycloadducts obtained from diphenylketene and phenyl azocarboxylates, which were originally believed to have the isomeric structure **128**.[47] Compounds of type **127** are readily decarboxylated on heating in ethanolic hydrochloric acid (see also Section 3.A).



127
R = C_6H_5 (70%)
R = C_6H_4Cl-4 (60%)

128

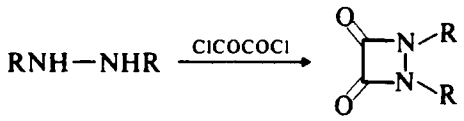
An attempt to synthesize 1,3-diphenyl-Δ^3-1,2-diazetine **129** by reacting α-bromoacetophenone with phenylhydrazine failed.[117] Subsequent investigations clearly showed that the reaction product had structure **130**.[118]



129

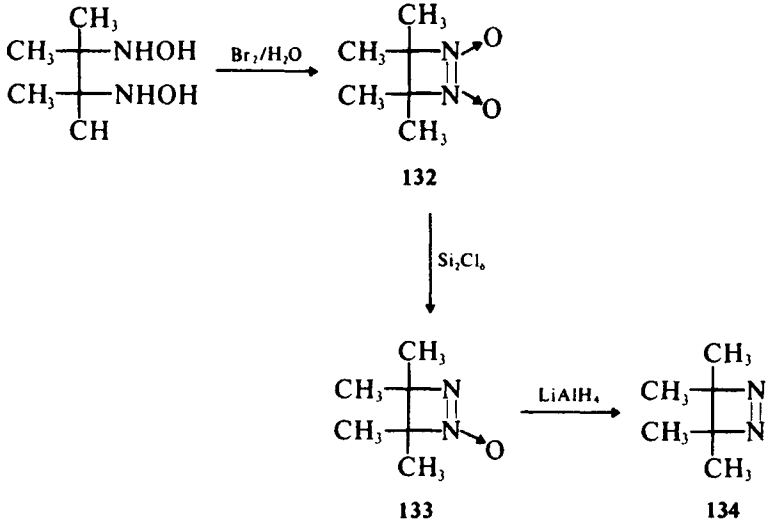
130

1,2-Dialkylhydrazines react also with oxalyl chloride in pentane or hexane solution to yield the 1,2-dialkyl-1,2-diazetidine-3,4-diones **131**.[5] The diisopropyl derivative, a yellow liquid, polymerizes at room temperature within a few hours but can be kept at −20°C. The di-*t*-butyl derivative is stable at ambient temperatures if stored under nitrogen; rapid decomposition takes place on exposure to moist air.



131
R = $(CH_3)_2CH$ (20%)
R = $(CH_3)_3C$ (58%)

Several *N*-alkylhydroxylamines having either another hydroxylamino or oxime group on the β-carbon of the *N*-alkyl group have been found to be excellent starting materials for the synthesis of Δ^1-1,2-diazetine dioxides. The oxidative cyclization of 2,3-dimethylbutane-2,3-bishydroxylamine with bromine or sodium periodate in aqueous solution at room temperature yields 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine-1,2-dioxide (**132**).[119-122] Compound **132**, which was found to be an excellent triplet quencher,[120] can be deoxygenated stepwise. Treatment with hexachlorodisilane in chloroform removes one *N*-oxygen to yield the monoxide **133**; further treatment with lithium aluminum hydride in diethyl ether gives the Δ^1-1,2-diazetine **134**.[122] These reduction steps provided proof for the structure of the dioxide **132**, for which several other formulae had been considered.[122]

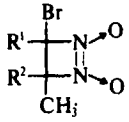


132

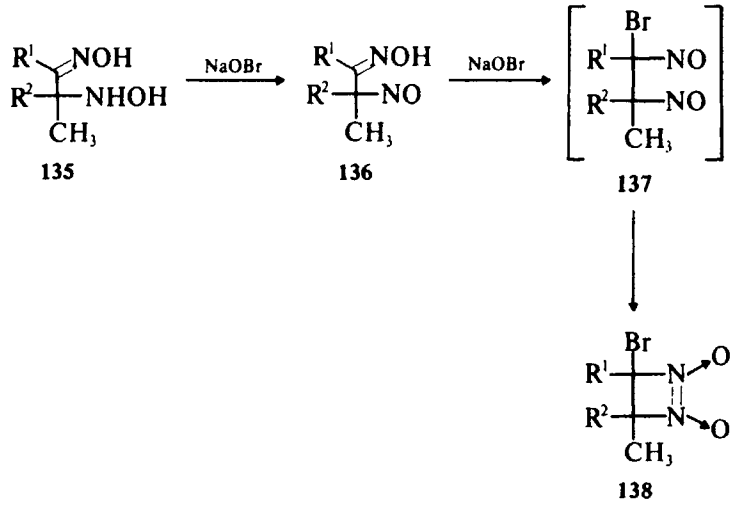
133 **134**

Tertiary α-hydroxylamino oximes with the general formula **135** are readily converted into Δ^1-1,2-diazetine-1,2-dioxides **138** (see Table 11) on treatment with excess aqueous sodium hypobromide.[123] The cyclizations, which are accompanied by bromination in position 3, are likely to proceed via the dinitroso intermediate **137**, which, in analogy to other nitroso compounds, dimerizes to **138**.[123-126] Evidence for the formation of another intermediate, the nitroso oxime **136**, was obtained from reactions with insufficient amounts of oxidizing agent. It is likely that the formation of the tetramethyl-Δ^1-1,2-diazetine-1,2-dioxide **132** also proceeds via a dinitroso intermediate.

TABLE 11. 3-BROMO-3-ALKYL(ARYL)-4,4-DIALKYL-Δ^1-DIAZETINE 1,2-DIOXIDES (138) FROM *N*-(1-OXIMINO-1-ALKYL [ARYL]-2-ALKYLPROPYL)-HYDROXYLAMINES (135)



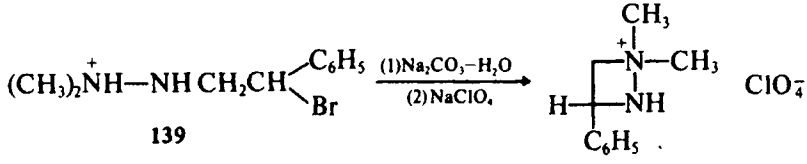
R^1	R^2	m.p. (°C)	Yield (%)	Ref.
C_6H_5	CH_3	110–112	82	123
CH_3	CH_3	125–127	53	123
C_2H_5	CH_3	94–95	51	123
$(CH_2)_3$		123–125	10	123
$(CH_2)_4$		118–120	40	123



135 136 137 138

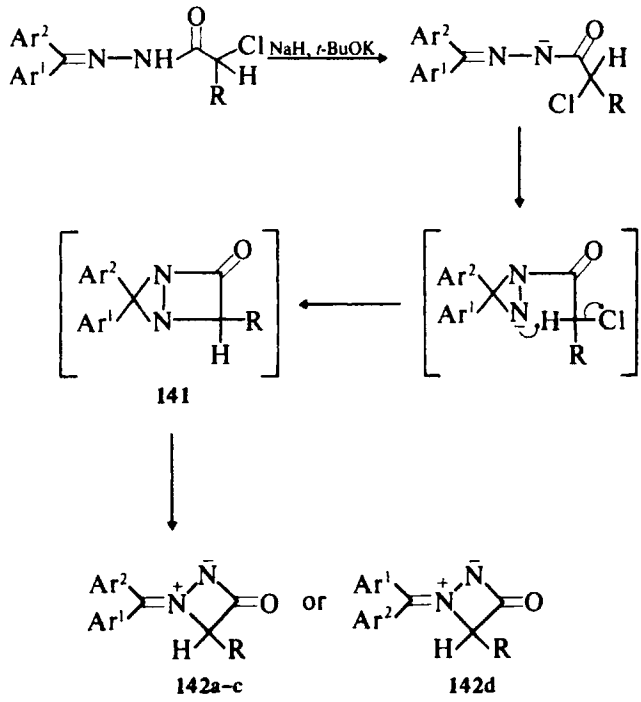
The oxidation of secondary α-hydroxylamino oximes with sodium hypobromide under similar conditions gives 4,5-disubstituted furoxanes instead of Δ^1-1,2-diazetine dioxides.[123]

Intramolecular dehydrohalogenation of certain halogenated hydrazine derivatives also leads to 1,2-diazetidines. Treatment of *N,N*-dimethyl-*N'*-(2-phenyl-2-bromoethyl)hydrazinium bromide (**139**) with dilute sodium carbonate solution and sodium perchlorate gave 1,1-dimethyl-4-phenyl-1,2-diazetidinium perchlorate (**140**) in good yield.[127]



139 **140**

m.p. = 82–83°C (65%)



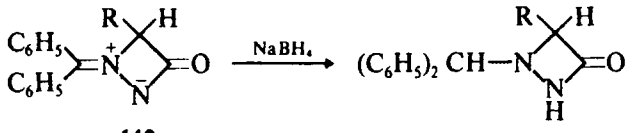
142a–c 142d

	R	Ar^1	Ar^2	m.p. (°C)
a.	H	C_6H_5	C_6H_5	199–200
b.	H	C_6H_5	C_6H_4Br-4	
c.	C_6H_5	C_6H_5	C_6H_5	
d.	H	C_6H_4Br-4	C_6H_5	

Similarly, benzophenone chloroacetylhydrazones were shown to yield 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salts (**142**) on treatment with strong bases such as sodium hydride or potassium *t*-butoxide. Bicyclic intermediates, such as **141**, are believed to be formed as precursors of **142**.[128] The reactions leading to these 1,2-diazetidinium inner salts were also found to be stereospecific: the *syn*- and *anti*-chloroacetylhydrazones of *p*-bromobenzophenone ($Ar^1 = C_6H_5$, $Ar^2 = C_6H_4Br$-4) gave two isomeric, non interconvertible azomethine imides (**142b** and **142d**).[128] Structurally identical compounds have also been prepared by thermolyzing 2-(methylenehydrazono)-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines.[129]

The structure of these inner salts was confirmed by x-ray analysis of the 4-bromophenyl derivative.[130] An unusually short distance between C–H · · · N was found, which was believed to be caused by a strong hydrogen bridge bonding.[131] Subsequent investigations showed that the short distance is predominantly a result of crystal packing; IR studies on solutions and in the solid state (KBr) support, at the most, very weak hydrogen bonding in the solid.

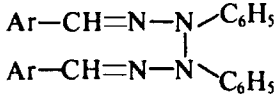
Reduction of the inner salts (**142**) with sodium borohydride in methanol gives 1-diarylmethyl-1,2-diazetidine-3-ones (**143**) in good yield.[132]



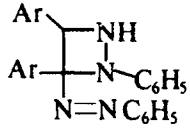
142 143

R	m.p. (°C)	Yield (%)
H	174–175	76
CH_3	163–165	55
C_6H_5	158–159	83

The oxidation of phenylhydrazones of aromatic aldehydes with mercuric oxide or isoamyl nitrite in ether or chloroform is known to yield, depending upon the reaction conditions, mixtures of tetrazones, osazones, and hydrazidines. A UV spectroscopic reexamination of the products seems to indicate that compounds believed to be tetrazones (**144**) are in reality the 1,2-diazetidines (**145**).[133] However, more evidence seems to be needed in support of the proposed structure.



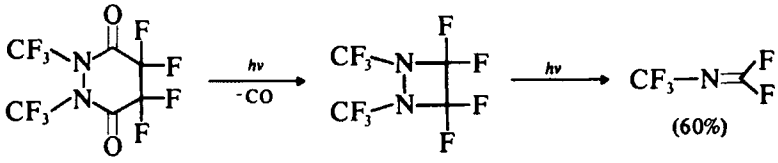
144



145

C. *Ring Contractions*

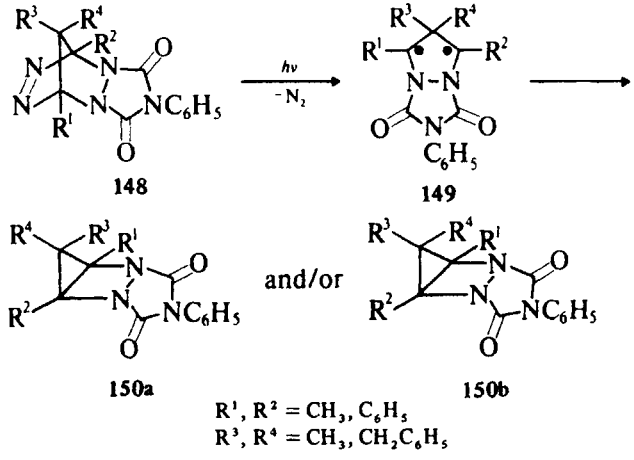
A number of substituted 1,2-diazetidine derivatives have been prepared from five- and six-membered ring heterocycles by either expulsion of one or several of the links in the ring chain (N_2, C=O) or by ring contraction, which involves opening of a heterocycle and reclosure in a different manner under the influence of light, thermal energy, or chemical agents. The irradiation of perfluoro-1,2-dimethylperhydrodiazine-3,6-dione (**146**) causes double decarbonylation of the heterocycle and formation of perfluoro-1,2-dimethyl-1,2-diazetidine (**147**). This product is itself photolabile and dissociates under the reaction conditions, giving perfluoro-2-azapropene as the end product.[134]



146 147 (40%) (60%)

Another photolytic ring contraction proceeds with elimination of N_2. Thus, irradiation of the Diels–Alder adducts **148**, obtained from 1,2,4-triazoline-3,5-diones and isopyrazoles (substituted 2,4,5,8,9-pentaazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-diones) in benzene below 10°C, leads to the evolution of nitrogen and formation of the liabile 1,5,7-triazatricyclo[3.1.0.$0^{2,4}$]octanes **150** in good yields.[135]

Isolation of the products in pure form was not possible because of their air and moisture sensitivity; they were identified by nmr and trapping with 4-phenyl-1,2,4-triazoline-3,5-dione. Esr spectral analyses clearly show that the reactions involve diradicals of type **149**, which can also be generated thermally from **148**. With two different substituents (R^3 and R^4) on the methylene bridge, two isomeric products (**150a** and **150b**) have been obtained in several cases. A thermal isomerization of pure **150a** and **150b**, leading to mixtures of both isomers as a result of an inversion around the $R^1C{-}CR^2$ bond (involving ring opening to a diradical), can be followed by monitoring the temperature dependence of the nmr spectra.

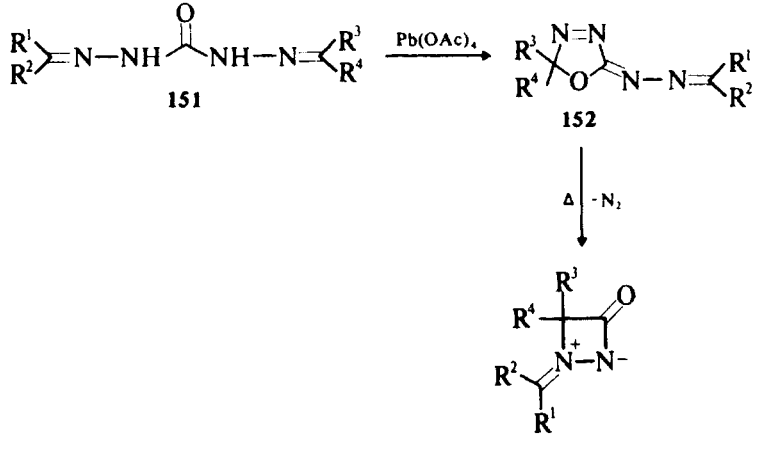


148 **149**

150a **150b**

$R^1, R^2 = CH_3, C_6H_5$
$R^3, R^4 = CH_3, CH_2C_6H_5$

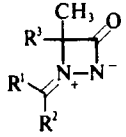
Thermolysis of 2-(methylenehydrazono)-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines **152** (obtained by oxidative cyclization of asymmetrically substituted carbohydrazones **151**) in refluxing chlorobenzene leads to loss of nitrogen and formation of 1-methylene-3-oxo-4,4-dialkyl-1,2-diazetidinium inner salts **153** (see Table 12) in yields ranging from 32 to 36%.[129] The structure of these compounds was confirmed by x-ray analysis.[136]



151 **152**

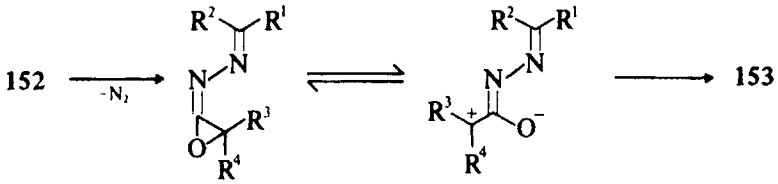
153

TABLE 12. 1-METHYLENE-3-OXO-4,4-DIALKYL-1,2-DIAZETIDINIUM INNER SALTS (153) FROM 2-(METHYLENEHYDRAZONO)-5,5-DIALKYL-Δ^3-1,3,4-OXADIAZOLINES (152)[129]



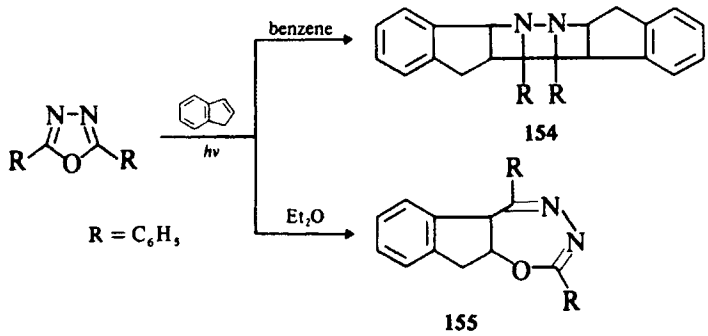
R^1	R^2	R^3	m.p. (°C)
C_6H_5	C_6H_5	CH_3	171–173
4-ClC_6H_4	4-ClC_6H_4	CH_3	200–201
4-BrC_6H_4	4-BrC_6H_4	CH_3	210–211
C_6H_5	H	CH_3	191
4-$CH_3C_6H_4$	H	CH_3	211
C_6H_5	H	$CH_2C_6H_5$	154

A mechanism involving dipolar intermediates has been suggested for the formation of the diazetidinium salts **153**.[129] Similar compounds have been obtained by cyclization of benzophenone chloroacetylhydrazones; these are described in Section 2.B.[128]

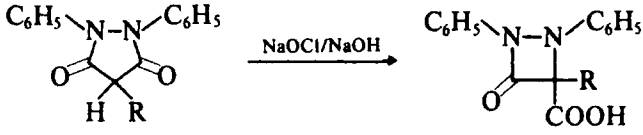


The photolysis of 2,5-diphenyl-1,3,4-oxadiazole in the presence of indene in benzene solution is claimed to yield the 1,2-diazetidine **154**. The reaction obviously involves two [2+2] cycloadditions followed or preceded by expulsion of oxygen.[137] If the reaction is carried out in diethyl ether as solvent, the oxadiazepine **155** is obtained instead.

Ring contractions involving *N*-arylsubstituted 3,4-dioxopyrazolidines (**156**) were shown to give 1,2-diazetidine-3-one-4-carboxylic acids (**157**). Treatment of 1,2-diphenyl-4-*n*-butyl-3,5-dioxopyrazolidine with sodium hypochloride in sodium



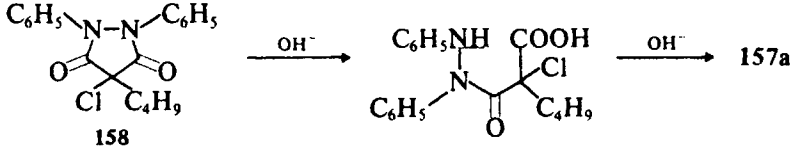
hydroxide solution at 0–5°C leads to the formation of 1,2-diphenyl-4-*n*-butyl-1,2-diazetidine-3-one-4-carboxylic acid.[138] Several other 4-alkyl-1,2-diazetidine-3-one carboxylic acids have been prepared similarly (no yields given); sodium hypobromide has also been used in these oxidative rearrangements.[138]



156 157a–h

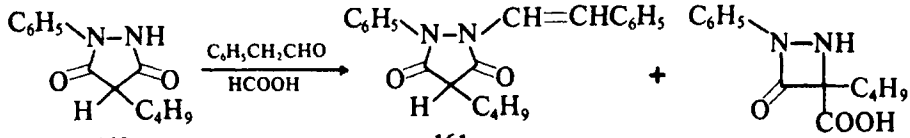
	R	m.p. (°C)
a.	Butyl	122
b.	Amyl	109
c.	$(CH_3)_2CH$	138
d.	Cyclopentyl	137
e.	$CH_2C_6H_5$	108
f.	Tetrahydrofuryl	80
g.	2 (4-pyridylethyl)	162
h.	Diethylaminoethyl	116

In a related reaction, 1,2-diphenyl-4-butyl-4-chloro-3,5-dioxopyrazolidine **158** (4-chlorophenylbutazone) is used as starting material for the rearrangement.[139] Treatment of **158** with two equivalents of sodium hydroxide leads to **157a** in about 77% yield. An intermediate in this reaction, the malonic acid derivative **159**, could also be isolated when less sodium hydroxide was used in the process. Both ring contractions are reminescent of the Favorskii reaction (i.e., ring contractions of α-halogenated ketones leading to carboxylic acids).



158 159

A similar ring contraction has been observed during treatment of 1-phenyl-4-butyl-3,5-dioxopyrazolidine (**160**) with phenylacetaldehyde in refluxing formic acid, which gave a mixture of 1-phenyl-2-styryl-4-butyl-3,5-dioxopyrazolidine (**161**) and 2-phenyl-4-butyl-1,2-diazetidine-3-one-4-carboxylic acid (**162**).[140]

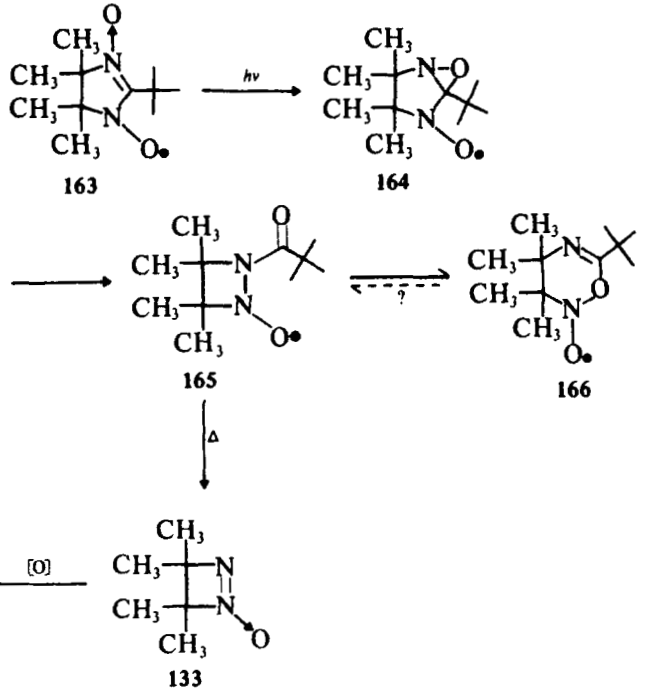


160 161 162

Another type of 1,2-diazetidine formation involves bond reorganizations in heterocycles. A number of pyrazoles, oxadizaoles, as well as imidazole and diazepine derivatives have been converted, mostly in photochemical processes, to four-

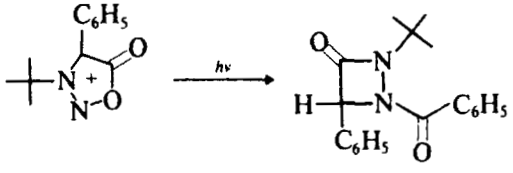
membered-ring heterocycles. Those involving intramolecular cycloadditions were described in Section 2.v.

The irradiation of a pentane solution of the cyclic radical nitronyl nitroxide **163** (> 410 nm at 20°C) produces a mixture of two new heterocyclic radicals, **165** and **166**, which are believed to be formed via the intermediate oxaziridine **164**.[141] This photorearrangement can be sensitized by a number of known photosensitizers. Both products are thermolabile and are readily converted on heating in benzene to a mixture of products containing 49% of 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine 1-oxide (**133**), which was identified by further oxidation (with *m*-chloroperbenzoic acid) to the known 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine-1,2-dioxide (**132**).[120]



163 **164** **165** **166** **132** **133**

On irradiation of a benzene solution of 3-*t*-butyl-4-phenylsydnone with a high pressure mercury lamp, 1-benzoyl-2-*t*-butyl-4-phenyl-1,2-diazetidine-3-one (**167**) is claimed to be formed in 59% yield (68% in toluene). The structure of **167** was confirmed spectroscopically.[142]



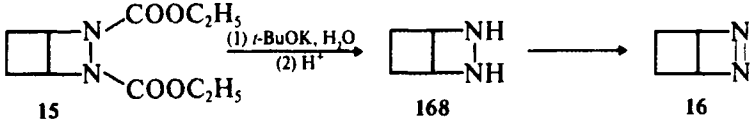
167
m.p. = 114–115°C

3. Reactions

A. *Reactions with Retention of the Heterocycle*

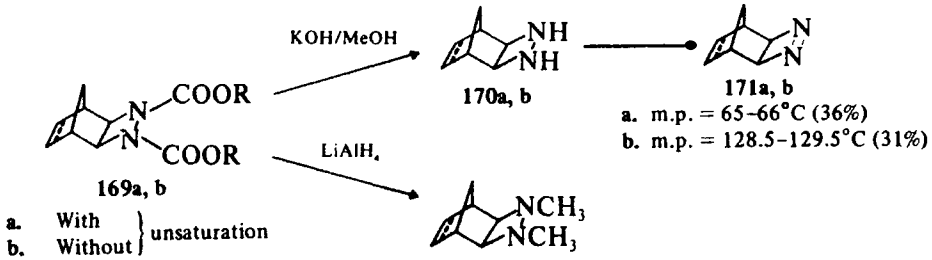
Small rings, including heterocycles, have a built-in ring strain, which renders these compounds susceptible to degradation under relatively mild conditions. Derivatives of 1,2-diazetines and 1,2-diazetidines are no exception. Consequently, only few reactions are known that can be used to modify substituents on the ring or the bond order in the ring.

Removal of electron-withdrawing substituents such as COOR or CN on one or both N atoms is occasionally difficult and will in many cases lead to ring cleavage or ring enlargement. Thus the attempted hydrolytic removal of both ethoxycarbonyl groups in **15** with potassium hydroxide in ethylene glycol or under acidic conditions destroyed the molecule. Treatment of **15** with anhydrous KOH, generated from potassium *t*-butoxide and water in diethylether,[143] followed by acidification of the reaction mixture gave the hydrazo compound **168**, which could be further dehydrogenated with cupric chloride–sodium sulfite to afford the Δ^1-1,2-diazetine **16**.[29]



15 **168** **16**

On the other hand, methanolic potassium hydroxide was used to saponify the alkoxycarbonyl groups in **169a** and **169b** (R = C_2H_5 or CH_3), although the hydrazo compounds **170a** and **170b** were not isolated; oxidation with $CuCl_2$ led to the Δ^1-1,2-diazetines **171a** and **171b**.[108] Treatment of **169a** and **169b** (R = C_2H_5) with lithium aluminum hydride in diethyl ether at room temperature for several hours gave the corresponding 1,2-dimethyl-1,2-diazetidine derivatives **172a** and **172b**.[115]



169a, b

a. With
b. Without
} unsaturation

R = CH_3 or C_2H_5

170a, b

171a, b

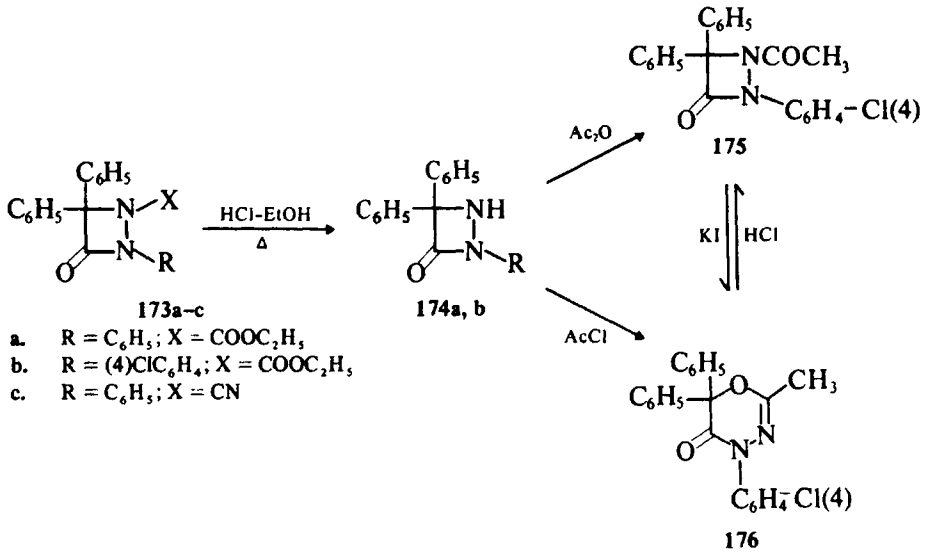
a. m.p. = 65–66°C (36%)
b. m.p. = 128.5–129.5°C (31%)

172a, b

a. b.p. = 55–60°C/3 mm (52%)
b. b.p. = 45–50°C/1 mm (60%)

Acid treatment of 1-aryl-3,3-diphenyl-1,2-diazetidin-4-ones (**173**) possessing an ethoxycarbonyl or nitrile group in the 2-position (aqueous HCl–ethanol, reflux) led to hydrolytic removal of these groups, yielding **174a** and **174b**.[68,116] *N*-acetylation of **174b** with acetic anhydride gave **175**, while acetyl chloride treatment produced

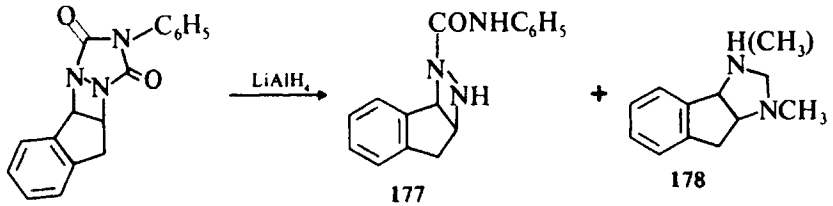
the dihydrooxadiazinone **176** (R = 4-ClC$_6$H$_4$). The same compound was also obtained when **175** was heated in xylene in the presence of small amounts of iodide.[68] The ring expansion of **175** to the oxadiazinone can be reversed by heating **176** with concentrated hydrochloric acid.



a. R = C_6H_5; X = $COOC_2H_5$
b. R = (4)ClC_6H_4; X = $COOC_2H_5$
c. R = C_6H_5; X = CN

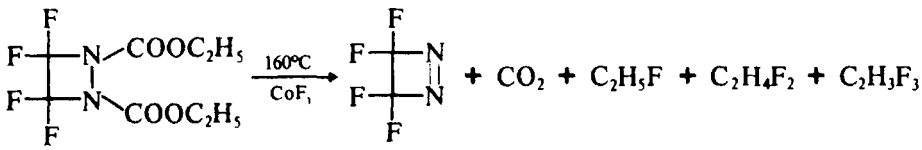
Similarly, diisopropyl 3,3,4,4-tetrafluoro-1,2-diazetidine-1,2-dicarboxylate is readily hydrolyzed and decarboxylated on treatment with excess concentrated sulfuric acid, affording 3,3,4,4-tetrafluoro-1,2-diazetidine in 88.5% yield.[17] When diisopropyl 3-methyl-1,2-diazetidine-1,2-carboxylate, however, is treated with 89 or 100% sulfuric acid or with cobalt fluoride (at 180°C), the heterocycle is destroyed.[16]

Hydrolytic methods failed to remove the CONR groups from the cycloadduct **8**, derived from indene and 4-phenyl-1,2,4-triazoline-3,5-dione; opening of the four-membered ring took place instead. Only with lithium aluminum hydride was **8** partially deacylated, giving **177**, although the reaction was accompanied by formation of the indeno[2,1-d]imidazole **178**.[9]



8 177 178

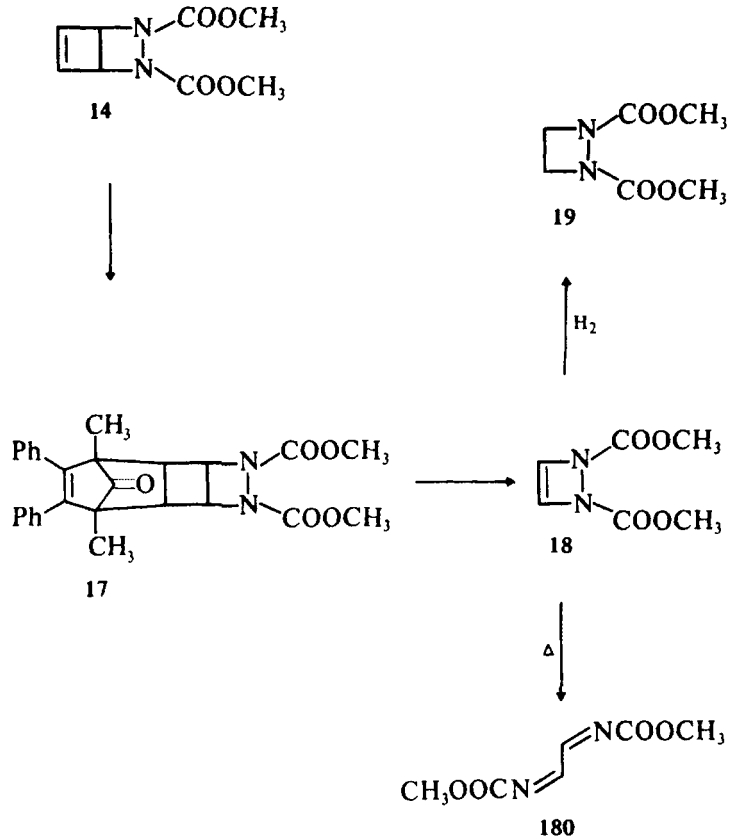
Both ethoxycarbonyl groups are removed thermally from diethyl tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (**179**) in the presence of cobalt(III)fluoride, affording 3,3,4,4,-tetrafluoro-Δ^1-1,2-diazetine (**118**) in 40% yield plus fluorinated ethanes and carbon dioxides.[144]



179 118

The stepwise removal of *N*-oxide groups in 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine-1,2-oxide, giving both the monoxide and 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine,[122] as well as the *N*-oxidation of the monoxide to the dioxide[120] have already been described in Section 2.B and 2.C.

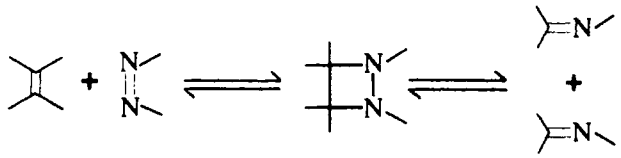
The 1:1 cycloadduct **17**, obtained from 2,3-bis(methoxycarbonyl)-2,3-diazabicyclo[2.2.0]hex-5-ene (**14**) and 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone, is cleaved on irradiation with a medium pressure mercury lamp at 0°C to produce carbon monoxide, 3′,6′-dimethyl-*o*-terphenyl, and the very unstable dimethyl Δ^3-1,2-diazetine-1,2-dicarboxylate (**18**).[18] The diazetine isomerizes at room temperature to the glyoxal derivative **180**; hydrogenation of **18** over Pd–C yields the stable dimethyl-1,2-diazetidine-1,2-dicarboxylate (**19**).



B. *Ring-Opening Reactions*

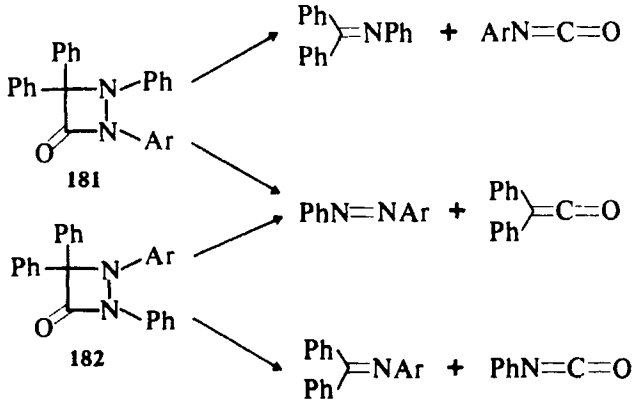
a. THERMAL AND PHOTOCHEMICAL FRAGMENTATION

A large number of 1,2-diazetines and 1,2-diazetidines dissociate at elevated temperatures. This is especially the case with 1,2-diazetidine derivatives that are formed by [2+2] cycloaddition. [2+2] Cycloreversion leads back either to the starting materials or to a set of new compounds.

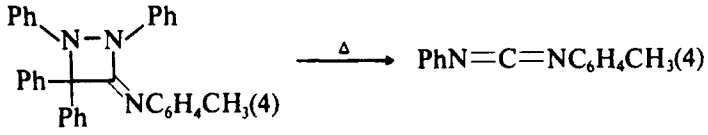


The thermal decompositions of 1,2-diaryl-1,2-diazetidinones, which were shown to dissociate into both imine/isocyanate and back to azobenzene/ketene mixtures, have received the most attention.[48-50, 53, 54]

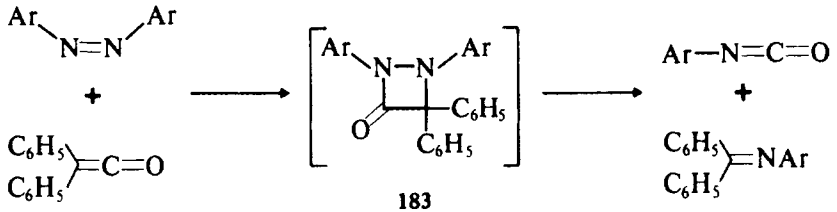
Mixtures of the [2+2] cycloadducts **181** and **182**, obtained from substituted *cis*-azobenzenes and diphenylketene, were found to afford mixtures of all possible products.



Kinetic studies, product distribution, and dissociation temperature were used to draw conclusions about the mechanisms involved in the cyclization–dissociation. The thermal decomposition of several tetraaryl-1,2-diazetidinones, having identical aryl groups (p-RC_6H_4) on both ring nitrogens, was accelerated when the R group was electron withdrawing. This was interpreted to mean that the reactions proceed by initial homolytic cleavage of the N–N bond, giving a diradical.[49] On the other hand, a low degree of regioselectivity in the formation of tetraaryl-1,2-diazetidinones from asymmetrically substituted azobenzenes with diphenylketene, coupled with only a small effect of substituents on reaction rates and product distribution, seems to disfavor a diradical process and could well be explained by a concerted, although not perfectly synchronous, process.[50] The thermolysis of 1,2,3,3-tetraphenyl-4-*p*-tolylimino-1,2-diazetidine, formed by cycloaddition from the corresponding ketenimine and azobenzene, gave *N*-phenyl-*N'*-*p*-tolycarbodiimide as the only identifiable product.[71]



Occasionally, the [2+2] cycloadditions lead to products that are extremely labile under the reaction conditions employed and decompose already during formation; the transient existence of 1,2-diazetidine derivatives is indicated only by their decomposition products. Thus, irradiating a benzene solution of 4,4′-bis(dimethylamino)azobenzene and diphenylketene does not give the expected 1,2-diazetidinone **183** but rather a mixture of its decomposition products: *p*-dimethylaminophenyl isocyanate and *N*-(*p*-dimethylaminophenyl)diphenyl ketimine.[49]



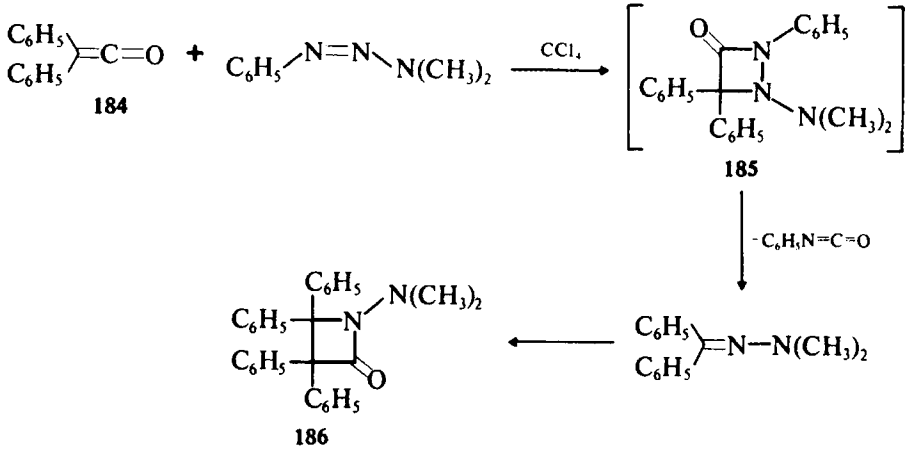
183

Ar = $C_6H_4N(CH_3)_2$-*p*

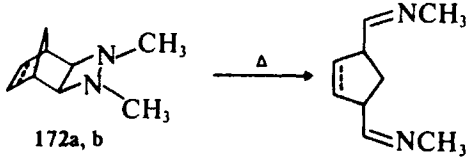
Similarly, the photolysis of *p*-*N*,*N*-dimethylaminobenzaldehyde anil in diethyl ether gives 4,4′-bis(dimethylamino)stilbene and azobenzene, probably via a labile [2+2] cycloadduct.[76]

Another case involves the reaction of *cis*-3-dimethyl-1-phenyltriazene with diphenylketene, which ultimately yields phenyl isocyanate and 3,3,4,4-tetraphenyl-1-dimethylaminoazetidine-2-one (**186**), which is believed to be formed via the labile [2+2] cycloadduct **185**.[50]

The flash vacuum photolysis of two fused-ring 1,2-diazetidine derivatives, **172a** and **172b**, at 450°C and above for ~ 0.5 sec led to formation of cyclopentane and

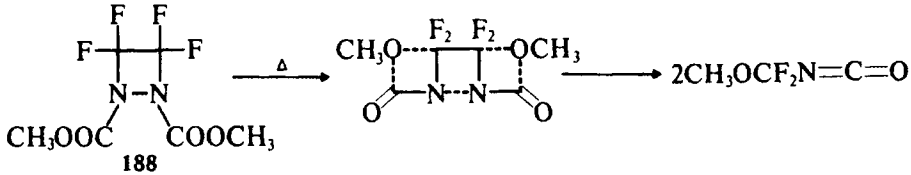


cyclopentene bisaldimines (**187a** and **182b**, respectively) as the sole reaction products.[145] It is believed that the reaction proceeds in a stepwise fashion, involving initial rupture of the N–N bond and not via concerted [2+2] cycloreversions.[145]



172a, b **187a, b**

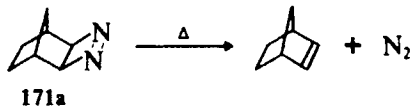
Rather unusual in regard to the pathway of the thermal decomposition, and consequently to the structure of the product, is the way in which dimethyl 3,3,4,4-tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (**188**) is cleaved. The formation of methoxy-1,1-difluoromethyl isocyanate at 600°C can best be explained by simultaneous bond breaking and bond formation.[15]



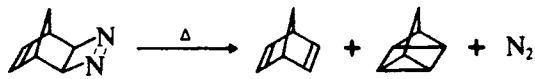
188

The thermal and photochemical decomposition of several alkylated Δ^1-1,2-diazetines has been studied. 3,3,4,4-Tetramethyl-Δ^1-1,2-diazetine was found to require more thermal energy for dissociation into nitrogen and 2,3-dimethyl-2-butene than other, similarly built cyclic azo compounds with larger rings.[122,146] Several explanations have been offered to account for the experimental results, one being the forbidden orbital symmetry of a concerted $[2_s+2_s]$ decomposition. The photochemical decomposition of the same heterocycle, which proceeds with N_2 formation, was also found not to be very efficient (quantum yield 0.65 in benzene).

The decomposition of the tricyclic Δ^1-1,2-diazetine derivatives **171a** and **172b** has also been studied, both in solution and in the gas phase.[108] Fragmentation of **171a** gave norbornene and nitrogen under either conditions. Thermolysis of **171b** led to nitrogen and a mixture of varying amounts of norbornadiene and quadricyclane (depending upon the decomposition temperature). Photolysis of **171b** gave the tetracyclic hydrocarbon as the major product.[108] The formation of norbornene and norbornadiene is an orbital symmetry-forbidden process, while dissociation into quadricyclane and N_2 is symmetry allowed.

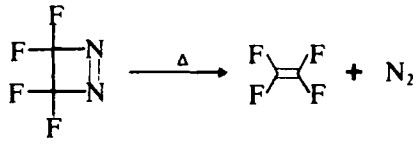


171a



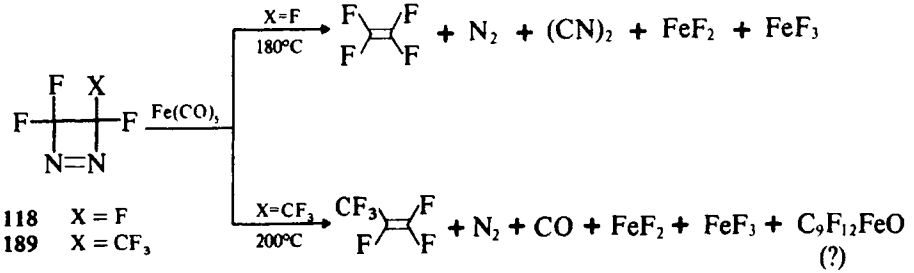
171b

Thermolysis of 3,3,4,4-tetrafluoro-Δ^1-1,2-diazetine (**118**) above 150°C gives tetrafluoroethylene and nitrogen in a unimolecular process.[8,147]



118

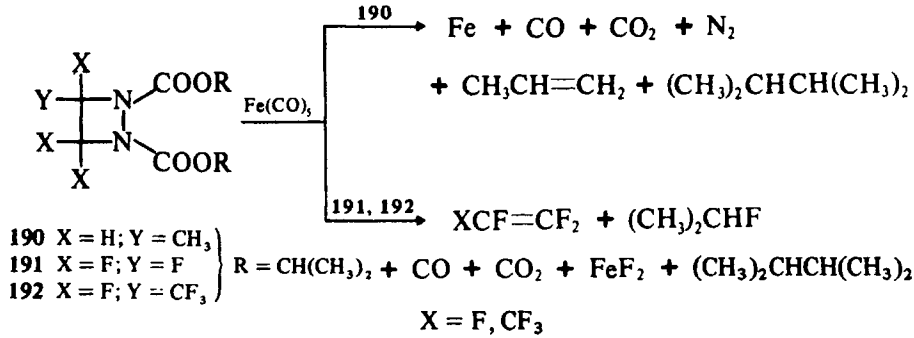
If **118** is heated to 180°C in presence of iron pentacarbonyl, dicyanogen is formed in addition to tetrafluoroethylene and nitrogen (FeF_2 and FeF_3 are also formed). The formation of dicyanogen can be explained by assuming that iron acts as a defluorinating agent.[118] This is, to some extent, a reversion of the formation of **118** from dicyanogen in the presence of argentic fluoride as the fluorinating agent.[8,149] No dicyanogen could be detected among the products of the thermal decomposition of 3,3,4-trifluoro-4-trifluoromethyl-Δ^1-1,2-diazetine (**189**) in the presence of iron pentacarbonyl at 200°C.[148]



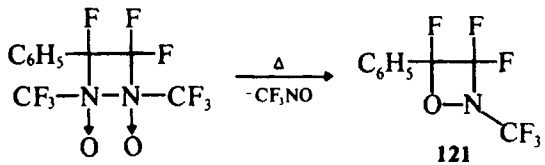
118 X = F
189 X = CF_3

In a number of similar experiments diisopropyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (**190**), as well as diisopropyl 3,3,4,4-tetrafluoro- and 3,3,4-trifluoro-4-trifluoromethyl-1,2-diazetidine-1,2-dicarboxylate (**191** and **192**), were heated in the presence of equimolar amounts of iron pentacarbonyl at 190–200°C, giving rise to mixtures of decomposition products via a radical mechanism.[150]

On heating of 3,3,4-trifluoro-4-phenyl-1,2-bis(trifluoromethyl)-1,2-diazetidine-1,2-dioxide (**120**) above its melting point (76°C), trifluoronitrosomethane is lost and 3,3,4-trifluoro-4-phenyl-2-trifluoromethyl-1,2-oxazetidine (**121**) is formed.[106]

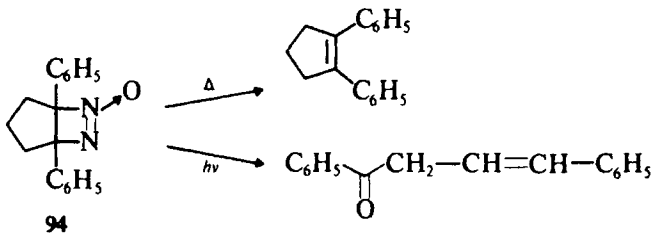


190 X = H; Y = CH_3
191 X = F; Y = F
192 X = F; Y = CF_3
R = $CH(CH_3)_2$
X = F, CF_3



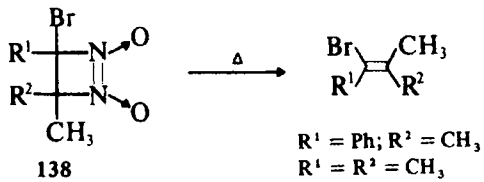
120 121

Bicyclic 1,4-diphenyl-2,3-diazabicyclo[3.2.0]hept-2-ene-2-oxide (**94**) was shown to slowly decompose on heating in diglyme to afford 1,2-diphenylcyclopentene. Photolysis of **94** in methylene chloride (450 W lamp, pyrex filter) gave the unsaturated ketone **193**.[86]



94 193

In a related elimination reaction, olefins were obtained from Δ^1-1,2-diazetine dioxides upon brief heating in benzene. Thus 1-bromo-1-phenyl-2-methylpropene-1 and 2-bromo-3-methylbutene-2 were obtained (aside from nitrogen oxide) from the corresponding 1,2-diazetines **138**.[123]

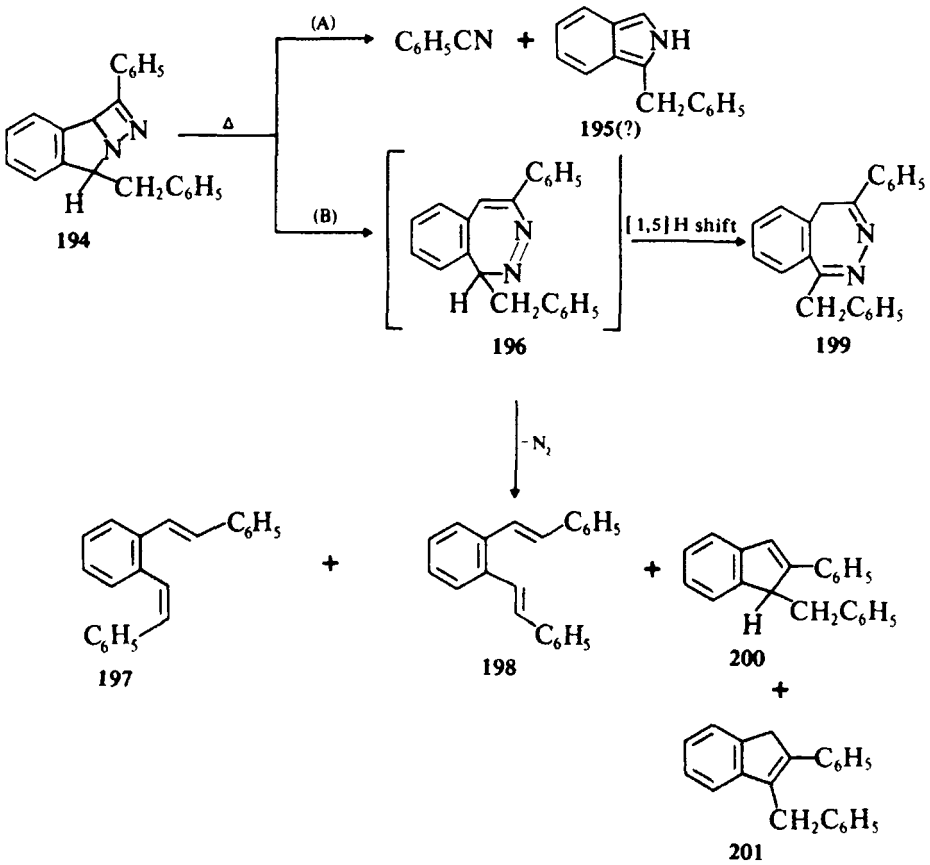


138

$R^1 = Ph; R^2 = CH_3$
$R^1 = R^2 = CH_3$

The pyrolysis of the tricyclic 7-benzyl-2a,7-dihydro-2-phenyl[1,2]diazeto[4,1-a]isoindole (**194**) in *t*-butylbenzene at 168°C gives a number of products as a result of decomposition by two different routes (A and B in the scheme below). Decomposition via route A gives benzonitrile (30%) and probably isoindole (which could not be isolated, probably because of thermal instability). Decomposition via route B gives *cis,trans*- and *trans,trans*-*o*-distyrylbenzene (**197** and **198**; 23 and 35%, respectively), 5H-2,3-benzodiazepine (**199**), and two isomeric compounds, believed to be the indenes **200** and **201**.[91] Most products are formed via route B from 1H-2,3-benzodiazepine **196**, which is formed by [2+2] cyclorevision from **194**. Higher decomposition temperatures (flash-vacuum photolysis at 500°C) favor the formation of products via route B.

Many 1,2-diazetidine derivatives, especially those prepared by [2+2] cycloaddition from azo compounds and activated olefins, are often extremely unstable and decompose on isolation attempts or slowly change (hydrolyze, isomerize) on storage. It is often impossible to isolate pure cycloadducts in cases where several



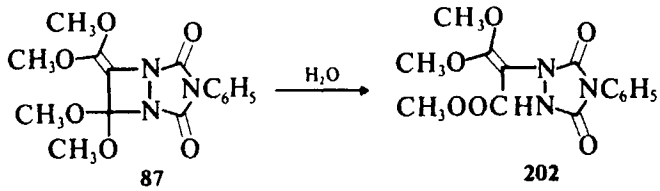
products are formed. All these cases are not treated here; they are discussed, when details about the course of decomposition are known, in the chapters related to their formation.

b. RING OPENING BY CHEMICAL AGENTS

A large number of 1,2-diazetidine derivatives have been treated with acids, bases, and reducing agents. This led in most cases to ring opening or to extensive molecular modifications (see also Section 3.C). Reports about the hydrolytic stability or lability of 1,2-diazetidines have been given for a number of isolated cases; systematic investigations are rare.

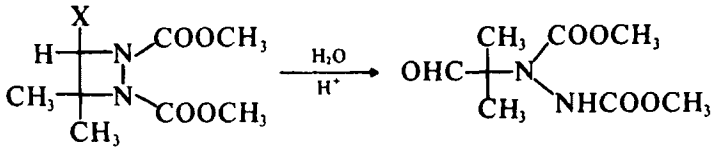
The hydrolytic instability of several 1,2-diazetidinones and 1,2-diazetidines toward water made purification or isolation of some [2+2] cycloadducts impossible.[13,26,38] The strained cycloadduct 7,7-dimethoxy-3-phenyl-6-dimethoxymethylene-1,3,5-triazabicyclo[3.2.0]heptadione-2,4 (**87**), obtained from tetramethoxyallene and 4-phenyl-1,2,4-triazolidine-3,5-dione at low temperature, is hydrolyzed completely on brief exposure to water with opening of the 1,2-diazetidine ring at the amide acetal group, giving the ester **202**.[74]

[2+2] Cycloadducts **203**, derived from enol ethers and enamines with azodicar-

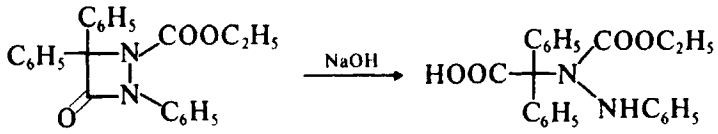


87 202

boxylate, are readily cleaved by aqueous acids at the N–CX bond (X = OR, NR_2).[13] Adducts of enol thioethers with dialkyl azodicarboxylate are similarly cleaved by methanol.[36] Treatment of ethyl-2,4,4-triphenyl-1,2-diazetidine-1-carboxylate (**204**) with dilute ethanolic sodium hydroxyde solution gives the hydrazinodiphenylacetic acid derivative **205**.[47,116]

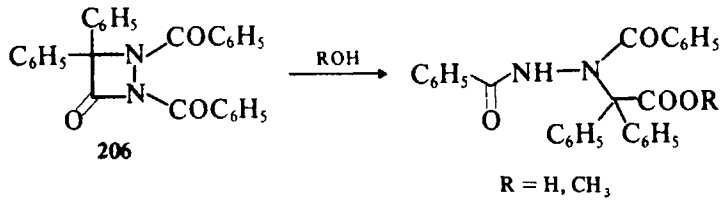


203



204 **205**

1,2-Diphenyl-1,2-diazetidinone is similarly cleaved by cold dilute sodium hydroxide solution to give the corresponding *N,N*-diphenylhydrazinoacetic acid.[53] Ring opening also takes place when 1-(4-chlorophenyl)-2-cyano-3,3-diphenyl-1,2-diazetidinone is treated with sodium hydroxide,[48] although the structure of the product is in doubt because of the revision of the structure of the starting material by Bird et al.[68,116] In the hydrolysis (moist air) and methanolysis of 4,4-diphenyl-1,2-dibenzoyl-1,2-diazetidinone (**206**), the cyclic amide bond is broken and the corresponding acid and ester are obtained.[151]



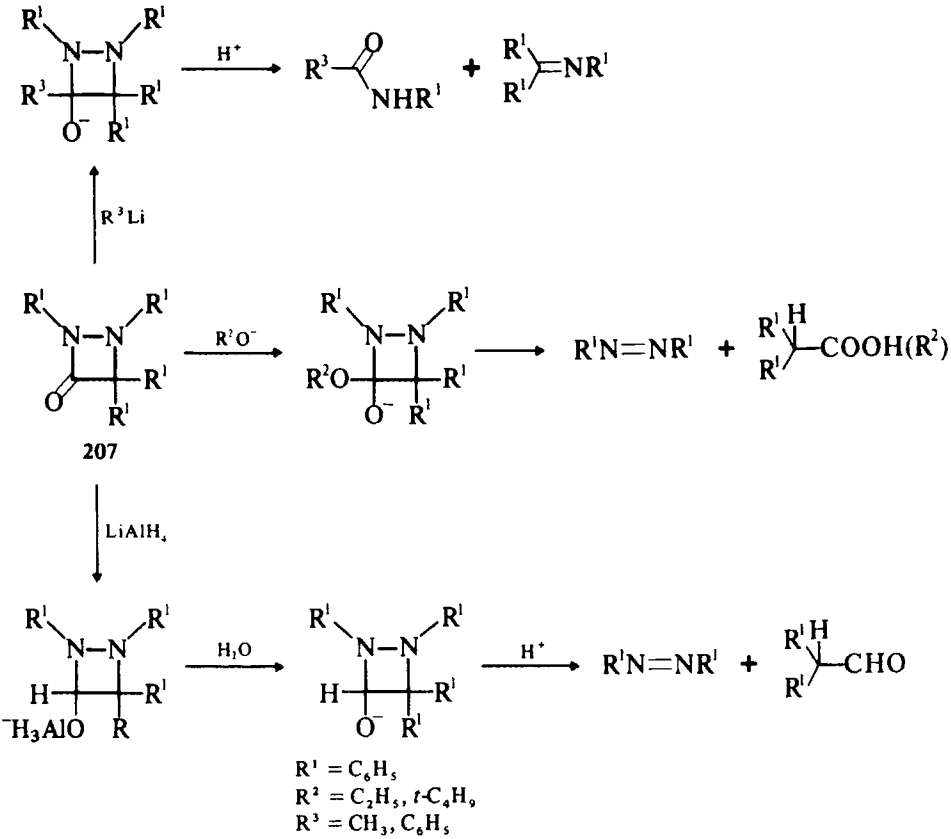
206

R = H, CH_3

A systematic study of the behaviour of 1,2,4,4-tetraphenyl-1,2-diazetidinone (**207**) toward bases such as sodium hydroxide, sodium alkoxide, lithium aluminum hydride, and methyl and phenyl lithium has been published by Hall.[152] Contrary to the preceding reports about the ease of cleavage of the 1,2-diazetidinone ring, it was found that **207** is stable toward cold alcoholic alkali[48] and is attacked only on

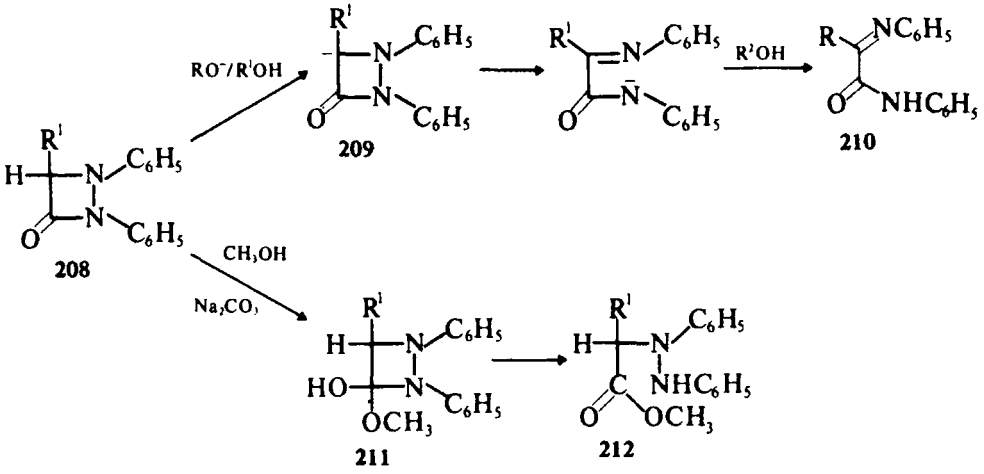
prolonged heating with 50% sodium hydroxide solution, producing diphenylacetic acid and azobenzene.[151] Refluxing **207** with sodium ethoxide or sodium *t*-butoxide in the corresponding alcohols gave the same products in high yield.[152] The formation of diphenylacetic acid instead of the esters is due, in both cases, to the facile hydrolysis of the latter during work-up.

A different type of ring cleavage takes place when **207** is treated with methyl- or phenyllithium in diethyl ether, during which benzophenone anil and benzophenone (as a secondary product), as well as acetanilide or benzanilide, are formed; traces of azobenzene were also isolated. Reductive cleavage of **207** with lithium aluminum hydride followed by work-up with water produced azobenzene along with diphenylacetaldehyde (the latter was oxidized to benzophenone during work-up). The formation of all these products can be rationalized by an initial attack of the base on the ring carbonyl group followed by cleavage of either the N–N/C–C or C–N/C–N bonds.



Related ring openings have been reported for 1,2,4-triaryl-1,2-diazetidinones. Thus treatment of 1,2,4-triphenyl-1,2-diazetidinone with 1% sodium carbonate solution in methanol leads to the formation of methyl *N,N'*-diphenylhydrazinophenylacetate (C–N bond cleavage), while brief refluxing with sodium methoxide/

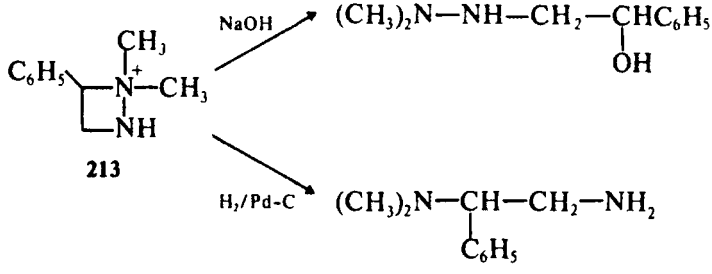
methanol or sodium *t*-butoxide/*t*-butanol leads to N–N cleavage with formation of the anil of phenylglyoxylic acid anilide.[153] When 1,2-phenyl-4-*p*-bromophenyl-1,2-diazetidinone is treated with 1% sodium carbonate solution, ring opening at both the N–N and C–N bonds takes place, and a mixture of the corresponding hydrazinoacetic acid and phenylglyoxylic acid derivatives (**210** and **212**) is obtained. Ring cleavage at the N–N bond by RO^- is believed to involve the formation of an anion of type **209**, while carbonate–methanol is likely to attack the carbonyl group, giving an intermediate (**211**) before the C–N bond is broken.



208 **209** **210** **211** **212**

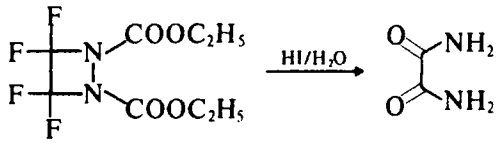
$R^1 = C_6H_5, C_6H_4Br(4), C_6H_4CH_3(4)$
$R^2 = CH_3, C_2H_5, C(CH_3)_3$

Base treatment (NaOH, Na_2CO_3) was also shown to open the diazetidine ring of 1,1-dimethyl-4-phenyl-1,2-diazetidinium hydroxide (**213**) at the 1,4-(NC) bond, giving *N,N*-dimethyl-*N'*-(2-phenyl-2-hydroxyethyl)hydrazine.[127] Hydrogenolysis of the same compound, however, opened the 1,2-bond of **213**, and 2-dimethylamino-2-phenylethylamine was obtained.[127]



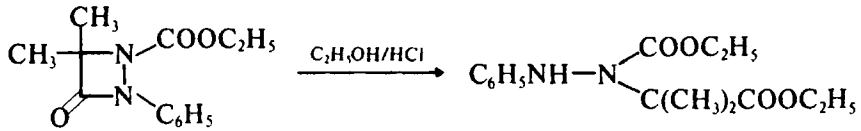
213

The effects of acids on 1,2-diazetidine derivatives has been studied in a few cases, and both C–N and N–N bond cleavage was encountered. 1,2-Di-*t*-butyl-1,2-diazetidinedione is readily hydrolyzed on treatment with methanolic hydrochloric acid, giving methyl (*N,N'*-di-*t*-butylhydrazido)oxalate in high yield.[5] The diethyl 3,3,4,4-tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (**214**) is cleaved on treatment with hydriodic acid, affording oxalamide.[144]



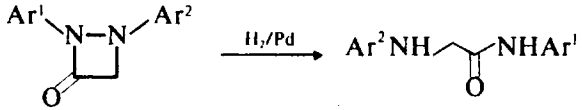
214

The effect of alcoholic hydrochloric acid on substituted 1,2-diazetidinones depends largely on the nature and positioning of the substituents. On refluxing a solution of ethyl 4,4-dimethyl-2-phenyl-1,2-diazetidine-1-carboxylate (**215**), the amide bond is broken and ethyl α-(*N*-carbethoxy-*N'*-phenylhydrazino)isobutyrate is formed.[57] On the other hand, treatment of 1-cyano-2-*p*-chlorophenyl-4,4-diphenyl-1,2-diazetidinone with ethanolic hydrogen chloride leads only to the removal of the cyano group, and the ring remains unchanged.[68] When ethyl 1,4,4-triphenyl-1,2-diazetidinone-2-carboxylate is heated with hydrochloric acid in ethanol, loss of the ethoxycarbonyl group is a side reaction; most of the diazetidine is converted to 1-ethoxycarbonylamino-3,3-diphenyloxindole[116] (see also Section 3.C).



215

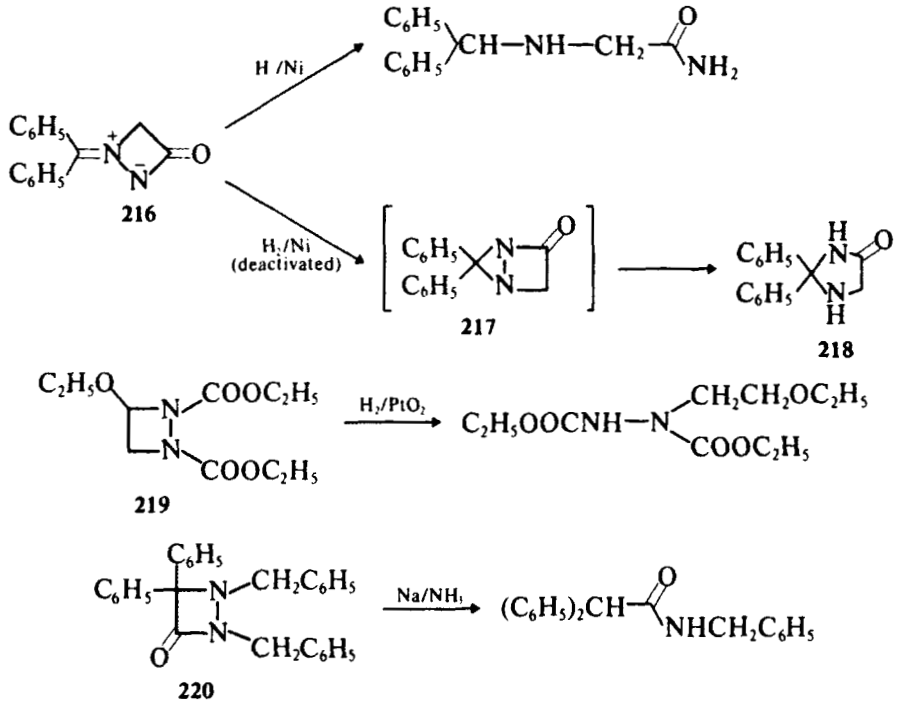
Catalytic hydrogenation usually, but not exclusively, cleaves the N–N bond of the 1,2-diazetidine (one) ring. The hydrogenation of 1,2-diphenyl-1,2-diazetidinone over palladium gave anilinoacetanilide;[53] similar reactions have been reported for related 1,2-diazetidinones.[62]



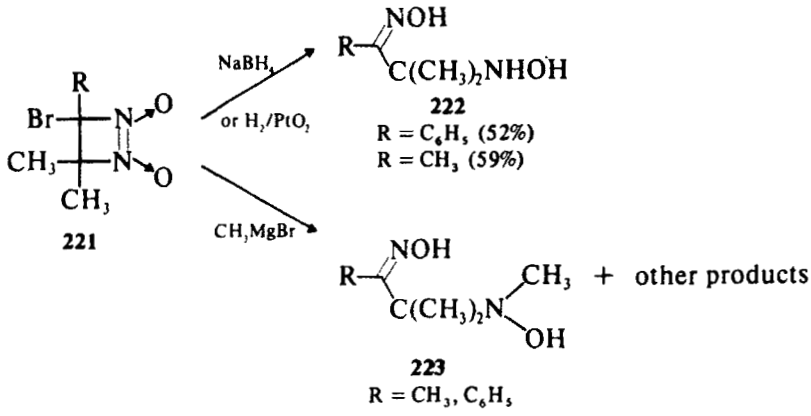
Two different products have been obtained from 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt **216**, depending upon the conditions of the catalyst. Hydrogenation of **216** over active Raney nickel gave α-diphenylmethylaminoacetamide, while deactivated Raney nickel led to the formation of 2,2-diphenylimidazolidine-4-one (**218**), probably via the bicyclic intermediate **217**.[132] The milder sodium borohydride does not attack the ring of **216** but reduces the exocyclic methylene double bond.[132]

Hydrogenation of diethyl 3-ethoxy-1,2-diazetidine-1,2-dicarboxylate (**219**) over platinum oxide proceeds with cleavage of the 2,3-(CN) bond and formation of *N*-(β-ethoxyethyl)-*N,N'*-bis(ethoxycarbonyl)hydrazine in 51% yield.[9]

In an attempt to reductively remove the benzyl groups on 1,2-dibenzyl-3,3-diphenyl-1,2-diazetidinone (**220**) with sodium in liquid ammonia, cleavage of the ring took place instead, and *N*-benzyldiphenyl-acetamide was obtained.[151]

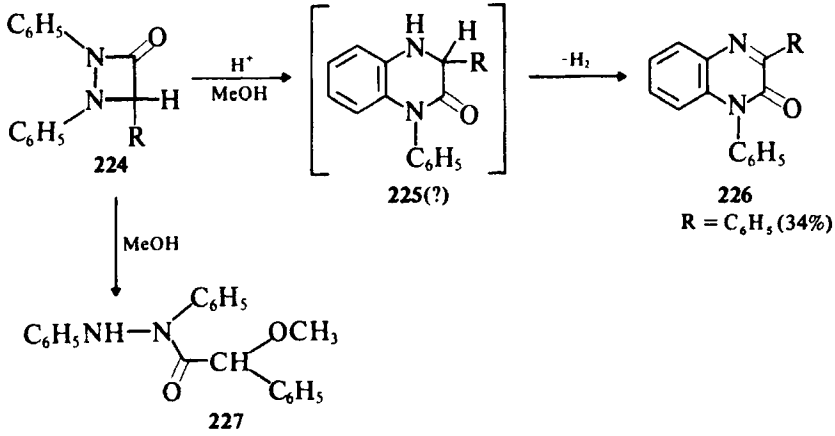


Several 3-alkyl- and aryl-substituted 4,4-dimethyl-3-bromo-Δ^1-1,2-diazetine dioxides of type **221** have been treated with reducing agents. In each case the N–N bond was cleaved, and the products were free of halogen. Sodium borohydride reduction of **221** ($R = C_6H_5$) gave a hydroxylamino ketoxime of type **222**. A similar product was obtained when **221** ($R = CH_3$) was hydrogenated over platinum oxide.[126] Treatment of both diazetine dioxides **221** ($R = CH_3$ and C_6H_5) with methylmagnesium bromide also resulted in N–N bond cleavage, but the reactions were more complex, giving several products, of which *N*-methylhydroxylamino ketoximes **223** were the major ones.[126]

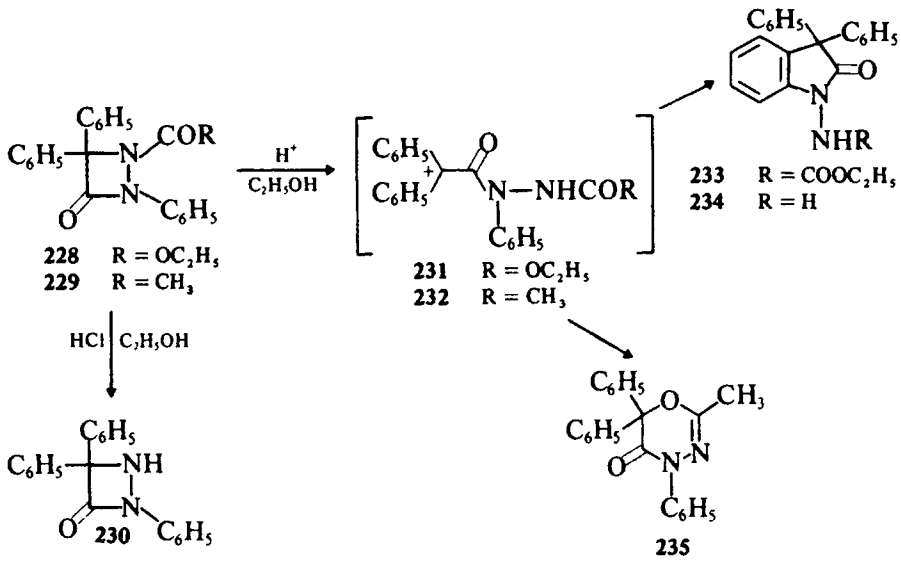


C. *Molecular Rearrangements*

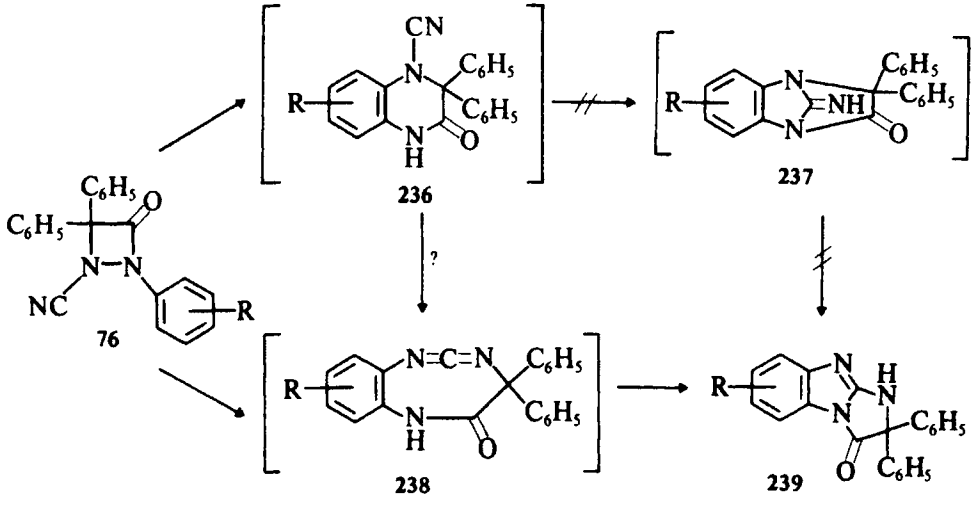
A number of 1,2-diazetidine derivatives have a tendency to undergo acid-catalyzed or thermally induced molecular rearrangements in which the four-membered rings are opened up and larger heterocycles are formed by incorporating other groups or parts of the molecule as building blocks into the new rings. 1,2,3-Triaryl-1,2-diazetidinones of type **224** undergo facile *ortho*-semidine rearrangement on heating in methanol that contains catalytic amounts of sulfuric acid to produce quinoxaline derivatives (**226**) in moderate yield, probably via a hydrogenated intermediate (**225**).[154] The reactions are also accompanied by formation of hydrazides (**227**) as a result of partial methanolysis of the starting material. The structure of **226** ($R = C_6H_5$) was verified by independent synthesis from phenylglyoxylic acid and *o*-aminodiphenylamine. These results disprove the claim by Wittig et al.[155] that only *N,N'*-diaryl-1,2-diazacycloalkanes with at least four methylene units in the ring are capable of undergoing *ortho*-semidine rearrangements.



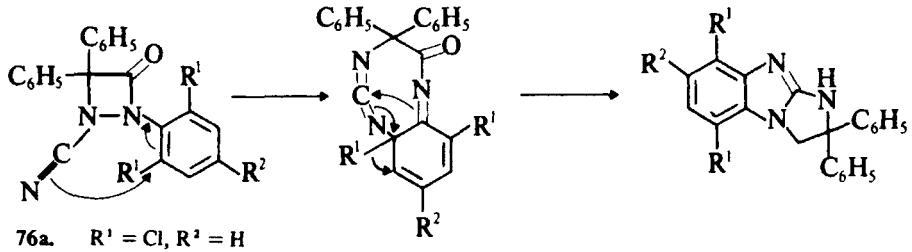
The acid-catalyzed rearrangement of ethyl 2,4,4-triphenyl-1,2-diazetidine-3-one-carboxylate (**228**) was originally believed to also yield a quinoxaline derivative,[47] but a more recent study could show that the product formed was 1-ethoxycarbonyl-amino-3,3-diphenyloxindole (**233**); small amounts of the decarbethoxylated 2,4,4-triphenyl-1,2-diazetidine-3-one (**230**) could be isolated too.[116] Interestingly, the related 2,4,4-triphenyl-1-acetyl-1,2-diazetidine-3-one **229** (prepared by acetyl chloride treatment of **230**) was found to rearrange to a mixture of 5,6-dihydro-2-methyl-4,5,5-triphenyl-5H-1,3,4-oxadiazine-5-one (**235**) and 1-amino-3,3-diphenyl-oxindol (**234**) on heating in ethanolic hydrochloric acid; here too, deacylated 1,2-diazetidinone **230** was formed as a by-product. Both rearrangements, leading either to oxindole or oxadiazine derivatives, are believed to proceed via carbonium ions **231** and **232**, which differ only in the *N*-acyl groups and can be visualized to result from fission of the 2,3-bond following protonation. Subsequent attack on either the *N*-phenyl or the acetyl group will lead to the products, as shown in the following scheme.



Much attention has been focused on the thermal rearrangements of 1-aryl-2-cyano-3,3-diphenyl-1,2-diazetidinones (**76**), which were shown to produce 2,3-dihydro-3-oxo-2,2-diphenyl-1H-imidazo[1,2-a]benzimidazoles (**239**) in very high yield.[68-70,156,157] Brief heating of the cyano-1,2-diazetidinones in refluxing xylene or higher-boiling hydrocarbons is sufficient for the rearrangement to take place. Two mechanisms have been considered for the formation of tricyclic products **239**. Labeling with ^{15}N has clearly shown that the reactions proceed via a [3,3]sigmatropic rearrangement of **76** to cyclic carbodiimides of type **238**, followed by intramolecular cyclization giving the imidazo[1,2-a]benzimidazoles **239**. The alternative mechanism would involve an *ortho*-semidine rearrangement to **236** in the first step (although it was impossible to synthesize **236** independently) and intramolecular cyclization to **237**, followed by N-to-N migration, giving **239**.

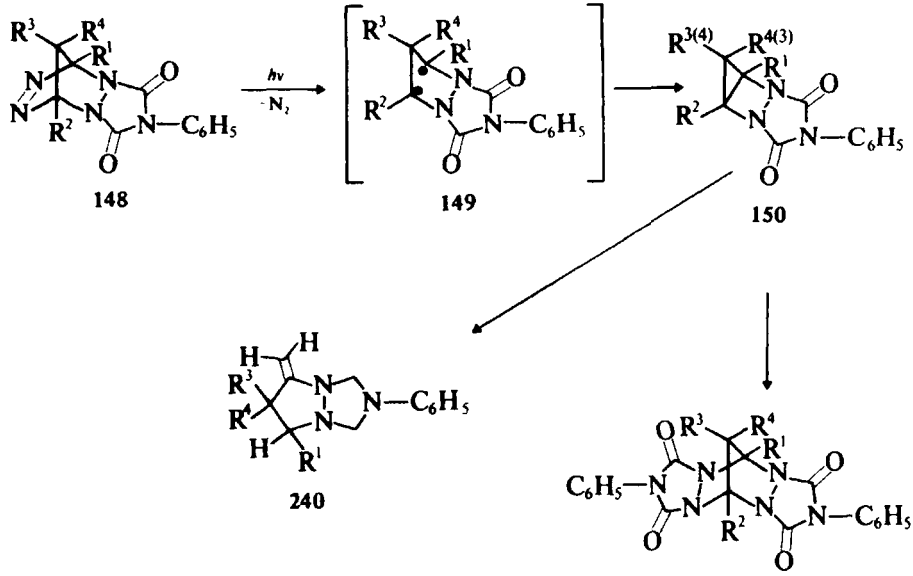


The rearrangements to imidazo[1,2-a]benzimidazoles also take place when both ortho positions of the 1-aryl group of **76** are blocked by halogen (Br, Cl). In these cases, (**76a** and **76b**), a 1,2-halogen shift takes place during the rearrangement, which is followed by rearomatization and hydrogen shift.[158, 70]



76a. $R^1 = Cl, R^2 = H$
b. $R^1 = R^2 = Br$

1,7,8,8-Tetraalkyl-4-phenyl-2,4,6-triazatricyclo[5.1.0.0]ocat-3,5-diones (**150**), which are formed from 1,7,10,10-tetraalkyl-4-phenyl-2,4,6,8,9-pentaazatricyclo-[5.2.1.$0^{2,6}$]dec-8-ene-3,5-diones **148** (Diels–Alder adducts of substituted isopyrazoles and 4-phenyl-1,2,4-triazoline-3,5-dione) by nitrogen extrusion, are thermally very labile and isomerize on heating with rupture of the strained C–C bond of the four-membered ring, followed by a hydrogen shift and formation of 1,3,5-triazabicyclo[3.3.0]octa-2,4-diones **240**.[135] Addition of 4-phenyl-1,2,4-triazoline-3,5-dione to solutions of **150** leads to the formation of products of type **241**, again via opening of the C–C bond of the 1,2-diazetidine ring.[135]



148 **149** **150**

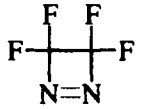
240

241
$R^1 = CH_3, C_6H_5$
$R^2, R^3, R^4 = CH_3$ or $CH_2C_6H_5$

4. Structure and Spectral Properties

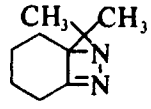
Spectroscopic methods have been used extensively to characterize and identify derivatives of 1,2-diazetines and 1,2-diazetidines. Structural features and steric aspects have become known through analyses of spectral data. In addition, the limited number of methods for structure verification by independent synthesis and chemical modification of these compounds (which very often results in the destruction of the heterocycle) makes these methods even more valuable. It has also been possible to ascertain spectroscopically the formation of very labile 1,2-diazetines at low temperature when isolation at ambient temperature failed.

Vibrational spectra have been recorded for a large number of 1,2-diazetidine and 1,2-diazetine derivatives.[5,6,9,29,50,59,62,63,86,88,103,122,142,158] They have often been compared with those of related cyclic and acyclic compounds; i.e., the IR and Raman spectra of dialkyl tetrafluoro-1,2-diazetidine-1,2-dicarboxylates were compared with those of acyclic azodicarboxylates,[158] and the IR spectra of tetrafluoro-Δ^1-1,2,-diazetine (**118**) and hexafluorocyclobutene were analyzed and compared.[103] The N=N stretching bond of **118** was found to be at 1484 cm^{-1}, while the C=N band of the tricyclic Δ^2-1,2-diazetine derivative **242** appeared at 1608 cm^{-1}.[88]



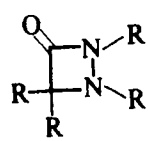
118

N=N: 1484 cm^{-1} (gas phase)



242

C=N: 1608 cm^{-1} (CH_2Cl)

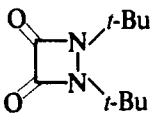


C=O: 1750–1780 cm^{-1}

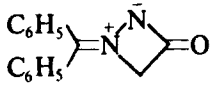
The IR spectra of 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine and of its *N*-oxide and *N,N'*-dioxide have also been recorded (in $CHCl_3$). The Δ^1-1,2-diazetine shows a band at 1480 cm^{-1}, which could be attributed to N=N absorption; the monoxide and the dioxide show several bands between 1465 and 1555 cm^{-1}.[122] The IR spectrum of the bicyclic azoxide 1,4-diphenyl-2,3-diazabicyclo[3.2.0]-hept-2-ene-2-oxide has also been recorded.[86]

The ring strain in 1,2-diazetidines causes a shift of the IR bands of semicyclic C=O and C=NR groups toward higher wave numbers. The cyclic hydrazide carbonyl groups of 1,2-diazetidinones have bands generally between 1750 and 1780 cm^{-1}, in a range very similar to the urea carbonyl absorption of 1,3-diazetidinones. The carbonyl band of 1,2-di-*t*-butyl-1,2-diazetidine-3,4-dione is shifted even further – to 1813 cm^{-1}.[5] The 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt shows two bands in the double bond region at 1740 and 1775 cm^{-1}.[128] The C=N band of 1,2,3,3-tetraphenyl-4-tolylimino-1,2-diazetidine is found at 1705 cm^{-1}.[71] The stretching bands of semicyclic C=C groups on two 1,2-diazetidine derivatives were found at 1628 and 1640 cm^{-1}.[74]

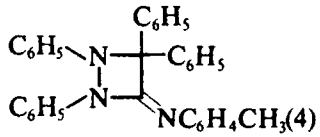
Nuclear magnetic resonance (nmr) spectra have been recorded for a large number and variety of 1,2-diazetines and 1,2-diazetidines. Proton-nmr spectra of several 1,2-dialkyl-1,2-diazetidines, which were measured at low temperature, showed



C=O: 1813 cm^{-1}

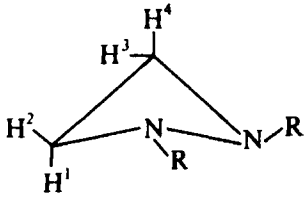


C=O/C=N: 1740 cm^{-1}
1775 cm^{-1}



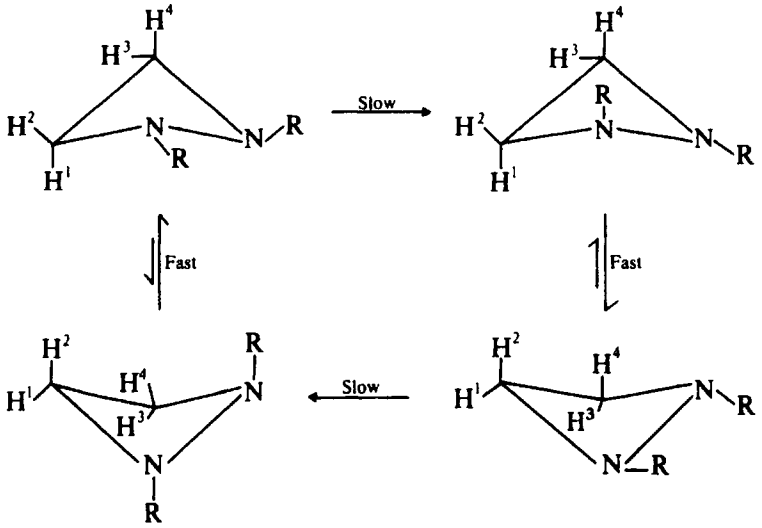
C=N: 1705 cm^{-1}

large J_{14} and J_{23} coupling constants for the ring methylene protons. This has been explained by assuming that the 1,2-diazetidine ring is highly puckered. An increase in the bulkiness of the alkyl groups on N^1 and N^2 (from methyl, ethyl, and isopropyl to *t*-butyl) causes an increasing flattening of the ring, as indicated by a decrease in J_{14} and an increase of J_{23}.[7]



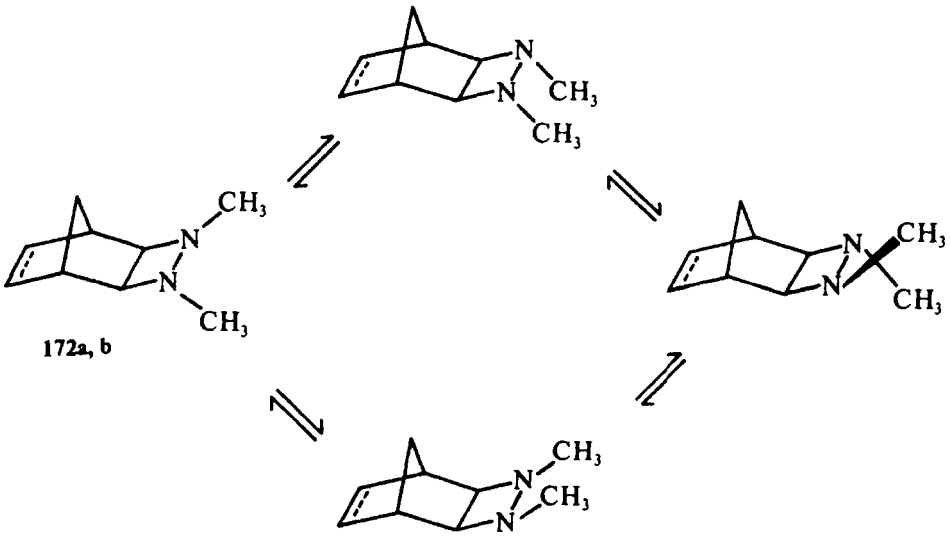
R	J_{14} (Hz)	J_{23} (Hz)
CH_3	10.14	2.76
C_2H_5	9.85	3.17
$(CH_3)_2CH$	8.79	4.57
$(CH_3)_3C$	9.80	4.61

Furthermore, the temperature-dependent coalescence of the bands of the AA'BB' spectrum of the methylene protons allows to quantitatively determine the nitrogen inversion (rate constants, activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) and to draw conclusions about all conformational changes (nitrogen inversion and ring inversion) taking place during the heating process.



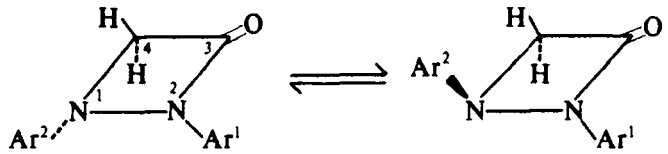
On the basis of these data, the free energy of activation of the nitrogen inversion in 1,2-dimethyl-1,2-diazetidine was calculated to be 16.4 kcal/mole.[7] This is a value considerably higher than the 7.25 kcal/mole reported for 1,2-bis(trifluoromethyl)-3,4-tetrafluoro-1,2-diazetidine on the basis of ^{19}F-nmr analysis.[159]

The fused-ring systems in 3,4-dimethyl-3,4-diazatricyclo[4.2.1.0.2.5]nonane (**172a**) and -non-7-ene (**172b**) minimize torsional effects and keep the four-membered ring nearly planar, with the two methyl groups in the trans position. Inversion on the nitrogens proceeds consecutively through two sterically and electronically destabilized cis forms (simultaneous inversion at both nitrogens is a higher energy process). The rates for the double inversion on **172a** and **172b** (determined by using variable-temperature H-nmr spectra) were found to be nearly equal, increasing slightly with increasing solvent polarity. The free energy of activation $\Delta G^{\ddagger}_{298}$ was found to be about 3.8 kcal/mole lower for **172a, b** when compared with 1,2-dimethyl-1,2-diazetidine.[115]



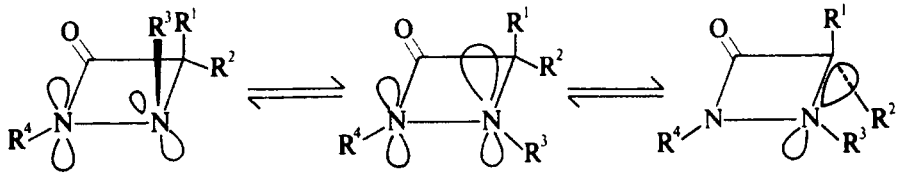
172a, b

Nitrogen inversion in 1,2-diaryl-1,2-diazetidinones is restricted to the N atom adjacent to the methylene group because of the planarity of the amide group. Thus 1-phenyl-2-*p*-tolyl-1,2-diazetidine-3-one shows a sharp singlet for the methylene protons at 35°C and signal splitting (AB spectrum, $J_{AB} = 13$ Hz) at -50°C.[62] Calculation of the free energy of activation $\Delta G^{\ddagger}$ for the inversion gave a value of 12.8 ± 0.3 kcal/mole.

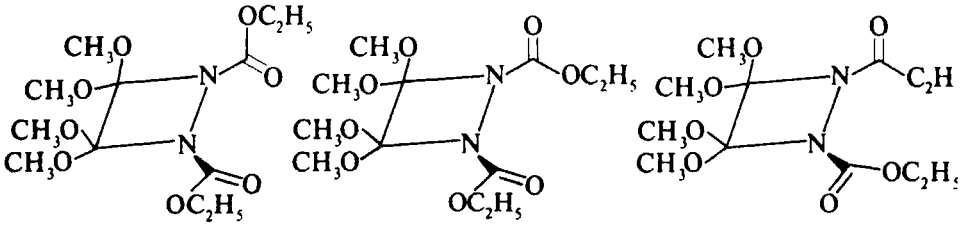


The N^1 inversion of a large number of C^4-substituted 1,2-diazetidine-3-ones has been determined similarly using temperature-dependent changes in the H-nmr spectra.[160] It was found that the free energy of activation ($\Delta G^{\ddagger}$) of the inversions is not very much influenced by the size of the substituents on N^1 (aryl, benzyl), although benzyl groups showed generally higher values (ca. 17 kcal/mole) than aryl

groups (14–15 kcal/mole), probably because of disruption of the resonance between the electrons on the nitrogen and the aryl substituent. It is interesting, however, that the rates of inversion were considerably slower than those of the structurally related azetidinones. This could be caused by electron repulsion of the two neighboring nitrogens in the transition state or by inductive effects of the two heteroatoms.[160]



The analysis of H-nmr spectra of 1,2-bis(alkoxycarbonyl)-1,2-diazetidine derivatives bearing additional substituents at C^3 and C^4 revealed a temperature-dependent restriction of rotation of the alkoxycarbonyl groups around the C–N bonds.[74,161] 1,2-Bis(ethoxycarbonyl)-3,3,4,4-tetramethoxy-1,2-diazetidine (**243**) shows signal splitting of the methoxy protons at $-65°C$ into four singlets (acetone-d_6, toluene-d_8), which coalesce on heating to -40 to $-20°C$. These features are consistent with the interconversion of the three isomers (**a**, **b**, and **c**) of **243**.[161]

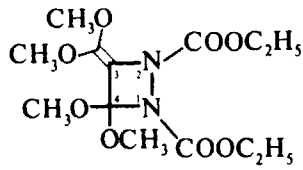


243a ("in-in") **243b** ("in-out") **243c** ("out-out")

On the basis of line-shape analysis of the methoxy signals of **243**, the free energy of activation ($\Delta G^{\ddagger}$) was calculated to be 13.6 kcal/mole (at $-27°C$), which is a value fairly close to those reported for other 1,2-diazetidine derivatives (see above).*

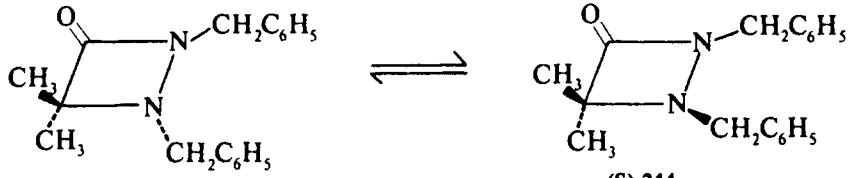
Methoxy signal splitting into four signals of equal intensity in the spectrum of diethyl 4,4-dimethoxy-3-dimethoxymethylene-1,2-diazetidine-1,2-dicarboxylate (**86**) can be observed at ambient temperatures. Coalescence of the two signals of the C^3 methoxy groups takes place around 80°C, while coalescence of the remaining two signals requires heating to 180°C. For both processes the free energy of activation (approximately 20 kcal/mole or more) was calculated on the basis of the spectral data.

* A substantially lower value for the activation energy (8.0 kcal/mole) has been reported for 1,2-bisethoxycarbonyl-3,3,4,4-tetrafluoro-1,2-diazetidine (apparently based on coalescence temperature) by W. D. Phillips, reported in *Determination of Organic Structure by Physical Methods*, Vol. 2, Academic Press, New York, 1962, p. 452.

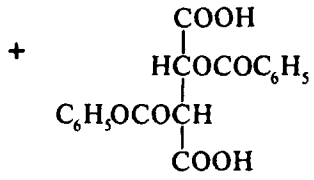


86

4,4-Dimethyl-1,2-dibenzyl-1,2-diazetidinone (**244**) also shows signal splitting for the diastereotopic methyl groups at $-55°C$ because of suppressed N-inversion. A further splitting of the methyl signal is observed on recording the spectra in the presence of the optically active (+)-(2R,3R)-O^2,O^3-dibenzoyltartaric acid (**245**), which causes the formation of diastereomeric association complexes between (R)-**244**, (S)-**244** and (+)-**245**.[162]

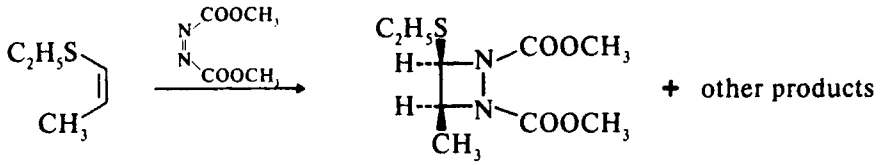


(R)-**244** (S)-**244**



(+)-**245**

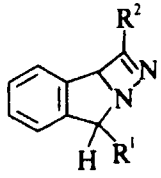
H-Nmr spectral analysis has also been used extensively for the determination of stereochemistry in the cycloadduct produced in the reaction of enol ether, enol thioether, 1,2-dialkoxyalkenes, and enamines with azodicarboxylate.[9,13,36] For example, *cis*-1-thioethylpropene and dimethyl azodicarboxylate form (aside from other products) stereospecifically the cis-substituted 1,2-diazetidine **246**.



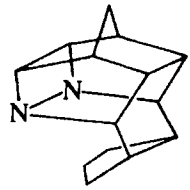
246

The ^1H and ^{13}C-nmr spectra of several 2a,7-dihydro[1,2]diazeto[4,1-a]isoindoles (**247**) have been recorded.[91]

The *Electron spin resonance* (esr) spectra of 1,2-dimethyl- and 1,2-diisopropyl-1,2-diazetidine have been recorded, and the splitting constants of the cation radicals were determined and compared with those of other cyclic and acyclic hydrazine derivatives.[100,115] The esr spectrum of 3,3,4,4-tetrafluoro-Δ^1-1,2-diazetine was recorded



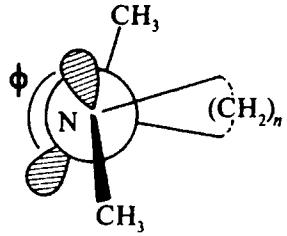
247



114

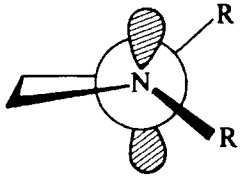
and compared with acyclic *N,N'*-perfluoroalkylazo compounds. In the radical cation of this heterocycle the ring seems to be planar, or the ring conformations are rapidly interconverted on the esr scale.[149] The spectrum of the caged hydrazine **114** was recorded and compared with that of 1,2-dimethyl-1,2-diazetidine.[100,115]

Photoelectron (PE) spectra are a very useful tool to obtain information about the conformation of many acyclic and cyclic tetraalkylhydrazine derivatives and azo compounds, among them several 1,2-diazetidine[115,163,164] and Δ^1-1,2-diazetines.[165,166,167] Calculation of the dihedral (torsional) angle φ of 1,2-dimethyl-1,2-diazetidine and other cyclic hydrazines by using the orbital energy differences of the lone pair electrons on the nitrogens, which are obtained from the spectra as the negative values of the vertical ionization potentials, indicates an increase in the folding of the ring system from diaziridine to 1,2-diazine.[163,164]

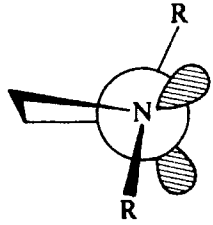


n	1	2	3	4
$\varphi°$	102	154	160	170

By increasing the size of alkyl substituents in 1,2-dialkyl-1,2-diazetidine (methyl, isopropyl), the two substituents trans to each other seem to be pushed further apart. Thus, of the two trans configurations T_e (equatorial) and T_a (axial), the dimethyl derivative exists exclusively in the T_e form, while both T_e and T_a are populated by the diisopropyl derivative.[115]



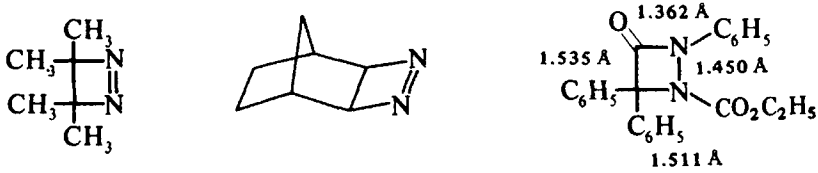
T_e ($\varphi > 120°$)



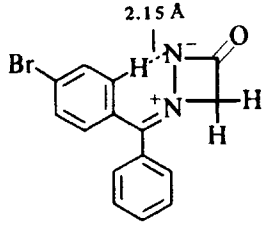
T_a ($\varphi < 120°$)

Photoelectron spectra and ionization potentials of cyclic azo compounds,[165-167] azo *N*-oxides, and azo *N,N'*-dioxides[165] were compared with corresponding derivatives of Δ^1-1,2-diazetines. The observed three ionization potentials (for n^-, n^+ and π) of tetramethyl-Δ^1-1,2-diazetine are very similar to the ones of 3,4-diazatricyclo [4.2.1.$0^{2,5}$] non-3-ene.[165,167]

x-Ray diffraction has been used in obtaining information about the structures of 1,2-diazetidines. Ethyl 2,4,4-triphenyl-1,2-diazetidine-3-one-1-carboxylate has been analyzed and was found to be slightly puckered, with the following bond distances: N–N, 1.450 Å, C–C, 1.535 Å (ketone); N–C, 1.362 and 1.511 Å.[168]



Determination of the structure of α-1-(*p*-bromophenyl)phenylmethylene-3-oxo-1,2-diazetidinium inner salt[128] revealed that the distance between the aromatic CH and the negatively charged ring nitrogen was shorter (2.15 Å) than the sum of the van der Waals radii (2.7 Å), suggesting a rare case of hydrogen bonding involving an aromatic hydrogen.[131] This shortening of the H · · · N distance has later been interpreted as being caused by crystal packing forces rather than by hydrogen bonding, since extensive IR investigations in solution and in the solid state failed to show the expected frequency shift due to C–H hydrogen bonding.[130]



UV spectra[5, 59, 86, 88, 119, 122, 128] and *mass spectra*[7, 9, 74, 86, 91, 122, 128, 135, 142, 144, 145] have been recorded without interpretation for a large number of 1,2-diazetidines and 1,2-diazetines.

5. References

1. T. Curtius and J. Thun, *J. Prakt. Chem.*, **44**, 175 (1891).
2. O. Hess, *Ann. Chem.*, **232**, 234 (1885).
3. A compilation of earlier claims about the successful synthesis of 1,2-diazetes, 1,2-diazetines, and 1,2-diazetidines, together with the results of newer investigations, can be found in J. A. Moore, "Trimethyleneimines", in A. Weissberger, Ed., *Heterocyclic Compounds with Three and Fourmembered Rings*, Part 2, Interscience, New York–London–Sydney, 1964, p. 885.
4. H. Staudinger, *Die Ketene*, F. Enke, Stuttgart, 1912, p. 591.
5. J. C. Stowell, *J. Org. Chem.*, **32**, 2360 (1967).
6. D. Horovitz, U.S. Patent 3,129,215 (1964) to FMC Corp.; *Chem. Abstr.*, **60**, 15874 (1964).
7. J. H. Hall and W. S. Bigard, *J. Org. Chem.*, **43**, 2785 (1978).

8. H. Emeleus and G. L. Hurst, *J. Chem. Soc.*, 3276 (1962).
9. (a) E. Koerner von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970); (b) A. Hassner, D. Y. Tang, and J. Keogh, *J. Org. Chem.*, **41**, 2102 (1976).
10. J. Firl and S. Sommer, *Tetrahedron Lett.*, 1929 (1970).
11. K. Adler and H. Niklas, *Ann. Chem.*, **585**, 97 (1954).
12. J. Firl and S. Sommer, *Tetrahedron Lett.*, 1133 (1969).
13. J. Firl and S. Sommer, *Tetrahedron Lett.*, 1137 (1969).
14. R. D. Cramer, U.S. Patent 2,456,176 (1948); *Chem. Abstr.*, **43**, 3445 (1949).
15. J. C. Kauer and A. K. Schneider, *J. Am. Chem. Soc.*, **82**, 852 (1960).
16. M. A. Englin, A. S. Filatov, and N. F. Sirotenkova, *Zh. Org. Khim.*, **5**, 1597 (1969).
17. S. A. Rodkin, A. Y. Yakubovich, and S. P. Makarov, *Zh. Org. Khim.*, **7**, 2271 (1971).
18. E. E. Nunn and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 818 (1972).
19. G. Ahlgren and B. Akermark, *Acta Chem. Scand.*, **21**, 2910 (1967).
20. O. Diels and K. Alder, *Ann. Chem.*, **450**, 237 (1926).
21. C. F. Huebner, P. L. Strachan, E. M. Donoghue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32**, 1126 (1967).
22. E. Koener von Gustorf and B. Kim, *Angew. Chem.*, **76**, 592 (1964).
23. C. F. Huebner, E. M. Donoghue, C. J. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.*, **35**, 1149 (1970).
24. (a) R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960); *J. Org. Chem.*, **27**, 1115 (1962); (b) T. J. Kealy, *J. Am. Chem. Soc.*, **84**, 966 (1962).
25. O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31**, 3862 (1966).
26. M. Lora-Tamayo, P. Navarro, and J. L. Soto, *Ann. Chem.*, **748**, 96 (1971).
27. R. E. Putnam, J. L. Anderson, and W. H. Sharkey, *J. Am. Chem. Soc.*, **83**, 386 (1961).
28. D. J. Pasto and A. Fu-Taichen, *Tetrahedron Lett.*, 2995 (1972).
29. E. A. Wildi and B. K. Carpenter, *Tetrahedron Lett.*, 2469 (1978).
30. L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 686 (1968).
31. S. Sommer, *Tetrahedron Lett.*, 117 (1977).
32. S. Sommer and U. Schubert, *Angew. Chem.*, **91**, 757 (1979).
33. K. B. Wagener, S. R. Turner, and G. B. Butler, *J. Org. Chem.*, **37**, 1454 (1972).
34. J. Firl and S. Sommer, *Tetrahedron Lett.*, 1925 (1970).
35. S. R. Turner, L. J. Giulbault, and G. B. Butler, *J. Org. Chem.*, **36**, 2838 (1971).
36. J. Firl and S. Sommer, *Tetrahedron Lett.*, 4713 (1972).
37. L. Marchetti and G. Tosi, *Tetrahedron Lett.*, 3071 (1971).
38. R. H. Rynbrandt, *J. Heterocyclic Chem.*, **11**, 787 (1974).
39. F. Effenberger, unpublished results.
40. F. Effenberger and R. Maier, *Angew. Chem. Int. Ed.*, **5**, 416 (1966).
41. D. H. Clemens, J. A. Bell, and J. L. O'Brian, *J. Org. Chem.*, **29**, 2932 (1964).
42. F. Effenberger, R. Gleiter, and G. Kiefer, *Chem. Ber.*, **99**, 3892 (1966).
43. J. H. Hall and M. Wojciechowska, *J. Org. Chem.*, **43**, 3348 (1978).
44. J. H. Hall and M. Wojciechowska, *J. Org. Chem.*, **43**, 4869 (1978).
45. J. Sauer, D. Lang, and H. Wiest, *Chem. Ber.*, **97**, 3208 (1964).
46. (a) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häuser, *Chem. Ber.*, **104**, 873 (1971); (b) R. W. Hoffmann and H. Häuser, *Angew. Chem. Int. Ed.*, **3**, 380 (1964).

47. C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, **127**, 378 (1925).
48. A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 184 (1941).
49. J. H. Hall and R. Kellog, *J. Org. Chem.*, **31**, 1079 (1966).
50. R. C. Kerber, T. J. Ryan, and S. D. Hsu, *J. Org. Chem.*, **39**, 1215 (1974).
51. R. C. Kerber and T. J. Ryan, *Tetrahedron Lett.*, 703 (1970).
52. D. Y. Curtin and J. L. Tveten, *J. Org. Chem.*, **26**, 1764 (1961).
53. G. O. Schenck and N. Engelhard, *Angew. Chem.*, **68**, 71 (1956).
54. S. Skraup and O. Binder, *Chem. Ber.*, **62**, 1127 (1929).
55. G. Brooks, M. A. Shah, and G. A. Taylor, *J. Chem. Soc. Perkin*, **I**, 1297 (1973).
56. M. Colonna and A. Risaliti, *Gazz. Chim. Ital.*, **90**, 1165 (1960).
57. C. W. Bird, *Tetrahedron*, **21**, 2179 (1965).
58. L. Horner, E. Spietschka, and A. Gross, *Ann. Chem.*, **573**, 17 (1951).
59. W. Fischer and E. Fahr, *Tetrahedron Lett.*, 5245 (1966).
60. S. Sommer, *Angew. Chem. Int. Ed.*, **15**, 432 (1976).
61. S. Sommer, *Angew. Chem. Int. Ed.*, **16**, 58 (1977).
62. E. Fahr, W. Fischer, A. Jung, L. Sauer, and A. Mannschreck, *Tetrahedron Lett.*, 161 (1967).
63. R. Huisgen and H. -U. Reissig, *J. Chem. Soc., Chem. Commun.*, 568 (1979).
64. W. Ried and E. Kahr, *Chem. Ber.*, **103**, 331 (1970).
65. T. Eicher and E. V. Angerer, *Chem. Ber.*, **103**, 339 (1970).
66. W. Ried and R. Dietrich, *Ann. Chem.*, **666**, 113 (1963).
67. W. Ried and R. Kraemer, *Ann. Chem.*, **681**, 52 (1965).
68. C. W. Bird, *J. Chem. Soc.*, 5284 (1964).
69. C. W. Bird and T. D. Twibell, *Tetrahedron*, **28**, 2813 (1972).
70. C. W. Bird, M. W. Kaczmar, and C. K. Wong, *Tetrahedron*, **30**, 2549 (1974).
71. M. W. Barker and M. E. Coker, *J. Heterocyclic Chem.*, **4**, 155 (1967).
72. M. W. Barker and R. H. Jones, *J. Heterocyclic Chem.*, **9**, 555 (1972).
73. M. W. Barker, S. Perumal, and C. J. Wierengo, *J. Heterocyclic Chem.*, **11**, 409, (1974).
74. R. W. Hoffmann and W. Schäfer, *Chem. Ber.*, **105**, 2437 (1972).
75. W. H. Knoth and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 3873 (1960).
76. S. Searles, Jr. and R. A. Clasen, *Tetrahedron Lett.*, 1627 (1965).
77. P. H. Ogden, *J. Chem. Soc. (C)*, 2920 (1970).
78. A. Padwa, W. Bergmark, and D. Pashayan, *J. Am. Chem. Soc.*, **90**, 4458 (1968).
79. G. Balogh and F. C. De Schryver, *Tetrahedron Lett.*, 1371 (1969).
80. R. O. Kan and R. L. Furey, *J. Am. Chem. Soc.*, **90**, 1666 (1968) assigned a wrong 1,3-diazetidine structure to these products.
81. J. G. Smith, *Can. J. Chem.*, **44**, 59 (1966).
82. W. Schlenk and E. Bergmann, *Ann. Chem.*, **463**, 32 (1928).
83. Y. Jean and A. Devaquet, *J. Am. Chem. Soc.*, **99**, 1949 (1977).
84. F. W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).
85. W. R. Dolbier, Jr. and W. M. Williams, *J. Am. Chem. Soc.*, **91**, 2818 (1969).
86. W. M. Williams and W. R. Dolbier, Jr., *J. Am. Chem. Soc.*, **94**, 3955 (1972).
87. G. L. Closs and W. A. Böll, *J. Am. Chem. Soc.*, **85**, 3904 (1963).
88. G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Am. Chem. Soc.*, **90**, 173 (1968).
89. W. J. Leigh and D. R. Arnold, *Can. J. Chem.*, **57**, 1186 (1979).
90. A. A. Reid, J. T. Sharp, and S. J. Murray, *J. Chem. Soc., Chem. Commun.*, 827 (1972).

91. A. A. Reid, H. R. Sood, and J. T. Sharp, *J. Chem. Soc. Perkin*, **I**, 362 (1976).
92. M. Pomerantz and G. W. Gruber, *J. Am. Chem. Soc.*, **93**, 6615 (1971).
93. R. McEwan and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 85 (1973).
94. M. A. Battiste and T. J. Barton, *Tetrahedron Lett.*, 1227 (1967).
95. (a) J. Sauer and G. Heinrichs, *Tetrahedron Lett.*, 4979 (1966); (b) G. Heinrichs, H. Krapf, B. Schröder, A. Steigel, T. Troll, and J. Sauer, *Tetrahedron Lett.*, 1617 (1970).
96. C. D. Anderson, J. H. Sharp, E. Stefaniuk, and R. S. Strathdee, *Tetrahedron Lett.*, 305 (1976).
97. T. Tsuchiya and J. Kurita, *J. Chem. Soc., Chem. Commun.*, 803 (1979).
98. D. J. Anderson and A. Hassner, *J. Chem. Soc., Chem. Commun.*, 45 (1974).
99. W. Berning and S. Hünig, *Angew. Chem. Int. Ed.*, **16**, 777 (1977).
100. S. F. Nelson, C. R. Kessel, and H. N. Brace, *J. Am. Chem. Soc.*, **101**, 1874 (1979).
101. J. A. Deyrup, *Tetrahedron Lett.*, 2191 (1971).
102. P. Robson, V. C. R. McLoughlin, J. B. Hynes, and L. C. Bigelow, *J. Am. Chem. Soc.*, **83**, 5010 (1961).
103. E. A. V. Ebsworth and G. L. Hurst, *J. Chem. Soc.*, 4840 (1962).
104. J. L. Gerlock, E. G. Janzen, and J. F. Ruff, *J. Am. Chem. Soc.*, **92**, 2558 (1970).
105. I. V. Vereshchinskii and A. T. Podkhalyuzin, *Dokl. Akad. Nauk SSSR*, **165**, 107 (1965); *Chem. Abstr.*, **64**, 5060 (1966).
106. (a) V. A. Ginsburg, L. L. Martynova, S. S. Dubov, B. I. Tetelbaum, and A. Y. Yakubovich, *Zh. Obshch. Khim.*, **35**, 851 (1965); *Chem. Abstr.*, **63**, 6995 (1965); (b) V. A. Ginsburg, S. S. Dubov, A. N. Medvedev, L. L. Martynova, B. I. Tetelbaum, M. N. Vasileva, and A. Y. Yakubovich, *Dokl. Akad. Nauk SSSR*, **152**, 1104 (1963); *Chem. Abstr.*, **60**, 1570 (1964).
107. D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 1881 (1955).
108. N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Am. Chem. Soc.*, **91**, 5668 (1969).
109. M. E. Landis and J. C. Mitchell, *J. Org. Chem.*, **44**, 2288 (1979).
110. M. Colonna and A. Risaliti, *Gazz. Chim. Ital.*, **87**, 923 (1957).
111. M. Colonna and A. Risaliti, *Gazz. Chim. Ital.*, **89**, 2493 (1959).
112. A. Risaliti and A. Monti, *Gazz. Chim. Ital.*, **90**, 397 (1960).
113. A. R. Katritzki and S. Musierowicz, *J. Chem. Soc. (C)*, 78 (1966).
114. J. Markert and E. Fahr, *Tetrahedron Lett.*, 4337 (1967).
115. S. F. Nelson, V. E. Peacock, G. R. Weisman, M. E. Landis, and J. A. Spencer, *J. Am. Chem. Soc.*, **100**, 2806 (1978).
116. C. W. Bird, *J. Chem. Soc.*, 674 (1963).
117. P. C. Freer, *Am. Soc.*, **21**, 14 (1899).
118. D. Y. Curtin and E. W. Tristram, *J. Am. Chem. Soc.*, **72**, 5238 (1950).
119. P. Singh, D. G. B. Boocock, and E. F. Ullman, *Tetrahedron Lett.*, 3935 (1971).
120. E. F. Ullman and P. Singh, *J. Am. Chem. Soc.*, **94**, 5077 (1972).
121. (a) P. Singh and E. F. Ullman (Syva Corp.), U.S. Patent 3,953,444 (1976); *Chem. Abstr.*, **85**, 47641 (1976); (b) E. F. Ullman (Syva Corp.), U.S. Patent 4,032,519 (1977); *Chem. Abstr.*, **87**, 102306 (1977).
122. F. D. Greene and K. E. Gilbert, *J. Org. Chem.*, **40**, 1409 (1975).
123. L. B. Volodarskii and L. A. Tikhonova, *Khim. Geterocycl. Soedin.*, 748 (1975).
124. L. B. Volodarskii, L. A. Tikhonova, and S. A. Amitina, U.S.S.R. Patent 481,593 (1975); *Chem. Abstr.*, **84**, 31039 (1975).
125. L. B. Volodarskii, L. A. Tikhonova, and S. A. Amitina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 738 (1974); *Chem. Abstr.*, **81**, 3797 (1974).

126. L. A. Tikhonova and L. B. Volodarskii, *Ivz. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 103 (1977); *Chem. Abstr.*, **87**, 5844 (1977).
127. W. J. Urry, P. Szecsi, C. Ikoku, and D. W. Moore, *J. Am. Chem. Soc.*, **86**, 2224 (1964).
128. R. B. Greenwald and E. C. Taylor, *J. Am. Chem. Soc.*, **90**, 5272 (1968).
129. P. C. Ip, K. Ramakrishnan, and J. Warkentin, *Can. J. Chem.*, **52**, 3671 (1974).
130. T. H. Gorrie and N. F. Haley, *J. Chem. Soc., Chem. Commun.*, 1081 (1972).
131. C. J. Fritchie, Jr. and J. L. Wells, *J. Chem. Soc., Chem. Commun.*, 917 (1968).
132. R. B. Greenwald and E. C. Taylor, *J. Am. Chem. Soc.*, **90**, 5273 (1968).
133. P. Grammaticakis, *Compt. Rend. Hebd. Sci.*, **259**, 2113 (1964).
134. P. H. Ogden, *J. Chem. Soc., Chem. Commun.*, 2920 (1971).
135. A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Am. Chem. Soc.*, **92**, 6218 (1970).
136. C. Calvo, P. C. Ip, N. Krishnamachari, and J. Warkentin, *Can. J. Chem.*, **52**, 2613 (1974).
137. K. Oe, M. Tashiro, and O. Tsuge, *Hukusokan Kagaku Toronkai Koen Yoshishu*, 14 (1975); *Chem. Abstr.*, **84**, 164742 (1976).
138. (a) R. Pfister and F. Häfliger (Geigy Chem. Corp.), U.S. Patent 2,859,211 (1958); *Chem. Abstr.*, **53**, 7196 (1959); (b) J. R. Geigy A.-G., Brit. Patent 813,474 (1959).
139. A. Blade Font and J. M. Torres, *Quim. Ind. (Madrid)*, **17**, 110 (1971); *Chem. Abstr.*, **75**, 20277 (1971).
140. F. Schatz, T. Wagner-Jauregg, and U. Jahn (Siegfried A.-G.), Swiss Patent 482,682 (1970); *Chem. Abstr.*, **72**, 90455 (1970); Brit. Patent 1,199,107 (1970); *Chem. Abstr.*, **74**, 13148 (1971).
141. E. F. Ulman, L. Call, and S. S. Tseng, *J. Am. Chem. Soc.*, **95**, 1677 (1973).
142. Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Japan*, **45** 3202 (1972).
143. P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).
144. A. S. Filatov, S. P. Makarov, and A. Y. Yakubovich, *Zh. Obshch. Khim.*, **38**, 1721 (1968); *Chem. Abstr.*, **70**, 3879 (1969).
145. M. E. Landis, L. M. Bell, D. C. Madoux, J. C. Mitchell, J. M. Schmidt, and J. A. Spencer, *J. Am. Chem. Soc.*, **102**, 837 (1980).
146. P. S. Engel, R. A. Hayes, L. Keifer, S. Szilagyi, and J. W. Timberlake, *J. Am. Chem. Soc.*, **100**, 1876 (1978).
147. J. J. Cosa, H. E. Gsponer, E. H. Staricco, and C. A. Vallana, *J. Chem. Soc. Faraday Trans. 1*, **69**, 1817 (1973).
148. M. A. Englin, A. S. Filatov, and N. F. Alekseeva, *Zh. Org. Khim.*, **7**, 2611 (1971).
149. J. L. Gerlock, E. G. Janzen, and J. K. Ruff, *J. Am. Chem. Soc.*, **92**, 2558 (1970).
150. M. A. Englin, A. S. Filatov, and N. F. Alekseeva, *Zh. Org. Khim.*, **7**, 2319 (1971).
151. L. Horner and E. Spietschka, *Chem. Ber.*, **89**, 2765 (1956).
152. J. H. Hall, *J. Org. Chem.*, **29**, 3188 (1964).
153. E. Fahr and W. Fischer, *Tetrahedron Lett.*, 3291 (1967).
154. W. Fischer and E. Fahr, *Angew. Chem. Int. Ed.*, **6**, 630 (1967).
155. G. Wittig, P. Börzel, F. Neumann, and G. Klar, *Ann. Chem.*, **691**, 109 (1965).
156. C. W. Bird, *Chem. and Ind.*, 1556 (1963).
157. C. W. Bird, *J. Chem. Soc., Chem. Commun.*, 1486 (1969).
158. S. S. Dubov and O. G. Strukov, *Tr. Soveshch. Fis. Metod. Issled. Organ. Soedin. Khim. Protsessov*, Akad Nauk Kirg. SSR, Inst. Organ. Khim., Frunze, 1962, p. 94; *Chem. Abstr.*, **62**, 4785 (1965).

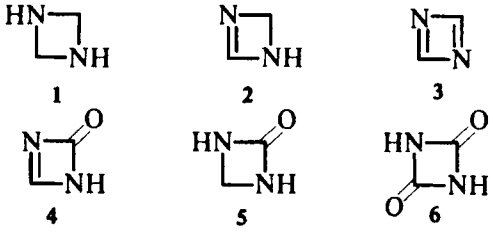
159. P. Ogden, *J. Chem. Soc., Chem. Commun.*, 1084 (1969).
160. E. Fahr, W. Rohlfing, R. Thiedemann, A. Mannschreck, G. Rissmann, and W. Seitz, *Tetrahedron Lett.*, 3605 (1970).
161. E. H. Carlson, A. P. Schaap, and M. Raban, *J. Org. Chem.*, **38**, 1605 (1973).
162. A. Mannschreck, V. Jonas, and B. Kolb, *Angew. Chem. Int. Ed.*, **12**, 583 (1973).
163. P. Rademacher, *Tetrahedron Lett.*, 83 (1974).
164. P. Rademacher and H. Koopmann, *Chem. Ber.*, **108**, 1557 (1975).
165. K. E. Gilbert, *J. Org. Chem.*, **42**, 609 (1977).
166. L. S. Domelsmith, K. N. Houk, J. W. Timberlake, and S. Szilagyi, *Chem. Phys. Lett.*, **48**, 471 (1977).
167. F. Brogli, W. Eberbach, E. Haselbach, E. Heilbronner, V. Hornung, and D. M. Lemal, *Helv. Chim. Acta*, **56**, 1933 (1973).
168. H. Ruben, H. Bates, A. Zalkin, and D. H. Templeton, *Acta Crystallogr.*, Sect. B, **30**, 1631 (1974).

II. 1,3-DIAZETIDINES

1. Introduction

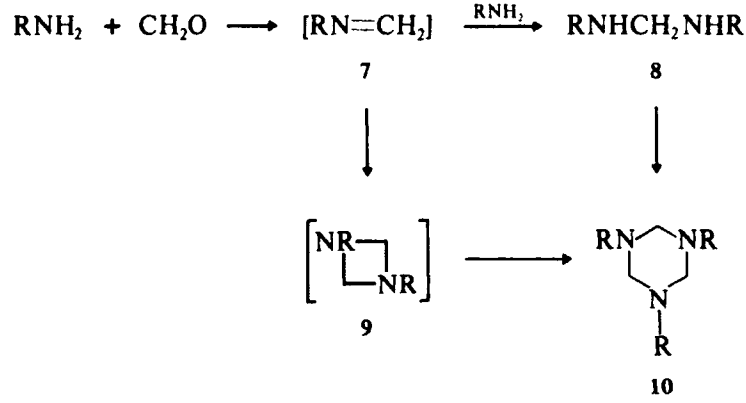
The synthesis of the parent 1,3-diazetidine **1** was reported by Tollens and Hölzer in 1884.[1] Even earlier, in 1869, Schiff claimed that he isolated substituted 1,3-diazetidinones.[2] In light of today's knowledge, we can safely conclude that almost all four-membered ring structures containing two nitrogen atom in positions 1 and 3, reported in the early literature, are incorrect. A noteworthy exception is the synthesis of 1,3-diphenyldiazetidine-2,4-dione, reported by Hofmann in 1858.[3] This compound was obtained in high yield by dimerization of phenyl isocyanate in the presence of triethylphosphine. The correct four-membered ring structure for the phenyl isocyanate dimer was proposed by Staudinger[4] in 1912, and it was later verified by x-ray crystallography.[5]

In the early literature the parent compound (**1**) of the four-membered ring heterocycles, containing two nitrogen and two carbon atoms alternately placed, was named uretidine. The corresponding unsaturated derivatives **2** and **3** were named uretine and urete, respectively. The carbonyl compounds, accordingly, were named uretone **4**, uretidinone **5**, and uretidinedione **6**. This nomenclature is still occasionally used today. The adapted nomenclature for heterocycles with two nitrogens in positions 1 and 3 is 1,3-diazetidine. This nomenclature was first introduced by Hale in 1918.[6]

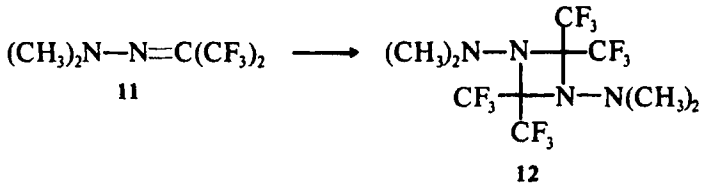


Of the structures indicated above, only a few derivatives of **1** are reported in the literature. Derivatives of compounds **2–4** have not as yet been synthesized. The majority of the synthesized 1,3-diazetidines are derived from **5** and **6**. The parent compound **6** is the hypothetical dimer of cyanic acid.

The most general method of synthesis of 1,3-diazetidines involves the [2+2] cycloaddition reaction of C=N double bond–containing substrates. Dimerization of azomethines could afford 1,3-diazetidines, and examples of this reaction are reported in the literature. These reactions often involve azomethines derived from amines and aliphatic aldehydes. However, the monomeric azomethines are usually unstable, and rapid oligomerization occurs. For example, azomethines **7**, derived from aromatic amines and formaldehyde, have never been isolated. Rapid reaction of **7** with another equivalent of arylamine produces the isolable aminals **8** and the also isolable six-membered-ring trimers **10**. It is presently not clear if the 1,3-diazetidine **9** is an intermediate in the formation of the six-membered-ring trimer **10**.



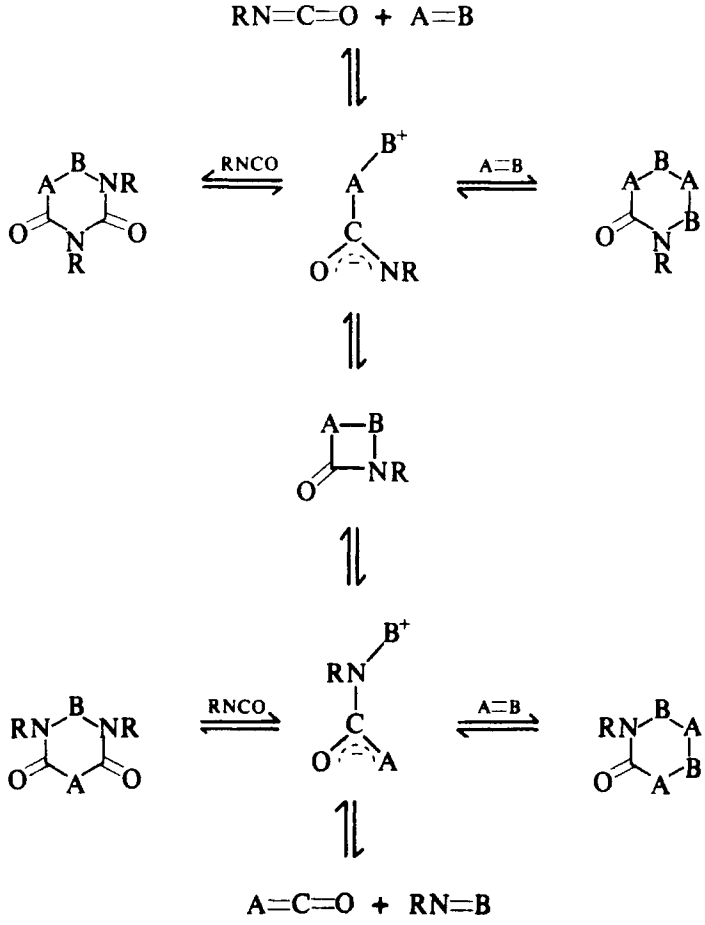
In view of the indicated reaction sequences, it is unlikely that a reaction product obtained from *p*-toluidine and formaldehyde has the reported 1,3-diazetidine structure.[7] Also, in the reaction of 2-thenylamine with formaldehyde, formation of a 1,3-diazetidine derivative was reported.[8,9] The boiling range reported for this compound indicates the formation of a complex reaction mixture, rather than the postulated four-membered-ring heterocycle. However, examples of cyclodimerization of hydrazine derivatives have been reported.[10] Traces of acid catalyze the dimerization of **11** to give the diazetidine derivative **12**.



Extension of the C=N double bond-containing system to a heterocumulene system favors [2+2] cycloaddition reactions to give four-membered-ring heterocycles. In this manner, 1,3-diazetidine derivatives having structures **5** and **6** are

readily synthesized. Reactions of this type include the dimerization of isocyanates, carbodiimides, and certain ketenimines. Also [2+2] cycloaddition reactions of isocyanates with carbodiimides and certain azomethines afford 1,3-diazetidines. In view of the fact that these reactions are often catalyzed, it can be concluded that stepwise processes involving polar, linear 1:1 adducts are intermediates in the formation of the cyclic adducts.

The polar [2+2] cycloaddition reaction of C=N double bond–containing substrates can lead to the four-membered-ring heterocycles, but more often six-membered-ring heterocycles are formed, as shown in Scheme 1.[11]

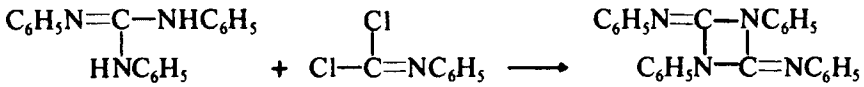


Scheme 1

The scheme assumes that the addition occurs across the C=N double bond of the heterocumulene system, with possible formation of a 1:1 cycloadduct with a 1,3-diazetidine structure if A is nitrogen. However, the reaction can also occur across the C=O double bond. For example, aroyl isocyanates add to carbodiimides to give 1,3-oxazetidines.[12] In contrast, the reaction of benzoyl and trichloroacetyl

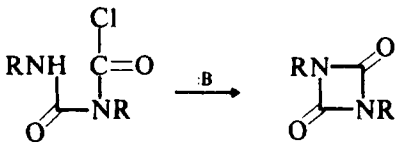
isocyanates with azomethines affords 1,3-diazetidine derivatives by addition across the C=N double bond.[13] Isothiocyanates react across their C=S double bond, and arenesulfonyl isocyanates form polar, linear 1:1 adducts. There are numerous examples in the literature where 1,3-diazetidine structures were erroneously assigned to the 1:1 adducts obtained by dimerization of heterocumulenes or by [2+2] cycloaddition of a heterocumulene with another C=N double bond–containing substrate.

Ring-closure reactions also leads to 1,3-diazetidines. For example, phenylcarbonimidoyl dichloride **13** reacts with triphenylguanidine to give 2,4-bisphenylimino-1,3-diphenyldiazetidine **14**.[14] The same compound can be obtained by cyclodimerization of diphenylcarbodiimide. This ring-forming reaction involves the combination of a one-carbon-containing segment with a three-carbon-containing segment,



13 **14**

Starting with a urea segment is also feasible. Reaction of certain *N,N*-dialkylureas (a three-carbon segment) with carbonyl chloride yields allophanoyl chlorides (**15**), which undergo ring closure in base to give 1,3-diazetidines (see Section 2.E).[15]



15

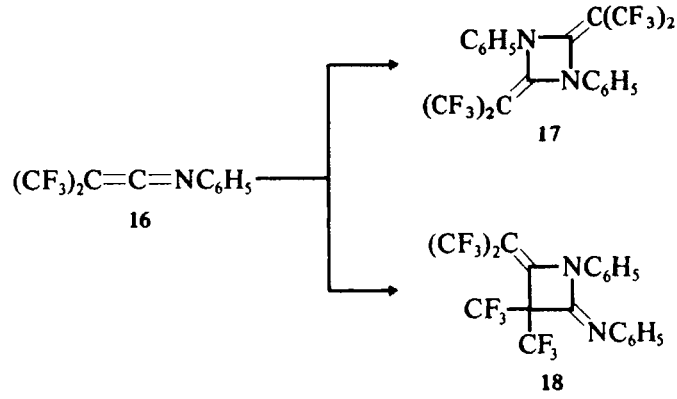
This reaction sequence is the most general method of synthesis for 1,3-diazetidine-2,4-diones with two different substituents on nitrogen.

2. Methods of Preparation

A. *Dimerization of Imines*

The formation of cyclic dimers of azomethines was described by Ingold and Piggott in 1922.[16b] Although their experiments establish an exchange reaction – most likely involving dimeric species as intermediates – the 1,3-diazetidine structures have not as yet been verified for the isolated dimeric products. However, photodimerization of benzaldehyde cyclohexylimine to give a low yield of the corresponding 1,3-diazetidine has been reported.[16a]

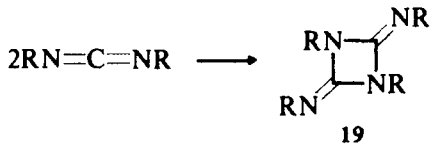
Imines with adjacent double bonds readily undergo cyclodimerization across their C=N double bonds. Examples include suitable substituted ketenimines and dialkyl- and diarylcarbodiimides. In the presence of pyridine, *N*-phenyl-bis



(trifluoromethyl)ketenimine **16** undergoes cyclodimerization to give the symmetric dimer **17**.[17] In the presence of triethylamine, ethylene oxide, DMF, or triethyl phosphite, **16** is converted to the unsymmetric dimer **18**.[17]

N-Aryl-substituted bis(trifluoromethyl)ketenimines with electron-withdrawing or electron-donating groups in the para position dimerize rapidly to give the symmetric dimers **17**.[18]

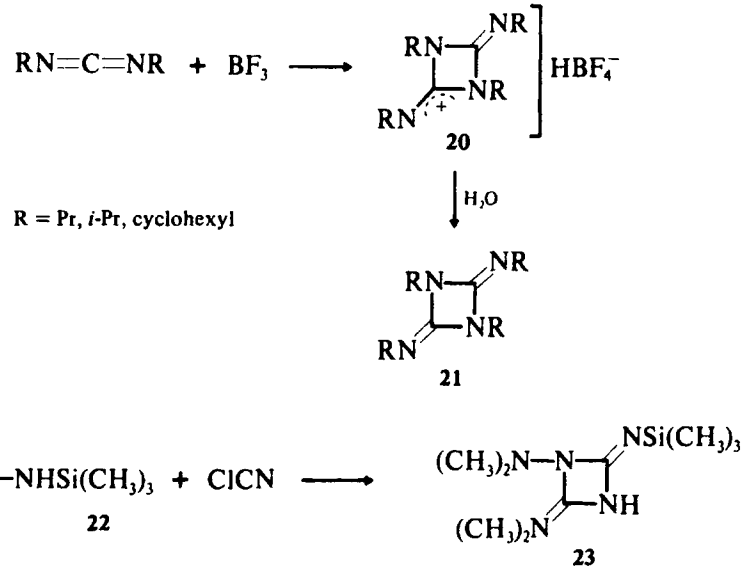
Carbodiimides also undergo a [2+2] cycloaddition to give 1,3-disubstituted 2,4-bisalkyl- or arylimino-1,3-diazetidines. Zetzsche and Fredrich[19] isolated a dimer (m.p. 102–103°C) from the distillation residue of dibenzylcarbodiimide. The authors proposed the 1,3-diazetidine structure **19** ($R = C_6H_5CH_2$) for the isolated product. The dimer of diphenylcarbodiimide (m.p. 162–163°C) was also isolated from the distillation residue of diphenylcarbodiimide, and it was shown that tributylphosphine catalyzes the cyclodimerization reaction.[14] Addition of 1% of tributylphosphine to diphenylcarbodimide, followed by heating at 90°C for 22 hours, gave 71% of the cyclic dimer. Heating of diphenylcarbodiimide in the absence of a catalyst at 165–170°C for 16 hours gave only 43% of the dimer. The heat-induced dimerization explains the presence of **19** in the distillation residues.



Reaction of dialkylcarbodiimides with boron trifluoride produced imino-1,3-diazetidine-4-yl iminium salts (**20**), which are readily hydrolyzed to give 2,4-bisalkylimino-1,3-bisalkyldiazetidines (**21**) in good yields.[20]

The formation of phosphorylated diazetidines by dimerization of phosphorylated carbodiimides has also been described, but evidence for the ring structure was not presented.[21]

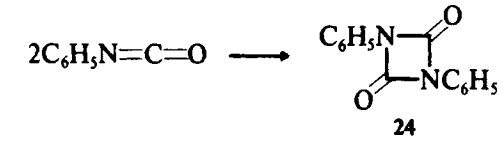
In the reaction of the hydrazine derivative **22** with cyanogen chloride, carbodiimide intermediates are generated, which cyclize in the reaction to give the 1,3-diazetidine derivative **23**.[22]



The dimeric carbodiimides were also obtained by ring-closure reactions (see Section 2.E).

B. *Dimerization of Isocyanates*

The dimerization of phenyl isocyanate to 1,3-diphenyldiazetidine-2,4-dione (**24**) in the presence of a trialkylphosphine catalyst was first observed by A. W. Hofmann in 1858.[3] In 1886 Snape obtained the same compound when he treated phenyl isocyanate with pyridine.[23] The correct 1,3-diazetidine structure for the phenyl isocyanate dimer was assigned in 1912 by Staudinger,[4] and x-ray crystallography established the symmetric structure in 1955.[5]



Over the years, numerous aryl isocyanates were dimerized to 1,3-diaryl diazetidine-2,4-diones (see Table 1). Trialkylphosphines and pyridine are still the catalysts of choice, because high selectivity for the four-membered-ring dimers is usually observed. Other trivalent phosphorus compounds, such as aryldialkylphosphines,[24,25] dialkylcarbamoyl diethyl phosphite,[26] hexaalkyl phosphortriamides,[26] and bis-*n*-dialkyl phosphoramidous acid ethyl ester[26] have also been reported to catalyze the dimerization of aryl isocyanates. Pyridine derivatives, such as methyl-substituted pyridines,[27] 4-dimethylaminopyridine,[28] and 4-ethoxypyridine[24] are also effective dimerization catalysts. Even tertiary amines sometimes produce mixtures of dimeric

TABLE 1. 1,3-DIARYLDIAZETIDINE-2,4-DIONES



R	Catalyst	m.p. (°C)	Yield (%)	Ref.
C_6H_5	PEt_3	175	80	3, 39
	PBu_3	175	90	48
	$PPhMe_2$	174–175	76	24
	$P(OCHMe_2)_3$	174	70	49
	C_5H_5N	175–176	–	23, 25
	4-$EtOC_5H_4N$	175	100	50
3-$CH_3C_6H_4$	PEt_3, $P(OCHMe_2)_3$	159–160	67	39, 49
4-$CH_3C_6H_4$	PEt_3, $P(NMe_2)_3$	185	70	26, 39
3-$CF_3C_6H_4$	$P(OCHMe_2)_3$	118–119	74	49
4-$C_2H_5C_6H_4$	$P(NMe_2)_3$	175–176	–	26
4-CH_2=CH-C_6H_4	C_5H_5N	198–198.5	–	51
4-$C_6H_5C_6H_4$	PEt_3	270[a]	38	39
2-ClC_6H_4	PEt_3	234–235	37	39
	$P(OCHMe_2)_3$	234–235	62	49
3-ClC_6H_4	$P(NMe_2)_3$	165–166	99	26
	PEt_3	153–154	72	39
	$P(OCHMe_2)_3$	154	80	49
4-ClC_6H_4	PEt_3	155–156	85	39
	$P(NMe_2)_3$	174	–	26
	$P(OCHMe_2)_3$	173–174	81	49
3,4-$Cl_2C_6H_3$	$P(NMe_2)_3$	178–179	–	26
4-BrC_6H_4	PEt_3	203–204	87	39
4-$C_2H_5OC_6H_4$	PEt_3	181–182	95	39
4-$O_2NC_6H_4$	PEt_3	208–211	67	39
4-C_6H_4N=NC_6H_4	PEt_3	281–282[a]	100	39
1-$C_{10}H_7$	PEt_3	296[b]	52	39
	Et_3N	295[a,b]	–	29
2-$C_{10}H_7$	PEt_3	196–197	87	39

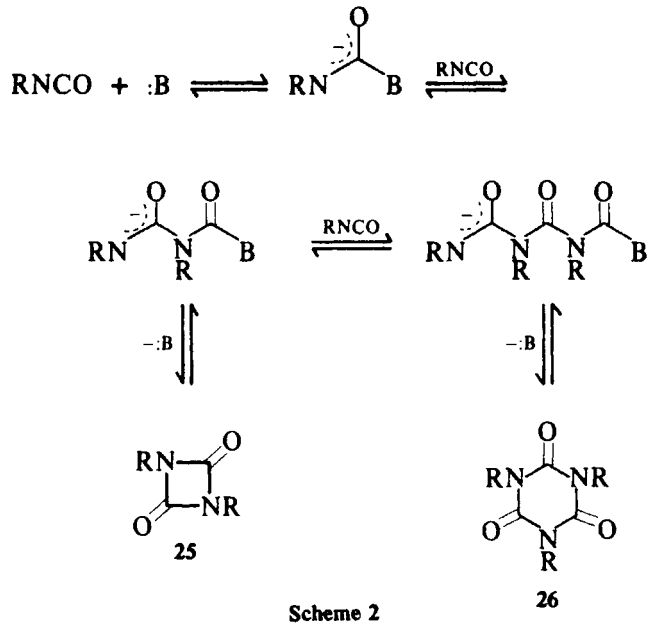
[a] Decomposition.
[b] Sublimation.

species.[29] Phenyl isocyanate also reacts at room temperature with Me_3SiPPh_2 to give a 72% yield of (**24**),[30] and Et_3SnSEt and Et_3SnPh also catalyze the trimerization of phenyl isocyante.[31]

The high selectivity for dimerization observed with trialkylphosphines and pyridine derivatives can be explained by a stepwise mechanism.[32] The general base catalysis of oligomerization of isocyanates involves the dimeric species **25** as low temperature intermediates in the formation of the more stable isocyanurates (**26**). The following scheme demonstrates the equilibria involved:

Phenyl isocyanate is also dimerized when heated under pressure, and the cyclic dimer is obtained in over 90% yield at 16 kilobars at a temperature range of 175–225°C, while higher temperatures and pressures lead to the formation of byproducts.[33]

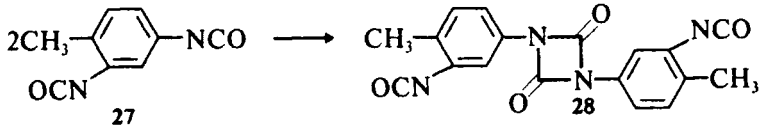
Some aryl isocyanates dimerize at a slow rate in the absence of catalyst. For



Scheme 2

example, 4,4′-diisocyanatodiphenylmethane dimerizes at a slow rate, even in the solid state. Since the rate of the uncatalyzed dimerization is temperature dependent, a concerted [2+2] cycloaddition reaction can be envisioned for this process.

Steric effects seem to play a role in the dimerization of aryl isocyanates. 2-Chlorophenyl isocyanate gave only a 37% yield of the corresponding 1,3-diazetidine dione,[34] while *ortho*-tolyl isocyanate did not dimerize. The steric hindrance was utilized in the selective dimerization of 2,4-diisocyanatotoluene (**27**). Treatment of **27** with typical dimerization catalysts gave a high yield of **28**.[35]



Until very recently, aliphatic isocyanates have not been dimerized. Treatment of aliphatic isocyanates with base catalysts usually afforded the corresponding six-membered-ring trialkylisocyanurates. Low conversion of some aliphatic mono- and diisocyanates to the corresponding 1,3-dialkyldiazetidine-2,4-diones has been reported in the patent literature using tributylphosphine as catalyst.[36] Methyl and ethyl isocyanates could be converted in yields of 21 and 32%, respectively, to the corresponding 1,3-dialkyldiazetidine-2,4-diones using antimony pentachloride as the catalyst.[37] Isopropyl isocyanate, under identical conditions, gave the corresponding trimer and higher oligomers.[37] Even better yields of 1,3-dialkyldiazetidine-2,4-diones were obtained in the cyclodimerization of benzyl isocyanates using 1,2-dimethylimidazole as the catalyst.[38] Byproducts in these reactions were the corresponding tribenzyltriisocyanurates.

TABLE 2. 1,3-DIALKYLDIAZETIDINE-2,4-DIONES



R	Catalyst	m.p. (°C)	Yield (%)	Ref.
CH_3	$SbCl_5$	94–95	21	37
$(CH_3)_2NCHF$	–[a]	40 (119–120/2.5)[b]	–	52
C_2H_5	$SbCl_5$	27/0.1[b]	32	37
	PBu_3	73–74	–[c]	36
$CH_2{=}CHCH_2$	PBu_3	66/1.0[b]	–[c]	36
CH_3OCH_2	PBu_3	86/1.0[b]	–[c]	36
n-C_4H_9	PBu_3	92–93	–[c]	36
$(C_2H_5)_3SiCH_2CH_2CH_2$	–[a]	167–170/1.0[b]	40	53
$C_6H_5CH_2$	1,2-Dimethylimidazole	92–93	76	38
4-$CH_3C_6H_4CH_2$	"	140	87	38
2-$ClC_6H_4CH_2$	"	108–109	80	38
4-$ClC_6H_4CH_2$	"	162–163	81	38
3-$CH_3OC_6H_4CH_2$	"	51–58	40	38
4-$CH_3OC_6H_4CH_2$	"	93-94	82	38
Cl	–[a]	68	50–70	54
$(Et_2N)_2PS$	–[a]	145	–	55
FCOS	–[a]	101	–	56
CF_3S	–[a]	79	20	57
ClF_2CS	–[a]	79	55	58
CH_3OCS	–[a]	170	100	59

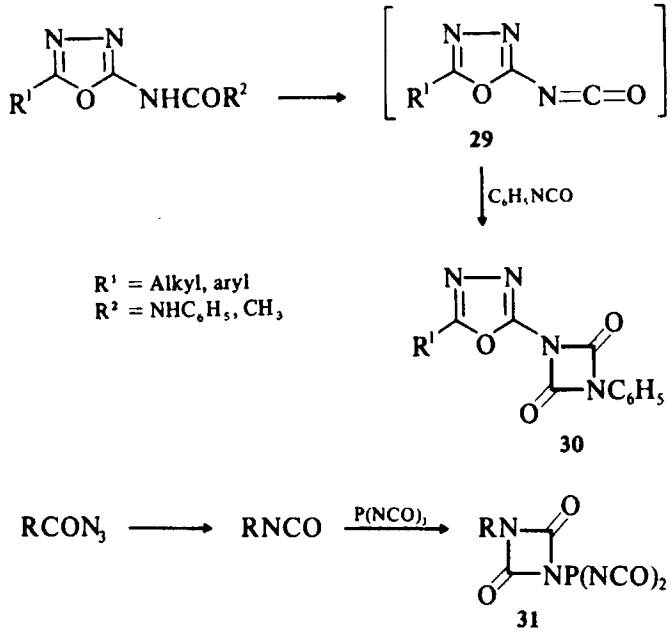
[a] No catalyst.
[b] b.p./torr.
[c] Low yield.

Certain highly reactive isocyanates with reactive groups or heteroatoms adjacent to the isocyanate group dimerize during synthesis or on standing at room temperature to give the corresponding 1,2-diazetidine-2,4-diones. Examples of aliphatic and heteroatom-containing isocyanate dimers are listed in Table 2.

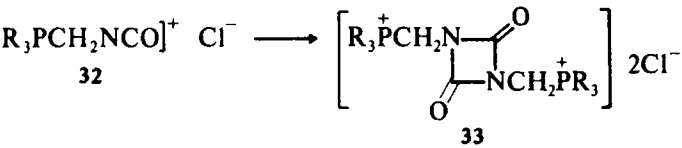
The formation of mixed dimers has also been reported. For example, addition of several drops of triethylphosphine to an equimolar mixture of *p*-tolyl and *p*-chlorophenyl isocyanates produced the mixed dimer in 88% yield.[39] Trapping of heterocyclic isocyanates by phenyl isocyanate has also been reported.[40] The heterocyclic isocyanate **29** was generated from the urea or acylamino precursor in the presence of excess phenyl isocyanate, and **29** underwent a [2+2] cycloaddition to phenyl isocyanate to give the 1,3-diazetidine-2,4-dione derivates **30** in good yields.

Another example of the formation of mixed isocyanate dimer **31** involves the reaction of triisocyanatophosphine with aroyl azides.[41]

The dimers of amino isocyanates and aroyl isocyanates, previously reported as 1,3-diazetidine-2,4-dione derivatives, were shown to have different structures.[42–45,63] Also, structural assignment for dimers obtained from dialkylcarbamoyl isocyanates was not possible.[46]



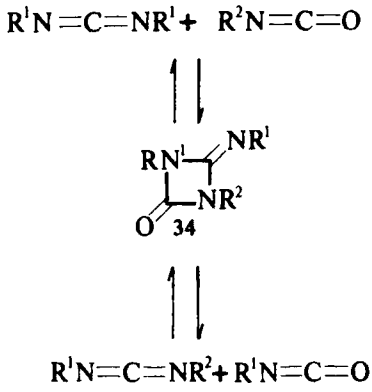
Reaction of chloromethyl isocyanate with triarylphosphines gives phosphonium salts (**32**), which dimerize in diethyl ether at 0–10°C in the presence of tripropylphosphine to give the four-membered-ring dimers **33**.[47]



C. *Cycloaddition of Isocyanates to Carbodiimides*

The formation of four-membered-ring cycloadducts **34** from dialkylcarbodiimides and alkyl and aryl isocyanates was first observed in 1957.[60] This reaction was catalyzed by cuprous and cupric salts, but it was later shown that no catalysts are necessary.[12] In contrast to dialkylcarbodiimides, the addition of aryl isocyanates to diarylcarbodiimides requires heating at 100–125°C.[61] If the substituents on the isocyanate and on the carbodiimide are different, thermal reorganization is observed, and the reaction can be utilized to prepare mixed carbodiimides by removing the lowest boiling isocyanate by distillation[62] (see Scheme 3).

The four-membered-ring structure **34** for the cycloadducts was established by ring-opening reactions[61] as well as by thermal degradation of the adducts derived from *t*-butylmethylcarbodiimide.[12] The latter method gave conclusive evidence that the cycloaddition of benzoyl isocyanate to carbodiimides proceeds across the C=O



Scheme 3

double bond of the isocyanate group to give 1,3-oxazetidine derivatives[12] rather than the originally proposed isomeric 1,3-diazetidines.[63]

In the reaction of arenesulfonyl isocyanates with carbodiimides, six-membered-ring compounds are usually isolated.[64] However, a few examples of formation of four-membered-ring 1 : 1 adducts have also been reported. Reaction of phenylsulfonyl isocyanate with bis(trimethylsilyl)carbodiimide gave a 1 : 1 adduct, for which a 1,3-diazetidine structure was proposed.[65] Also, addition of chlorosulfonyl isocyanate to dicyclohexylcarbodiimide gave the 1,3-diazetidine cycloadduct in good yield.[66] If the addition is reversed, only a six-membered-ring cycloadduct is obtained.

In the reaction of phenyl isocyanate with bis(tributylstannyl)carbodiimide, a 2 : 1 adduct was isolated, for which the 1,3-diazetidine structure **36** was proposed.[67] This reaction occurs by insertion of the isocyanate group into the tin–nitrogen bond to give the 1 : 1 adduct **35**, which adds another phenyl isocyanate molecule across the newly generated C=N double bond.

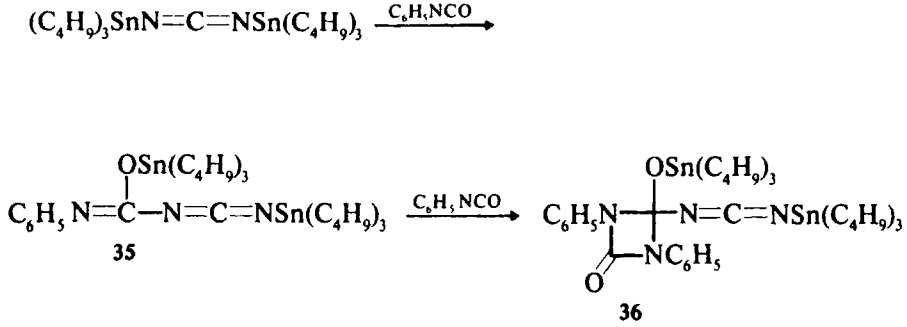
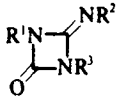


TABLE 3. 2-IMINO-1,3-DIAZETIDINE-4-ONES



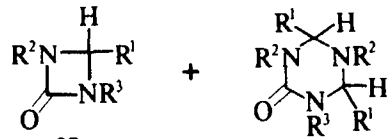
R^1	R^2	R^3	m.p. (°C)	Yield (%)	Ref.
C_2H_5	C_2H_5	C_2H_5	38–40/0.1[a]	–	69
i-C_3H_7	i-C_3H_7	C_6H_{11}	Oil	–	60
C_6H_{11}	C_6H_{11}	C_2H_5	Oil	–	69
i-C_3H_7	i-C_3H_7	C_6H_5	38	–	60
i-C_3H_7	i-C_3H_7	1-$C_{10}H_7$	Oil	–	60
CH_3	t-C_4H_9	C_6H_5	52	45.4	12
t-C_4H_9	t-C_4H_9	C_6H_5	68	–	60
C_6H_5	C_6H_5	C_6H_5	139–140[b]	25.0	61
			136	–	69

[a] b.p./torr.
[b] Decomposition.

D. *Cycloaddition of Isocyanates to Imines*

Imines derived from aromatic amines and benzaldehyde derivatives having electron-donating groups in the para position undergo a [2+2] cycloaddition reaction with aryl isocyanates to give the 1:1 adducts.[70–72] If an excess of the azomethine derivative is used, the six-membered-ring triazine derivatives **38** are formed exclusively.[71] The formation of **37** and **38** is consistent with a stepwise dipolar mechanism (see Scheme 1).

$$R^1CH{=}NR^2 + R^3NCO \longrightarrow$$

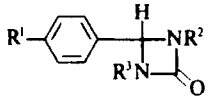


37 **38**

Anils derived from benzophenones with electron-donating groups in the para position react with aryl isocyanates to give six-membered-ring cycloadducts exclusively.[70] A four-membered-ring structure proposed for the reaction product of methylene aniline and phenyl isocyanate is most likely in error.[73] Arbuzov and co-workers have proposed 1,3-diazetidine structures for the reaction products of azomethines with electron-donating groups and benzoyl and trichloroacetyl isocyanate, respectively.[13,74–76] The reaction product derived from 6-isocyanatopenicillanic acid and *N,N*-dimethylbenzamidine has been formulated as a 1,3-diazetidine derivative.[77]

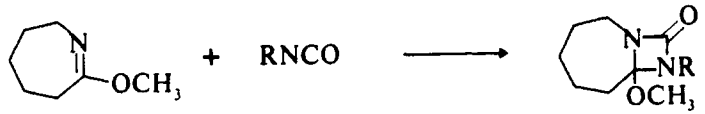
Heterocyclic imines are also known to react rapidly with isocyanates. In most

TABLE 4. 1,3-DIAZETIDINE-4-ONES



R^1	R^2	R^3	m.p. (°C)	Yield (%)	Ref.
CH_3O	C_6H_5	C_6H_5	190–194	5	70
CH_3O	4-ClC_6H_4	C_6H_5	169–170	4	70
$(CH_3)_2N$	C_6H_5	C_6H_5	181	47	70
$(CH_3)_2N$	4-$CH_3C_6H_4$	C_6H_5	180	31	71
$(CH_3)_2N$	2-ClC_6H_4	C_6H_5	–	43	71
$(CH_3)_2N$	3-ClC_6H_4	C_6H_5	–	34	71
$(CH_3)_2N$	4-ClC_6H_4	C_6H_5	171–173	85	70
$(CH_3)_2N$	4-ClC_6H_4	4-ClC_6H_4	165–167	50	70
$(CH_3)_2N$	2-BrC_6H_4	C_6H_5	–	38	71
$(CH_3)_2N$	4-$C_2H_5OCOC_6H_4$	C_6H_5	–	32	71
$(CH_3)_2N$	4-$C_4H_9OCOC_6H_4$	C_6H_5	–	34	71
$(CH_3)_2N$	2-C_5H_4N	C_6H_5	173–176	33	72
H	4-$CH_3OC_6H_4$	C_6H_5CO	119–121	30	13
O_2N	C_6H_5	C_6H_5CO	132–134	32	13
$(CH_3)_2N$	C_6H_5	C_6H_5CO	113–115	62	13
$(C_2H_5)_2N$	C_6H_5	C_6H_5CO	107–108	27	13
$(CH_3)_2N$	4-$CH_3OC_6H_4$	C_6H_5CO	104–106	24	13
$(CH_3)_2N$	C_6H_5	CCl_3CO	126–128	83	13
$(C_2H_5)_2N$	4-$O_2NC_6H_4$	CCl_3CO	170–172	96	13

cases heterocyclic six-membered-ring adducts are formed, but in one instance 1,3-diazetidine derivatives were isolated. Room temperature reaction of aryl isocyanates with the lactim ether **39** gave the 1 : 1 cycloadducts **40** in 45–87% yields.[78]



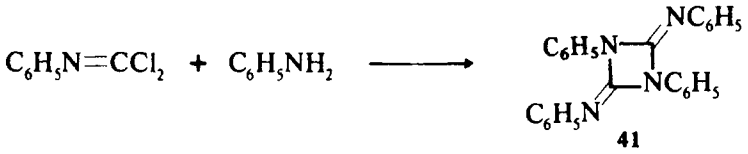
39 **40**

The formation of a four-membered-ring 1,3-diazetidine derivative from benzylidene aniline and cyanic acid has also been described.[80] However, the structure of this product has never been verified. The 1 : 1 adducts derived from *N,N*-dimethylbenzamidine and phenyl isocyanate,[81] as well as the 1 : 1 adducts obtained from tosyl isocyanate and *N*-phenyl-*N'*-dimethylformamidine and tetramethylphenylguanidine, respectively,[82] were shown to be dipolar linear adducts rather than 1,3-diazetidine derivatives.

Treatment of a thiazolium chloride derivative with 4-chlorobenzenesulfonyl isocyanate gave an adduct for which, again, a 1,3-diazetidine structure was postulated, based on the carbonyl absorption of 1800 cm^{-1}.[79] The 1,3-diazetidines obtained in the cycloaddition of azomethines with aryl isocyanates are listed in Table 4.

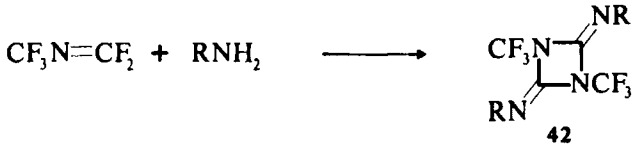
E. *Ring-Closure Reactions*

The reaction of triphenylguanidine with phenylcarbonimidoyl dichloride produces the diphenylcarbodiimide dimer **41** in good yield.[14] It is not necessary to start with the trisubstituted guanidine, because it can be generated *in situ*. For example, reaction of phenylcarbonimidoyl dichloride with aniline gave the same compound in 77% yield.[83]



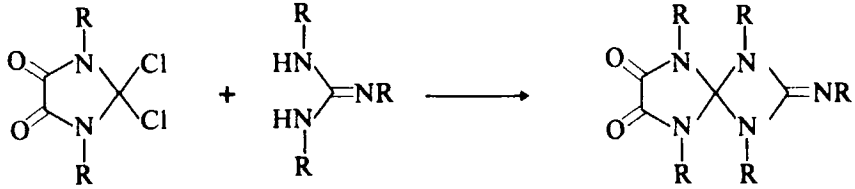
41

In a similar manner, perfluoroazapropene reacts with aromatic amines to give 1,3-di(trifluoromethyl)-2,4-bis(arylmino)-1,3-diazetidines (**42**).[84]



42

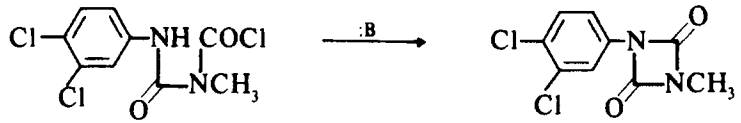
Geminal dichlorides such as 2,2-dichloroimidazolidine-3,4-diones, obtained from carbodiimides and oxalyl chloride, undergo a similar reaction with triphenylguanidine to give the spiro compounds **43**.[85]



43

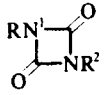
The second general method for the synthesis of 1,3-diazetidine derivatives involves cyclization of linear allophanoyl chlorides. This reaction has been used to synthesize 1-alkyl-3-aryldiazetidine-2,4-diones with herbicidal properties.[86] For example, reaction of 1-(3,4-dichlorophenyl)-3-methylurea with $COCl_2$ gave the allophanoyl chloride **44**, which was cyclized with *N,N*-dimethylcyclohexylamine to give the 1,3-diazetidine derivative **45**.[86]

A number of similar derivatives are described in some patents[86] (see Table 5).



44 **45**

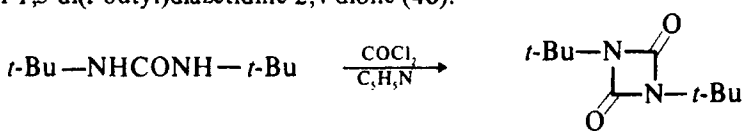
TABLE 5. 1,3-DIAZETIDINE-2,4-DIONES



R^1	R^2	m.p. (°C)	Yield (%)	Ref.
CH_3	CH_3	96–98	79	90
i-C_3H_7	i-C_3H_7	80–83/14[a]	86	90
t-C_4H_9	t-C_4H_9	89–90	52	87
C_6H_{11}	C_6H_{11}	92–94	84	90
CH_3	4-FC_6H_4	117–118	–	85
CH_3	4-BrC_6H_4	130–131	–	85
CH_3	3-$CF_3C_6H_4$	75–76	–	85
CH_3	3,4-$Cl_2C_6H_3$	124–125	–	85, 86
CH_3	4-Br-3-ClC_6H_3	116–117	–	85
CH_3	4-CH_3O-3-ClC_6H_3	138–139	–	85
CH_3	3,4-$(CH_3)_2C_6H_3$	80–81	–	85
CH_3	4-CH_3-3-ClC_6H_3	101	–	85
CH_3	3-$CH_3NHCOOC_6H_4$	118–119	–	85
CH_3	3-$(CH_3)_2CHNHCOOC_6H_4$	134–135	–	85
$C_6H_5CH_2$	C_6H_5	63–64	43	15
C_6H_5	C_6H_5	176–177	95	15
2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	131–132	43	15
3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	163–164	65	15
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	180–181	70	15
2-ClC_6H_4	2-ClC_6H_4	141–142	35	15
3-ClC_6H_4	3-ClC_6H_4	173–174	66	15
4-ClC_6H_4	4-ClC_6H_4	176–177	63	15
3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	183–185	45	15
4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	203[b]	52	15
4-$C_6H_5C_6H_4$	4-$C_6H_5C_6H_4$	240–241	78	15
1-$C_{10}H_7$	1-$C_{10}H_7$	181–182	42	15
2-$C_{10}H_7$	2-$C_{10}H_7$	210–211	75	15

[a] b.p./torr.
[b] Decomposition.

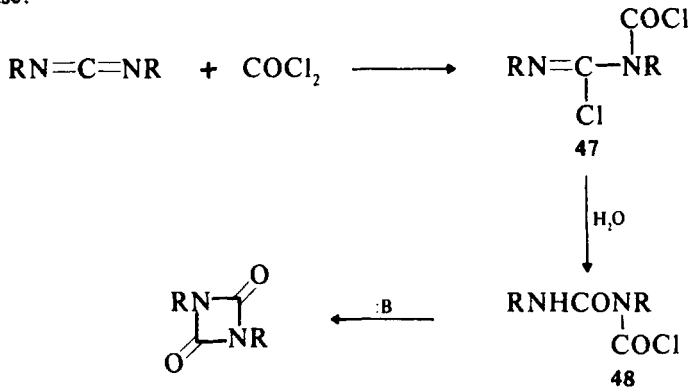
1,3-Dialkyldiazetidine-2,4-diones can be synthesized in a similar manner. Treatment of di-t-butylurea with phosgene in the presence of pyridine gave a 50–60% yield of 1,3-di(t-butyl)diazetidine-2,4-dione (**46**).[87]



46

Allophanoyl chlorides are also produced from aryl isocyanates and boron trichloride. The 2,4-diarylallophanoyl chlorides obtained by this method are readily cyclized by addition of excess pyridine to give the corresponding 1,3-diazetidinediones in 24–70% yield.[15] We had previously investigated the formation of allophanoyl chlorides from 1,3-dialkylureas and noted that preferential reaction

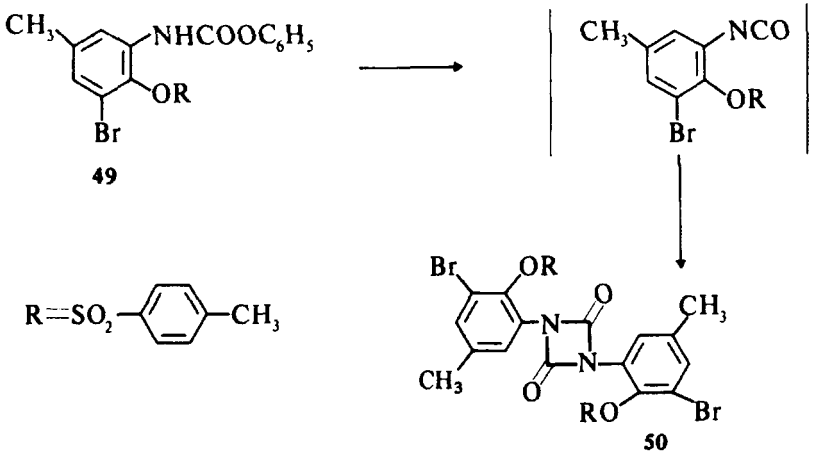
on the nitrogen occurs if the substituent group is a primary alkyl group.[88,89] An alternate route to allophanoyl chlorides, starting with dialkylcarbodiimides, has been found recently.[90] Addition of phosgene to dialkylcarbodiimides produces chloroformamidine-*N*-carbonyl chlorides (**47**) in quantitative yields.[91] Selective hydrolysis of **47** with aqueous acetone produces the corresponding allophanoyl chlorides (**48**), which are readily cyclized in diethyl ether using triethylenediamine as the base.[90]



This method works well with primary, secondary and tertiary alkyl substituents, and it should also be applicable for the synthesis of 1,3-diazetidinediones with different substituents on nitrogen. The 1,3-diazetidinediones synthesized by cyclization of allophanoyl chlorides are listed in Table 5.

F. *Miscellaneous Methods of Synthesis of 1,3-Diazetidines*

Masked isocyanates can also be used to synthesize 1,3-diazetidine derivatives. For example, the phenylcarbamate **49**, upon treatment with pyridine, dissociates into the free isocyanate, which dimerizes in pyridine to give the 1,3-diazetidinedione **50**.[92]

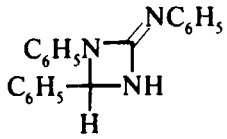


Another route to 1,3-diphenyldiazetidinedione involves the reaction of phenyl carbamate with thionyl chloride.[93,94]

Reaction of diphenylcarbodiimide with *N*-benzylidenealuminum amide (**51**) gave 1,2-diphenyl-4-phenylimino-1,3-diazetidine (**52**) in 47% yield.[95]

$$C_6H_5N{=}C{=}NC_6H_5 + [(C_2H_5)_3AlN{=}CHC_6H_5]^-Na^+ \longrightarrow$$

51



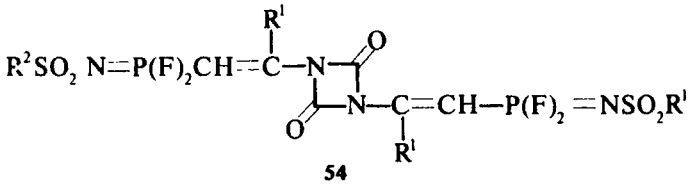
52

This reaction formally resembles the cycloaddition of an azomethine to a carbodiimide. The cyclic dimer derived from *N*-*p*-toluensulfonyl-*N'*-phenylcarbodiimide has been isolated recently.[96] Cyclodimerization of the reaction product derived from isocyanate **53** and arenesulfonamides has also been observed. The 1,3-diazetidine derivatives **54** were obtained in 85–94% yield.[97]

$$F_4PCH{=}C(R^1)NCO + R^2SO_2N(SiMe_3)_2 \longrightarrow$$

53

$$[R^1SO_2N{=}PCH{=}C(R^1)NCO] \longrightarrow$$



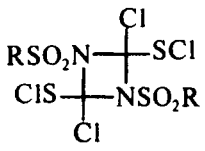
54

The cyclic dimer of di-*p*-tolylcarbodiimide was also isolated in 32% yield in the reaction of the carbodiimide with succinoyl chloride.[83]

Reaction products **55** derived from arenesulfonamides and trichloromethanesulfenyl chloride, upon treatment with triethylamine, are dehydrohalogenated to give dimeric species having the 1,3-diazetidine structure (**56**).[98]

$$RSO_2NHSCCl_3 \xrightarrow{Et_3N}$$

55



56

It has also been reported recently that isothiocyanate dimers with a 1,3-diazetidine-2,4-dithione structure are formed in the reaction of an oxalic acid monoarylamide derivative with lead thiocyanate.[99,100] However, in view of the preferential reaction of isothiocyanates across the C=S double bond, further verification of the postulated structures is necessary.

3. Physical and Spectral Properties

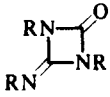
The 1,3-diazetidine derivatives with aryl substituents on nitrogen are usually high melting crystalline solids, while alkyl derivatives often are liquid at room temperature. Since fragmentation of the four-membered ring occurs at elevated temperatures, decomposition is sometimes observed at the melting point.

Spectral data have been used extensively to verify the cyclic structure. This is best done by infrared spectroscopy if the 1,3-diazetidine derivatives contain C=O or C=N double bonds. These absorptions are significantly shifted from the corresponding open-chain urea and guanidine derivates. The nature of the substituents on nitrogen influences the position of the infrared absorptions, as shown in Table 6.

Conclusive evidence for the symmetric 1,3-diazetidine structure of isocyanate dimers was provided by x-ray crystallography.[5,37,102] A planar four-membered-ring structure was found for 1,3-dimethyldiazetidine-2,4-dione. The two methyl groups are bent ~ 22° out of the plane, while the oxygen atoms are in the plane. Contrary to 1,3-diphenyldiazetidine-2,4-dione,[5] both carbon-to-nitrogen distances as well as the NCO angle are identical in the methyl derivative.[37]

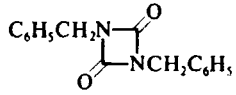
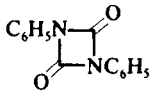
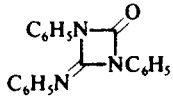
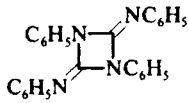
Further identification of the cyclic structure can be obtained by ^{13}C-nmr spectroscopy. The carbon atoms in the four-membered-ring structures have defined chemical shifts (see Table 7).[103]

TABLE 6. INFRARED ABSORPTION OF 1,3-DIAZETIDINE DERIVATIVES

Structure	R	C=O (cm^{-1})	C=N (cm^{-1})	Ref.
	Cl	1819	–	54
	CF_3S	1824	–	101
	FCOS	1831 (1790)[a]	–	56
	CH_3	1778	–	37
	C_6H_5	1781	–	–
	C_6H_5	1730	1700	61
	C_6H_5	–	1675–1700	14

[a] Substituent carbonyl absorption.

TABLE 7. ^{13}C-NMR SPECTRA OF 1,3-DIAZETIDINE DERIVATIVES ($CDCl_3$)

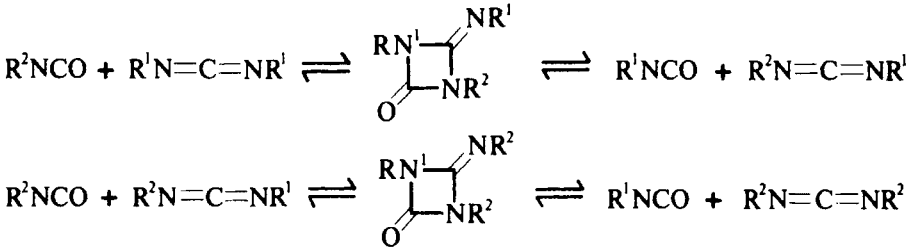
Structure	C=O (ppm)	C=N (ppm)
	156.8	–
	151.1–151.3	–
	151.7–153.6	140.1–143.1
	–	144.2–144.6

4. Reactions

A. *Fragmentation*

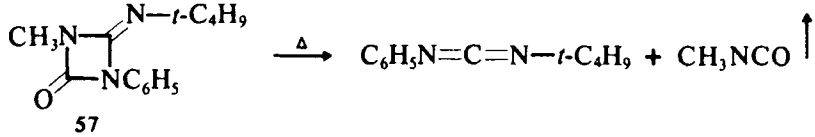
The 1,3-diazetidine derivatives synthesized by dimerization of heterocumulenes are in equilibrium with the starting monomers. Dissociation usually occurs at elevated temperatures, but in solution, in the presence of dimerization catalysts, detectable amounts of the monomers are in equilibrium at room temperature.

In the case of the [2+2] cycloaddition of two different heterocumulenes, all possible fragments are formed. For example, reaction of α-naphthyl isocyanate with dicyclohexylcarbodiimide affords a 1,3-diazetidine derivative which, upon thermal dissociation, produces the exchange products cyclohexyl isocyanate and α-napththylcyclohexylcarbodiimide. If this reaction is conducted with an additional equivalent of α-naphthyl isocyanate and the generated cyclohexyl isocyanate is simultaneously removed by distillation, the totally exchanged carbodiimide is obtained exclusively.[62] The reactions involved are shown in Scheme 4.



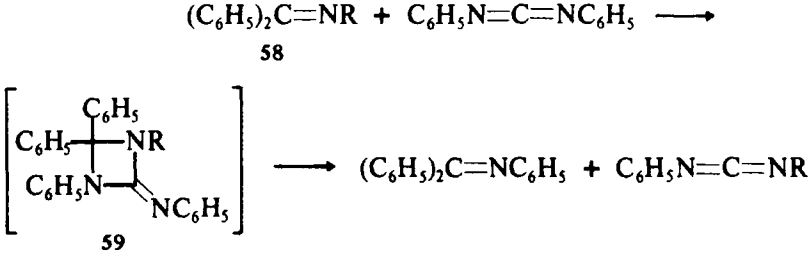
Scheme 4

In a similar manner, heating 1-methyl-3-phenyl-4-*t*-butylimino-1,3-diazetidine-2-one (**57**), with simultaneous removal of the volatile methyl isocyanate, affords *t*-butylphenylcarbodiimide in 64% yield.[12] This fragmentation reactions has been used to determine the structure of cycloadducts formed in the reaction of carbodiimides with aryl isocyanates, aroyl isocyanates, and isothiocyanates. Only in the case of the aryl isocyanates were 1,3-diazetidine derivatives formed.[12]



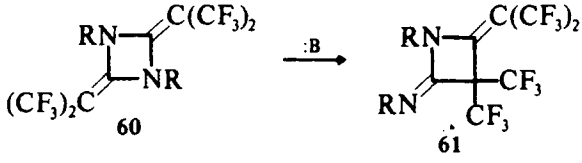
57

Cycloadducts derived from imines and carbodiimides are not reported in the literature. However, heating of anils (**58**) with diphenylcarbodiimide gave rise to the formation of the expected exchange products, indicating that the reaction may have proceeded via the 1,3-diazetidine derivative **59**.[104]



58 **59**

The rate of dissociation of the [2+2] cycloadduct derived from phenyl isocyanate and diphenylcarbodiimide is in agreement with an equilibrium process in which a first-order forward reaction is opposed by a second-order reverse reaction.[61] Photolytic dissociation of 1,3-di-*t*-butyldiazetidine-2,4-dione occurs already at room temperature in cyclohexane.[87] Base-catalyzed isomerization of the symmetric ketenimine dimer **60** to give the unsymmetric dimer **61** has also been observed.[18]



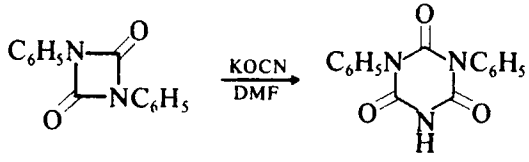
60 **61**

B. *Ring Expansion to Six-Membered-Ring Heterocycles*

The four-membered-ring isocyanate dimers are intermediates in the formation of six-membered-ring cyclic trimers (see Scheme 1).[38] This reaction occurs in the presence of base catalysts. Even in the absence of catalysts dissociation to the monomer with subsequent trimer formation has been demonstrated. For example, heating of

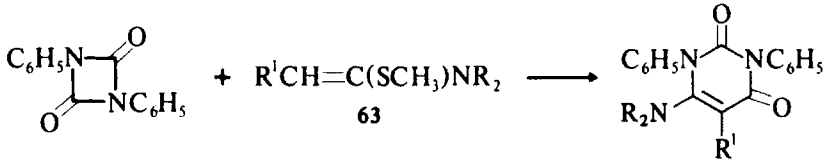
1,3-dichlorodiazetidine-2,4-dione to its melting point of 68°C gives rise to the formation of the trichloroisocyanurate trimer.[54]

Reaction of 1,3-diphenyldiazetidine-2,4-dione with potassium cyanate in *N,N*-dimethylformamide gave a 79% yield of diphenylisocyanurate (**62**).[105]



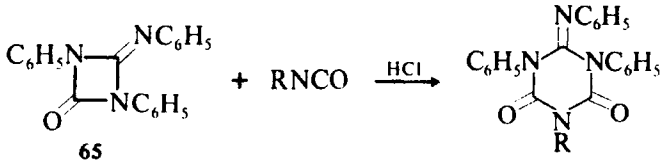
62

A ring expansion to the six-membered-ring heterocycle **64** was also observed when the phenyl isocyanate dimer was treated with the ketene derivative **63**.[106]



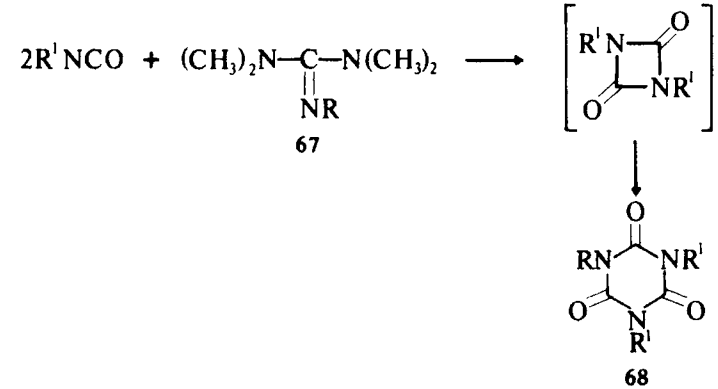
64

Ring expansion of the cycloadduct **65**; derived from phenyl isocyanate and diphenylcarbodiimide, occurs upon treatment of **65** with aryl isocyanates in the presence of a catalytic amount of hydrogen chloride. The *s*-triazine derivatives **66** were isolated in 47–82% yield.[107]



65 **66**

The formation of isocyanate dimer intermediates in the formation of triphenyl isocyanurate, derived from phenyl isocyanates and tetramethylphenylguanidine (**67**), was also observed.[108]

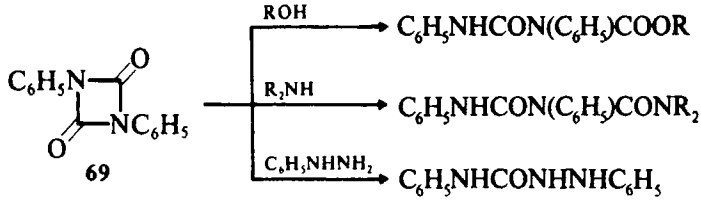


67 **68**

C. *Nucleophilic Ring-Opening Reactions*

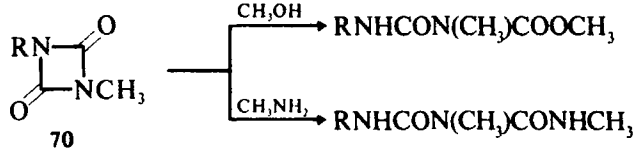
The reactions of 1,3-diphenyldiazetidine-2,4-dione (**69**) with ammonia and aliphatic amines to give biuret derivatives was already reported by A. W. Hofmann in 1871.[109] He also reported the formation of allophanates upon prolonged heating in alcohol. In contrast, reaction with phenylhydrazine gave a semicarbazide, rather than the expected biuret derivative. Apparently, the latter reaction occurred only after dissociation of the phenyl isocyanate dimer into monomers. In a similar manner, phenylcarbamate was obtained upon heating **69** with phenol at 150°C.

The reaction of aromatic amines, such as aniline, with **69** does not proceed below 100°C. However, in the presence of glacial acetic acid, a quantitative yield of triphenylbiuret was obtained at 25°C within 3 hours.[35] The catalysis with glacial acid works equally well for aliphatic amines. For example, reaction of **69** with dimethylamine gave a 98% yield of 1,3-diphenyl-5,5-dimethylbiuret.[48]



69

In 1,3-diazetidinediones with two different substituents on nitrogen, mixtures of reaction products are expected. However, reaction of **70** with alcohols and amines occurs exclusively at positions 1 and 2.[110]



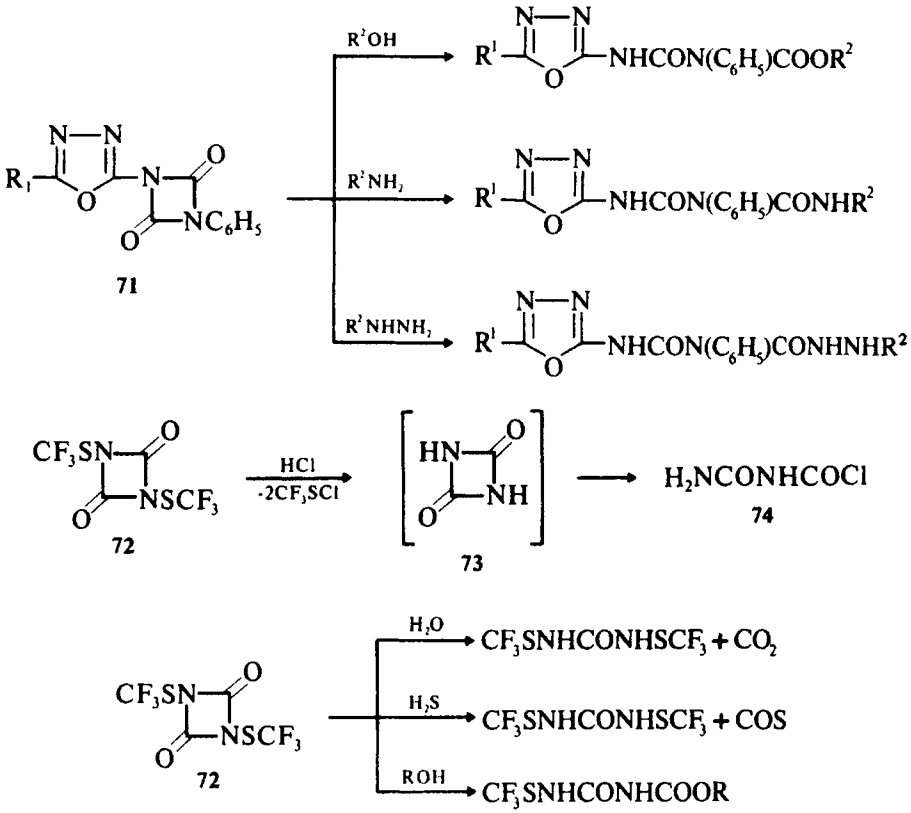
70

In contrast, ring opening in the mixed isocyanate dimers **71** occurs at the nitrogen–carbon bond having the heterocyclic substituents. In all cases only one reaction product was obtained.[40] In the reaction of **71** with hydrazine, the expected ring-opening product was observed.[40]

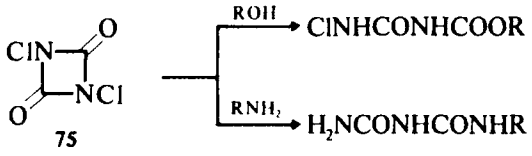
The ring-opening reactions are also catalyzed with 0.1% sodium ethoxide.[40]

Ring opening of the trifluorosulfenyl isocyanate dimer **72** has also been studied.[111] In these reactions it is not clear if the hydrolysis of the sulfur-to-nitrogen bond occurs prior to ring opening or afterwards. In the former case the reactions could involve 1,3-diazetidine-2,4-dione **73** as an intermediate. For example, ring opening with hydrogen chloride gives rise to the formation of allophanoyl chloride **74**.[111]

Reaction of **72** with water gives a urea derivative,[57] and a similar reaction occurs with hydrogen sulfide.[111] The reaction of **72** with ammonia gives biuret, and in the reaction with alcohols partially solvolyzed allophanates are obtained.[111]



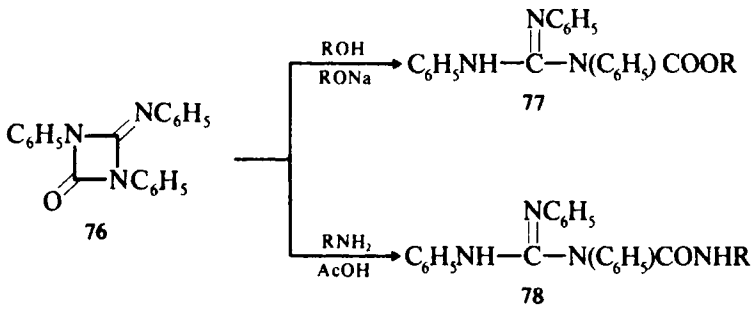
A similar reaction occurs upon treatment of 1,3-dichlorodiazetidinedione **75** with ethanol.[54] However, reaction of **75** with ammonia gives a biuret derivative.[54]



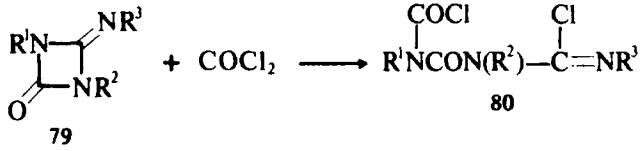
The ring opening of 1,3-diphenyl-4-phenylimino-1,3-diazetidine-2-one (**76**) with alcohols occurs only in the presence of a catalytic amount of sodium alkoxide. The reaction proceeds at room temperature. An 80% yield of the guanidine derivative **77** was isolated in the reaction of **76** with *n*-butanol.[61] The ring-opening reaction with *n*-butylamine required catalysis with glacial acetic acid, and the guanidine derivative **78** was obtained in good yield.[61]

The ring-opening of 1,3-dialky-4-alkylamino-1,3-diazetidine-2-ones (**79**) with phosgene affords the chloroformamidine derivatives **80**.[69]

Selective reaction of the isocyanato group in **81** can be achieved without opening of the four-membered ring. Thus reaction of **81** with a wide variety of alcohols

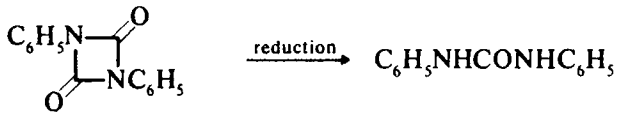


76 77 78



79 80

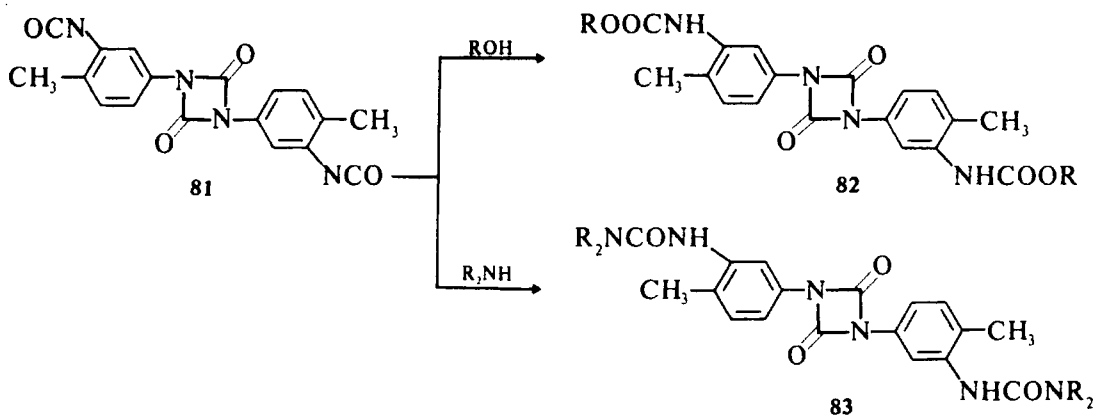
at 90°C gave the biscarbamates **82** in high yields.[112] Also, selective reaction of **81** with diallylamine,[113] diisobutylamine,[112] and dibenzylamine[112] to give **83** was observed, provided the reaction was conducted at room temperature. Di-*n*-butylamine reacts more rapidly with **81** in *o*-dichlorobenzene at 170–180°C. Four equivalents of di-*n*-butylamine are consumed to give the bisurea derivative derived from toluene-2,4-diisocyanate.[114]

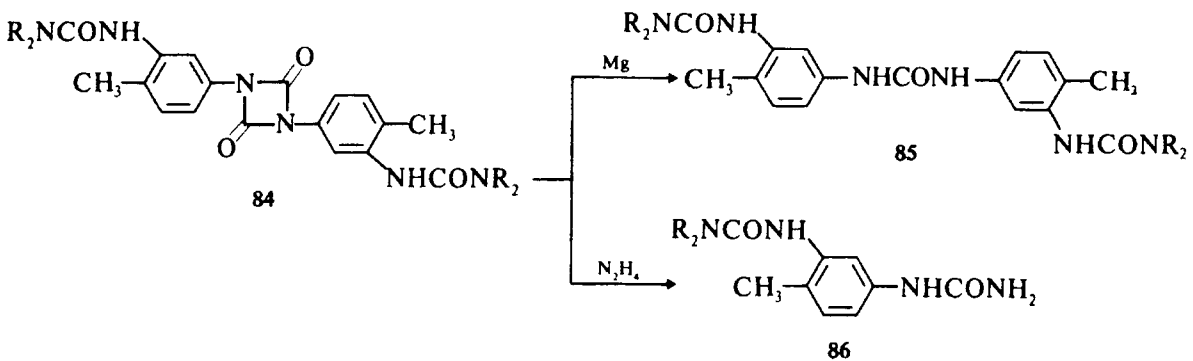


Reduction of 1,3-diphenyldiazetidinedione with either Grignard reagents[115] or lithium aluminum hydride[116] results in ring opening with formation of *N,N*-diphenylurea.

Reduction of the urea derivative **84**, derived from **81**, with magnesium in methanol gives the ring-opened urea derivative **85** and with hydrazine hydrate **86** was obtained.[117]

Dissociation of **84** gives rise to the substituted *p*-tolylisocyanate.[118] In this manner, selective reaction of the less reactive isocyanato group in toluene-2,4-diisocyanate can be achieved. Reaction of **81** with hydroxyl-terminated bifunctional polyesters affords a linear polyurethane, provided that the reaction is conducted below 120°C. Heating at higher temperature leads to cross-linking, because of ring opening.[119]


OCN
CH3
N
O
N
O
CH3
NCO
81
ROH
ROOCNH
CH3
NHCOOR
82
R2NH
R2NCONH
CH3
NHCONR2
83


R2NCONH
CH3
NHCONR2
84
Mg
R2NCONH
CH3
NHCONH
CH3
NHCONR2
85
N2H4
R2NCONH
CH3
NHCONH2
86

5. References

1. Tollens and Hölzer, *Chem. Ber.*, **17**, 659 (1884).
2. H. Schiff, *Justus Liebigs Ann. Chem.*, **151**, 206 (1869).
3. A. W. Hofmann, *Jahresberichte*, 349 (1858).
4. H. Staudinger, *Die Ketene*, Enke, Stuttgart, 1912, p. 126.
5. C. J. Brown, *J. Chem. Soc.*, 2931 (1955).
6. W. J. Hale, *J. Am. Chem. Soc.*, **40**, 370 (1918).
7. K. D. Petrov, E. S. Lagucheva, and V. I. Pukhova, *Zh. Obshch. Khim.*, **23**, 1771 (1953).
8. H. D. Hartough, S. L. Meisel, E. Koft, and J. W. Shick, *J. Am. Chem. Soc.*, **70**, 4013 (1948).
9. H. D. Hartough, J. W. Shick, and J. J. Dickert, Jr., *J. Am. Chem. Soc.*, **72**, 1572 (1950).
10. (a) C. D. Wright and J. L. Zollinger, *J. Org. Chem.*, **38**, 1975 (1973); (b) H. W. Roesky and E. Janssen, *Z. Naturforsch.*, **29b**, 177 (1974).
11. H. Ulrich, *Acc. Chem. Res.*, 187 (1969).
12. H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Am. Chem. Soc.*, **94**, 3484 (1972).
13. B. A. Arbuzov and N. N. Zobova, *Synthesis*, 461 (1974).
14. R. Richter, *Chem. Ber.*, **101**, 174 (1968).
15. H. Helfert and E. Fahr, *Angew. Chem. Int. Ed.*, **9**, 372 (1970).
16. (a) R. O. Kan and R. L. Furey, *J. Am. Chem. Soc.*, **90**, 1666 (1968); (b) C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, **121**, 2793 (1922).
17. D. P. Deltsova, N. P. Gambaryan, Y. V. Zeifman, and I. L. Knunyants, *Zh. Org. Khim.*, **8**, 856 (1972).
18. N. P. Gambaryan and E. A. Avetisyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 358 (1976).
19. F. Zetzsche and A. Fredrich, *Ber.*, **73**, 1114 (1940).
20. K. Hartke, F. Rossbach, and M. Radau, *Justus Liebigs Ann. Chem.*, **762**, 167 (1972).
21. A. V. Narbut and G. I. Derkach, *Zh. Obshch. Khim.*, **39**, 1698 (1969).
22. L. Ruppert, *Angew. Chem.*, **89**, 336 (1977).
23. H. L. Snape, *J. Chem. Soc.*, **49**, 254 (1886).
24. W. J. Balon and O. Stallmann, U.S. Patent 2,683,144 (1952); *Chem. Abstr.*, **48**, 12465 (1954).
25. J. S. Blair and G. E. P. Smith, *J. Am. Chem. Soc.*, **56**, 907 (1934).
26. G. Oertel and H. Holtschmidt, U.S. Patent 3,290,288 (1966); *Chem. Abstr.*, **67**, 90788 (1967).
27. W. H. Lookwood, FIAT Final Rept. No. 1301 (1947).
28. H. J. Wild and F. E. G. Tate, U.S. Patent 3,144,452 (1964); *Chem. Abstr.*, **61**, 16068 (1964).
29. J. M. Lyon and R. H. Thomson, *J. Chem. Soc.*, 1971 (1950).
30. S. Y. Han, T. J. Min, D. Y. Lee, and I. K. Lee, *Daehan Hwahak Hwoejee*, **15**, 318 (1971); *Chem. Abstr.*, **76**, 140740 (1972).
31. S. Y. Han, U. H. Paek, D. Y. Lee, and I. K. Lee, *Daehan Hwahak Hwoejee*, **17**, 188 (1973); *Chem. Abstr.*, **79**, 78906 (1973).
32. H. Ulrich, *Cycloaddition Reactions of Heterocumulenes*, Academic Press, New York, pp. 124–125.
33. J. L. Bach, W. M. Beyleveld, and C. Woolf, NASA Accession No. N66-30268 Report No. AD631374 (1965); *Chem. Abstr.*, **66**, 32376 (1967).
34. W. Frentzel, *Chem. Ber.*, **21**, 411 (1888).

35. R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957).
36. Farbenfabriken Bayer A. G., Fr. Patent 1,532,054 (1968); *Chem. Abstr.*, **71**, 81328 (1969).
37. N. Kuhn, W. Schwarz, and A. Schmidt, *Chem. Ber.*, **110**, 1130 (1977).
38. R. Richter and H. Ulrich, *Synthesis*, 463 (1975).
39. L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943).
40. H. Gehlen and M. Just, *Justus Liebigs Ann. Chem.*, **692**, 151 (1966).
41. E. S. Gubnitskaja and G. I. Derkach, *Zh. Obshch. Khim.*, **42**, 296 (1972).
42. R. Richter and H. Ulrich, *J. Org. Chem.*, **43**, 3060 (1978).
43. M. Kutz and W. Reichen, *Tetrahedron Lett.*, 1433 (1978).
44. O. Tsuge and R. Mizuguchi, *Nippon Kagaku Zasshi*, **86**, 325 (1965); *Chem. Abstr.*, **63**, 4299 (1965).
45. (a) O. Tsuge and R. Mizuguchi, *Kogyo Kagaku Zasshi*, **69**, 939 (1966); *Chem. Abstr.*, **66**, 85552 (1967); (b) O. Tsuge and K. Sakai, *Bull. Chem. Soc. Japan*, 1534 (1972); *Chem. Abstr.*, 77, 48411 (1972).
46. G. Zinner and G. Isensee, *Chem. Ztg.*, **97**, 73 (1973).
47. B. N. Kozhushko, A. V. Gumenyuk, and Y. A. Paliichuk, *Zh. Obshch. Khim.*, **47**, 333 (1977).
48. E. Meisert and W. Altner, Germ. Patent 1,164,395 (1964); *Chem. Abstr.*, **60**, 14434 (1964).
49. F. L. Kligman, M. I. Bakhitov, E. V. Kuznetsov, and S. L. Zainutdinova, *Zh. Org. Khim.*, **12**, 2026 (1976).
50. E. G. Tate and J. H. Wild, Brit. Patent 821,148 (1959); *Chem. Abstr.*, **54**, 14284 (1960).
51. V. G. Sinyavskii and V. F. Kovaleva, *Zh. Org. Khim.*, **5**, 1888 (1969).
52. M. Brown, U.S. Patent 3,214,412 (1965); *Chem. Abstr.*, **64**, 3542 (1966).
53. N. P. Smetankina, N. I. Miryan, and V. E. Didkovskii, *Zh. Obshch, Khim.*, **39**, 2016 (1969).
54. W. Gottardi and D. Henn, *Mh. Chem.*, **100**, 1860 (1969); *Mh. Chem.*, **101**, 264 (1970).
55. G. Boden, W. Grosskreutz, G. Kessler, and H. Scheler, *J. Chem.*, **12**, 299 (1972).
56. A. Haas and H. Reinke, *Chem. Ber.*, **102**, 2718 (1969).
57. A. Haas, *Chem. Ber.*, **98**, 111 (1965).
58. A. Haas and Doug-Young Oh, *Chem. Ber.*, **100**, 480 (1967).
59. J. Goerdler and K. Jonas, *Chem. Ber.*, **99**, 3572 (1968).
60. R. Hofmann, E. Schmidt, A. Reichle, and F. Moosmüller, Germ. Patent 1,012,601 (1957), *Chem. Abstr.*, **53**, 19892 (1959).
61. W. J. Farrissey, Jr., R. J. Riccardi, and A. A. R. Sayigh, *J. Org. Chem.*, **33**, 1913 (1968).
62. W. Neumann and P. Fischer, *Angew. Chem. Int. Ed.*, **1**, 621 (1962).
63. R. Neidlein, *Arch. Pharm.*, **297**, 623 (1964).
64. H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Am. Chem. Soc.*, **90**, 528 (1968).
65. Y. I. Dergunov, A. S. Gordetsov, I. A. Vostokov, and V. A. Galperin, *Zh. Obshch. Khim.*, **45**, 2234 (1975).
66. H. Suschitzky, R. E. Walround, and R. Hull, *J. Chem. Soc. Perkin I*, 47 (1977).
67. Y. I. Dergunov, A. S. Gordetsov, I. A. Vostokov, and V. F. Gerega, *Zh. Obshch. Khim.*, **44**, 2166 (1974).
68. Y. I. Dergunov, A. S. Gordetsov, A. I. Vostokov, and V. F. Gerega, *Zh. Obshch. Khim.*, **44**, 1523 (1974).

69. Farbenfabriken Bayer A. G., Brit. Patent 959,997 (1964); *Chem. Abstr.*, **61**, 6924 (1964).
70. R. Richter, *Chem. Ber.*, **102**, 938 (1969).
71. N. S. Kozlov, V. D. Pak, and N. A. Ivanov, *Tr. Perm. Gos. Selskokhoz. Inst.*, **68**, 149 (1970); *Chem. Abstr.*, **77**, 139856 (1972).
72. J. Bödeker and K. Courault, *Tetrahedron*, **34**, 101 (1978).
73. A. Senier and F. G. Shephard, *J. Chem. Soc.*, **95**, 494 (1909).
74. N. N. Zobova, G. N. Rusanov, and B. A. Arbuzov, *Izv. Akad. Nauk SSSR, Ser Khim.*, 2016 (1972).
75. B. A. Arbuzov and N. N. Zobova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2607 (1973).
76. B. A. Arbuzov, N. N. Zobova, and N. R. Rubinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 953 (1977).
77. J. H. Sellstedt, D. M. Teller, and C. J. Guinosso, U.S. Patent 3,720,666 (1973); *Chem. Abstr.*, **79**, 5329 (1973).
78. U. Kraatz, *Tetrahedron Lett.*, 1219 (1973).
79. G. Entenmann, *Tetrahedron Lett.*, 3279 (1974).
80. W. J. Hale and N. A. Lange, *J. Am. Chem. Soc.*, **41**, 379 (1919).
81. G. Schwenker and R. Kolb, *Tetrahedron*, **25**, 5437 (1969).
82. H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Angew. Chem. Int. Ed.*, 7, 291 (1968).
83. G. Zinner and R. Vollrath, *Chem. Ztg.*, **97**, 38 (1973).
84. W. T. Flowers, R. Franklin, R. N. Haszeldine, and R. J. Perry, *J. Chem. Soc., Chem. Commun.*, 567 (1976).
85. G. Zinner and R. Vollrath, *Z. Chem.*, **10**, 30 (1970).
86. (a) K. H. Koenig, A. Fischer, and B. Zech, Germ. Offen. 2,027,345 (1971); *Chem. Abstr.*, **76**, 72500 (1972); (b) A. G. Jelinek, U.S. Patent 3,579,500 (1971); *Chem. Abstr.*, **75**, 35991 (1971).
87. J. C. Stowell, F. D. Greene, and W. R. Bergmark, *J. Org. Chem.*, **36**, 3056 (1971).
88. H. Ulrich, J. N. Tilley, and A. A. R, Sayigh, *J. Org. Chem.*, **29**, 2401 (1964).
89. H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Int. Ed.*, **5**, 704 (1966).
90. D. K. White and F. D. Greene, *J. Org. Chem.*, **43**, 4530 (1978).
91. H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **28**, 1427 (1963).
92. L. C. Raiford and R. J. Shelton, *J. Org. Chem.*, **4**, 207 (1939).
93. W. H. Warren and F. E. Wilson, *Chem. Ber.*, **68**, 957 (1935).
94. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 174 (1943).
95. H. Hoberg and J. Korff, *Justus Liebigs Ann. Chem.*, 1111 (1978).
96. E. Schaumann and E. Kausch, *Justus Liebigs Ann. Chem.*, 1560 (1978).
97. L. N. Markovskij and E. A. Stookalo, *Phosphorus*, **4**, 237 (1974).
98. M. M. Kremlev, A. D. Biba, N. A. Kirsanova, G. I. Derkach, E. V. Bryukhova, and G. K. Semin, *Ukr. Khim. Zh.*, **37**, 1026 (1971); *Chem. Abstr.*, **76**, 14008 (1972).
99. M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pelkis, *Dopov. Akad. Nauk Ukr. RSR, Ser. B*, **30**, 266 (1968); *Chem. Abstr.*, **69**, 59144 (1968).
100. M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pelkis, *Khim. Geterotsikl. Soedin. Sb.*, 176 (1971); *Chem. Abstr.*, **77**, 114292 (1972).
101. A. J. Downs and A. Haas, *Spectrochim. Acta*, Part A, **23**, 1023 (1967).
102. J. L. Baudour, Y. Delugeard, and M. Sanquer, *Acta Crystallogr.*, Sect. B, **30**, 691 (1974).
103. R. Richter and H. Ulrich, unpublished results.

104. M. W. Barker and R. H. Jones, *J. Heterocyclic Chem.*, **9**, 169 (1972).
105. P. A. Argabright, Fr. Patent 1,582,371 (1969); *Chem. Abstr.*, **73**, 35410 (1970).
106. R. Gompper and J. Stetter, *Tetrahedron Lett.*, 233 (1973).
107. R. Richter and H. Ulrich, *Tetrahedron Lett.*, 1875 (1974).
108. R. Richter, *Tetrahedron Lett.*, 5037 (1968).
109. A. W. Hofmann, *Chem. Ber.*, **4**, 246 (1871).
110. D. E. Thurman and C. E. Moyer, Jr., *J. Heterocyclic Chem.*, **9**, 459 (1972).
111. A. Haas and P. Schott, *Chem. Ber.*, **99**, 3103 (1966).
112. P. Singh and J. L. Boivin, *Can. J. Chem.*, **40**, 935 (1962).
113. C. B. Puchalski, *Anal. Chem.*, **45**, 787 (1973).
114. J. H. Saunders and E. E. Hardy, *J. Am. Chem. Soc.*, **75**, 5439 (1953).
115. L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943).
116. N. G. Gaylord and J. H. Crowdle, *Chem. Ind. (London)*, 145 (1955).
117. P. Singh and J. L. Boivin, *Can. J. Chem.*, **40**, 2411 (1962).
118. W. Siefken, *Justus Liebigs Ann. Chem.*, **562**, 75 (1949).
119. P. Müller, K. Wagner, R. Müller, and B. Quiring, *Angew. Macrom. Chem.*, **65**, 23 (1977).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

CHAPTER IV

Diaziridines, 3H-Diazirines, Diaziridinones, and Diaziridinimines

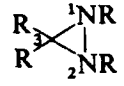
Harold W. Heine

Department of Chemistry, Bucknell University, Lewisburg, Pennsylania

I. Diaziridines (1,2-Diazacyclopropanes) 549
1. Introduction 549
2. Methods of Preparation 549
A. Reaction of Imines with NH_2Cl and RNHCl (Method A) and H_2NOSO_3H and $RNHOSO_3H$ (Method B). 549
B. Reactions of Aminals with Sodium Hypochlorite (Method C) 551
C. 3-Alkyl- and 3-Aryldiaziridines from Acid Hydrolysis of 1,3,5-Triazabicyclo[3.1.0]hexanes (Method D) 551
D. 3,3-Disubstituted and 1,3,3-Trisubstituted Diaziridines from *N*-Haloketimines and Ketoxime-*O*-sulfonates (Method E). 552
E. Diaziridines from Diazirines (Method F) 553
F. Photochemical Synthesis of Diaziridines 553
G. Reactions of Azodicarbonyl Compounds with Aliphatic Diazo and Organomercury Substrates 555
H. Miscellaneous Preparations of Diaziridines 557
3. Preparation of Diaziridines Utilizing Other Diaziridines 558
A. 1-(2,4-Dinitrophenyl)- and 1-(2,4,6-Trinitrophenyl)diaziridines 558
B. *N*-Alkyldiaziridines 559
C. 1-(Dialkylaminomethyl)diaziridines 559
D. Chloral Adducts of Diaziridines 559
E. *N*-(2-Hydroxyalkyl)diaziridines 559
F. Acylated Diaziridines 559
G. *N*-Arylsulfonyldiaziridines 560
H. Diaziridinyl Phosphinyl Derivatives 561
I. 1-Diaziridinecarboxamides and 1,2-Diaziridinedicarboxamides 561
J. Adducts of Diaziridines with Michael-Type Substrates 561
K. *N*-Silyldiaziridines 562
4. Ring-Opening Reactions 562
A. Reactions Proceeding Through Azomethine Imine Intermediates . . . 562
B. Reactions Resulting in Nitrogen–Nitrogen Bond Breaking of the Ring 566
C. Hydrolysis of Diaziridines 568
D. Reaction of Diaziridines with Acyl Anhydrides 569

E. Reaction of 1,2-Dialkyl- and 1,2,3-Trialkyldiaziridines with Ketones and Isocyanates 569
F. Reaction of Diaziridines with Diphenylcyclopropenone 570
G. Reaction of Diaziridines with Lead Tetraacetate 571
5. Isolable Invertomers and Optical Antipodes 572
6. Physical Properties 572
7. Diaziridines of Pharmacological Interest 573
8. Tables 574
9. References 584
II. 3H-Diazirines (1-Diazirines) 588
1. Introduction 588
2. Methods of Preparation 589
A. Dehydrogenation of 1,2-Unsubstituted Diaziridines 589
B. Reaction of Imines with Dichloro- and Difluoroamines 592
C. Halogenation of Amidines 593
D. Reductive Deflorinative Cyclization 594
E. Photochemical Isomerization of Diazo Compounds 595
F. Miscellaneous Methods for Preparing 3H-Diazirines 597
3. Reactions 598
A. 3H-Diazirines and Nucleophilic Reagents 598
B. 3H-Diazirines and Electrophiles 599
C. Thermal and Photolytic Decomposition of 3H-Diazirines 602
4. Physical Properties 603
5. 3H-Diazirines of Pharmacological Interest 604
6. Tables 605
7. References 612
III. Diaziridinones 616
1. Methods of Preparation 616
2. Reactions 619
A. Reaction of Diaziridinones with Acids 619
B. Reaction of Diaziridinones with Nucleophiles 619
C. Thermal Decomposition of Diaziridinones 623
D. Reactions of Diaziridinones with Unsaturated Substrates 624
3. Physical Properties 625
4. References 625
IV. Diaziridinimines (3-Iminodiaziridines) 626
1. Methods of Preparation 626
2. Reactions 627
A. Diaziridinimines and Heat 627
B. Diaziridinimines and Unsaturated Substrates 627
3. References 628

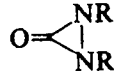
The present chapter includes the chemistry of diaziridines (**1**), 3H-diazirines (**2**), diaziridinones (**3**) and diaziridinimines (**4**). The literature has been surveyed from 1959 to 1980, and compilations of the methods of preparation, reactions, and physical properties of compounds **1**–**4** are given.



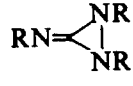
1



2



3



4

I. DIAZIRIDINES (1,2-DIAZACYCLOPROPANES)

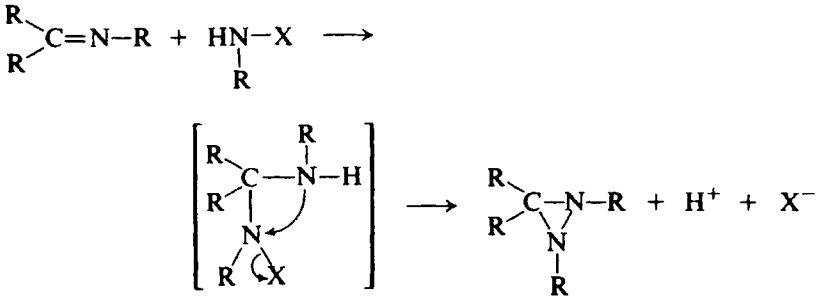
1. Introduction

Diaziridines were first synthesized in 1959 by three groups of investigators employing essentially the same methods of preparation.[1-3] Since then, 1-monosubstituted; 1,2-, 1,3-, 3,3-disubstituted; 1,2,3- and 1,3,3-trisubstituted; and 1,2,3,3-tetrasubstituted diaziridines have been made (Tables 1, 3–7). 3-Monosubstituted diaziridines (Table 2), although not isolable, can be generated *in situ* and reacted with many reagents. Professor E. Schmitz, a pioneer in the field, has published several reviews on diaziridines.[4-6]

2. Methods of Preparation

A. *Reaction of Imines with NH_2Cl and RNHCl (Method A) and H_2NOSO_3H and $RNHOSO_3H$ (Method B)*

The reaction of imines with NH_2Cl, RNHCl, H_2NOSO_3H, and $RNHOSO_3H$ is a general procedure for the synthesis of diaziridines. In many instances the imine is generated *in situ*. All possible variants of substituted diaziridines can be prepared by methods A and B except 3-monoalkyl- and 1,2-dialkyldiaziridines. Although not isolable, diaziridine itself is formed in solution by both of these methods.[7,8] The formation of the three-membered ring probably proceeds by the addition of the chloramine or hydroxylamine-*O*-sulfonic acid to the imine, followed by an intramolecular nucleophilic displacement (Eq. 1).



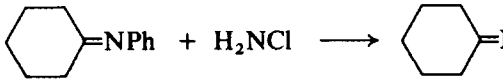
(1)

X = Cl, OSO_3H

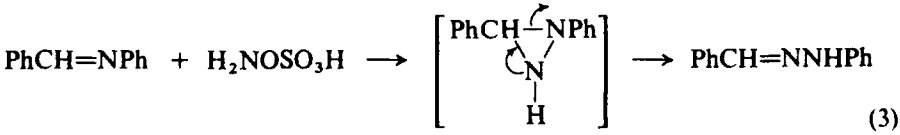
Ketones react with ammonia and NH_2OSO_3H to provide 3,3-dialkyldiaziridines.[9] Steric and electronic factors impose some restrictions on this reaction. For example, dicyclopropyl ketone and quinuclidin-3-one fail to react, as do 3-oxosteroids with adjacent *gem*-dimethyl substituents or with α,β-unsaturated moieties.[10] Regardless of these limitations, a host of 3,3-dialkyldiaziridines (Table 5) have been synthesized

from simple ketones, 3-oxo-[11-13a] and 17-oxosteroids,[13b] tropinone derivatives,[14] and yohimban-16- and 17-ones.[15]

Another limitation to methods A and B is that anils fail to yield diaziridines. Cyclohexylidene anil reacts with chloramine to give aniline and *N*-chlorocyclohexanimine[16] (Eq. 2), and *N*-benzylidene anil reacts with hydroxylamine-*O*-sulfonic acid to form benzaldehyde phenylhydrazone[17] (Eq. 3). In the latter case the desired diaziridine may have formed and isomerized.

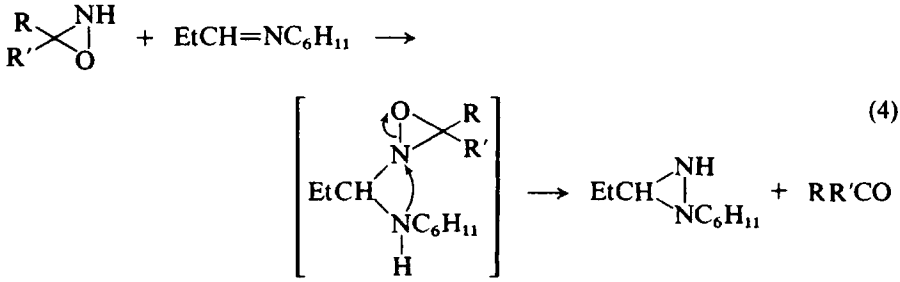


(2)



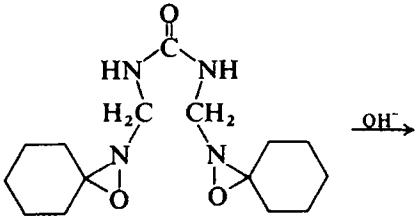
(3)

Oxaziridines also add to imines to yield diaziridines in 75% yields.[18] The reaction has not been examined in detail. A possible mechanism for the reaction is as follows (Eq. 4). 3-Ethyl-3-methyloxaziridine, like hydroxylamine-*O*-sulfonic acid,

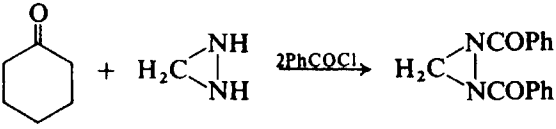


(4)

reacts with benzylideneaniline to give benzaldehyde phenylhydrazone instead of 1,3-diphenyldiaziridine.[17] A related reaction involves the heating of **5** in concentrated sodium hydroxide solution to give diaziridine, which was trapped by benzoyl chloride as 1,2-dibenzoyldiaziridine.[19]

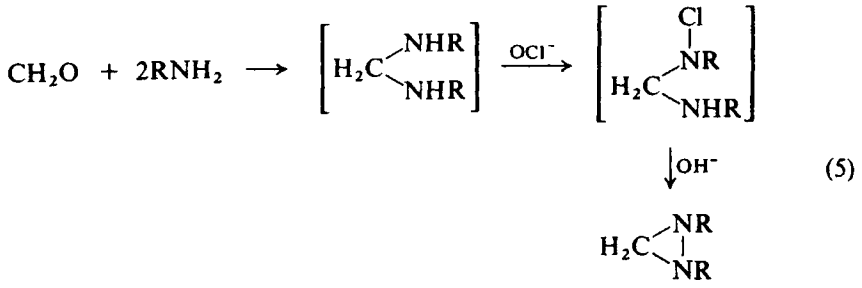


5



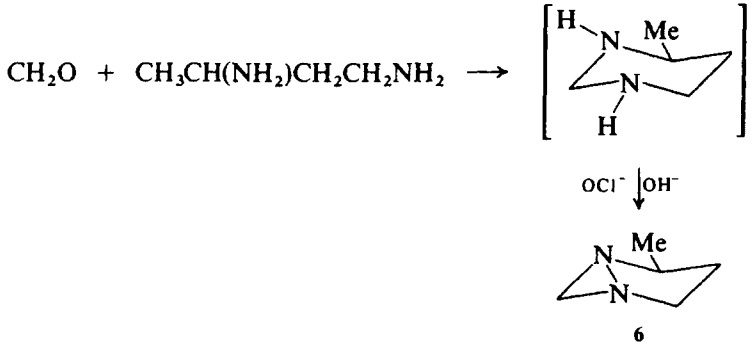
B. *Reaction of Aminals with Sodium Hypochlorite (Method C)*

1,2-Dialkyldiaziridines (Table 3) are made by the interaction of an aminal (produced *in situ* by reaction of formaldehyde and a primary amine) with an alkaline sodium hypochlorite solution (Eq. 5). The method has been employed to



(5)

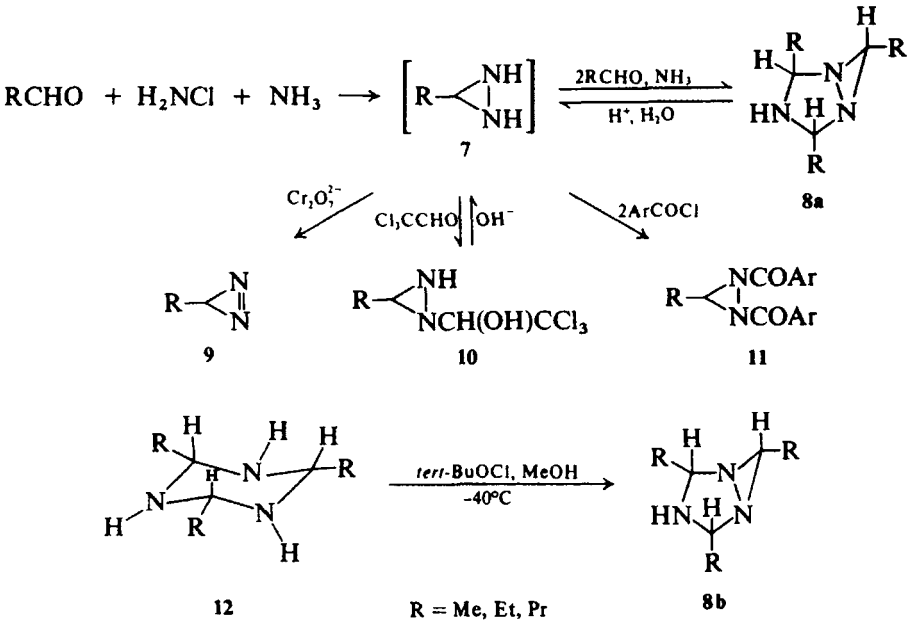
prepare the bicyclic diaziridine **6** in 93% yield from 1,3-diaminobutane and formaldehyde.[20]



6

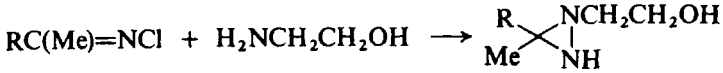
C. *3-Alkyl- and 3-Aryldiaziridines from Acid Hydrolysis of 1,3,5-Triazabicyclo[3.1.0]hexanes (Method D)*

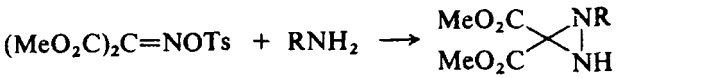
Reaction of aldehydes with ammonia and chloramine (or hydroxylamine-*O*-sulfonic acid) forms transient 3-alkyl- and 3-aryldiaziridines (**7**). Compound **7** condenses with additional aldehyde and ammonia to give *trans*-2,4,6-trialkyl- and 2,4,6-triaryl-1,3,5-triazabicyclo[3.1.0]hexanes (**8a**) (Table 10). Acid hydrolysis of **8a** regenerates **7**, which can be intercepted by oxidizing agents and by chloral hydrate to form diazirines (**9**)[7,21a,21b] and chloral adducts (**10**), respectively. Alkaline hydrolysis of **10**, followed by extraction of **7** from the reaction mixture by ether and addition of aroyl chlorides to the extracts, affords 1,2-diaroyl-3-alkyldiaziridines (**11**).[22–24] *Cis*-2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes (**8b**) are obtained by oxidation of 1,3,5-hexahydrotriazines (**12**) with *tert*-butyl hypochlorite.[25,26]

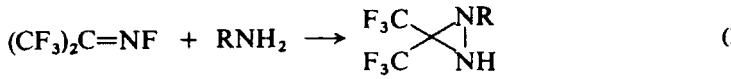


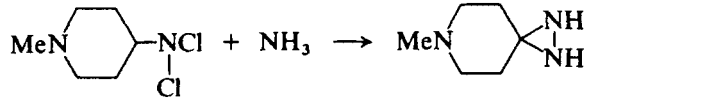
D. *3,3-Disubstituted and 1,3,3-Trisubstituted Diaziridines from N-Haloketimines and Ketoxime-O-sulfonates (Method E)*

An important modification of methods A and B is the addition of ammonia or aliphatic primary amines to *N*-haloketimines and ketoxime-*O*-sulfonates. The method is especially useful for forming highly functionalized 3,3-disubstituted and 1,3,3-trisubstituted diaziridines. The *N*-chloroketimines may be generated *in situ*. Illustrative examples follow.



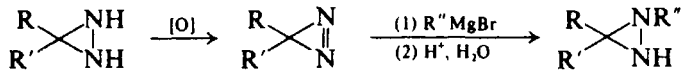






E. *Diaziridines from Diazirines (Method F)*

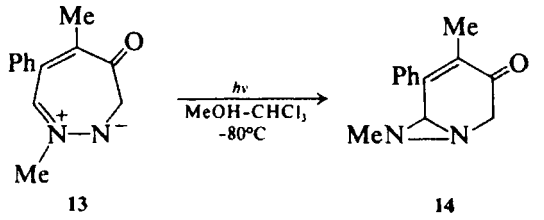
Addition of alkyl Grignard reagents to 3H-diazirines leads to 1-alkyldiaziridines,[7,8,20,21a] 1,3-dialkyldiaziridines,[7,31] and 1,3,3-trialkyldiaziridines.[31-33]



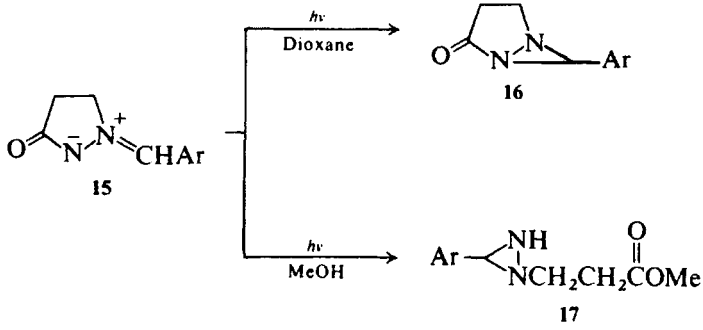
Phenylmagnesium bromide reacts with 3,3-pentamethylenediazirine to give (in 60% yield) 1-phenyl-3,3-pentamethylenediaziridine, which could not be isolated.[31]

F. *Photochemical Synthesis of Diaziridines*

Photolysis of azomethine imines frequently produces diaziridines. For example, exposure of **13** to sunlight at −80°C afforded **14**.[34] Similarly, ultraviolet irradiation of betaines (**15**) in dioxane forms the bicyclic diaziridines **16**.[35,36] An aryl-substituted azomethine imine system appears necessary for the latter cyclization, since 1-isopropylidenepyrazolidone-3-betaine does not yield a diaziridine. If the azomethine imides **15** are irradiated in methanol rather than in dioxane, diaziridines **17** are the products.[37]

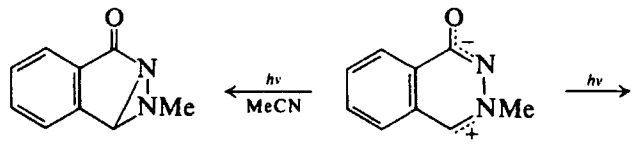


13 **14**

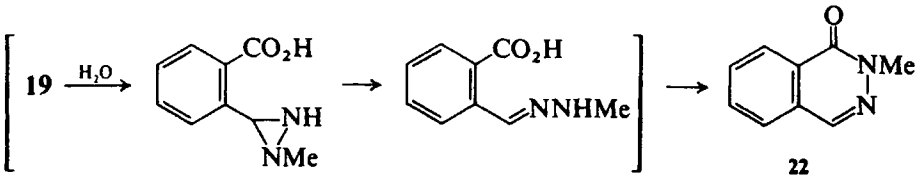


15 **16** **17**

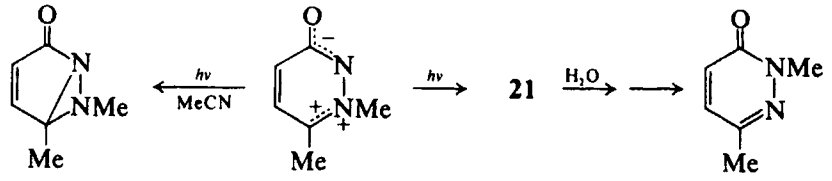
Photolysis of the 3-oxopyridazinium betaines **18** and **20** gives diaziridines **19** and **21**, respectively.[38] Diaziridines **19** and **21** are postulated to be intermediates in the photoconversion in water of **18** to **22** and **20** to **23**.



19 18

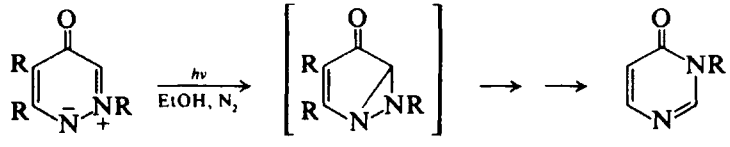


22

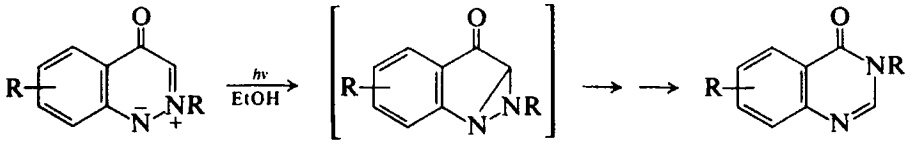


21 20 23

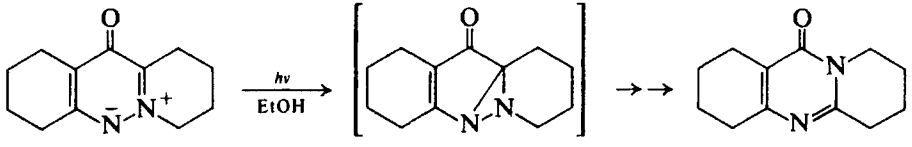
It is likely that diaziridines intervene as intermediates in the photoisomerization of **24a**, **24b**, and **24c** to **25**,[39] **26**,[40] and **27**,[41] respectively.



24a 25

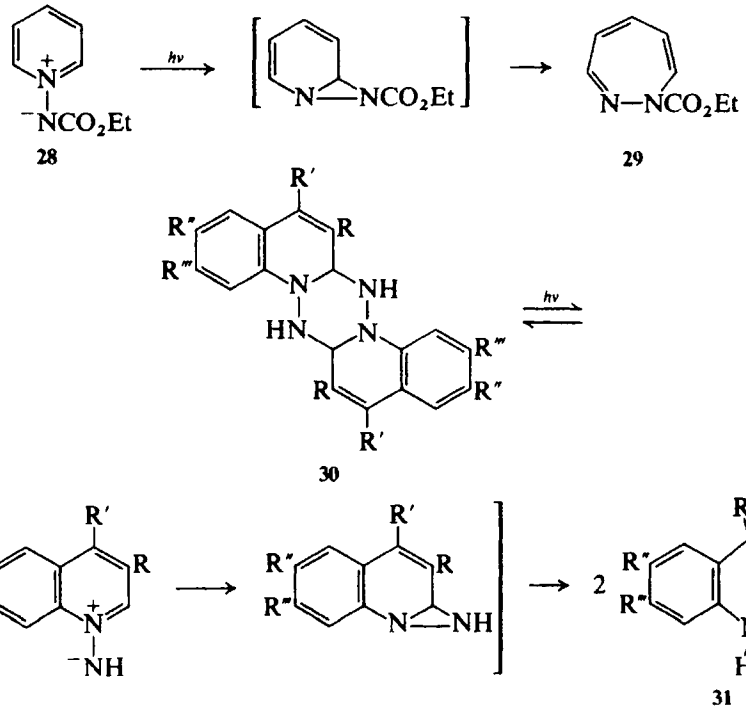


24b 26

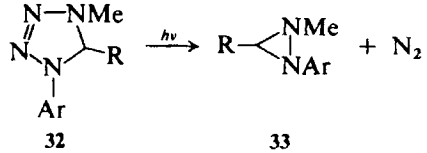


24c 27

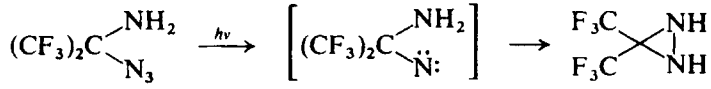
A recent report by Streith summarizes the considerable work done on the photochemically induced ring expansions of 1-iminopyridinium ylides (**28**) into diazepines (**29**).[42a] Undoubtedly the ring enlargements occur through the intermediacy of a diaziridine. The photoconversion of **30** to **31** is thought to proceed analogously.[42b]



Photodecomposition of Δ^2-tetrazolines (**32**) affords 1,2,3-trisubstituted diaziridines and nitrogen.[43] The procedure has been utilized to produce the elusive *N*-aryldiaziridines (**33**).



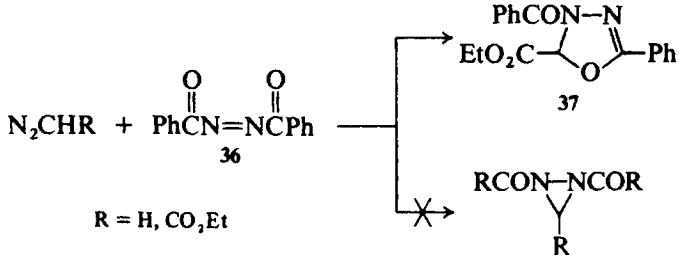
Both photolysis and pyrolysis of azide **34** gives diaziridine **35**.[44] An intramolecular insertion reaction by a nitrene intermediate is presumed to occur in the conversion of **34** to **35**.



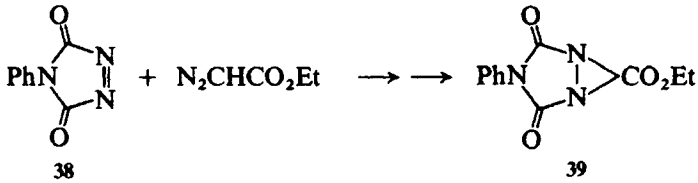
G. *Reaction of Azodicarbonyl Compounds with Aliphatic Diazo and Organomercury Substrates*

Reaction of diethyl azodicarboxylate or of diazomethane with the *trans* form of **36** leads to oxadizaolines **37**,[45a] and not diaziridines as purported.[45b] This result

renders suspect the earlier reports[45c,d] that diaziridines are products of the reaction of diazoalkanes with **36**, azodicarboxylates, and 2,2′-azopyridine.

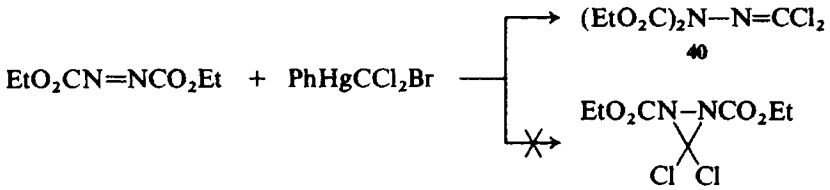


However, the reaction of diethyl azodicarboxylate with the *cis*-azo compound **38** in benzene at 0°C gives the diaziridine **39** in near quantitative yield.[46] Because of the mild reaction conditions employed, it was proposed that the reaction proceeds by a 1,3-dipolar cycloaddition of ethyl diazoethanoate to **38**, rather than by an addition of a free carbene to **38**.



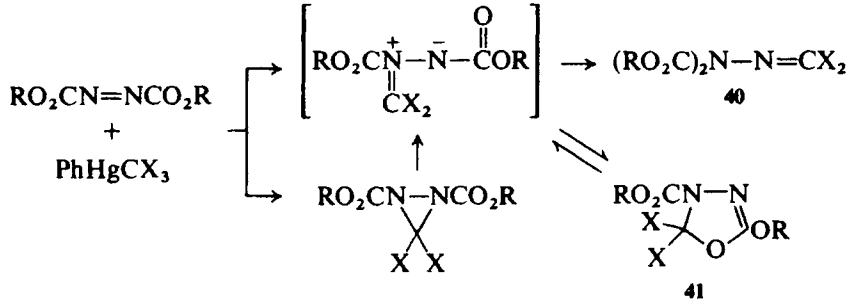
38 **39**

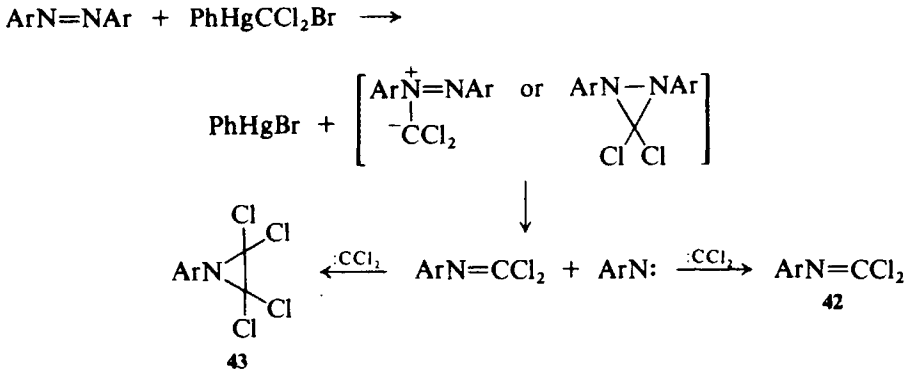
Reaction of phenyl(bromodichloromethyl)mercury with diethyl azodicarboxylate in benzene results in the formation of **40**, and not the anticipated diaziridine.[47] Decarboxylation of sodium trichloroacetate in 1,2-dimethoxyethane containing diethyl azodicarboxylate also gives **40**.[47]



^{1}H- and ^{13}C-nmr spectroscopic studies of the reaction between the organomercury compound and the diethyl azodicarboxylate suggest that intermediate **41** forms – possibly via an azomethine imine – and accumulates during the early stages of the reaction. Rearrangement of **41** to **40** then slowly takes place through the azomethine imine. The possibility also exists that a diaziridine is initially formed and subsequently isomerizes to the azomethine imine.

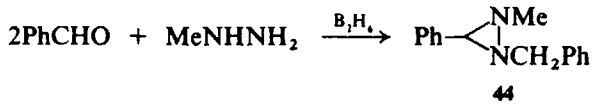
Addition of phenyl(bromodichloromethyl)mercury to an excess of azoarenes gives the carbonimidoyl dichlorides **42**. If an excess of the organomercury substrate is employed, aziridines **43** are the products.[48] Likely intermediates are diaziridines or azomethine imines.



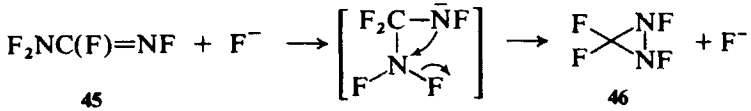


H. *Miscellaneous Preparations of Diaziridines*

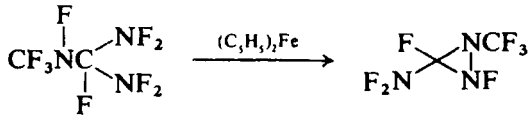
An unusual synthesis of the diaziridine **44** involves the interaction of diborane with a solution of benzaldehyde and methylhydrazine.[49] Presumably the diborane reacts with preformed benzaldehyde methylhydrazone. The resulting adduct condenses with a second equivalent of benzaldehyde to give a carbinolamine intermediate, which subsequently undergoes cyclization and elimination. The scope of this reaction is yet to be investigated.



The explosive 3-difluoroamino-1,2,3-trifluorodiaziridine and the tetrafluorodiaziridine **46** are products of the interaction of rubidium fluoride and potassium fluoride with pentafluoroguanidine and tetrafluoroamidine **45**, respectively.[50] A likely mechanism follows.

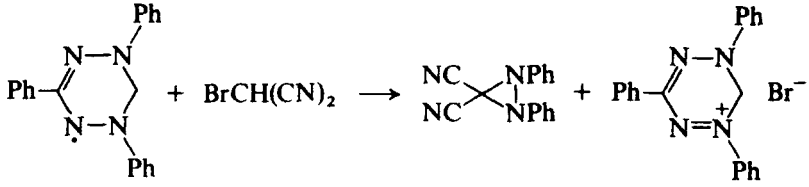


Diaziridine **48** is made in 33% yield by the reaction of dicyclopentadienyliron with **47**.[51]



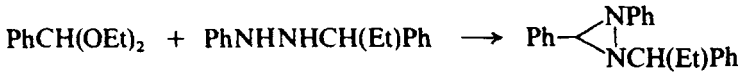
47 **48**

It has been claimed that treatment of 1,3,5-triphenylverdazyl (**49**) with bromomalononitrile in benzene gave **50** (13%) and **51** (50%).[52]



49 **50** **51**

A report on the formation of the diaziridine **53** by heating the ethyl acetal of benzaldehyde with hydrazine **52** is yet to be confirmed.[53]

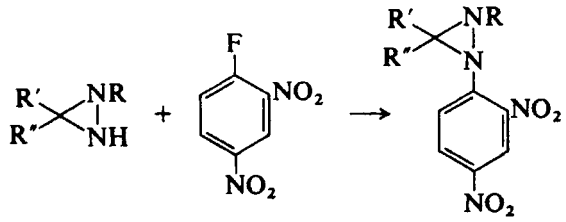


52 **53**

3. Preparation of Diaziridines Utilizing Other Diaziridines

A. *1-(2,4-Dinitrophenyl)- and 1-(2,4,6-Trinitrophenyl)diaziridines*

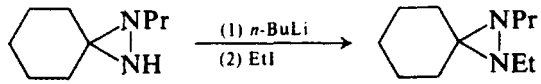
The only general method presently available to obtain 1-aryldiaziridines (other than irradiation of Δ^2-tetrazolines[43]) is the reaction of 2,4-dinitrofluorobenzene and 2,4,6-trinitroanisole at ambient temperature with 1- or 1,2-unsubstituted diaziridines.[54]



R = H or alkyl

B. *N-Alkyldiaziridines*

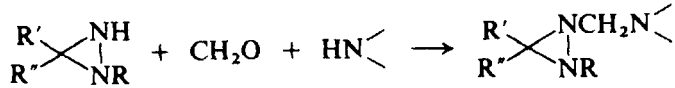
N-Lithiodiaziridines, generated from diaziridines with butyllithium, are readily alkylated with alkyl iodides. For example, addition of iodoethane to a mixture of *n*-butyllithium and diaziridine **54** gives **55** in 75% yield.[55] Similar alkylations occur when the lithium salts of 1-ethyl-3,3-pentamethylenediaziridine and 3-ethyl-3-methyldiaziridines are reacted with 1-iodopropane and 2-iodopropane, respectively.



54 **55**

C. *1-(Dialkylaminomethyl)diaziridines*

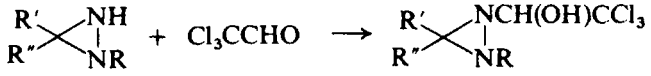
Applying Mannich conditions to 1,3-disubstituted and 1,3,3-trisubstituted diaziridines gives rise to the 1-(dialkylaminomethyl)diaziridines **56** (Table 9).[33,59]



56

D. *Chloral Adducts of Diaziridines*

Admixing of chloral hydrate with 1- or 1,2-unsubstituted diaziridines affords **57**.[7,8,20,22,56–59] The reaction has been employed frequently in the isolation, purification, and characterization of diaziridines. Alkaline hydrolysis of the chloral adducts regenerates the parent diaziridines.



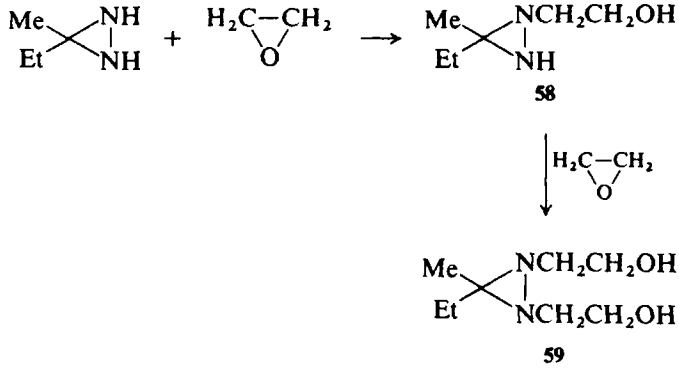
57

E. *N-(2-Hydroxyalkyl)diaziridines*

Reaction of 3,3-disubstituted and 1,3,3-trisubstituted diaziridines with epoxides yields 1-(2-hydroxyethyl)diaziridines. For example, 3-ethyl-3-methyldiaziridine reacts with 1,2-epoxyethane to form **58** and **59**.[60]

F. *Acylated Diaziridines*

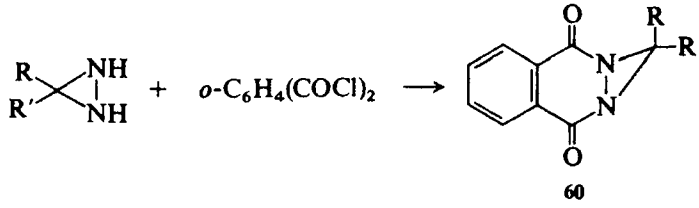
Aroyl derivatives of 1,3-disubstituted and 1,3,3-trisubstituted diaziridines have been prepared,[23,61] as have the 1,2-diacyl- and 1,2-diaroyl derivatives of



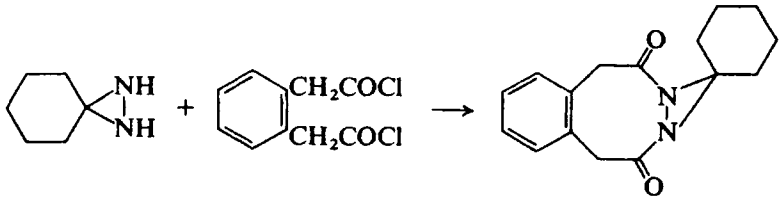
58

59

3-alkyl- and 3,3-dialkyldiaziridines.[22,23,62] Reaction of *o*-phthaloyl chloride and *o*-benzenediacetyl chloride with 3,3-dialkyldiaziridines forms **60**[24] and **61**,[61] respectively. It will be recalled that azomethine imides **15** and **18** are converted by photolysis to *N*-acylated diaziridines.



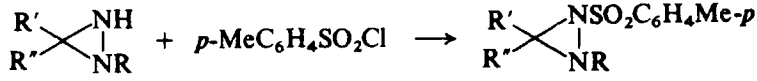
60



61

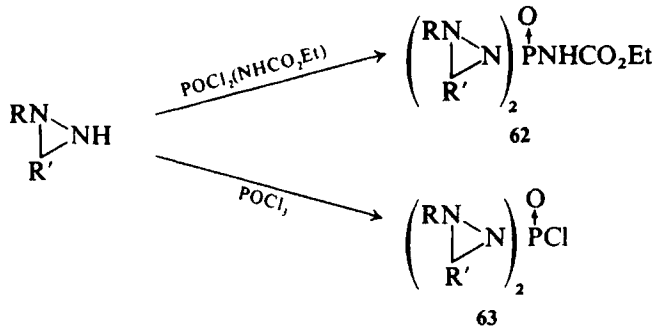
G. *N-Arylsulfonyldiaziridines*

Only one *N*-sulfonated diaziridine had been reported in the earlier literature,[23] but the reaction is quite general.[63] High yields are realized if pulverized *p*-toluenesulfonyl chloride is added portionwise to a mixture of a liquid diaziridine and triethylamine held at 0°C.



H. *Diaziridinyl Phosphinyl Derivatives*

Reaction of diaziridines with dichlorophosphinylurethan and with phosphorus oxychloride forms **62** and **63**, respectively. The latter compound is an unstable hygroscopic oil.[64]

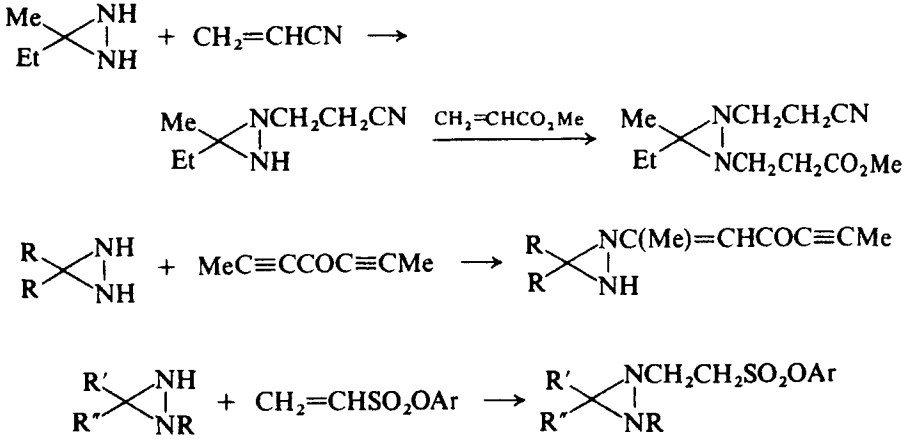


I. *1-Diaziridinecarboxamides and 1,2-Diaziridinedicarboxamides*

2,3-Disubstituted 1-diaziridinecarboxanilides,[17,23] 3,3-disubstituted 1-diaziridinecarboxamides,[65,66] 2,3,3-trisubstituted 1-diaziridinecarboxanilides,[17,22,67,68] 3-monosubstituted 1,2-diaziridinedicarboxanilides,[23] and 3,3-disubstituted 1,2-diaziridinedicarboxanilides[66,69] have been prepared by the interaction of isocyanates with the appropriate diaziridines.

J. *Adducts of Diaziridines with Michael-Type Substrates*

Diaziridines undergo conjugate addition to acrylonitrile,[70] buten-2-one,[70] α,β-acetylenic ketones,[71,72] and esters of vinylsulfonic acid.[73]



Many of the adducts of diaziridines and α,β-acetylenic ketones are not isolable because of their penchant to rearrange to hydrazones (see below).[54,74] The reaction of diaziridines with diphenylcyclopropenone is discussed in Section 4.F.

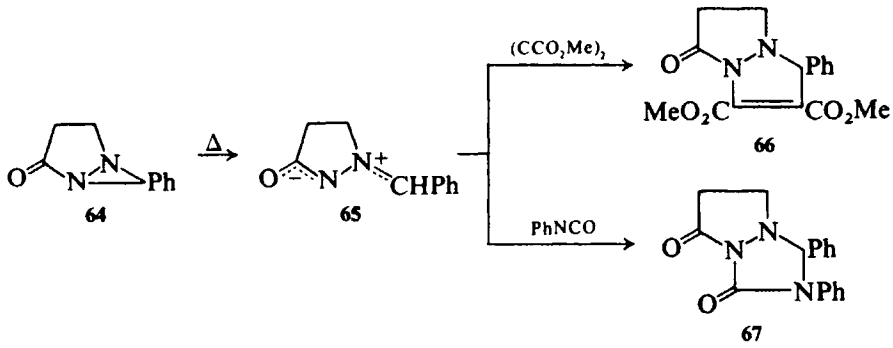
K. *N-Silyldiaziridines*

Treating 3,3-disubstituted diaziridines with triorganochlorosilanes at 50–150°C in the presence of a hydrogen chloride acceptor leads to *N*-silyldiaziridines.[75]

4. Ring-Opening Reactions

A. *Reactions Proceeding Through Azomethine Imine Intermediates*

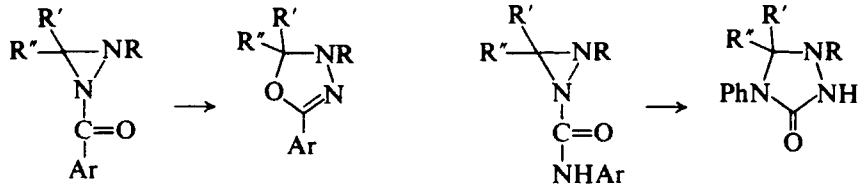
Diaziridines substituted with electron-withdrawing groups at the 1- or the 1,2-positions of the ring frequently rearrange upon heating to acyclic or ring-expanded isomers. Such diaziridines also react with enamines, ynamines, isocyanates, and nitrones to form five- and six-membered heterocycles. An attractive rationale for these transformations is that the diaziridine first forms a labile azomethine imine derivative, which then rearranges or undergoes cycloadditions. Supportive of this view is the fact that heating diaziridine **64** affords a 78% yield of the isolable azomethine imide **65**.[35] Reaction of **65** with dimethyl acetylenedicarboxylate and phenylisocyanate gives the cycloadducts **66** and **67**, respectively.[76]



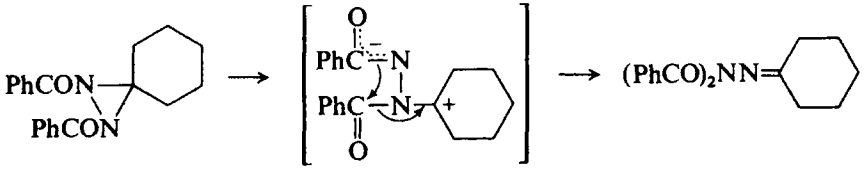
64 65 66 67

Azomethine imides similar to **65** have been postulated as intermediates for the thermal isomerization of 1-aroyl-2,3,3-trialkyldiaziridines (**68**) to 4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines (**69**)[61] and of 1-(arylcarbamoyl)-2,3-dialkyl-3-aryldiaziridines (**70**) to 1,2,4-triazolid-3-ones (**71**).[17,77]

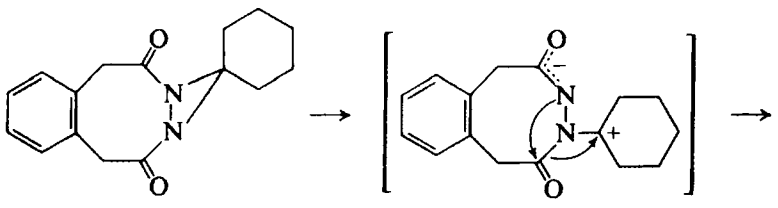
Thermolysis of diaziridines **72**[22] and **75**[61] forms hydrazones **74** and **77**, respectively. However, thermolysis of **78**[24] leads to **80**. The difference in reaction pathways between **78** and **72** and **75** is attributed to the constraints to hydrazone formation inherent in the rigid azomethine imide intermediate **79**.



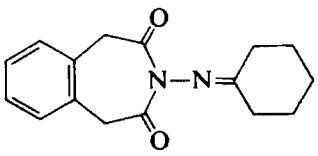
68 69 70 71



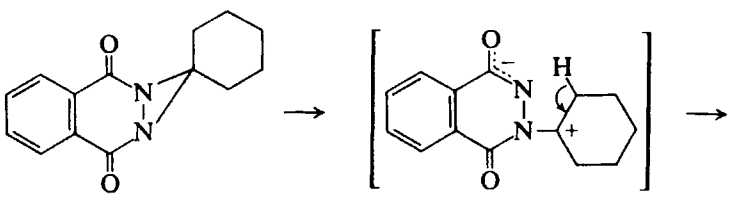
72 73 74



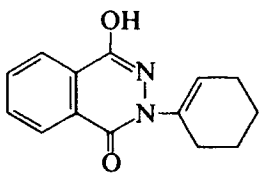
75 76



77

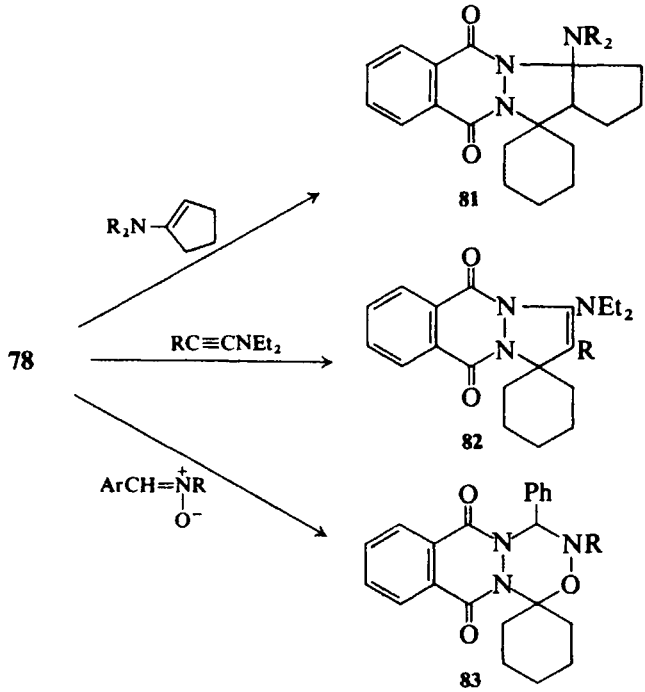


78 79

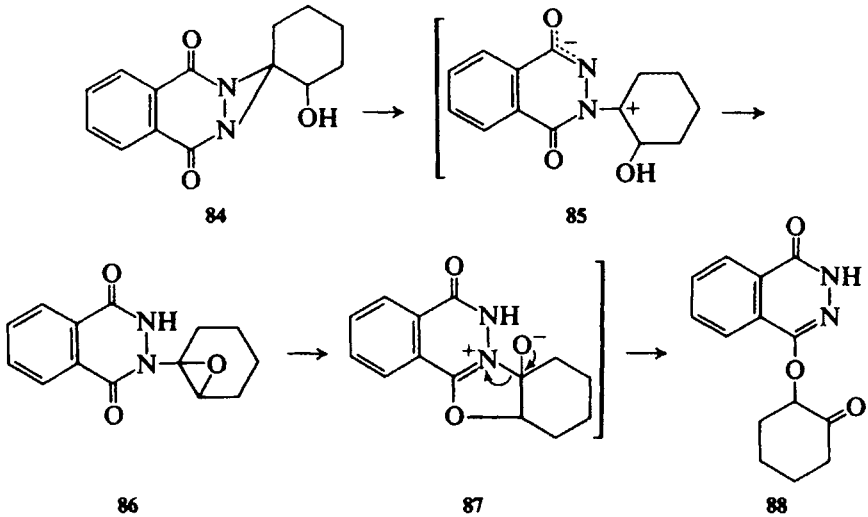


80

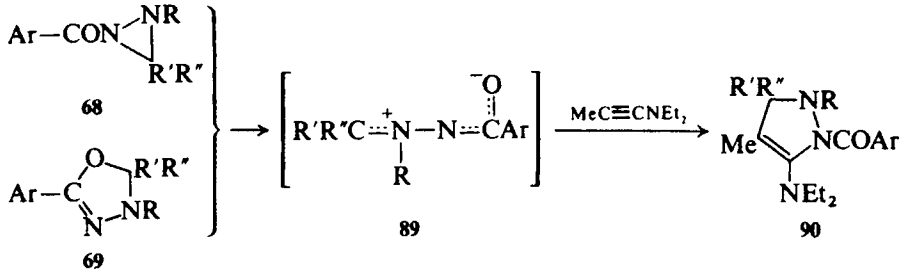
Azomethine imides like **79** have been trapped by heating **78** with enamines,[24] ynamines,[24] and nitrones.[78] The products are **81–83**, respectively.



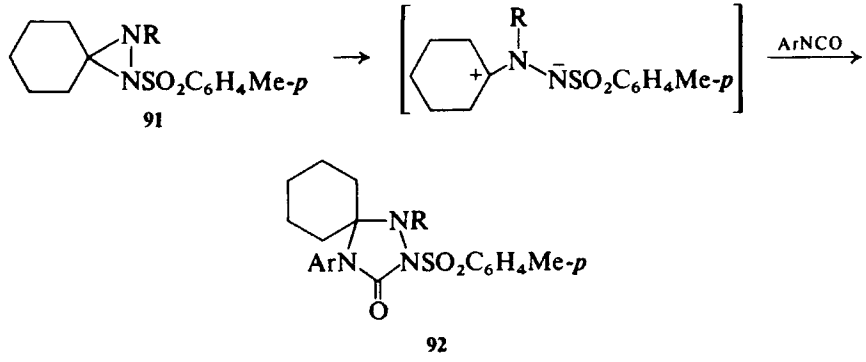
Diaziridine **84** in refluxing toluene isomerizes to **88**.[79] The formation of **88** is thought to occur via the intermediacy of **85**. Transformation of **85** into **86** and subsequent attack by the amido oxygen of **86** on the epoxide ring gives **87**, which is the immediate precursor of **88**.



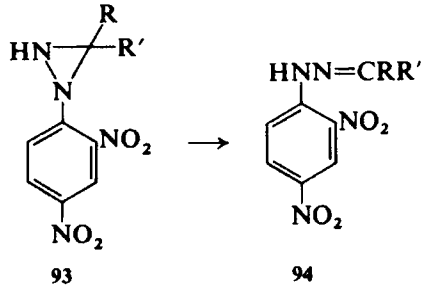
Both the *N*-aroyldiaziridine **68** and the 1,3,4-oxadiazoline **69** give **90** when heated with ynamines.[61] A reasonable supposition is that both **68** and **69** form the azomethine imide **89**, which then undergoes a cycloaddition with the ynamine.



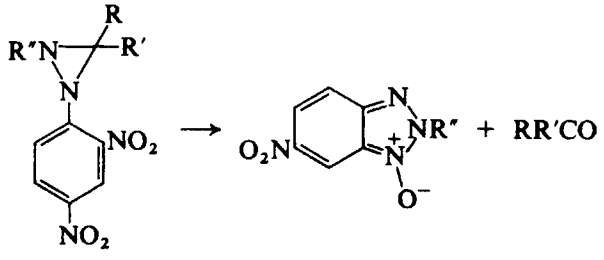
Heating 1-*p*-toluenesulfonyl-2-alkyl-3,3-pentamethylenediaziridines (**91**) with aryl isocyanates or benzoyl isocyanate results in the formation of triazolidin-3-one derivatives (**92**).[63] The product **92** was characterized by x-ray analysis. Azomethine imines seem likely intermediates for these reactions.



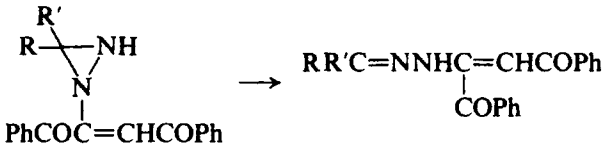
Diaziridines **93** isomerize in refluxing toluene to **94**, but under the same conditions diaziridines **95** form **96** and ketones.[54] Both reactions are thought to involve azomethine imine intermediates.

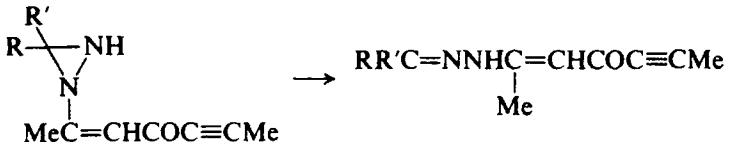


Diaziridines substituted at the 1-position with α,β-unsaturated keto moieties are thermally unstable and rearrange to hydrazones.[71,72] Once again azomethine imines can be evoked as intermediates.



95 96



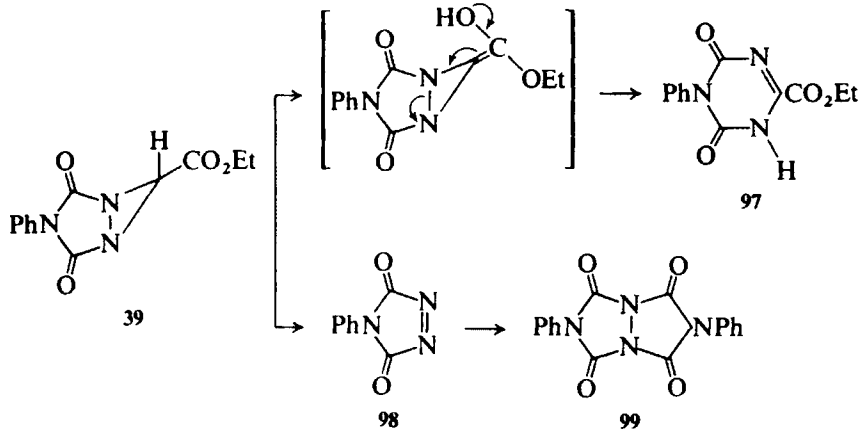


The formation of azomethine imines from diaziridines often requires two stabilizing substitutents at the diaziridinyl carbon as well as one or two electron-withdrawing groups at the 1- or 1,2-positions. Thus, while 1-aroyl-2,3,3-trialkyldiaziridines (**68**),[61] 1-(arylcarbamoyl)-2,3-dialky-3-aryldiaziridines (**70**),[17,77] and 1,1-dialkyl-1-H-diazirino[1,2-b]phthalazine-3,8-diones (**78**)[24] undergo ring opening via the azomethine imine to **69**, **71**, and **80** respectively, the same diaziridinyl systems with but one substituent on the diaziridinyl carbon do not isomerize. Similarly, 1-(*p*-toluenesulfonyl)-2-alkyl-3,3-pentamethylenediaziridines (**91**) react with aroyl isocyanates to form triazolidin-3-ones (**92**), but 1-(*p*-toluenesulfonyl)-2,3-dialkyl-diaziridines are inert toward the same reagents. Exceptions to these observations are the conversions of **64** to **65**,[35] 1-(2,4-dinitrophenyl)-2-cyclohexyl-3-ethyldiaziridine (**95**) to 2-cyclohexyl-6-nitrobenzotriazole-1-oxide (**96**),[54] and 1,2-dibenzoyl-3-*t*-butyldiaziridine to the β,β-dibenzoylhydrazone of pivalaldehyde.[22]

B. *Reactions Resulting in Nitrogen–Nitrogen Bond Breaking of the Ring*

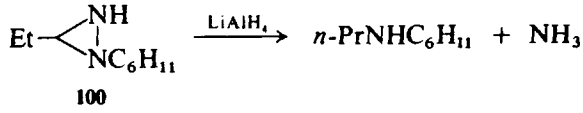
Pyrolysis of diaziridine **39** forms **97** (76%) and **99** (17%).[46] The enol of **39** is a possible precursor of **97**. Compound **99** could arise by elimination of carbethoxy carbene from **39** to afford **98**. The conversion of **98** to **99** is a known reaction.

Reaction of most diaziridines with hydriodic acid cleaves the nitrogen–nitrogen bond to give iodine, amine salts, and carbonyl compounds.[1,3,5,80,81] Titration of the liberated iodine with thiosulfate is a useful method for estimating the purity of the diaziridine.

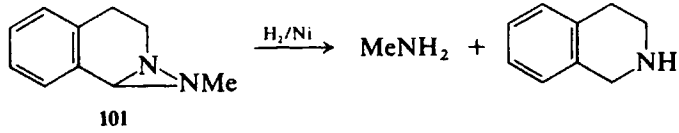


$$\begin{matrix} R'' & NR \\ R''' & NR' \end{matrix} + 4HI \longrightarrow I_2 + RNH_3^+ I^- + R'NH_3^+ I^- + R''R'''CO$$

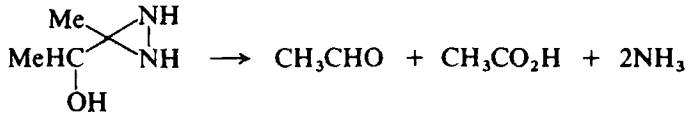
3,3-Diethyldiaziridine and 1-cyclohexyl-3-ethyldiaziridine (**100**) are reduced by lithium aluminum hydride to amines and ammonia.[81] 1,2-Di-*n*-butyl-3-*n*-propyldiaziridine and diaziridine **101** failed to react in boiling ether containing lithium aluminum hydride.



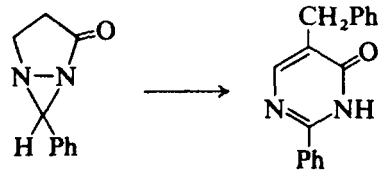
Catalytic hydrogenation of 1-cyclohexyl-3-ethyldiaziridine over Raney nickel gives *n*-propylamine and cyclohexylamine. Similarly, diaziridine **101** forms methylamine and tetrahydroisoquinoline.[81]



Simple diaziridines are stable toward aqueous sodium hydroxide, but diaziridine **102** reacts with hot 2 *N* sodium hydroxide to form acetaldehyde, acetic acid, and ammonia.[5]

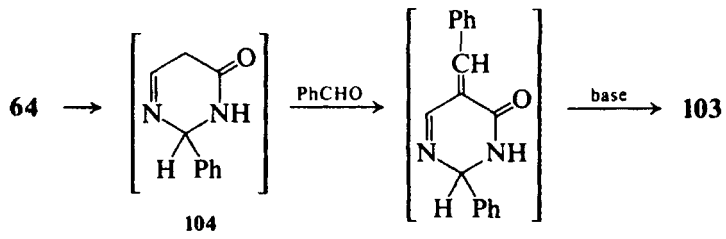


Compound **64** when treated with equimolar quantities of potassium *t*-butoxide at room temperature undergoes nitrogen–nitrogen bond breaking to give **103** in 52% yield.[82] The structure of **103** was authenticated by an independent synthesis.



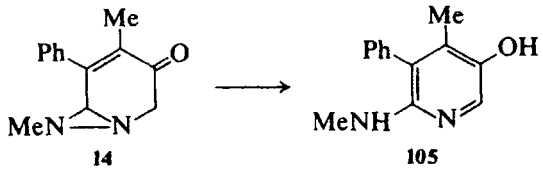
64 **103**

It was suggested that **64** undergoes ring opening to **104** and that **104** condenses with benzaldehyde (somehow produced in a side reaction) to finally give **103**.



104

Compound **14** in methanolic sodium methoxide rearranges to the pyridine **105**.[34]



14 **105**

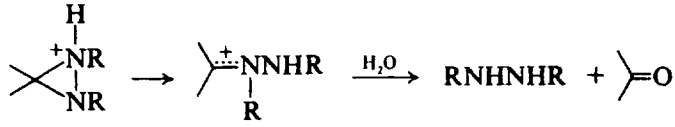
C. *Hydrolysis of Diaziridines*

Diaziridines are cleaved hydrolytically in acid media into carbonyl derivatives and substituted hydrazines. The method is useful for the preparation of 1-alkylhydrazines and symmetrical and unsymmetrical 1,2-dialkylhydrazines. Almost all diaziridines undergo this reaction regardless of the nature of the *C*- or *N*-substituents.[1, 3, 16, 20, 24, 54, 80, 81, 83, 84]



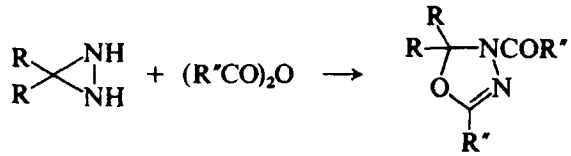


The hydrolytic ring opening of diaziridines in acid solution proceeds by first-order kinetics and is fastest when the diaziridinyl carbon is disubstituted. This suggests a mechanism in which the rate-determining step involves ring opening of the protonated diaziridine to a stabilized carbonium ion.



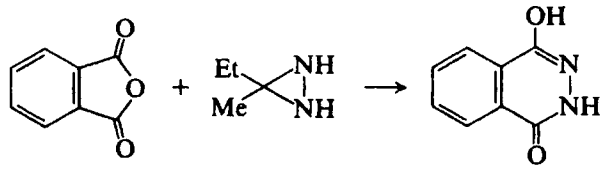
D. *Reaction of Diaziridines with Acyl Anhydrides*

1,3,4-Oxadiazolines (**106**) are obtained in 40–50% yields by heating 3,3-dialkyldiaziridines with acid anhydrides at 160°C.[85,86] The reaction is reminiscent of the isomerization of 1-aroyl-2,3,3-trialkyldiaziridines (**68**) to 1,3,4-oxadiazolines (**69**).



106

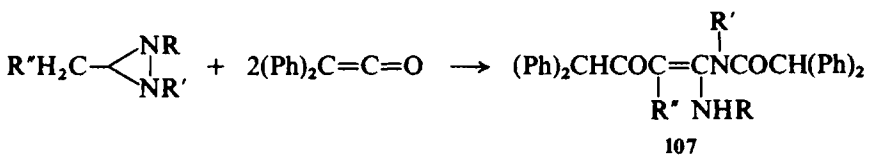
If 3-ethyl-3-methyldiaziridine is added to an aqueous solution of sulfuric acid and maleic anhydride or phthalic anhydride, the corresponding maleic and phthalic hydrazides are formed.[87] It would appear that hydrolysis of the diaziridine to hydrazine occurs, followed by reaction of the hydrazine with the anhydride.



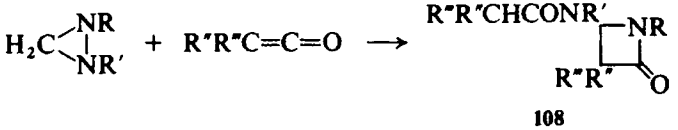
It will be recalled that under milder conditions and employing acyl halides, mono- and diacetylated diaziridines can be prepared (Section 3.F).

E. *Reaction of 1,2-Dialkyl- and 1,2,3-Trialkyldiaziridines with Ketenes and Isocyanates*

1,2,3-Trialkyldiaziridines react with diphenylketene in benzene at 80°C to give acyclic 1:2 adducts (**107**) in 6–53% yields.[88,89] On the other hand, 1,2-dialkyldiaziridines and ketenes form azetidinones **108** in approximately 25% yields.[90]

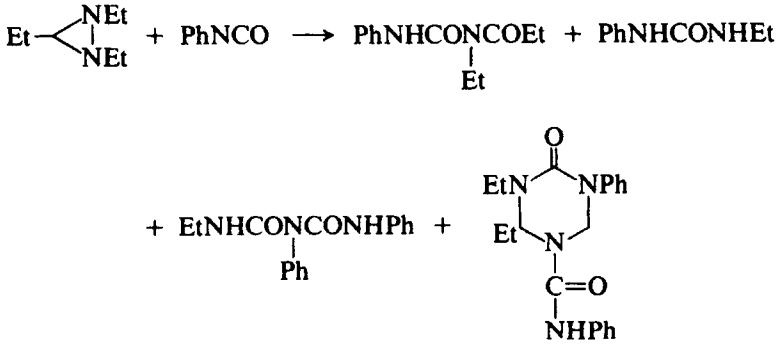


107

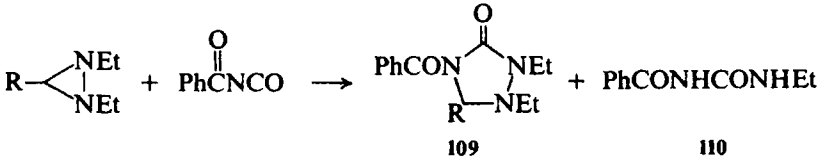


108

1,2,3-Triethyldiaziridine reacts with phenyl isocyanate to give a melange[89] of products – all isolated in low yields:



However, interaction of 1,2,3-trialkyldiaziridines with benzoyl isocyanate afforded triazolidinones **109** (30–44%) and the urea **110** (18–39%).[89]



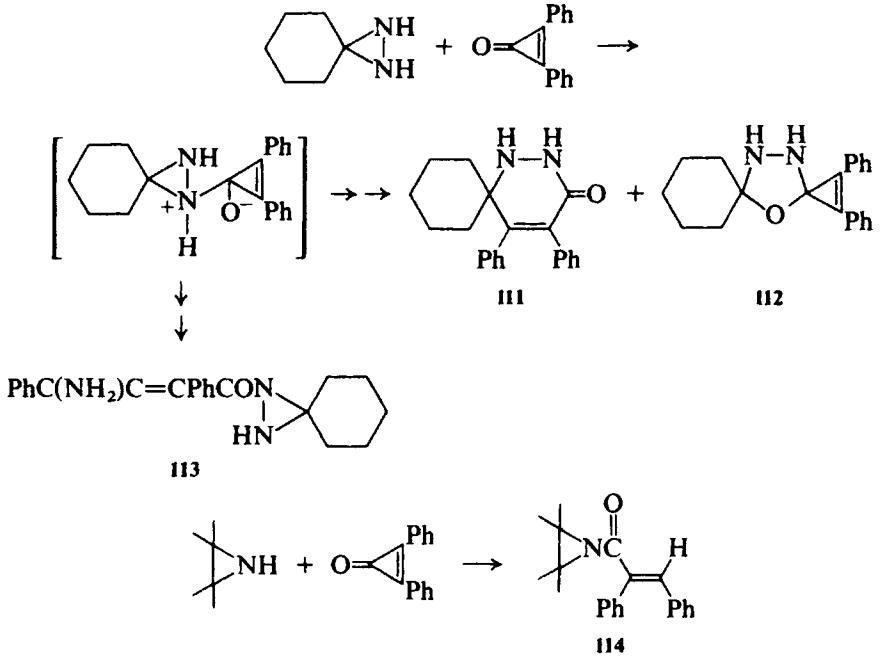
109 110

As discussed previously (Section 3.I), diaziridines unsubstituted in the 1- and 1,2-positions react with isocyanates to give 1-diaziridinecarboxamides and 1,2-diaziridinedicarboxamides.

F. *Reaction of Diaziridines with Diphenylcyclopropenone*

It was observed (Section 3.J) that diaziridines undergo a normal Michael-type addition to buten-2-one, but, in contrast, 3,3-pentamethylenediaziridine in methanol adds to the carbonyl carbon of diphenylcyclopropenone to give **111** and **112**.[91] In benzene or ether and a twofold excess of pentamethylenediaziridine,

compound **113** is produced.[92] Interestingly, aziridines react in methanol with diphenylcyclopropenone to yield **114**.[93]



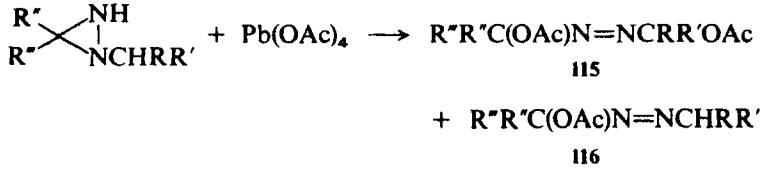
111 **112**

113

114

G. *Reaction of Diaziridines with Lead Tetraacetate*

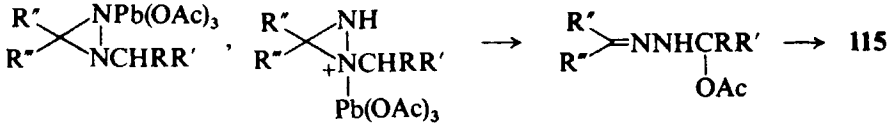
1,3,3-Trialkyldiaziridines in which the *N*-substitutent is a methyl or isopropyl group are oxidized by lead tetraacetate in methylene chloride at 0°C to the azo compounds **115** and **116**, possibly through the intermediacy of **117** or **118**.[94,95]



115

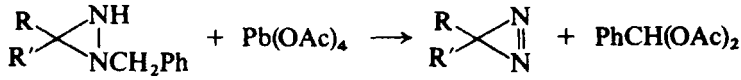
116

It is suggested that the intermediate **118** could lose $Pb(OAc)_2$ to form **119** and that **119** interacts with additional $Pb(OAc)_4$ to give **115**.



117 **118** **119**

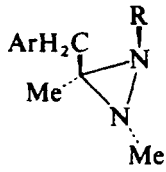
If the *N*-substituent of the 1,3,3-trialkyldiaziridine is a benzyl group, the products are diazirines **120** and benzaldiacetate.[96]



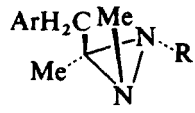
120

5. Isolable Invertomers and Optical Antipodes

Nmr studies revealed that inversion of the nitrogen atom is a relatively slow process and that the isolation of invertomers should therefore be possible.[67] In 1969 the separations of invertomers **121a** and **121b** and **122a** and **122b** were achieved by Mannschreck and Seitz.[97a,b]

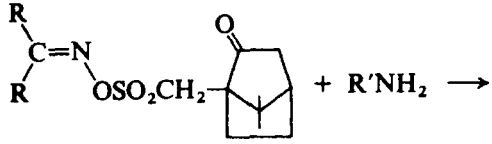


121a R = $PhCH_2$
122a R = H

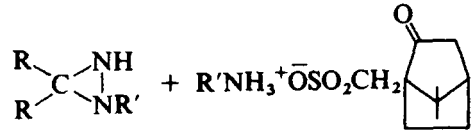


121b R = $PhCH_2$
122b R = H

Kostyanovskii and his colleagues resolved the optical antipodes of 1-methyl-3,3-pentamethylenediaziridine[68] and have established their absolute configuration.[98] The separation of racemic 1-methyl-3,3-dicarbomethoxydiaziridine into optical antipodes has also been accomplished by this research group.[99] An asymmetric synthesis of diaziridines has been devised involving the reaction of *l*-10-*O*-camphorsulfonylketoximes **123** with primary amines.[28]



123



6. Physical Properties

BASICITY. Diaziridines are weak bases. Their basicity is comparable to that of aniline. Stable oxalate salts of 1,3-dialkyldiaziridines have been isolated, and treatment of these salts with alkali regenerates the diaziridines.[81] In some cases

diaziridines can be extracted from organic solvents with aqueous mineral acids and then be reformed by reaction with alkali.[81]

INFRARED SPECTRUM. One- and 1,2-unsubstituted diaziridines exhibit absorption bands ranging from 3175 to 3370 cm^{-1} for the NH group.[17,33,59,21a] Infrared absorption between 1380 and 1490 cm^{-1} is characteristic of three-membered fluorinated heterocycles containing one or two heteroatoms. For example, diaziridine **124** has an absorption band of medium strong intensity at 1410 cm^{-1}.

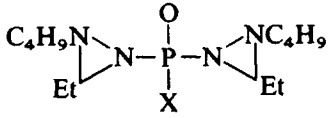


124

ULTRAVIOLET SPECTRUM. Simple diaziridines do not absorb in the UV range.

7. Diaziridines of Pharmacological Interest

Compounds **125** and **126** showed some cytotoxicity against a Sarcoma 180 cell line.[64] Calf thymus DNA, on incubation with **125** and **126** at 37°C, showed a significant decrease in its ability to serve as "template" in the RNA polymerase system.[64]

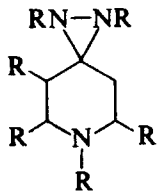


125 X = $NHCO_2Et$
126 X = Cl

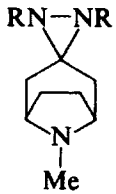
3-Spiro-3′-diaziridine steroids are peroral anabolic agents,[13,14] and 17-spiro-3′-diaziridine steroids showed in rats the same hypotensive activity as guanethidine.[13b] 1,3,5(10)-Estratrien-3-ol-17-spiro-3′-diaziridine exhibits a strong gonadotropic blocking effect.[13b]

Compounds of the general structure **127** and **128** are reported[14] to possess antihypertensive, anti-inflammatory, and (or) local anesthetic activities.[14]

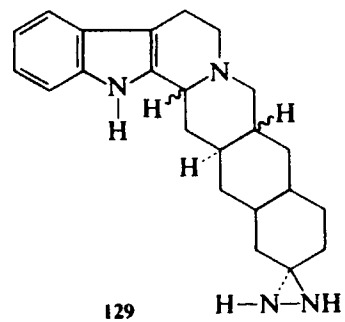
Substituted hydraziyohimbans (**129**) are central nervous system depressants.[15]



127



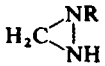
128



129

8. Tables

TABLE 1. 1-ALKYLDIAZIRIDINES



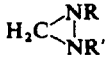
R	Method of Prep.	Mol. Formula	b.p., °C (mm)	Yield %	Ref.
i-Pr	B	$C_4H_{10}N_2$	107–108 (760)	11.3	8
n-Bu	B	$C_5H_{12}N_2$	54 (23)	15	8
s-Bu	B	$C_5H_{12}N_2$	134–135 (760)	28	8
t-Bu	B, F	$C_5H_{12}N_2$	31–35 (17)	12, 27	8, 20
C_6H_{11}[a]	F	$C_7H_{14}N_2$	82 (16)	35–40	7, 21a
CH_2Ph	F	$C_8H_{10}N_2$	62–69 (0.035)	29	20

[a] Cyclohexyl group.

TABLE 2. 3-ALKYL- and 3-ARYLDIAZIRIDINES

R	Generated from	Mol. Formula	Ref.
Me	8	$C_2H_6N_2$	7
Et	8	$C_3H_8N_2$	7, 21a
n-Pr	8, 10	$C_4H_{10}N_2$	7, 21a, 23, 24
t-Bu	8, 10	$C_5H_{12}N_2$	23, 24, 100
Ph	8	$C_7H_8N_2$	21b

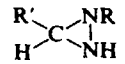
TABLE 3. 1,2-DIALKYLDIAZIRIDINES

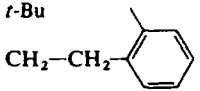


R	R'	Method of Prep.	Mol. Formula	b.p., °C (mm)	Yield,[a] %	Ref.
Me	Me	C	$C_3H_8N_2$	49 (766)	48	20
CH(Me)CH_2CH_2		C	$C_5H_{10}N_2$	57–58 (12)	93	20
Et	Et	C	$C_5H_{12}N_2$	96–97 (760)	31	20, 101, 102
Et	*n*-Pr	C	$C_6H_{14}N_2$	–	–	20
n-Pr	*n*-Pr	C	$C_7H_{16}N_2$	37.5–38 (11–12)	53	20
i-Pr	*i*-Pr	C	$C_7H_{16}N_2$	125–126 (760)	28	20
n-Bu	*n*-Bu	C	$C_9H_{20}N_2$	34–36 (0.015)	72	20
CH_2Ph	CH_2Ph	C	$C_{15}H_{16}N_2$	Not isolated	–	20

[a] As determined by iodometric titration of the reaction mixture.

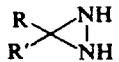
TABLE 4. 1,3-DISUBSTITUTED DIAZIRIDINES



R	R′	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield, %	Ref.
Me	Me	B	$C_3H_8N_2$	78.5–79.5 (760)	75	59
Et	Me	A, B, F	$C_4H_{10}N_2$	103.5–104 (760)	18–69	7, 59, 81, 103
n-Bu	Me	B	$C_6H_{14}N_2$	33 (8)	68	59
i-Bu	Me	B	$C_6H_{14}N_2$	42 (12)	75	59
n-Bu	Et	B	$C_7H_{16}N_2$	69–73 (16)	27.5	64
Me	Ph	B	$C_8H_{10}N_2$	72–75 (0.4)	77.5	33
C_6H_{11}[a]	Me	A	$C_8H_{16}N_2$	34–36 (0.2)	46	81
n-Bu	Pr	B	$C_8H_{18}N_2$	77–79 (12)	–	104
t-Bu	Pr	F	$C_8H_{18}N_2$	53–54 (10)	78	105
		B	$C_9H_{10}N_2$	72	37.8	106
C_6H_{11}[a]	Et	A, F	$C_9H_{18}N_2$	99–100 (12)	27–80	7, 18, 21a, 81, 107
C_6H_{11}[a]	*n*-Pr	F	$C_{10}H_{20}N_2$	25–26, 57–59 (0.3)	55	7, 21a
$MeO_2C(CH_2)_2$	*m*-ClC_6H_4		$C_{11}H_{13}ClN_2O_2$	69	75	37
$MeO_2C(CH_2)_2$	*p*-ClC_6H_4		$C_{11}H_{13}ClN_2O_2$	20–23	84	37
$MeO_2C(CH_2)_2$	*m*-$O_2NC_6H_4$		$C_{11}H_{13}N_3O_4$	89	45	37
$MeO_2C(CH_2)_2$	*p*-$O_2NC_6H_4$		$C_{11}H_{13}N_3O_4$	103	40	37
$MeO_2C(CH_2)_2$	Ph		$C_{11}H_{14}N_2O_2$	36	85, 91	35, 37
$C_6H_5CH_2$	*n*-Pr	A	$C_{11}H_{16}N_2$	12–13, 100–103 (0.6)	26	81
n-Bu	*n*-Hex	A	$C_{11}H_{24}N_2$	70–73 (1)	53	81
$MeO_2C(CH_2)_2$	*p*-MeC_6H_4		$C_{12}H_{16}N_2O_2$	33–34	92	37
$MeO_2C(CH_2)_2$	*p*-$MeOC_6H_4$		$C_{12}H_{16}N_2O_3$	29–30	89	37
C_6H_{11}[a]	*p*-BrC_6H_4	B	$C_{13}H_{17}BrN_2$	74–76	26	10
C_6H_{11}[a]	Ph	B	*cis*-$C_{13}H_{18}N_2$	102–104	2	10
C_6H_{11}[a]	Ph	B	*trans*-$C_{13}H_{18}N_2$	53–54	23	10
C_6H_{11}[a]	*n*-Hex	A	$C_{13}H_{26}N_2$	17–18, 114 (0.2)	54	81
$C_6H_5CH_2$	Ph	B	*cis*-$C_{14}H_{14}N_2$	63	13	10
$C_6H_5CH_2$	Ph	B	*trans*-$C_{14}H_{14}N_2$	38–40	2	10

[a] Cyclohexyl group.

TABLE 5. 3,3-DISUBSTITUTED DIAZIRIDINES

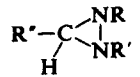


R	R′	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield %	Ref.
CF_3	CF_3	E	$C_3H_2F_6N_2$	78–80	43–94	29, 44, 108, 109
CF_3	F_2NCF_2	E	$C_3H_2F_7N_3$	84–85 (760)	82.5	29
Me	CF_3	E	$C_3H_5F_3N_2$	58–60	85	109
Me	Me	B	$C_3H_8N_2$	40–44, 106 (760)	36, 80	1, 31, 110
Me	$HOCH_2$	B	$C_3H_8N_2O$	43–45, 62–63 (0.05)	45	69
Me	Et	A	$C_4H_{10}N_2$	21.5–22, 32 (17)	99	80
Me	MeCH(OH)	B	$C_4H_{10}N_2O$	51–52, 58–62 (0.04)	58	69
Me	*n*-Pr	A	$C_5H_{12}N_2$	−10, 48 (15)	–	80
Me	*i*-Pr	A	$C_5H_{12}N_2$	55–56, 67 (50)	–	80
Et	Et	A	$C_5H_{12}N_2$	56, 58 (24)	91	80
	$(CH_2)_5$	B	$C_6H_{12}N_2$	105	59–70	31, 111
	$(CH_2)_4CH(OH)$	B	$C_6H_{12}N_2O$	133	45	112
Me	*i*-Bu	A	$C_6H_{14}N_2$	55 (13)	–	113
Me	$(Me)_2C(OH)CH_2$	B	$C_6H_{14}N_2O$	51–52, 84–87 (0.07)	46	69
Me	$(Me)_2C(OH)CH(OH)$	B	$C_6H_{14}N_2O_2$	118–120	46	69
	CH_2–CH(CH_2)$_2$CHCH_2 (S)	B	$C_7H_{12}N_2S$	169–171	33	114
	$(CH_2)_5CH(OH)$	B	$C_7H_{14}N_2O$	66–67	50	69
n-Pr	*n*-Pr	A	$C_7H_{16}N_2$	73–74 (11)	33	31
CF_3	Ph	E	$C_8H_7F_3N_2$	33–35	81	109
Me	Ph	B	$C_8H_{10}N_2$	41–42, 88–95 (16)	9	31
Et	*n*-C_5H_{11}	A	$C_8H_{18}N_2$	78 (2)	–	113

TABLE 5. CONTINUED

R	R'	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield %	Ref.
Me	$(Et)_2N(CH_2)_2$	B	$C_8H_{19}N_3$	63–64 (0.4)	56	69
Me	$PhCH_2$	A	$C_9H_{12}N_2$	73	52	33
n-Bu	Ph	B	$C_{11}H_{16}N_2$	–	–	115

TABLE 6. 1,2,3-TRISUBSTITUTED DIAZIRIDINES



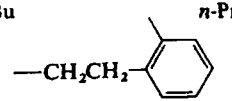
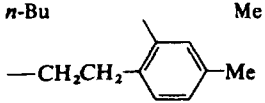
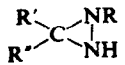
R	R′	R″	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield, %	Ref.
Et	Et	Me	A	$C_6H_{14}N_2$	53–55 (70)	14	89
Me	*n*-Pr	Et	A	$C_7H_{16}N_2$	63 (60)	16	89
Me	*i*-Pr	Et	A	$C_7H_{16}N_2$	74–77 (62)	4	89
Et	Et	Et	A	$C_7H_{16}N_2$	56 (40)	35	89
Me	Me	Ph		$C_9H_{12}N_2$	65–68 (2)	16	43
Me	Ph	Me		$C_9H_{12}N_2$	68–71 (2)	71	43
Me	Me	*n*-C_6H_{13}–	A	$C_9H_{20}N_2$	42–43 (1)	68	105
Me	*n*-Bu	*n*-Pr	A	$C_9H_{20}N_2$	49–51 (0.02)	42	105
Me			A	$C_{10}H_{12}N_2$	111.5–113 (10)	50	116
Me	C_6H_{11}[a]	Et	A	$C_{10}H_{20}N_2$	92–93 (12)	57	105
Et	C_6H_{11}[a]	Me	A	$C_{10}H_{20}N_2$	75–78 (0.3)	–	117
Et	*n*-Bu	*n*-Pr	A	$C_{10}H_{22}N_2$	55–57 (0.02)	55	105
n-Bu	*n*-Bu	Me	A	$C_{10}H_{22}N_2$	50–51 (1.5)	64	105
Me			A	$C_{11}H_{14}N_2$	68.5–70, 126.5–128 (11)	69	116
n-Pr	*n*-Bu	*n*-Pr	A	$C_{11}H_{24}N_2$	60–62 (0.02)	50	105
Me	*n*-Bu	*n*-C_6H_{13}–	A	$C_{12}H_{26}N_2$	79–81 (0.6), 111–112 (10)	63	105,118
n-Bu	*n*-Bu	Pr	A	$C_{12}H_{26}N_2$	64–66 (0.02)	71	105,118
Me	Ph	Ph		$C_{14}H_{14}N_2$	98–101 (0.25)	62	43
Me	$PhCH_2$	Ph		$C_{15}H_{16}N_2$	Oil	60	49
C_6H_{11}[a]	2,4-$(O_2N)_2C_6H_3$	Et		$C_{15}H_{20}N_4O_4$	115–116	88	54
n-Bu	*n*-Bu	C_6H_{11}[a]		$C_{15}H_{30}N_2$	–	–	119
Et	*n*-Bu	$CH_3(CH_2)_3CH(Et)CH_2$		$C_{15}H_{32}N_2$	–	–	119

TABLE 6. CONTINUED

R	R'	R''	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield %	Ref.
n-Bu	*n*-Bu	*n*-C_6H_{13}	A	$C_{15}H_{32}N_2$	106–107 (0.8)	53	105
n-Bu	*n*-Bu	*n*-$C_{12}H_{25}$	–	$C_{21}H_{44}N_2$	–	–	119
Ph	EtCH(Ph)	Ph		$C_{22}H_{22}N_2$	240–243 (14)	–	53

[a] Cyclohexyl group.

TABLE 7. 1,3,3-TRISUBSTITUTED DIAZIRIDINES



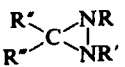
R	R′	R″	Method of Prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield, %	Ref.
Me	Me	Me	B, E	$C_4H_{10}N_2$	17, 30 (10)	22	5, 27, 28
Et	CF_3	CF_3	E	$C_5H_6F_6N_2$	82–83 (760)	57–98	28, 29
Et	CF_3	F_2NCF_2	E	$C_5H_6F_7N_3$	99–100 (760)	71.6	29
Me	Me	Et	B, E	$C_5H_{12}N_2$	113 (760)	75	5
i-Pr	CF_3	CF_3		$C_6H_8F_6N_2$	69–70 (760)	30, 50	28, 68
Me	Et	Et		$C_6H_{14}N_2$	60 (39)		74
i-Pr	Me	Me	A	$C_6H_{14}N_2$	−11, 54–55 (60)	40	81
$HO(CH_2)_2$–	Me	Et		$C_6H_{14}N_2O$	91–94 (0.5)		60
$MeO_2CCH(Me)$–	CF_3	CF_3	E	$C_7H_8F_6N_2O_2$	66–68 (14)	30	68
$NC(CH_2)_2$–	Me	Et		$C_7H_{13}N_3$	120 (6)	–	70
Me		$(CH_2)_5$	B	$C_7H_{14}N_2$	34–36, 42–43 (1.5)	45	32
$MeCH(OH)CH_2$	Me	Et		$C_7H_{16}N_2O$	–	–	60
$(Me)_2N(CH_2)_2$–	Me	Me	B	$C_7H_{17}N_3$	50–50.5 (4)	8	68
$MeCO(CH_2)_2$	Me	Et		$C_8H_{16}N_2O$	124 (12)	–	70
C_6H_5	CF_3	CF_3	B	$C_9H_6F_6N_2$	74 (42)	79.5	29
Me	Me	Ph	B	$C_9H_{12}N_2$	67 (0.8)	54	33
n-Pr		$(CH_2)_5$	B	$C_9H_{18}N_2$		–	110
C_6H_{11}[a]	Me	Me	A	$C_9H_{18}N_2$	16–17, 48–50 (0.6)	64	81
$2,4\text{-}(O_2N)_2C_6H_3$	Me	Et		$C_{10}H_{12}N_4O_4$	73–75	75	54
Me	Me	$PhCH_2$	B	$C_{10}H_{14}N_2$	76 (0.75)	60	33
Me	Me	$PhCH_2$	B	$C_{10}H_{14}N_2$	27,[b] 5[c]	–	97
$PhCH_2$	Me	Me	B	$C_{10}H_{14}N_2$	87 (0.8)	37	73
C_7H_7O[d]	Me	Me		$C_{10}H_{14}N_2O$	79–81	~ 50	72
MeCH(Ph)	Me	Me	B	$C_{11}H_{16}N_2$	74–75 (0.4)	62	73
$PhCH_2CH_2$	Me	Me	B	$C_{11}H_{16}N_2$	95 (0.6)	42	73
p-$MeOC_6H_4CH_2$	Me	Me	B	$C_{11}H_{16}N_2O$	114–115 (0.2)	34	73

TABLE 7. CONTINUED

R	R′	R″	Method of prep.	Mol. Formula	m.p. or b.p., °C (mm)	Yield, %	Ref.
C_5H_9[e]		$(CH_2)_5$	B	$C_{11}H_{20}N_2$	78–79 (0.01)	74	73
$HC{\equiv}CCH_2$	Me	$PhCH_2$	F	$C_{12}H_{14}N_2$	107 (0.75)	60	33
C_7H_7O[d]	Me	*n*-Pr		$C_{12}H_{18}N_2O$	52–53	~ 50	72
C_7H_7O[d]	Me	*i*-Pr		$C_{12}H_{18}N_2O$	62–63	~ 50	72
C_7H_7O[d]	Et	Et		$C_{12}H_{18}N_2O$	84–85	~ 50	72
C_6H_{11}[a]		$(CH_2)_5$	A, F	$C_{12}H_{22}N_2$	35–36, 92–93 (0.5)	71	31, 32, 81
C_7H_7O[d]		$(CH_2)_5$		$C_{13}H_{18}N_2O$	78–79.5	~ 50	72
C_6H_{11}[a]	Me	Ph	B	$C_{14}H_{20}N_2$	96–97	35	10
$PhCH_2$	Me	Ph	B	$C_{15}H_{16}N_2$	60–62	29	10
C_7H_7O[d]	Me	$PhCH_2$		$C_{16}H_{18}N_2O$	91.5–93	~ 50	72

[a] Cyclohexyl group.
[b] R, R′ cis.
[c] R, R″ cis.
[d] C_7H_7O = MeC≡CCOCH=C(Me)–.
[e] Cyclopentyl group.

TABLE 8. 1,2,3,3-TETRASUBSTITUTED DIAZIRIDINES



R	R′	R″	R‴	Method of Prep.	Mol. Formula	m.p.	Yield, %	Ref.
Me	Me	Me	Me	A	$C_5H_{12}N_2$	–	–	120
Et	Et	Me	Me	A	$C_7H_{16}N_2$	–	–	120
Me	Me	Me	$PhCH_2$	B	$C_{11}H_{16}N_2$	24–26.5	–	97
2,4-$(O_2N)_2C_6H_3$	*i*-Pr	Me	Me		$C_{12}H_{16}N_4O_4$	100–103	93	54
2,4,6-$(O_2N)_3C_6H_2$	Me		$(CH_2)_5$		$C_{13}H_{15}N_5O_6$	108–109	94	54
2,4-$(O_2N)_2C_6H_3$	Me		$(CH_2)_5$		$C_{13}H_{16}N_4O_4$	92–93	81	54
Me	$PhCH_2$	Me	$PhCH_2$	B	$C_{17}H_{20}N_2$	Oil	–	97

TABLE 9. 1-[(DIALKYLAMINO)METHYL]-2,3- AND 1-[(DIALKYLAMINO)METHYL]-2,3,3-TRIALKYLDIAZIRIDINES



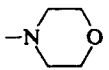
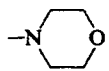
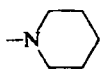
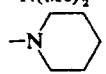
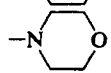
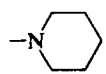
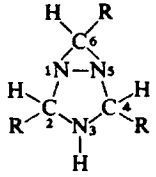
R	R′	R″	R‴	Mol. Formula	b.p., °C (mm)	Yield, %	Ref.
	Me	Me	H	$C_8H_{17}N_3O$	102–103 (10)	82	59
$-N(Me)_2$	Me	$-(CH_2)_5-$		$C_{10}H_{21}N_3$	63–64 (0.5)	58	59
	*i*-Bu	Me	H	$C_{11}H_{23}N_3O$	120–121 (7)	95	59
$-NEt_2$	Me	$-(CH_2)_5-$		$C_{12}H_{25}N_3$	83–84 (0.6)	82	59
	*n*-Bu	Me	H	$C_{12}H_{25}N_3$	136–137 (8)	80	59
$-N(Me)_2$	Me	$PhCH_2$	Me	$C_{13}H_{21}N_3$	81 (0.3)	75	33
	Me	$-(CH_2)_5-$		$C_{13}H_{25}N_3$	122–123 (0.5)	67	59
	Me	$PhCH_2$	Me	$C_{15}H_{23}N_3O$	132 (0.175)	77	33
$-N(CH_3)_2$	$-CH_2N(CH_3)_2$	$PhCH_2$	Me	$C_{15}H_{26}N_4$	110 (0.125)	75	33
	Me	$PhCH_2$	Me	$C_{16}H_{25}N_3$	115 (0.175)	46	33

TABLE 10. 2,4,6-TRIALKYL- AND 2,4,6-TRIARYL-1,3,5-TRIAZABICYCLO[3.1.0]HEXANES



R	Mol. Formula	C_2–C_3 Stereochem.	m.p., °C	Yield, %	Ref.
Me	$C_6H_{13}N_3$	*trans*	114–115	46	25, 121
Me	$C_6H_{13}N_3$	*cis*	106–108	6–20	25
Et	$C_9H_{19}N_3$	*trans*	104–105.5	74	25, 121
Et	$C_9H_{19}N_3$	*cis*	91–93	6–20	25
n-Pr	$C_{12}H_{25}N_3$	*trans*	84–86	80	25, 121
n-Pr	$C_{12}H_{25}N_3$	*cis*	66–69	6–20	25
i-Pr	$C_{12}H_{25}N_3$	*trans*	140–143	30–60	25
i-Pr	$C_{12}H_{25}N_3$	*cis* and *trans*		30–60	25
n-Bu	$C_{15}H_{31}N_3$	*trans*	68–69	30–60	25
i-Bu	$C_{15}H_{31}N_3$	*trans*	134–139	30–60	25
t-Bu	$C_{15}H_{31}N_3$	*trans*	93–95	30–60	25, 100
n-C_5H_{11}	$C_{18}H_{37}N_3$	*trans*	51–55	30–60	25
$(Et)_2CH$	$C_{18}H_{37}N_3$	*trans*	145–147	30–60	25
Ph	$C_{21}H_{19}N_3$	*trans*	162–164	32	25, 121, 122
n-C_6H_{13}	$C_{21}H_{43}N_3$	*trans*	65–67	30–60	25
$PhCH_2$	$C_{24}H_{25}N_3$	*trans*	172–175	~ 65	26
p-MeC_6H_4	$C_{24}H_{25}N_3$	–		28	122
p-$MeOC_6H_4$	$C_{24}H_{25}N_3O_3$	–		27	122
PhCH(Me)	$C_{27}H_{31}N_3$	*trans*	161–165	–	26

9. References

1. H. J. Abendroth and G. Henrich, *Angew. Chem.*, 71, 283 (1959); Ger. Patent 1,082,889 (1960); *Chem. Abstr.*, 55, 16930b (1961).
2. S. R. Paulsen, Belg. Patent 588,352 (1959).
3. E. Schmitz, *Angew. Chem.*, 71, 127 (1959).
4. E. Schmitz, *Advances in Heterocyclic Chemistry*, Vol. 2, Academic Press, New York, 1963, pp. 83–130.
5. E. Schmitz, *Dreiringe mit zwei Heteroatomen*, Springer-Verlag, Berlin and New York, 1967.
6. E. Schmitz, *Advances in Heterocyclic Chemistry*, Vol. 24, Academic Press, New York, 1979, pp. 63–107.
7. E. Schmitz and R. Ohme, *Chem. Ber.*, 95, 795 (1962).
8. A. A. Dudinskaya, L. I. Khmelnitski, I. D. Petrova, E. B. Baryshnikova, and S. S. Novikov, *Tetrahedron*, 27, 4053 (1971).
9. R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Am. Chem. Soc.*, 87, 2665 (1965).
10. R. F. R. Church and M. J. Weiss, *J. Org. Chem.*, 35, 2465 (1970).

11. American Cyanamid Co., Neth. Patent 6,509,356 (1966); *Chem. Abstr.*, **65**, 3942f (1966).
12. P. Borrevang, Fr. Patent 1,462,185 (1966); *Chem. Abstr.*, **68**, 114853q (1968).
13. (a) Novo Terapeutisk Laboratorium AIS, Neth. Patent 6,609,384 (1967); *Chem. Abstr.*, **68**, 105449k (1968); (b) Novo Terapeutisk Laboratorium AIS, Neth. Patent 6,605,966 (1966); *Chem. Abstr.*, **66**, 115864q (1967).
14. P. Borrevang and E. Guddal, Fr. Patent 1,562,790 (1969); *Chem. Abstr.*, **72**, 66923 (1970).
15. A. E. Lazilotti and L. Goodman, U.S. Patent 3,373,165 (1968); *Chem. Abstr.*, **69**, 44094n (1968).
16. E. Schmitz, *Angew. Chem.*, **72**, 23 (1961).
17. A. Nabeya, Y. Tamura, T. Kodama, and Y. Iwakura, *J. Org. Chem.*, **38**, 3758 (1973).
18. E. Schmitz, R. Ohme, and S. Schramm, *Chem. Ber.*, **97**, 2521 (1964).
19. E. Schmitz, R. Ohme, and S. Schramm, *Tetrahedron Lett.*, 1857 (1965).
20. R. Ohme, E. Schmitz, and P. Dolge, *Chem. Ber.*, **99**, 2104 (1966).
21. (a) E. Schmitz and R. Ohme, *Tetrahedron Lett.*, 612 (1961); (b) G. F. Bradley, W. B. L. Evans, and I. D. R. Stevens, *J. Chem. Soc. Perkin*, **II**, 1214 (1977).
22. E. Schmitz, D. Habisch, and C. Gründemann, *Chem. Ber.*, **100**, 142 (1967).
23. E. Schmitz and D. Habisch, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **7**, 1281 (1962); *Chem. Abstr.*, **61**, 4331 (1964).
24. H. W. Heine, R. Henrie, L. Heitz, and S. R. Kovvali, *J. Org. Chem.*, **39**, 3187 (1974).
25. A. T. Nielsen, R. L. Atkins, D. W. Moore, D. Mallory, and J. M. LaBerge, *Tetrahedron Lett.*, 1167 (1973).
26. A. T. Nielsen, R. L. Atkins, J. Dipol, and D. W. Moore, *J. Org. Chem.*, **39**, 1349 (1974).
27. K. W. Eichenhofer and R. Schliebs, Ger. Offen. 2,338,761 (1975); *Chem. Abstr.*, **83**, 28209n (1975).
28. R. G. Kostyanovskii, G. B. Shustov, A. I. Mishchenko, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2026 (1976); *Chem. Abstr.*, **86**, 121215h (1977).
29. B. L. Dyatkin, K. N. Makarov, and I. L. Knunyants, *Tetrahedron*, **27**, 51 (1971).
30. R. J. Sauer, U.S. Patent 3,682,889; *Chem. Abstr.*, **77**, 126605j (1972).
31. E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961).
32. E. Schmitz, R. Ohme, and R-D. Schmidt, *Chem. Ber.*, **95**, 2714 (1962).
33. C. J. Paget and C. S. Davis, *J. Med. Chem.*, **7**, 626 (1964).
34. M. G. Pliess and J. A. Moore, *J. Am. Chem. Soc.*, **90**, 4738 (1968).
35. M. Schulz and G. West, *J. Prakt. Chem.*, **312**, 161 (1970).
36. M. Schulz and G. West, *J. Prakt. Chem.*, **315**, 711 (1973).
37. M. Schulz, G. West, U. Müller, and D. Henke, *J. Prakt. Chem.*, **318**, 946 (1976).
38. Y. Maki, M. Kawamura, H. Okamoto, M. Suzuki, and K. Kaji, *Chem. Lett.*, 1005 (1977).
39. Y. Maki, M. Suzuki, T. Furuta, T. Hiramitsu, and M. Kuzuya, *Tetrahedron Lett.*, 4107 (1974).
40. D. E. Ames, S. Chandrasekhar, and R. Simpson, *J. Chem. Soc. Perkin*, **I**, 2035 (1975).
41. R. Y. Ning, J. F. Blount, W. Y. Chen, and P. B. Madan, *J. Org. Chem.*, **40**, 2201 (1975).
42. (a) T. Kiguchi, J-L. Schuppiser, J-C. Schwaller, and J. Streith, *J. Org. Chem.*, **45**, 5095 (1980); (b) T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.*, **42**, 1856 (1977).
43. T. Akiyama, T. Kitamura, T. Isida, and M. Kawanisi, *Chem. Lett.*, 185 (1974).
44. W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

45. (a) R. Breslow, C. Yaroslavsky, and S. Yaroslavsky, *Chem. Ind. (London)*, 1961 (1961); (b) E. Müller, *Chem. Ber.*, **47**, 3001 (1914); (c) H. Staudinger and A. Gaule, *Chem. Ber.*, **49**, 1961 (1916); (d) M. Colonna and A. Risaliti, *Gazz. Chim. Ital.* **87**, 923 (1957); *Chem. Abstr.*, **52**, 4642e (1958).
46. R. A. Izydore and S. McLean, *J. Am. Chem. Soc.*, **97**, 5611 (1975).
47. D. Seyferth and H. Shih, *J. Am. Chem. Soc.*, **94**, 2508 (1972).
48. D. Seyferth, W. Tronich, and H. Shih, *J. Org. Chem.*, **39**, 158 (1974).
49. J. A. Blair and R. J. Gardner, *J. Chem. Soc. Perkin Trans I*, 485 (1972).
50. W. C. Firth, *J. Org. Chem.*, **33**, 3489 (1968).
51. R. A. Mitsch, *J. Org. Chem.*, **33**, 1847 (1968).
52. E. I. Jomilenko, V. I. Staninets, and G. P. Vdovin, *Khim. Geterotsikl. Soedin.*, 417 (1977); *Chem. Abstr.*, **87**, 39433 (1977).
53. P. Grammaticakis, *Compt. Rend. Serie C Sciences Chimiques*, **229**, 1338 (1949).
54. H. W. Heine, P. G. Williard, and T. R. Hoye, *J. Org. Chem.*, **37**, 2980 (1972).
55. H. W. Heine, S. Riseman, and F. Martens, unpublished work.
56. R. Ohme and E. Schmitz, *Chem. Ber.*, **97**, 297 (1964).
57. R. Ohme and E. Schmitz, *Z. Chem.*, **7**, 226 (1967).
58. E. Hoehne, *J. Prakt. Chem.*, **312**, 862 (1971).
59. A. A. Dudinskaya, A. E. Bova, L. I. Khmel'nitskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1523 (1971); *Chem. Abstr.*, **75**, 98473 (1971).
60. M. D. Hinchliffe and J. Miller, Brit. Patent 1,085,794 (1967); *Chem. Abstr.*, **68**, 29243 (1968).
61. H. W. Heine, L. M. Baclawski, S. M. Bonser, and G. Wachob, *J. Org. Chem.*, **41**, 3229 (1976).
62. S. R. Paulsen, Ger. Patent 1,136,343 (1962); *Chem. Abstr.*, **58**, 3436 (1963).
63. L. S. Lehman, L. M. Baclawski, S. Harris, H. W. Heine, J. P. Springer, W. J. A. Vanden-Heuvel, and B. H. Arison, *J. Org. Chem.*, **45**, 320 (1981).
64. C. Szantay, Z. F. Chmielewicz, and T. J. Bardos, *J. Med. Chem.*, **10**, 101 (1967).
65. H. J. Abendroth, *Angew Chem.*, **73**, 67 (1961).
66. R. G. Kostyanovskii, K. S. Zakharov, V. F. Rudtchenko, and M. Zaripova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 875 (1975).
67. A. Mannschreck, R. Radeglia, E. Gruendemann, and R. Ohme, *Chem. Ber.*, **100**, 1778 (1967).
68. R. G. Kostyanovskii, A. E. Polyakov, G. V. Shustov, K. S. Zakharov, and V. I. Markov, *Dokl. Akad. Nauk SSSR*, **219**, 873 (1974); *Chem. Abstr.*, **82**, 97576w (1975).
69. E. Schmitz, C. Hoerig, and C. Gruendemann, *Chem. Ber.*, **100**, 2093 (1967).
70. J. Miller, Brit. Patent 1,081,292 (1967); *Chem. Abstr.*, **68**, 114071h (1968).
71. H. W. Heine, T. R. Hoye, P. G. Williard, and R. C. Hoye, *J. Org. Chem.*, **38**, 2984 (1973).
72. V. N. Yandovskii and T. K. Klindukhova, *Zh. Org. Khim.*, **10**, 1510 (1974); *Chem. Abstr.*, **81**, 105356w (1974).
73. H. Dorn and K. Walter, *Justus Liebigs Ann. Chem.*, **720**, 98 (1968).
74. T. K. Klindukhova and V. N. Yandovskii, *Zh. Org. Khim.*, **10**, 877 (1974); *Chem. Abstr.*, **81**, 24980t (1974).
75. N. S. Nametkin, V. N. Perchenko, and E. S. Vasil'eva, U.S.S.R. Patent 232,256 (1968); *Chem. Abstr.*, **70**, 96929d (1969).
76. H. Dorn and A. Otto, *Chem. Ber.*, **101**, 3287 (1968).

77. A. Nabeya, J. Saito, and H. Koyama, *J. Org. Chem.*, **44**, 3935 (1979).
78. H. W. Heine and L. Heitz, *J. Org. Chem.*, **39**, 3192 (1974).
79. H. W. Heine, L. S. Lehman, A. Glaze, and A. P. Douglas, *J. Org. Chem.*, **45**, 1317 (1980).
80. S. R. Paulsen and G. Huck, *Chem. Ber.*, **94**, 968 (1961).
81. E. Schmitz and D. Habisch, *Chem. Ber.*, **95**, 680 (1962).
82. M. Schulz and G. West, *J. Prakt. Chem.*, **316**, 999 (1974).
83. (a) C. Szantay and E. Schmitz, *Chem. Ber.*, **95**, 1759 (1962); (b) C. Szantay and E. Schmitz, *Magy. Kem. Folyoirat*, **69**, 292 (1963); *Chem. Abstr.*, **59**, 8167b (1963).
84. Whiffen and Sons, Ltd., Belg. Patent 650,329 (1965); *Chem. Abstr.*, **63**, 16355c (1965).
85. V. N. Yandovskii, L. B. Koroleva, and P. M. Adrov, *Zh. Org. Khim.*, **12**, 435 (1976); *Chem. Abstr.*, **84**, 150572m (1976).
86. V. N. Yandovskii, P. M. Adrov, and I. A. Zamorina, U.S.S.R. Patent 523,092 (1976); *Chem. Abstr.*, **86**, P29825j (1977).
87. M. Otsuka, S. Yukimura, H. Yamaguchi, and T. Kawasaki, Japan Patent 7,005,544 (1970); *Chem. Abstr.*, **72**, 111106v (1970).
88. M. Komatsu, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, 3999 (1972).
89. M. Komatsu, N. Nishikaze, M. Sakamoto, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **39**, 3198 (1974).
90. T. Agawa, Y. Ohshiro, and M. Komatsu, Japan Kokai 75,117,765 (1975); *Chem. Abstr.*, **84**, 59159w (1976).
91. J. W. Lown, *J. Chem. Soc. (C)*, 1338 (1969).
92. E. V. Dehmlow and J. Schönefeld, *Z. Naturforsch.*, **30B**: *Anorg. Chem., Org. Chem.*, 824 (1975).
93. E. V. Dehmlow, R. Zeisberg, and S. S. Dehmlow, *Z. Naturforsch.*, **30B**: *Anorg. Chem., Org. Chem.*, 404 (1975).
94. V. N. Yandovskii and P. M. Adrov, *Zh. Org. Khim.*, **10**, 2235 (1974); *Chem. Abstr.*, **82**, 43217m (1975).
95. V. N. Yandovskii, P. M. Adrov, and L. B. Koroleva, *Zh. Org. Khim.*, **11**, 156 (1975); *Chem. Abstr.*, **83**, 9066x (1975).
96. V. N. Yandovskii and L. B. Koroleva, *Zh. Org. Khim.*, **11**, 2221 (1975); *Chem. Abstr.*, **84**, 59268f (1976).
97. (a) A. Mannschreck and H. Seitz, *Angew. Chem. Int. Ed.*, **8**, 212 (1969); (b) H. Häkli and A. Mannschreck, *Angew. Chem. Int. Ed.*, **16**, 405 (1977).
98. R. G. Kostyanovskii, A. E. Polyakov, and G. V. Shustov, *Tetrahedron Lett.*, 2059 (1976).
99. R. G. Kostyanovskii, V. F. Rudchenko, and G. V. Shustov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1898 (1976).
100. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 3101 (1965).
101. Solvay et Cie, Belg. Patent 715,868 (1968); *Chem. Abstr.*, **71**, 81327 (1969).
102. Solvay et Cie, French Demande 2,009,634 (1970); *Chem. Abstr.*, **74**, 3600 (1971).
103. D. M. Lemal, F. Menger, and E. Coats, *J. Am. Chem. Soc.*, **86**, 2395 (1964).
104. P. G. Williard, M.Sc. Thesis, Bucknell University, Lewisburg, PA, July, 1972.
105. E. Schmitz and K. Schinkowski, *Chem. Ber.*, **97**, 49 (1964).
106. E. Schmitz and R. Ohme, *Chem. Ber.*, **95**, 2012 (1962).
107. R. Appel, H. Heinen, and R. Schöllhorn, *Chem. Ber.*, **99**, 3118 (1966).

108. D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Am. Chem. Soc.*, **88**, 3617 (1966).
109. Yu. V. Zeifman, E. G. Abduganiev, E. M. Rokhlin, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2737 (1972).
110. H. J. Abendroth, *Angew Chem.*, **73**, 67 (1961).
111. E. Schmitz and R. Ohme, *Org. Synth.*, **45**, 83 (1965).
112. E. Schmitz, A. Stark, and C. Hörig, *Chem. Ber.*, **98**, 2509 (1965).
113. S. R. Paulson, Ger. Patent 1,126,395 (1962); *Chem. Abstr.*, **57**, 9857 (1962).
114. J. J. Uebel and J. C. Martin, *J. Am. Chem. Soc.*, **86**, 4618 (1964).
115. M. T. H. Liu and B. M. Jennings, *Can. J. Chem.*, **55**, 3596 (1977).
116. E. Schmitz, *Chem. Ber.*, **95**, 676 (1962).
117. P. R. Farina and H. Tieckelmann, *J. Org. Chem.*, **40**, 1070 (1975).
118. E. Schmitz, Ger. Patent 1,107,238 (1959); *Chem. Abstr.*, **56**, 7325 (1962).
119. S. Ishida, K. Sato, and N. Fujita, U.S. Patent 3,376,263 (1968); *Chem. Abstr.*, **68**, 105651 (1968).
120. H. J. Abendroth, Ger. Patent 1,127,907 (1962); *Chem. Abstr.*, **57**, 9665 (1962).
121. E. Schmitz, *Chem. Ber.*, **95**, 688 (1962).
122. R. A. G. Smith and J. R. Knowles, *J. Chem. Soc. Perkin*, **II**, 686 (1975).

II. 3H-DIAZIRINES (1-DIAZIRINES)

1. Introduction

Two isomeric diazacyclopropenes are possible, namely the 3H-diazirine (or 1-diazirine) system (**A**) and the 1H-diazirine (or 2-diazirine) system (**B**), though only examples of the former have been isolated. Like the 2-azirines,[1] the ring system **B** is anti-aromatic and therefore much less stable than **A**. Both **A** and **B** are isomeric with the acyclic diazoalkane **C**.



A



B

$CH_2{=}N_2$

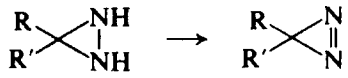
C

The first preparations of 3H-diazirines were reported by Paulsen (1960)[2a] and by Schmitz and Ohme (1961).[2b] By 1966 examples of 3-alkyl- and 3-aryl-3H-diazirines (Table 1), 3,3-dialkyl- and 3-alkyl-3-aryl-3H-diazirines (Table 2), and 3-alkyl-3-halo- and 3-aryl-3-halo-3H-diazirines (Tables 3–5) were known. 3H-Diazirines having vinyl, acetoxy, methoxy, trimethylsilyl, and carboxamido substituents at the 3-position have been synthesized, as have a host of 3H-diazirine derivatives of biologically active molecules[3] and steroids.[4,5] Because of the explosive nature of 3H-diazirines[1,6–9] precautions should be taken in handling and distilling these compounds. Explosions have occurred by opening with a file ampules containing 3-chloro-3-methyl-3H-diazirine.[10] 3-Chloro-3H-diazirines are frequently mentioned as being unstable. Some 3-fluorodiazirines are relatively stable,[11a,b] while others are highly explosive.

2. Methods of Preparation

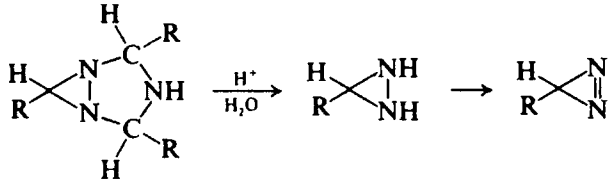
A. *Dehydrogenation of 1,2-Unsubstituted Diaziridines*

Dehydrogenation of 3-alkyl, 3-aryl-, 3,3-dialkyl, and 3-alkyl-3-aryldiaziridines (**1**) by oxidizing agents (silver oxide, chromic acid, yellow mercuric oxide, bromine, iodine, lead tetraacetate, and cupric salts) leads to the corresponding 3-substituted and 3,3-disubstituted diazirines (**2**).



1 **2**

3-Alkyl-3H-diazirines (**5**) are usually obtained by the dichromate oxidation of 3-alkyldiaziridines (**4**), which are generated *in situ* from 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes (**3**).[6,7] For example, 3-*t*-butyl-3H-diazirine was prepared by adding a suspension of **3** (R = *t*-Bu) in dilute sulfuric acid to an excess of sodium dichromate in dilute sulfuric acid.[12] Using this procedure, **3** (R = Ph) was converted in 45–80% yields to 3-phenyl-3H-diazirine.[13] The latter compound is also formed in 48% yield by the direct oxidative cleavage of **3** (R = Ph) with *t*-butyl hypochlorite at 0°C.[14,15] 3-*p*-Tolyl-, 3-*p*-methoxyphenyl-, and 3-*p*-carboxymethoxyphenyl-3H-diazirine could not be isolated by treating the corresponding **3** compounds with acid dichromate.[14,15] Low yields (1–3.6%) of these substances were obtained by adding yellow mercuric oxide to a mixture of aromatic aldehydes, methanolic ammonia, and chloramine.[14,15] This approach was based on the idea that as the 3-aryldiaziridine **4** was being formed from the starting reagents, it would be intercepted by the dichromate to give **5** faster than **4** would react with additional aldehyde and ammonia to give **3**. It is interesting to note that in the successful oxidation[13] of **3** (R = Ph), potassium dichromate in 2 *N* sulfuric acid was added to **3**, while in the unsuccessful oxidations[14,15] of **3** (R = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$MeO_2CC_6H_4$, and Ph in 4% yield) the addition sequence was reversed; that is, an acetone solution of **3** was added at 0°C to a mixture of dichromate, acetone, water, and sulfuric acid.

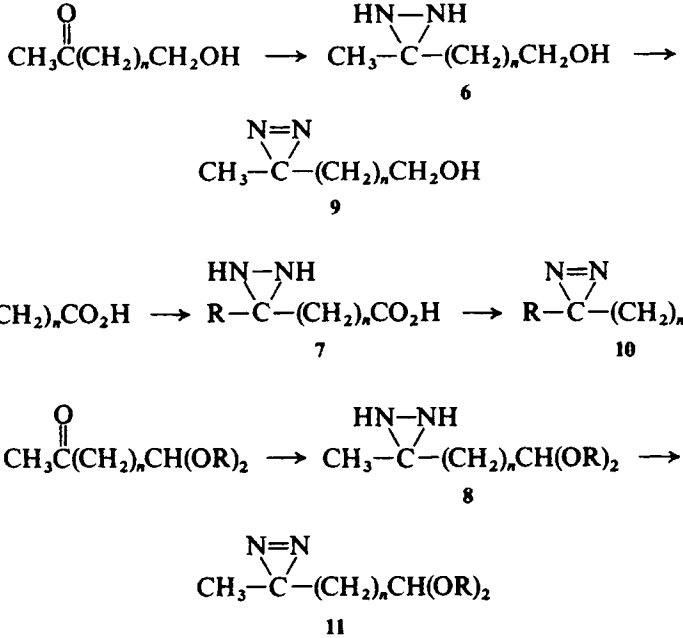


3 **4** **5**

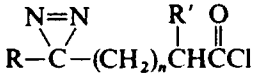
Condensation of formaldehyde with ammonia and chloramine in methanol forms a variety of diaziridine products, but addition of acid to the mixture liberates diaziridine, which in acid dichromate gives diazirine.[6,7]

Most known 3,3-dialkyl- and 3-alkyl-3-aryldiazirines have been prepared by the dehydrogenation of the corresponding 3,3-disubstituted diaziridines with silver oxide.[2,4,5,16-18] Bromine,[19] chlorine,[20a,b] and particularly iodine[21,22] in basic media are promising alternative oxidizing agents to silver oxide. The use of iodine circumvents the danger involved with metallic silver deposits, and iodine has the additional advantage of not interacting with most other functional groups that might be incorporated into the 3-substituent of the diaziridine precursor. No ammonia should be present in the reaction mixture when the iodine is added because of the possible formation of nitrogen triiodide. The patent literature claims that 3,3-dialkyldiazirines can be prepared in a one-step process in which it is not necessary to isolate the progenitorial 3,3-dialkyldiaziridine.[20a] Typically, a mixed stream of ammonia, chlorine, and nitrogen is introduced (with good agitation) into a ketone cooled to about 5°C. The ammonia chloride that is formed is filtered, and the filtrate is distilled to give the diazirine and unreacted ketones.[20a] In a similar process,[20b] chlorine and ammonia gases are brought into contact with a solution or suspension of a ketone or aldehyde in an inert medium (alcohol, chlorinated hydrocarbons, or ether) under intensive mixing at about −20° to 20°C. If, after the initial mixing or reagents, catalytic amounts of cuprous or cupric salts (acetates, chlorides) are added, the yields of diazirines improve considerably.[20b]

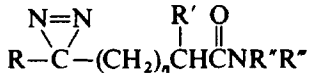
Diazirines containing aliphatic alcohol, carboxylic acid, and acetal side chains (**9–11**; Table 2) have been made by Church and Weiss.[21,22] They reacted hydroxyketones, keto acids, and dialkoxyketones with ammonia and hydroxylamine-*O*-sulfonic acid and then dehydrogenated the diaziridines generated *in situ* by adding either silver oxide or iodine and triethylamine to the reaction mixture.



The hydroxy, acid, and acetal groups of **9–11** have been converted into tosylates, acyl halides, amides, amines, and aldehydes (Table 2). In turn, acyl halides **12**, derived from **10**, have been reacted with amines, diamines, and 7-aminocephalosporanic acids to give a myriad of diazirine derivatives, illustrated by structures **13**,[23] **14**,[24] and **15**,[25] respectively.

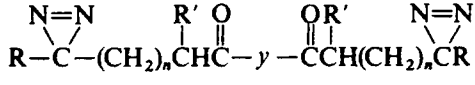


12

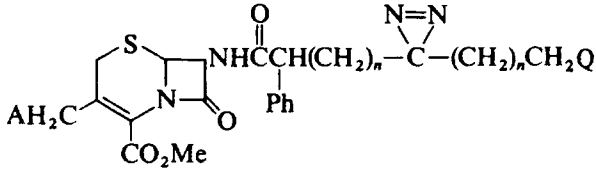


13

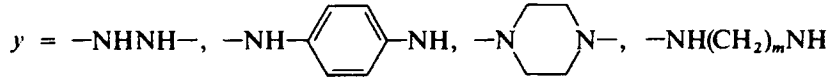
$n = 0, 1, 2, 3$



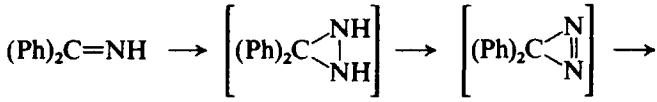
14



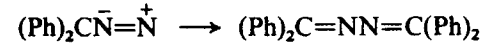
15



In an attempt to prepare 3,3-diphenyl-3H-diazirine **17**, benzophenone imine hydrochloride was reacted in liquid ammonia at −70°C with hydroxylamine-*O*-sulfonic acid.[26] Introduction of oxygen or the addition of yellow mercuric oxide to the reaction mixture gave **18**, identified by its conversion to benzophenone azine **19**. One explanation for these results is that 3,3-diphenyldiaziridine **16** was formed at the outset and then oxidized to **17**, which rearranged to **18** spontaneously.



16 **17**



18 **19**

As of 1981, no 3,3-diaryl-3H-diazirines have been prepared.

B. *Reaction of Imines with Dichloro- and Difluoroamines*

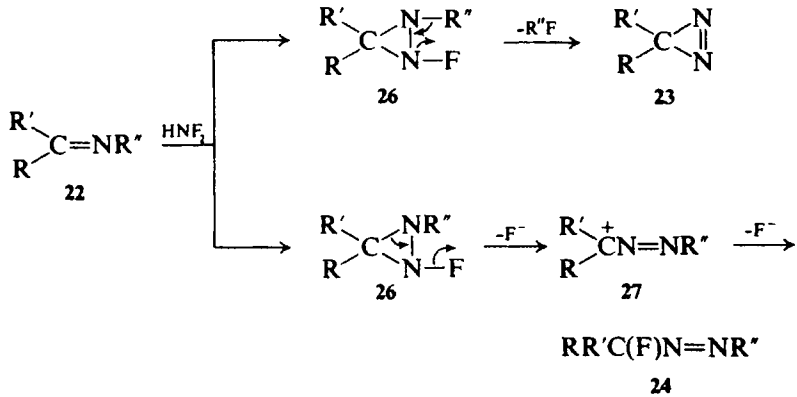
Treatment of **20** with difluoramine[27a] or dichloramine[28] formed 3H-diazirine **21** in 25–62% yields. Mono- or dideuterated-3H-diazirine can also be prepared in this manner.

$$\underset{\mathbf{20}}{CH_2{=}NC(Me)_2CH_2C(Me)_3} \xrightarrow{NHF_2} \underset{\mathbf{21}}{H_2C\begin{smallmatrix}N\\ \|\\ N\end{smallmatrix}}$$

Extending the reaction to imines of 2-amino-2,4,4-trimethylpentane or *t*-butylamine (**22**) gave, depending upon the structure of the imine, 3-substituted 3H-diazirines (**23**), α-fluoroazo compounds (**24**), mixtures of **23** and **24**, or tautomers of **24**, namely compounds **25**.[27b] It has been proposed that interaction of **22** with difluoramine gives rise to a 1-fluorodiaziridine (**26**), which either eliminates an alkyl

$$\underset{\mathbf{22}}{RR'C{=}NR''} \xrightarrow{HNF_2} \underset{\mathbf{23}}{\begin{smallmatrix}R'\\ R\end{smallmatrix}C\begin{smallmatrix}N\\ \|\\ N\end{smallmatrix}} \qquad \underset{\mathbf{24}}{RR'C(F)N{=}NR''} \qquad \underset{\mathbf{25}}{\begin{smallmatrix}RC{=}NNHR''\\ |\\ F\end{smallmatrix}}$$

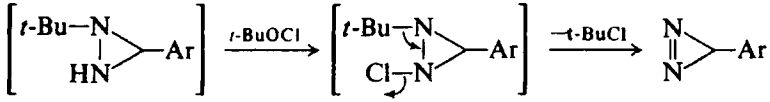
fluoride to form **23** or ionizes to the carbonium ion **27**. Subsequent attack of fluoride ion on **27** yields **24**. Intermediate **27** is prone to form if R or R and R′ are electron-releasing groups.



Tautomerization of RR′C(F)N=NR″ (**24**) to **25** is likely to occur if R′ is hydrogen.

$$\underset{\mathbf{24}}{\begin{smallmatrix}H\\ |\\ RC(F)N{=}NR''\end{smallmatrix}} \longrightarrow \underset{\mathbf{25}}{RC(F){=}NNHR''}$$

A variation of the synthesis of diazirines depicted above involves reaction of 3-aryl-1-(*tert*-butyl)diaziridine **28** (generated *in situ*) with *tert*-butyl hypochlorite.[15] Presumably **29** is produced and goes on to **30** by elimination of *t*-butyl chloride.

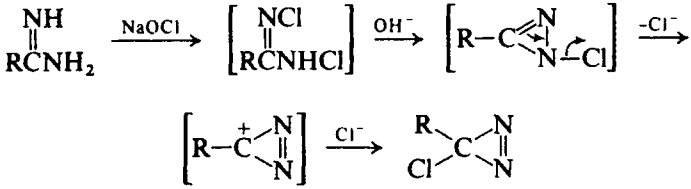


28 29 30

In this manner, 3-(3-pyridyl)-, 3-(4-pyridyl)-, and 3-(*m*-nitrophenyl)-3H-diazirines have been obtained in 3–15% yields.

C. *Halogenation of Amidines*

Virtually all of the known 3-chloro- and 3-bromo-3H-diazirines (Tables 3 and 4) have been prepared by an elegant reaction first described and developed by Graham.[9] In general, aqueous sodium hypochlorite containing excess chloride ion is added to a solution of an alkyl- or arylamidine in dimethyl sulfoxide. Graham suggested the following mechanism for the reaction:

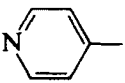


This reaction pathway no longer appears tenable. By employing Graham's procedure but controlling the reaction temperature, Berneth and Hünig[29] were able to convert the arylamidines **31a, b** to the corresponding diaziridines **32a, b** in 60 and 71% yields, respectively. Furthermore, **32a** under Graham's conditions gave rise to the diazirine **33a** in 50% yield.

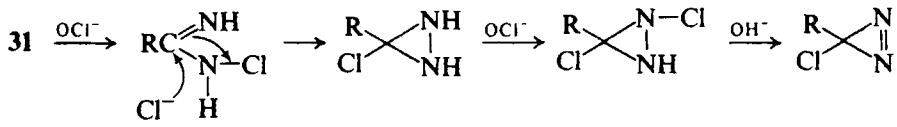


31a b 32a,b 33a,b

a. R = Ph

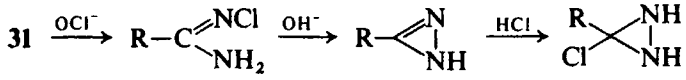
b. R = 

It was proposed that **31** undergoes monohalogenation to form **34**. Attack of **34** by chloride ion gives **32**, which interacts with hypochlorite to produce the *N*-chlorodiaziridine **35**. In the presence of hydroxide ion, **35** is converted to **33**.



34 32 35 33

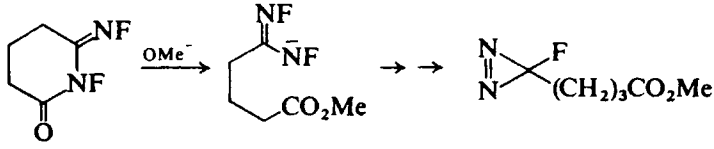
An alternate mechanism involves halogenation of **31** to form **36** instead of **34**. Reaction of **36** with hydroxide ion affords **37**, which undergoes addition of the elements of hydrogen chloride to yield **32**.



36 **37** **32**

In the chlorination of acetamidine, addition of acetate ion produced a mixture of 3-methyl-3-chloro-3H-diazirine and 3-methyl-3-acetoxy-3H-diazirine.[9] This result can be explained by assuming a competition between acetate and chloride ions for intermediate **34**. A judicious selection of nucleophiles other than acetate ion that are stable toward the halogenation medium could lead to novel 3-subsituted 3H-diazirines.

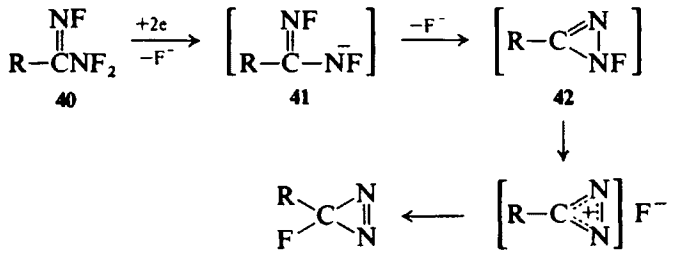
Graham's procedure has been employed to prepare 3-chloro-3-methyl-d_3-3H-diazirine.[30] Chlorination of *O*-methylisourea-*p*-toluenesulfonate by the same procedure forms 3-chloro-3-methoxy-3H-diazirine.[31-33] The propensity of many 3-chloro- and 3-bromo-3H-diazirines to explode often prompts their use without prior isolation. It has been reported that pure 3-phenyl-3-chloro-3H-diazirine is considerably more shock sensitive than nitroglycerin,[34] but it can be safely handled in solution.[34,35] Intermediates similar to those implicated in the halogenation of amidines may be involved in the conversion of **38** into **39** by methoxide ion.[36]



38 **39**

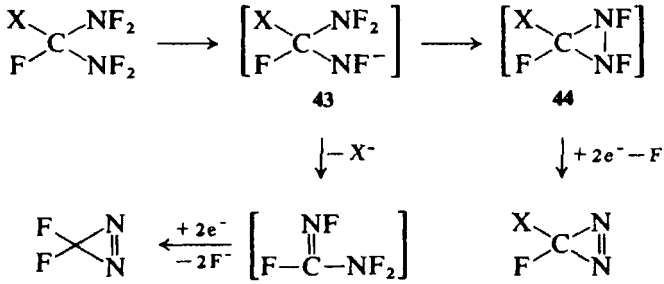
D. *Reductive Deflorinative Cyclization*

Reduction of $F_2C(NF_2)_2$, $FC(NF_2)_3$, $(NC)(NF_2)C{=}NF$, and $MeOC(NF_2)_2NFH$ by dicyclopentadienyliron or dicumenechromium yields 3,3-difluoro-, 3-difluoroamino-3-fluoro-, 3-cyano-3-fluoro-, and 3-fluoro-3-methoxy-3H-diazirines, respectively.[11a-c] Mitsch has suggested that the reduction of trifluoroformamidino derivatives (**40**) occurs at the NF_2 group, accompanied by loss of fluoride ion to form **41**. Ring closure of **41** to **42** followed by isomerization of **42**, possibly through



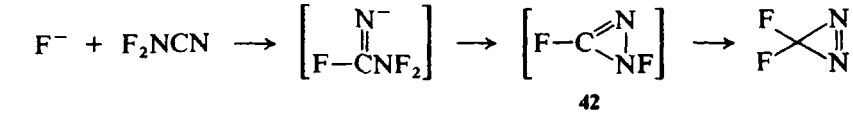
40 **41** **42**

the intermediacy of an ion pair, affords the 3H-diazirine. An analogous reduction of $F_2C(NF_2)_2$ and $FC(NF_2)_3$ leads to the anion **43**, which either undergoes ring closure to the diaziridine **44** or proceeds to a formamidine. Further reduction of **44** or the formamidine gives the 3H-diazirine.[11a,c]



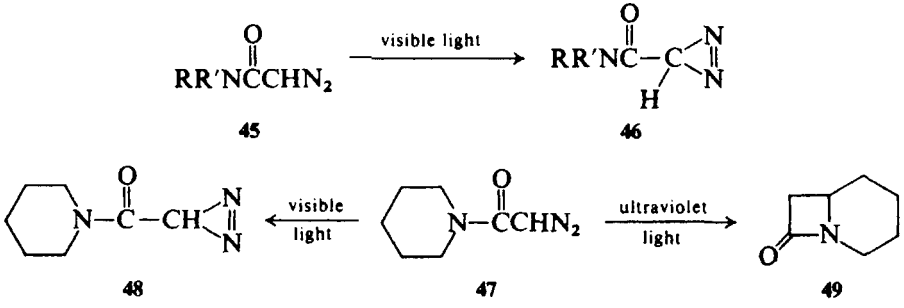
The physical and chemical properties of a variety of 3-fluoro-3H-diazirines made by these procedures appear in several publications.[11b,37a-c]

Intermediates analogous to **43** may be involved in the conversion of $F_2C(NF)_2$ and $Cl_2C(NF_2)_2$ by tetrabutylammonium iodide into 3,3-difluoro-3H-diazirine.[38] The 1H-diazirine **42** (R = F) has been suggested[11a] as one of the precursors of 3,3-difluoro-3H-diazirine when gaseous difluorocyanamide is passed over CsF.[39a,b]

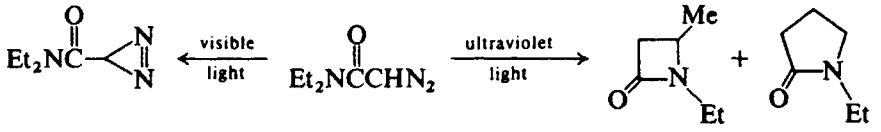


E. *Photochemical Isomerization of Diazo Compounds*

Diazoamides (**45**), when exposed to visible light, isomerize to 3-carboxamido-3H-diazirines (**46**), in some cases in 20–30% yields.[40,41] The photoisomerization proceeds regardless of the degree of substitution on the amido nitrogen. Interestingly, irradiation of **46** at the frequency of the diazirine absorption band brings about the re-formation of **45**. Ultraviolet irradiation of **45** does not give **46** but isomeric lactams instead. For example, in visible light **47** gives **48**, but in ultraviolet light **47** yields **49**.[42-44]

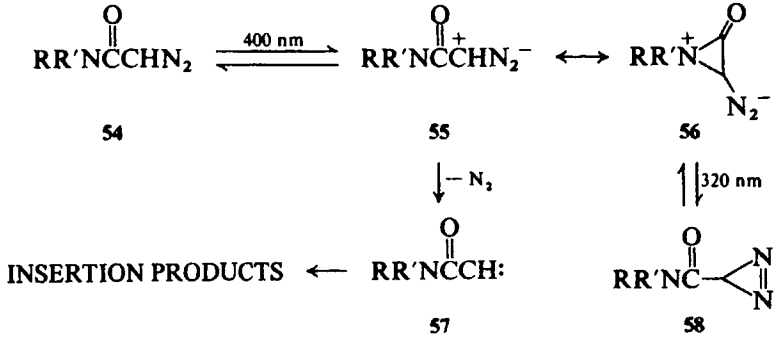


Similarly, **50** with visible light produces **51**, but **50** exposed to ultraviolet light gives a mixture of **52** and **53**.



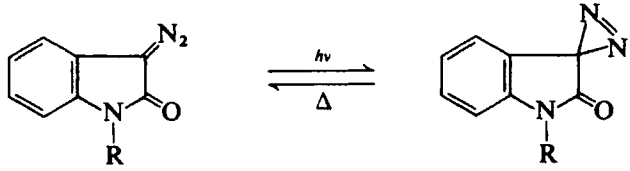
51 **50** **52** **53**

These transformations have been rationalized by assuming that the excited state of the diazoamide **54** may be represented by **55** and the canonical structure **56**.[41] It is further assumed that the contribution of **56** to the excited state suppresses the formation of the carbene **57** and prompts instead an intramolecular attack by the diimide anion to produce the diazirine **58**. Irradiation of **58** at a frequency near its absorption maximum, on the other hand, reverses the process, thereby facilitating the generation of **57** and the corresponding insertion products derived from **57**.



54 **55** **56** **57** **58**

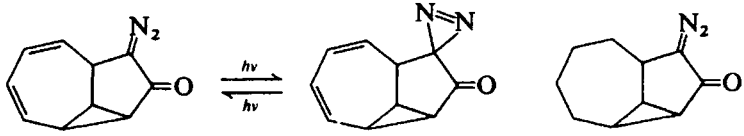
A thermally reversible, photochemically induced isomerization of the diazomethane derivatives **59a, b** to the 3H-diazirines **60a, b** has also been observed.[45,46]



59a,b **60a,b**

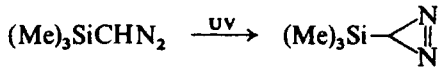
a; R = H
b; R = Me

A reversible photochemical valence isomerization between α-diazoketone **61** and α-ketodiazirine **62** takes place in aqueous dioxane.[47] The saturated α-diazoketone **63** also isomerizes upon irradiation to give an 11% yield of the corresponding diazirine. The latter result has been interpreted as evidence against the stabilization of the excited state of **61** by π-bond participation, and therefore, by inference, perhaps the excited state of **55** is not stabilized by the canonical structure **56**.



61 62 63

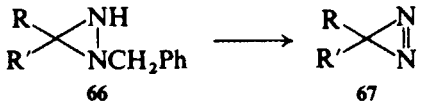
Another example of a photochemically induced isomerization of a diazomethane derivative to a diazirine is the conversion of **64** to **65**.[48a,b]



64 65

F. *Miscellaneous Methods for Preparing 3H-Diazirines*

Treatment of 1-benzyl-3,3-dialkyldiaziridines (**66**) with lead tetraacetate produces the diazirines **67**.[49] Other 1,3,3-trialkyldiaziridines (**68**), however, are oxidized by lead tetraacetate to the azo compounds **69** and **70**.[50,51]



66 67

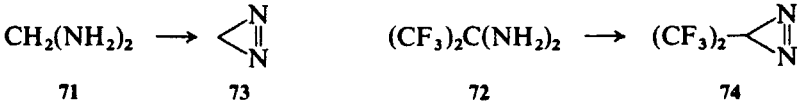


68

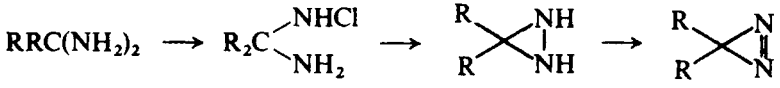


69 70

The sulfuric acid salts of the *gem*-diamines **71** and **72**, when treated with alkaline sodium hypochlorite, formed diazirines **73** and **74**, respectively.[52,53] Presumably the *gem*-diamines are *N*-chlorinated to form **75**, which undergoes ring closure to the diaziridine **76**. Subsequent oxidation of **76** gives the diazirine.

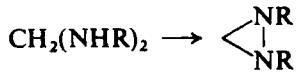


71 73 72 74



75 76

Extension of the same reaction conditions to secondary *gem*-diamines **77** produces the 1,2-dialkyldiaziridines **78**.[54]

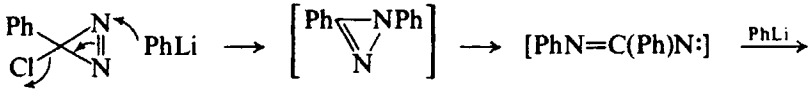


77 78

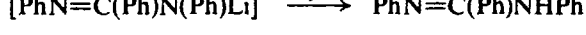
3. Reactions

A. *3H-Diazirines and Nucleophilic Reagents*

Grignard reagents add to the N–N double bond of 3H-diazirine, 3-alkyl-, and 3,3-dialkyl-3H-diazirines to give 1-alkyl-, 1,3-dialkyl-, and 1,3,3-trialkyldiaziridines, respectively, as discussed under method F for the preparation of diaziridines. Reaction of organometallics with 3-chloro-3H-diazirines, however, does not produce simple adducts. For example, mixing two equivalents of phenyllithium with **79** in ether gives **82** in near quantitative yield.[35] When equivalent quantities of phenyllithium and **79** are reacted, only 45% of **82** is isolated, together with 50% of unreacted **79**. Phenylmagnesium bromide and **79** also gives **82**. One view of the mechanism of the reaction involves the initial formation of **80** and its subsequent rearrangement to the nitrene **81**. Interaction of **81** with a second equivalent of phenyllithium leads to **82**.

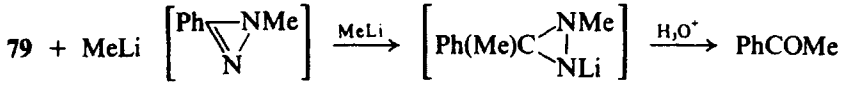


79 80 81



82

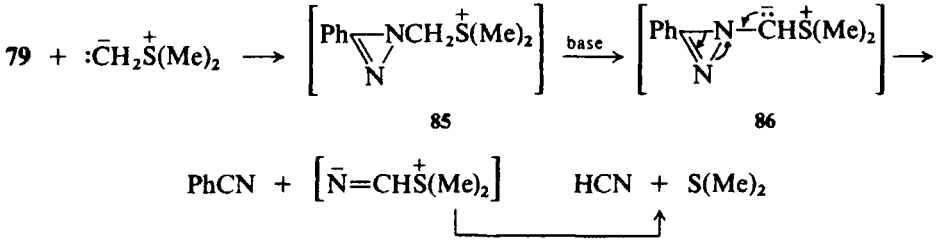
In contrast, methyllithium reacts with **79** to produce acetophenone (**84**). Here, apparently, an analog of **80** – namely **83** – is formed and undergoes addition of methyllithium across the carbon–nitrogen double bond faster than **83** can rearrange to a nitrene.



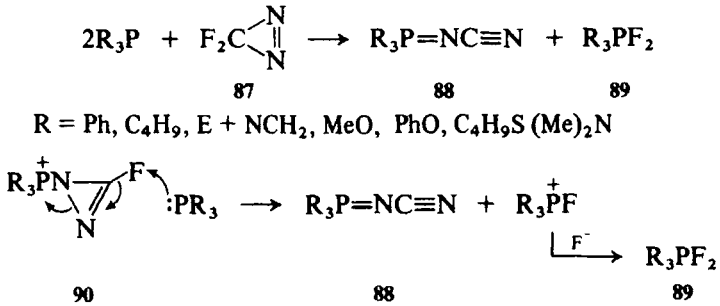
83 84

Treatment of **79** with dimethylsulfonium ylide gives mostly benzonitrile and dimethyl sulfide, together with lesser quantities of benzaldehyde and benzal chloride.[35] It is presumed that **85** is formed and converted by base to the ylide **86**. Fragmentation of **86** leads to the major products. The benzaldehyde and benzal chloride appear to arise from the decomposition of **79** in the work-up of the reaction mixture. Reaction of **79** with toluylmethylene triphenylphosphorane gave only 4% benzonitrile.

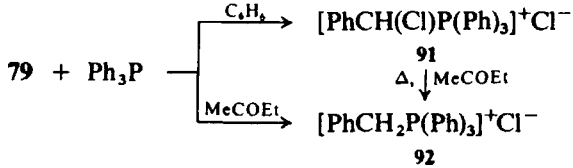
3,3-Difluoro-3H-diazirine (**87**) reacts at low temperatures with trivalent phosphorus compounds such as phosphines, phosphites, and thiophosphites to produce



N-cyanophosphorus imides (**88**) and difluorophosphoranes (**89**).[55] Suggested steps leading to the products involve the interaction of **87** with R_3P to produce **90**. Nucleophilic attack on the fluorine atom of **90** by a second equivalent of R_3P affords **88** and the progenitor of **89**.



Reaction of **79** with triphenylphosphine in benzene gave a 26% yield of **91**, while in butanone the same reactants formed **92**.[35] Compound **91** can be transformed into **92** in refluxing butanone. The products **91** and **92** can be explained by assuming that **79** decomposes to phenylchlorocarbene, which then interacts with the triphenylphosphine.

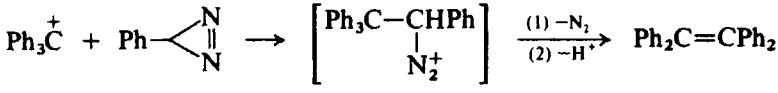


Bis(trifluoromethyl)-3H-diazirine does not react with triphenylphosphine,[56] nor does 3,3-pentamethylene-3H-diazirine.[13] The latter 3H-diazirine is also unaffected by lithium dimethylamide.[13] The former 3H-diazirine is reduced by lithium aluminum hydride to $(CF_3)_2C(NH_2)_2$.[53]

B. *3H-Diazirines and Electrophiles*

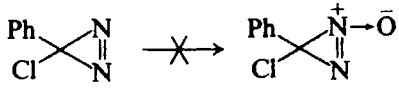
3H-Diazirines are remarkably unreactive toward a number of electrophilic reagents (for example, hydrochloric acid,[57] phosphoric acid,[58] and acid dichromate). 3,3-Pentamethylene-3H-diazirine is insensitive to methyl iodide, peracetic acid, boron trifluoride etherate, tetracyanoethene, and bromine, but it does decompose

in concentrated sulfuric acid to cyclohexene and nitrogen.[13] Electrophilic attack on a 3H-diazirine is observed when 3-phenyl-3H-diazirine is added to a solution of triphenylmethyl tetrafluoroborate in acetonitrile. Tetraphenylethene is obtained in high yield. Presumably, the reaction occurs through the intermediacy of **93**.[13]



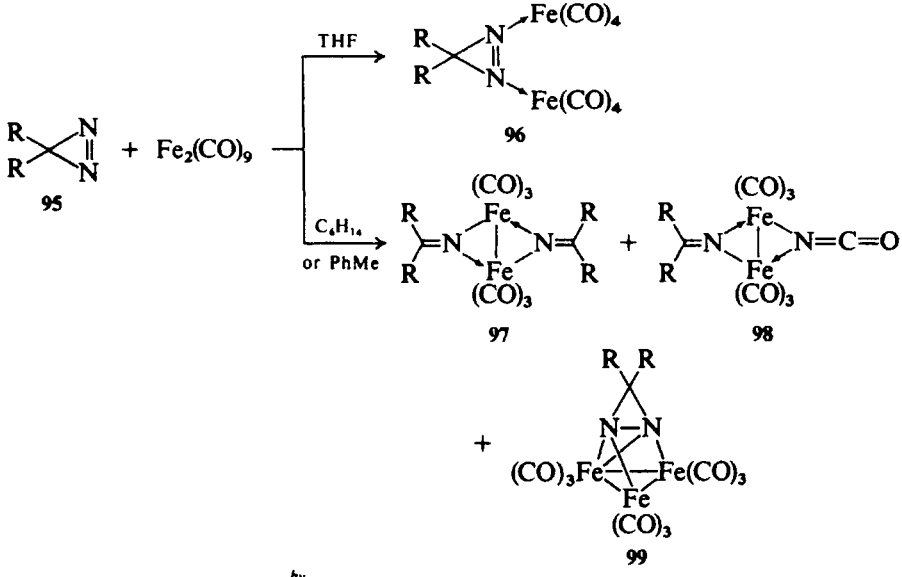
93

The reaction of **79** with *m*-chloroperbenzoic acid (to give benzoyl chloride in 45–50% yields) was originally thought to involve the initial formation of the *N*-oxide **94**.[59] Subsequent studies on the reaction of 3-*n*-butyl-3-phenyl-3H-diazirine with the same oxidizing agent indicated that direct attack on the 3H-diazirine to give intermediates similar to **94** is unlikely.[60] Instead, the products could be ascribed to the interaction of *m*-chloroperbenzoic acid with the thermal decomposition products of **79**.



79 **94**

3,3-Dimethyl- and 3,3-pentamethylene-3H-diazirines (**95**) react with enneacarbonyldiiron in tetrahydrofuran at room temperature to give **96** in 40–60% yields.[61] Compounds **96** in solution are slowly transformed into **97** and **98**. The complexes **97**, **98**, and **99** are prepared directly in 40, 12 and 0.8% yields, respectively, by mixing **95** and $Fe_2(CO)_9$ in hexane or toluene instead of tetrahydrofuran. Compounds **97** and **98** are also formed by irradiating a solution of $Fe(CO)_5$ and **95**.

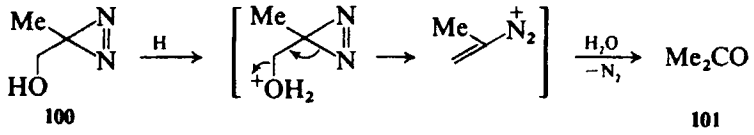


95 **96** **97** **98** **99**

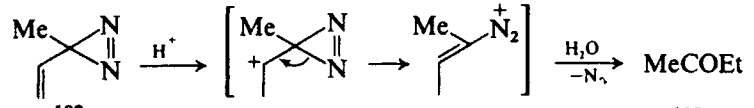
$$Fe(CO)_5 + \mathbf{95} \xrightarrow[C_6H_{14}]{h\nu} + \mathbf{97} + \mathbf{98}$$

The rupture of the nitrogen–nitrogen double bond of the ring that occurs in the formation of **97** and **98** is unique in the chemistry of 3H-diazirines.

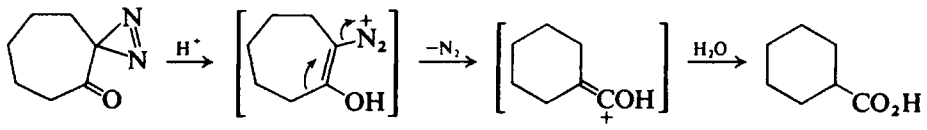
The generation of a positive charge on a carbon atom bonded to the 3-position of 3H-diazirines, usually by protonation of a functional group on that carbon, brings about the cleavage of the carbon–nitrogen bond of the ring to form a diazonium ion. Subsequent displacement of nitrogen from the diazonium ion, either by the solvent or by a neighbouring sigma bond, produces the progenitors of the observed products. Examples are the conversion of **100** to **101**,[18] **102** to **103**,[18] **104** to **105**,[62] and **106** to **107**.[63]



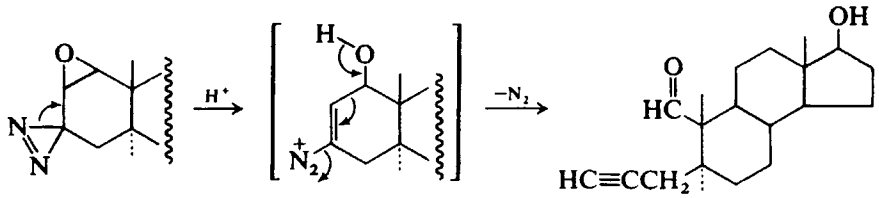
100 **101**



102 **103**

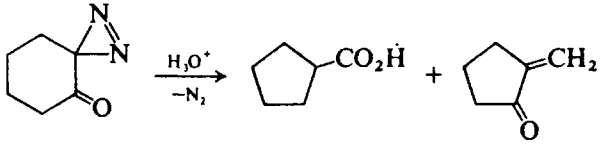


104 **105**

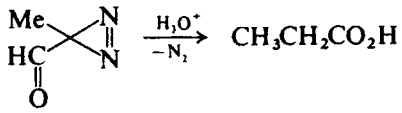


106 **107**

Still other examples are transformations of **108** to a mixture of **109** and **110**[64] and of **111** to **112**.[62]



108 **109** **110**

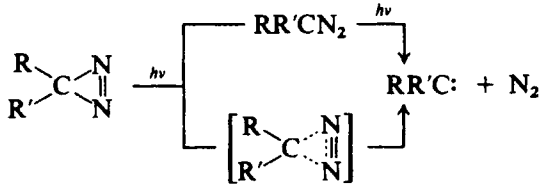


111 **112**

C. *Thermal and Photolytic Decomposition of 3H-Diazirines*

Carbenes are generated with ease by thermal or photolytic decomposition of 3H-diazirines. The reactions are useful because of the availability of 3H-diazirines and because free carbenes can be produced under neutral conditions, thus avoiding the difficulties associated with working in strongly basic media and the uncertainties of whether free carbenes or carbenoids are the reactive intermediates. Over 60 carbenes have been formed in this manner (Table 6).

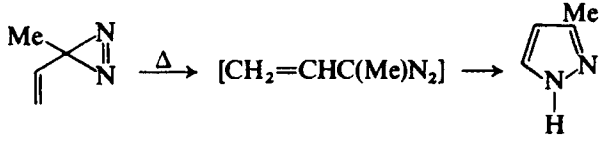
Two competing pathways appear to be operating in the photolytic decomposition of 3H-diazirines. One pathway involves the photoisomerization of 3H-diazirines into diazo compounds, which are known, of course, to lose nitrogen and form carbenes upon photolysis. The alternative pathway has carbene and nitrogen arising by a synchronous breaking of the two carbon–nitrogen bonds of the 3H-diazirine ring.



The photointerconversions of **54** and **58**,[41] as well as of **61** and **62**,[47] and the isolation of 1-phenyl-1-diazopentane from the photolysis of 3-butyl-3-phenyl-3H-diazirine[65] are examples of isomerizations of 3H-diazirines into diazo derivatives. Evidence also exists for the formation of diazo compounds during the photolysis of 3-aryl-3H-diazirines[14,15] and 3,3-hexamethylene- and 3,3-heptamethylene-3H-diazirines.[13] Amrich and Bell[66] claim to have identified diazomethane during the gas phase photolysis of 3H-diazirine. However, other investigators[67] have presented evidence that the photolysis of diazirine leads to methylene and nitrogen and that the latter compounds recombine to form diazomethane.

The duality of mechanism noted for the photolysis of 3H-diazirines may be operating as well in the thermolysis of these compounds. Convincing evidence for a two-step process in the thermal conversion of 3H-diazirines to carbenes is the isolation of 1-phenyl-1-diazopentane and 1-phenyl-1-diazoethane when 3-butyl-3-phenyl- and 3-methyl-3-phenyl-3H-diazirine are heated briefly in DMSO.[65,68,69] Further, the conversion of **113** to **115** suggests the intermediacy of the diazo intermediate **114**.[18,70]

On the other hand, the results of a kinetic study on the thermal decomposition of 3-chloro-3-methoxy-3H-diazirine are best rationalized in terms of a mechanism



113 **114** **115**

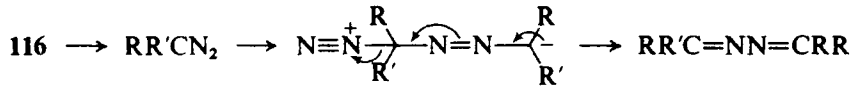
involving direct formation of carbene and nitrogen by the simultaneous breaking of the two carbon–nitrogen bonds of the 3H-diazirine ring.[33] Discussion abounds concerning the mechanism of the thermolysis reaction.[13,16,33,65,71–78] Whether the concerted one-step or the two-step process is operative may depend in large part upon the nature of the substituent groups on the ring.

The thermolysis of 3H-diazirines often affords azines (**118**).[8,9,13,31,33,34,56,65,69,79–82] It has been postulated that azine formation occurs by the partial decomposition of **116** to a carbene, which then adds to unconsumed **116** to produce **117**. Bond rearrangement of **117** yields **118**.[56]



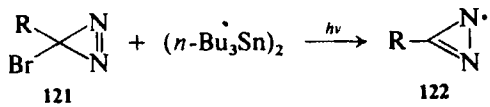
116 **117** **118**

An alternative mechanism involves the isomerization of **116** to the diazo compound **119**. Dimerization of **119** to **120** followed by elimination of nitrogen from **120** gives rise to **118**.[80] The conversion of diazoalkanes to azines is a known reaction.[83a,b] Persuasive evidence has been advanced to support the reaction pathway proceeding via the intermediates of **119** and **120**.[80]

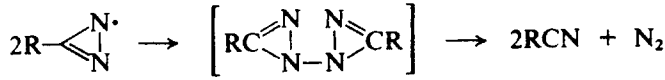


119 **120** **118**

A promising new area of investigation of 3H-diazirines has been initiated by Maeda and Ingold.[84] They generated the diazirinyl radicals **122** by photolyzing 3-alkyl-3-bromo-3H-diazirines (**121**) in the presence of hexa-*n*-butylditin. The diazirinyls that are formed are converted to nitriles possibly by dimerization of **122** to **123**, which subsequently loses nitrogen.



121 **122**



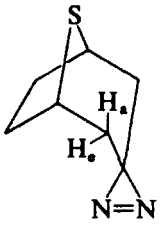
123

4. Physical Properties

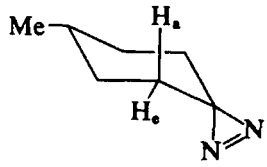
INFRARED SPECTRUM. The most characteristic infrared absorption band of medium to strong intensity of 3H-diazirines is in the range 1560–1600 cm^{-1} and represents the nitrogen–nitrogen double bond stretching vibration.[12,21,37c,72,85–87] The gas phase infrared spectrum of diazirine itself exhibits multiple peaks in the range 1610–1660 cm^{-1}.[27a] In contrast, 3,3-difluoro-3H-diazirine has a strong absorption band at 1565 cm^{-1}.[8]

ULTRAVIOLET SPECTRUM. Many investigators have reported on the ultraviolet absorption of diazirines, which typically show a family of absorption peaks in the 280–350 nm region.[4,8,12,13,15,21,27a,37c,87,96,129]

NMR SPECTRUM. The diazirine group of 3-methyl-3-alkyl-3H-diazirines has virtually no shielding or deshielding effect on the methyl protons.[21] However, with compounds **124** and **125**, the equatorial protons of the methylene groups adjacent to the diazirinyl carbon are found very much upfield (e.g., δ0.68 and δ0.60, respectively).[17] The shielding of these protons probably results from the magnetic anisotropy of the diazirine ring.



124

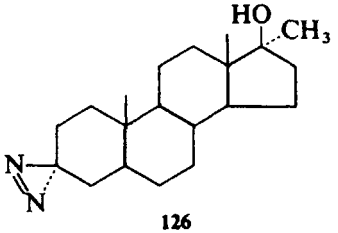


125

Similarly, the signals for the protons of the equatorial methyl groups in ring A of 3,3-azo-2α,17α-dimethyl- and 3,3-azo-4α,17α-dimethyl-5α-androstan-17β-ols[4] are more upfield than usual.

5. 3H-Diazirines of Pharmocological Interest

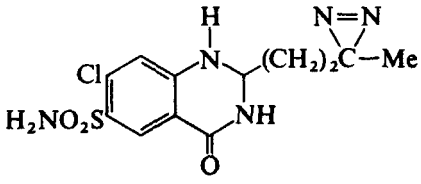
3H-Diazirine **126** had an anabolic potency three times that of 17-methyltestosterone and an androgenic potency (ventral prostate) about one-fifth that of the same standard.[4] Derivatives of **15** have been claimed to be antibacterial agents.[25] Compound **127**, an analog of tranylcypramine, was active as an antidepressant in the tetrabenazine reversal assay, and compound **128** induced diuresis.[3]



126



127



128

6. Tables

TABLE 1. 3-MONOSUBSTITUTED 3H-DIAZIRINES



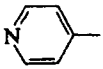
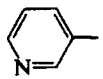
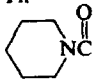
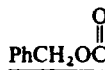
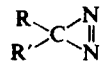
R	Mol. Formula	m.p. b.p., °C (mm)	Yield, %	Ref.
H	CH_2N_2	−14 (760)	27	6, 7, 27, 28, 52
Me	$C_2H_4N_2$			7, 85–89
MeNHCO	$C_3H_5N_3O$	107–110	31	41
Et	$C_3H_6N_2$			7
$HOCH_2CH_2$	$C_3H_6N_2O$			90
Pr	$C_4H_8N_2$	60–78 (760)	51	6, 7
i-Pr	$C_4H_8N_2$	38–42 (760)		86, 91, 92
$(Me)_3Si$	$C_4H_{10}N_2Si$			48a, 48b
t-Bu	$C_5H_{10}N_2$	61–62 (760)		12, 85, 86, 89, 91, 92
	$C_6H_5N_3$			15
	$C_6H_5N_3$			15
	$C_6H_{11}N_3O$	97–100 (1.3)	22	41
m-$O_2NC_6H_4$–	$C_6H_5N_3O_2$			15
p-$O_2NC_6H_4$–	$C_6H_5N_3O_2$	64–66	83	27b
Ph–	$C_7H_6N_2$	Oil	48–80	13–15, 93
	$C_7H_{11}N_3O$			40, 41
p-MeC_6H_4–	$C_8H_8N_2$	Oil	2–4	14, 15
p-$MeOC_6H_4$–	$C_8H_8N_2O$	Oil		14, 15
(Bu)(Et)CH–	$C_8H_{16}N_2$			20a
$HO_2CCH_2OC_6H_4$–	$C_9H_8N_2O_3$			15
	$C_9H_9N_3O$		21	41
	$C_{12}H_{13}N_3O_3$	104–105		40, 41
	$C_{14}H_{11}N_3O$	82–83	16	41
	$C_{14}H_{15}N_3O_3$	98–100		40, 41

TABLE 2. 3,3-DISUBSTITUTED 3H-DIAZIRINES



R	R'	Mol. Formula	m.p. b.p., °C (mm)	Yield, %	Ref.
$CClF_2$	CF_3	$C_3ClF_5N_2$	28 (760)	45	11
$CClF_2$	$CClF_2$	$C_3Cl_2F_4N_2$	57 (760)	48	94
CF_3	CF_3	$C_3F_6N_2$	−12 (760)	87	53, 56, 95
Me	HC(=O)–	$C_3H_4N_2O$			21, 62
Me	Me	$C_3H_6N_2$	21 (755)	80	2, 16, 61, 78, 96–99
Me	$HOCH_2$	$C_3H_6N_2O$	41–42 (11), 29–32 (4)	40	18, 22
Me	$H_2C{=}CH–$	$C_4H_6N_2$			62, 70
Me	$HCCH_2–$ (C=O)	$C_4H_6N_2O$	49–49.5 (37)		21, 22
Me	$CH_3CO_2–$	$C_4H_5N_2O_2$			9
Me	HO_2CCH_3	$C_4H_6N_2O_2$	49–51 (0.16)	35	21, 22
Me	$BrCH_2CH_2$	$C_4H_7BrN_2$	53 (32)		22
Me	Et	$C_4H_8N_2$	48 (760)	89	20b, 100
Me	MeCH(OH)	$C_4H_8N_2O$	42 (12)	72	18
Me	$HO(CH_2)_2$	$C_4H_6N_2O$	32 (3), 44 (6)	35–40	21, 22
Me	$H_2N(CH_2)_2$	$C_4H_9N_3$	170–172 (as HCl salt)	34	21, 22
Me	$ClC(=O)(CH_2)_2$	$C_5H_7ClN_2O$	38 (5)	88	21, 22
$Cl(CH_2)_2$	$Cl(CH_2)_2$	$C_5H_8Cl_2N_2$	Oil		22
Me	$HO_2C(CH_2)_2$	$C_5H_8N_2O$	8.5–10, 66 (0.12)		21, 22
Me	$H_2NC(=O)(CH_2)_2$	$C_5H_9N_3O$	89.5–91, 94–96		3, 21, 23

TABLE 2. CONTINUED

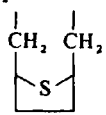
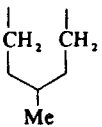
R	R′	Mol. Formula	m.p. b.p., °C (mm)	Yield, %	Ref.
Et	Et	$C_5H_{10}N_2$			100
Me		$C_6H_9ClN_2O$	51 (1.5)		22
$Cl(CH_2)_2$	$HO_2C(CH_2)_2$	$C_6H_9ClN_2O_2$	Gum		22
Me	$NC(CH_2)_3$	$C_6H_9N_3$	36–44 (0.2)		20a
$(CH_2)_2C(NOH)(CH_2)_2$		$C_6H_9N_3O$	88–89	5.4	21
$(CH_2)_5$		$C_6H_{10}N_2$	33 (30), 28 (35)	67	2, 19
Me	$HO_2C(CH_2)_3$	$C_6H_{10}N_2O_2$	14–16	38	21
Me	*i*-Bu	$C_6H_{12}N_2$	40–41 (100)		20a
Me	$(Me)_2C(OH)CH_2$–	$C_6H_{12}N_2O$	55–56 (12)	68	18
Me	$(MeO)_2CHCH_2$	$C_6H_{12}N_2O_2$	45 (12)	22	21, 22
$HO_2C(CH_2)_2$	$HO_2C(CH_2)_2$	$C_7H_{10}N_2O_4$	121–123	28	21, 22, 101
		$C_7H_{10}N_2S$	101–104	79	17
Me		$C_7H_{11}ClN_2O$	50–54 (0.6)		22
		$C_7H_{12}N_2$		37	17
Me	$MeO_2C(CH_2)_3$	$C_7H_{12}N_2O_2$	50 (3)		22
Me		$C_7H_{13}N_3O$	94–96		3, 7
Pr	Pr	$C_7H_{14}N_2$	24–25 (11)	81	2
Me	*n*-C_5H_{11}	$C_7H_{14}N_2$	50–51 (4)		20a
Me	$(EtO)_2CH$	$C_7H_{14}N_2O_2$	37 (8)	40	3, 21
Me	Ph	$C_8H_8N_2$	−5, 58–59 (11)	76 (23)	2, 65, 80

TABLE 2. CONTINUED

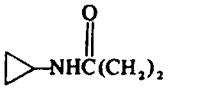
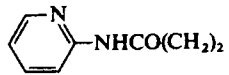
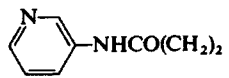
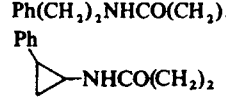
R	R′	Mol. Formula	m.p. b.p., °C (mm)	Yield, %	Ref.
Me		$C_8H_{13}N_3O$	39–41		3, 23
Me	$MeO_2C(CH_2)_4$	$C_8H_{14}N_2O_2$	50 (3)		3
Me	n-C_6H_{13}	$C_8H_{16}N_2$	44 (10)		20a
Me	$(Et)_2N(CH_2)_2$	$C_8H_{17}N_3$	62–63 (17)	71	18
Me		$C_9H_{11}N_5O$	96–97		3, 23
Et	n-C_6H_{13}	$C_9H_{18}N_2$	36–37 (1.4–1.5)		20a
Me	$(EtO)_2CH(CH_2)_2$	$C_9H_{16}N_2O_2$	43 (2.5)	40	21, 22, 102
Me		$C_{10}H_{12}N_4O$	147–148 (as HCl salt)		3, 23
Me		$C_{10}H_{12}N_4O$	78.5–80		3, 23
Me	$PhCO_2(CH_2)_2$	$C_{11}H_{12}N_2O_2$	82 (0.1)		3, 23
Me	$HO_2CCH(Ph)CH_2$	$C_{11}H_{12}N_2O_2$	73.5–75		22
Me	$PhNHCO(CH_2)_2$	$C_{11}H_{13}N_3O$	81.5–82		3
Ph	n-Bu	$C_{11}H_{14}N_2$	Oil		60, 65, 68, 80
Me	p-$MeC_6H_4SO_3(CH_2)_2$	$C_{11}H_{14}N_2O_3S$	25.5–28		22
Me	$C_6H_{11}NHCO(CH_2)_2$	$C_{11}H_{19}N_3O$	70.5–72.5		3
Me	$CH_3(CH_2)_8$	$C_{11}H_{22}N_2$	40–41 (0.3)		20a
Me	$PhCH_2NHCO(CH_2)_2$	$C_{12}H_{15}N_3O$	64–65		3, 23
Me	$Ph(CH_2)_2NHCO(CH_2)_2$	$C_{13}H_{17}N_3O$	65–66		3
Me		$C_{14}H_{17}N_3O$	81–81.5		3
Me	$PhCH_2CH(Me)NHCO(CH_2)_2$	$C_{14}H_{19}N_3O$	68–69		3
Me	$C_6H_{11}CH_2CH(Me)N(Me)CO(CH_2)_2$	$C_{15}H_{27}N_3O$	90–95 (0.14)		3
Me	$(PhCH_2)_2NCO(CH_2)_2$	$C_{19}H_{21}N_3O$	Oil		3

TABLE 3. 3-CHLORO 3-SUBSTITUTED 3H-DIAZIRINES



Y	Mol. Formula	b.p., °C (mm)	Yield, %	Ref.
F	$CClFN_2$			37c
F_2N	$CClF_2N_3$	5 (760)		37c
CF_3	$C_2ClF_3N_2$	−19 (760)	45	79
CCl_3	$C_2Cl_4N_2$			103
CD_3	$C_2ClD_3N_2$			30, 104
Me	$C_2H_3ClN_2$			9, 10, 71, 105–109, 126
MeO	$C_2H_3ClN_2O$			9, 31–33, 110
CH_2=CH–	$C_3H_3ClN_2$			9
Et	$C_3H_5ClN_2$			75, 111
	$C_4H_5ClN_2$			9, 73, 112–114, 117
Pr	$C_4H_7ClN_2$			75
i-Pr	$C_4H_7ClN_2$			75
	$C_5H_7ClN_2$	−5 (2–8)		115
t-Bu	$C_5H_9ClN_2$			9, 75
m-$O_2NC_6H_4$	$C_7H_4ClN_3O_2$			73
p-$O_2NC_6H_4$	$C_7H_4ClN_3O_2$		23	72
m-ClC_6H_4	$C_7H_4Cl_2N_2$			73
p-ClC_6H_4	$C_7H_4Cl_2N_2$		59	72, 73
Ph	$C_7H_5ClN_2$	33–35 (0.5)	60	9, 34, 35, 59, 60, 72, 73
m-MeC_6H_4	$C_8H_7ClN_2$			73
p-MeC_6H_4	$C_8H_7ClN_2$			73
p-$MeOC_6H_4$	$C_8H_7ClN_2O$			9, 72, 73
Cycloheptyl	$C_8H_{13}ClN_2$			73

TABLE 4. 3-BROMO 3-SUBSTITUTED 3H-DIAZIRINES[a]



Y	Mol. Formula	Ref.
Me	$C_2H_3Br_2N_2$	9, 77, 105
Et	$C_3H_5BrN_2$	77, 84
	$C_4H_5BrN_2$	112, 117
t-Bu	$C_5H_9BrN_2$	84
Ph	$C_7H_5BrN_2$	9, 77, 105
$PhCH_2$	$C_8H_7BrN_2$	84

[a] No melting points or boiling points reported.

TABLE 5. 3-FLUORO 3-SUBSTITUTED 3H-DIAZIRINES



Y	Mol. Formula	b.p., °C (mm)	Ref.
Cl	$CClFN_2$		37c
F	CF_2N_2		8, 11a, b, 37b, 55, 81, 82, 118–123
F_2N	CF_3N_3		11a, b, 37c
CN	C_2FN_3		11b, 37c
O=C=N–	C_2FN_3O		11b
MeO	$C_3H_3FN_2O$	5 (760)	11b, 37c
CH_3CO_2	$C_3H_3FN_2O_2$		11b
$MeO_2C(CH_2)_3$	$C_6H_9FN_2O_2$		36

TABLE 6. GENERATION OF CARBENES FROM 3H-DIAZIRINES



R	R′	Mol. Formula	Ref. for Mode and Decomposition of Diazirine	
			Thermal	Photolytic
H	H	CH_2N_2		66
Cl	F	$CClFN_2$		37c
Cl	NF_2	$CClF_2N_3$	39	
F	F	CF_2N_2	8, 38	8, 37a, b, 124, 125
F	NF_2	CF_3N_3	39	
Cl	CCl_3	$C_2Cl_4N_2$	103	
Cl	CF_3	$C_2ClF_3N_2$	79	
F	CN	C_2FN_3	39	
Br	Me	$C_2H_3BrN_2$	84	84
Cl	Me	$C_2H_3ClN_2$	9, 71	107, 108, 122, 126
Cl	MeO	$C_2H_3ClN_2O$	9, 31–33, 110	
F	MeO	$C_2H_3FN_2O$	39	
H	Me	$C_2H_4N_2$		87
CF_3	CF_3	$C_3H_6N_2$	95	
Br	Et	$C_3H_5BrN_2$		84
Cl	Et	$C_3H_5ClN_2$	75	
Me	Me	$C_3H_6N_2$	16, 78	96
$HOCH_2$	Me	$C_3H_6N_2O$	18	
MeNHC(=O)	H	$C_3H_6N_3O$	41	
Cl		$C_4H_5ClN_2$	73, 113	113, 114
CH_2=CH	Me	$C_4H_6N_2$	18, 70	
Cl	Pr	$C_4H_7ClN_2$	75	
Cl	*i*-Pr	$C_4H_7ClN_2$	75	

TABLE 6. CONTINUED

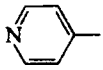
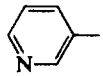
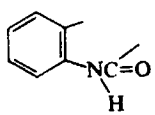
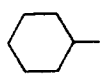
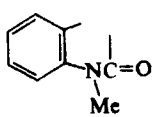
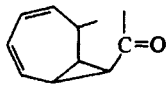
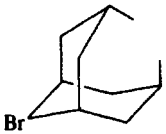
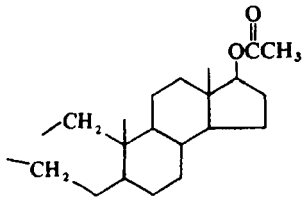
R	R′	Mol. Formula	Ref. for Mode and Decomposition of Diazirine	
			Thermal	Photolytic
H	*i*-Pr	$C_4H_8N_2$	91, 92	92
Me_3Si	H	$C_4H_{10}N_2Si$		48a, b
Cl		$C_5H_7ClN_2$		115
$(CH_2)_4$		$C_5H_8N_2$	13	13
Br	*t*-Bu	$C_5H_9BrN_2$		84
Cl	*t*-Bu	$C_5H_9ClN_2$	75	
H	*t*-Bu	$C_5H_{10}N_2$	91, 92	12, 92
H		$C_6H_5N_3$		15
H		$C_6H_5N_3$		15
				
	$C(CH_2)_4$	$C_6H_8N_2O$	64	
	$(CH_2)_5$	$C_6N_{10}N_2$	2, 13	
	$(CH_2)_4CH(OH)$	$C_6H_{10}N_2O$	64	13
Cl	*m*-$O_2NC_6H_4$	$C_7H_4ClN_3O_2$	72	
Cl	*p*-$O_2NC_6H_4$	$C_7H_4ClN_3O_2$	73	
Cl	*p*-ClC_6H_4	$C_7H_4Cl_2N_2$	72	
Br	Ph	$C_7H_5BrN_2$		84, 116
Cl	Ph	$C_7H_5ClN_2$	9, 34, 35, 72, 73, 80	116, 127
H	*m*-$O_2NC_6H_4$	$C_7H_7ClN_2$	73	
				
	$C(CH_2)_4$	$C_7H_{10}N_2O$	62	
	$(CH_2)_6$	$C_7H_{12}N_2$	13, 91	13
		$C_8H_5N_2O$		46
Br	$PhCH_2$	$C_8H_7BrN_2$	84	
Cl	*m*-MeC_6H_4	$C_8H_7ClN_2$	73	
Cl	*p*-MeC_6H_4	$C_8H_7ClN_2$	72	
Cl	*p*-$MeOC_6H_4$	$C_8H_7ClN_2$	72	
Me	Ph	$C_8H_8N_2$	2, 65, 80	
H	*p*-$MeOC_6H_4$	$C_8H_8N_2O$		15
Cl		$C_8H_{13}ClN_2$	73	
$(CH_2)_7$		$C_8H_{14}N_2$	13	13
		$C_9H_7N_2O$		46

TABLE 6. CONTINUED

R	R′	Mol. Formula	Ref. for Mode and Decomposition of Diazirine: Thermal	Photolytic
H	$HO_2CCH_2OC_6H_4$	$C_9H_8N_2O_3$		15
		$C_{10}H_8N_2O$		47
		$C_{10}H_{14}N_2$	128	
n-Bu	Ph	$C_{11}H_{14}N_2$	65, 68	
H	$(Ph)_2NC(=O)-$	$C_{14}H_{11}N_3O$	41	
		$C_{21}H_{32}O_2$	4	

7. References

1. V. Nair, in A. Hassner, Ed., *Heterocycles*, Vol. 24, Part 1, Ch. 2, Wiley, New York, 1982.
2. (a) S. R. Paulsen, *Angew. Chem.*, **72**, 781 (1960); (b) E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961).
3. R. F. R. Church, R. R. Maleike, and M. J. Weiss, *J. Med. Chem.*, **15**, 514 (1972).
4. R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Am. Chem. Soc.*, **87**, 2665 (1965).
5. American Cyanamid Co., Neth. Appl. 6,509,356, Feb. 28, 1966; *Chem. Abstr.*, **65**, 3942 (1966).
6. E. Schmitz and R. Ohme, *Tetrahedron Lett.*, 612 (1961).
7. E. Schmitz and R. Ohme, *Chem. Ber.*, **95**, 795 (1962).
8. R. A. Mitsch, *J. Heterocyclic Chem.*, **1**, 59 (1964).
9. W. H. Graham, *J. Am. Chem. Soc.* **87**, 4396 (1965).
10. M. T. H. Liu, *Chem. Engineering News*, **52**, 3 (1974).
11. (a) R. A. Mitsch, *J. Org. Chem.*, **33**, 1847 (1968); (b) R. A. Mitsch, U.S. Patent 3,637,663 (1972); *Chem. Abstr.*, **76**, 113195 (1972); (c) R. A. Mitsch, *J. Heterocyclic Chem.*, **3**, 245 (1966).
12. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 3101 (1965).

13. G. F. Bradley, W. B. L. Evans, and I. D. R. Stevens, *J. Chem. Soc. Perkin II*, 1214 (1977).
14. R. A. G. Smith and J. R. Knowles, *J. Am. Chem. Soc.*, **95**, 5072 (1973).
15. R. A. G. Smith and J. R. Knowles, *J. Chem. Soc. Perkin II*, 686 (1975).
16. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 3865 (1962).
17. J. J. Uebel and J. C. Martin, *J. Am. Chem. Soc.*, **86**, 4618 (1964).
18. E. Schmitz, C. Hörig, and C. Gründemann, *Chem. Ber.*, **100**, 2093 (1967).
19. H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, **35**, 2048 (1962).
20. (a) J. J. Fuchs, U.S. Patent 3,287,354, Nov. 22, 1966; *Chem. Abstr.*, **66**, 65453 (1967); (b) Bergwerksverband G.M.B.H., Brit. Patent 1,097,238, Jan. 3, 1968; *Chem. Abstr.*, **69**, 19137 (1968).
21. R. F. R. Church and M. J. Weiss, *J. Org. Chem.*, **35**, 2465 (1970).
22. R. F. R. Church and M. J. Weiss, U.S. Patent 3,525,736, Aug. 25, 1970; *Chem. Abstr.*, **73**, 109777 (1970).
23. R. F. R. Church and M. J. Weiss, U.S. Patent 3,509,131, Apr. 28, 1970; *Chem. Abstr.*, **73**, 25431 (1970).
24. R. F. R. Church and M. J. Weiss, U.S. Patent 3,514,447, May 26, 1970; *Chem. Abstr.*, **73**, 35355 (1970).
25. B. A. Lewis, M. L. Sassiver, and R. G. Shepherd, U.S. Patent 3,345,369, Oct. 3, 1967; *Chem. Abstr.*, **67**, 116891 (1967).
26. C. G. Overberger and J-P. Anselme, *Tetrahedron Lett.*, 1405 (1963).
27. (a) W. H. Graham, *J. Am. Chem. Soc.*, **84**, 1063 (1962); (b) W. H. Graham, *J. Am. Chem. Soc.*, **88**, 4677 (1966).
28. W. H. Graham, *J. Org. Chem.*, **30**, 2108 (1965).
29. H. Berneth and S. Hünig, *Chem. Ber.*, **113**, 2040 (1980).
30. M. T. H. Liu, N. H. Chishti, C. D. Burkholder, W. E. Jones, and J. S. Wasson, *J. Org. Chem.*, **45**, 4515 (1980).
31. N. P. Smith and I. D. R. Stevens, *Tetrahedron Lett.*, 1931 (1978).
32. R. A. Moss and W-C. Shieh, *Tetrahedron Lett.*, 1935 (1978).
33. N. P. Smith and I. D. R. Stevens, *J. Chem. Soc. Perkin II*, 213 (1979).
34. C. D. DeBoer, *Chem. Commun.*, 377 (1972).
35. A. Padwa and D. Eastman, *J. Org. Chem.*, **34**, 2728 (1969).
36. T. E. Stevens and W. H. Graham, *J. Am. Chem. Soc.*, **89**, 182 (1967).
37. (a) R. A. Mitsch, *J. Heterocyclic Chem.*, **1**, 223 (1964); (b) R. A. Mitsch, *J. Am. Chem, Soc.*, **87**, 758 (1965); (c) R. A. Mitsch, E. W. Neuvar, R. J. Koshar, and D. H. Dybvig, *J. Heterocyclic Chem.*, **2**, 371 (1965).
38. R. L. Rebertus, J. J. McBrady, and John G. Gagnon, *J. Org. Chem.*, **32**, 1944 (1967).
39. (a) M. D. Myers and S. Frank, *Inorg. Chem.*, **5**, 1455 (1966); (b) M. D. Myers, U.S. Patent 3,257,381, June, 1966; *Chem. Abstr.*, **65**, 8917 (1966).
40. G. Lowe and J. Parker, *Chem. Commun.*, 1135 (1971).
41. R. A. Franich, G. Lowe, and J. Parker, *J. Chem. Soc. Perkin I*, 2034 (1972).
42. D. M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc. (C)*, 3756 (1971).
43. R. H. Earle, D. T. Hurst, and M. Viney, *J. Chem. Soc. (C)*, 2093 (1969).
44. F. Moll, *Arch. Pharm.*, **201**, 230 (1968).
45. E. Voigt and H. Meier, *Angew. Chem. Int. Ed.*, **14**, 103 (1975).
46. E. Voigt and H. Meier, *Chem. Ber.*, **108**, 3326 (1975).
47. T. Miyashi, T. Nakajo, and T. Mukai, *Chem. Commun.*, 442 (1978).

48. (a) O. L. Chapman, C.-C. Chang, J. Kolc, M. E. Jung, J. A. Lowe, T. J. Barton, and M. L. Tumey, *J. Am. Chem. Soc.*, 98, 7844 (1976); (b) M. R. Chedekel, M. Skoglund, R. L. Kreeger, and H. Shechter, *J. Am. Chem. Soc.*, 98, 7846 (1976).
49. V. N. Yandovskii and L. B. Koroleva, *Zh. Org. Khim.*, 11, 2221 (1975); *Chem. Abstr.*, 84, 59268 (1976).
50. V. N. Yandovskii and P. M. Adrov, *Zh. Org. Khim.*, 10, 2235 (1975); *Chem. Abstr.*, 82, 43217 (1975).
51. V. N. Yandovskii, P. M. Adrov, and L. B. Koroleva, *Zh. Org. Khim.*, 11, 156 (1975); *Chem. Abstr.*, 83, 9066 (1975).
52. R. Ohme and E. Schmitz, *Chem. Ber.*, 97, 297 (1964).
53. R. B. Minasyan, E. M. Rokholin, N. P. Gambaryau, Z. V. Zeifman and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 761 (1965); *Chem. Abstr.*, 63, 2964 (1965).
54. R. Ohme, E. Schmitz, and P. Dolge, *Chem. Ber.*, 99, 2104 (1966).
55. R. A. Mitsch, *J. Am. Chem. Soc.*, 89, 6297 (1967).
56. D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Am. Chem. Soc.*, 88, 3617 (1966).
57. E. Schmitz, *Advances in Heterocyclic Chemistry*, Vol. 2, Academic Press, New York, 1963, pp. 126–130.
58. A. Lau, *Spectrochim. Acta*, 20, 97 (1964).
59. M. T. H. Liu and J. C. W. Li, *Tetrahedron Lett.*, 1329 (1974).
60. M. T. H. Liu and I. Yamamoto, *Can. J. Chem.*, 57, 1299 (1979).
61. A. Albini and H. Kisch, *J. Organomet. Chem.*, 94, 75 (1975).
62. E. Schmitz and C. Hörig, *Chem. Ber.*, 100, 2101 (1967).
63. P. Borrevang, J. Hjort, R. T. Rapala, and R. Edie, *Tetrahedron Lett.*, 4905 (1968).
64. E. Schmitz, A. Stark, and C. Hörig, *Chem. Ber.*, 98, 2509 (1965).
65. M. T. H. Liu and B. M. Jennings, *Can. J. Chem.*, 55, 3596 (1977).
66. M. J. Amrich and J. A. Bell, *J. Am. Chem. Soc.*, 86, 292 (1964).
67. C. B. Moore and G. C. Pimental, *J. Chem. Phys.*, 41, 3504 (1964).
68. B. M. Jennings and M. T. H. Liu, *J. Am. Chem. Soc.*, 98, 6416 (1976).
69. M. T. H. Liu and K. Ramakrishnan, *J. Org. Chem.*, 42, 3450 (1977).
70. M. T. H. Liu and K. Toriyama, *Can. J. Chem.*, 51, 2393 (1973).
71. M. R. Bridge, H. M. Frey, and M. T. H. Liu, *J. Chem. Soc. (A)*, 91 (1969).
72. M. T. H. Liu and K. Toriyama, *Can. J. Chem.*, 50, 3009 (1972).
73. M. T. H. Liu and D. H. T. Chien, *J. Chem. Soc. Perkin, II*, 937 (1974).
74. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 4700 (1964).
75. H. M. Frey and M. T. H. Liu, *J. Chem. Soc. (A)*, 1916 (1970).
76. W. J. Engelbrecht and M. J. DeVries, *J. S. Afr. Chem. Inst.*, 24, 205 (1971); *Chem. Abstr.*, 76, 13579 (1972).
77. M. T. H. Liu and K. Toriyama, *J. Phys. Chem.*, 76, 797 (1972).
78. G. A. Bottomley and G. L. Nyberg, *Aust. J. Chem.*, 17, 406 (1964).
79. M. W. Grayston and D. M. Lemal, *J. Am. Chem. Soc.*, 98, 1278 (1976).
80. M. T. H. Liu and K. Ramakrishan, *Tetrahedron Lett.*, 3139 (1977).
81. P. H. Ogden and R. A. Mitsch, *J. Heterocyclic Chem.*, 5, 41 (1968).
82. E. W. Neuvar and R. A. Mitsch, *J. Phys. Chem.*, 71, 1229 (1967).
83. (a) P. Yates, D. G. Farnum, and D. H. Wiley, *Tetrahedron*, 18, 881 (1962); (b) C. G. Overberger and J.-P. Anselme, *J. Org. Chem.*, 29, 1188 (1964).
84. Y. Maeda and K. U. Ingold, *J. Am. Chem. Soc.*, 101, 837 (1979).

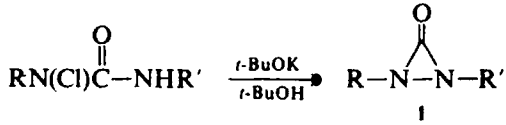
85. L. Albrecht, E. Schmitz, and R. Ohme, *Z. Physik. Chem.*, **223**, 417 (1963).
86. A. Lau and R. Ohme, *Monatsber. Deut. Akad. Wiss. Berlin*, **6**, 186 (1964); *Chem. Abstr.*, **61**, 15539 (1964).
87. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 1700 (1965).
88. J. W. Mitchell and J. A. Merritt, *J. Mol. Spectrosc.*, **29**, 174 (1969).
89. J. M. Figuera, J. M. Perez, and A. Tobar, *An. Quim.*, **72**, 737 (1976); *Chem. Abstr.*, **87**, 167159 (1977).
90. V. I. Trofimov and I. I. Chkeide, *Khim. Vys. Energ.*, **1**, 402 (1967); *Chem. Abstr.*, **67**, 86426 (1967).
91. E. Schmitz, D. Habisch, and A. Stark, *Angew. Chem. Int. Ed.*, **2**, 548 (1963).
92. K. T. Chang and H. Schechter, *J. Am. Chem. Soc.*, **101**, 5082 (1979).
93. H. Bayleg and J. R. Knowles, *Biochemistry*, **17**, 2420 (1978).
94. M. S. Raasch, *J. Org. Chem.*, **35**, 3470 (1970).
95. W. J. Middleton, D. M. Gale, and C. G. Krespan, *J. Am. Chem. Soc.*, **90**, 6318 (1968).
96. H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 3514 (1963).
97. H. M. Frey, *Chem. Commun.*, 260 (1965).
98. J. M. Figuera and E. Fernandez, *An. Quim.*, **67**, 213 (1971); *Chem. Abstr.*, **75**, 75884 (1971).
99. L. N. Domelsmith, K. N. Houk, J. W. Timberlake, and S. Szilagyi, *Chem. Phys. Lett.*, **48**, 471 (1977).
100. A. Jankowski and S. R. Paulsen, *Angew. Chem. Int. Ed.*, **3**, 229 (1964).
101. M. L. Sassiver and B. A. Lewis, U.S. Patent 3,345,369, Oct. 3, 1967; *Chem. Abstr.*, **67**, 116891 (1967).
102. R. F. R. Church and M. J. Weiss, U.S. Patent 3,459,752, Aug. 5, 1969; *Chem. Abstr.*, **71**, 112968 (1969).
103. T. Liu and K. Toriyama, *Int. J. Chem. Kinet.*, **4**, 229 (1972).
104. L. C. Robertson and J. A. Merritt, *J. Mol. Spectrosc.*, **42**, 403 (1972).
105. J. A. Merritt, W. N. Knopka, R. W. Mitchell, and L. C. Robertson, U.S. Clearinghouse Fed. Sci. Tech. Inform., AD 658988; *Chem. Abstr.*, **68**, 105056 (1968).
106. P. Cadman, S. Lotz, and S. W. J. Van der Merwe, *J. S. Afr. Chem. Inst.*, **27**, 149 (1974); *Chem. Abstr.*, **82**, 178111 (1975).
107. W. E. Jones, J. S. Wasson, and M. T. H. Liu, *J. Photochem.*, **5**, 311 (1976).
108. H. M. Frey and D. E. Penny, *J. Chem. Soc., Faraday Trans. 1*, **73**, 2010 (1977).
109. J. M. Figuera and A. Tobar, *J. Photochem.*, **10**, 473 (1979).
110. R. A. Moss, M. Fedorynski, and W-C. Shien, *J. Am. Chem. Soc.*, **101**, 4736 (1979).
111. M. T. H. Liu and D. H. T. Chien, *Can. J. Chem.*, **52**, 246 (1974).
112. W. J. Engelbrecht and S. W. J. Van der Merwe, *J. S. Afr. Chem. Inst.*, **28**, 148 (1975); *Chem. Abstr.*, **83**, 42651 (1975).
113. R. A. Moss and M. E. Fantina, *J. Am. Chem. Soc.*, **100**, 6788 (1978).
114. R. A. Moss, M. Vezza, W. Guo, R. Munjal, K. N. Houk, and N. G. Rondan, *J. Am. Chem. Soc.*, **101**, 5088 (1979).
115. R. A. Moss, M. E. Fantina, and R. C. Munjal, *Tetrahedron Lett.*, 1277 (1979).
116. R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974).
117. W. J. Engelbrecht and S. W. J. Van der Merwe, *J. S. Afr. Chem. Inst.*, **28**, 144 (1975); *Chem. Abstr.*, **83**, 42650 (1975).
118. M. D. Myers and S. Frank, *Inorg. Chem.*, **5**, 1455 (1966).
119. M. D. Myers, U.S. Patent 3,257,381, June, 1966; *Chem. Abstr.*, **65**, 8917 (1966).

120. R. A. Mitsch and J. E. Robertson, *J. Heterocyclic Chem.*, **2**, 152 (1965).
121. R. A. Mitsch, U.S. Patent 3,776,950, Dec., 1973; *Chem. Abstr.*, **81**, 63769 (1974).
122. R. A. Mitsch, U.S. Patent 3,896,188, July, 1975; *Chem. Abstr.*, **83**, 164373 (1975).
123. M. J. Dewar and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 58 (1978).
124. P. K. Pandey and P. Chandra, *Ind. J. Chem.*, Sect. A, 218 (1979).
125. D. E. Milligan, D. E. Mann, M. E. Jacox, and R. A. Mitsch, *J. Chem. Phys.*, **41**, 1199 (1964).
126. R. A. Moss and A. Mamantov, *J. Am. Chem. Soc.*, **92**, 6951 (1970).
127. R. A. Moss, J. R. Whittle, and P. Freidenreich, *J. Org. Chem.*, **34**, 2220 (1969).
128. S. D. Isajev, A. G. Jurtschenko, F. N. Stepanow, G. G. Koljada, and S. S. Novikov, *Zh. Org. Khim.*, **9**, 430 (1973).
129. A. Lau, E. Schmitz, and R. Ohme, *Z. Phys. Chem.*, **223**, 417 (1963).

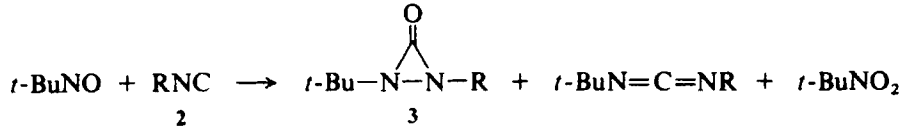
III. DIAZIRIDINONES

1. Methods of Preparation

Nearly all the methods of synthesis of diaziridinones have originated in the laboratories of F. D. Greene. The best procedure for the preparation of diaziridinones (**1**) is to treat *N,N'*-di-*tert*-alkyl-*N*-chloroureas (usually generated *in situ*) with potassium *tert*-butoxide or similar bases.[1-5] The yields range from 70 to 90% (Table 1). A variation to this method involves interaction of the progenitorial chlorourea with the potassium salt of the urea.[4] The latter approach is said to be applicable to the synthesis of diaziridinones in which the *N,N'*-alkyl groups are primary or secondary.[4]

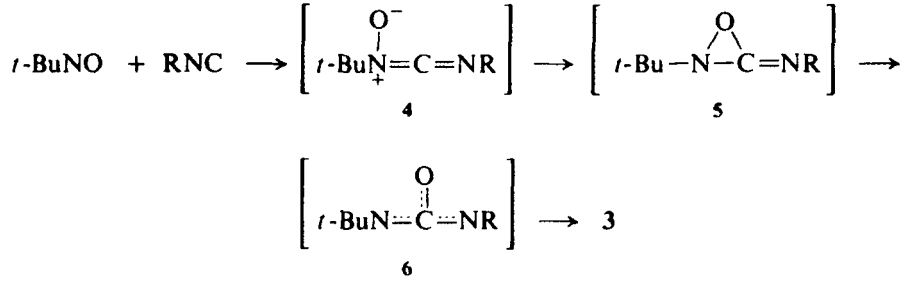


Condensation of alkyl isocyanides (**2**; R = *t*-Bu, *i*-Pr, Me) with 2-methyl-2-nitrosopropane give diaziridinones (**3**), carbodiimides, and 2-methyl-2-nitropropane.[6] Very little diaziridinone was formed in the reaction of methyl isocyanide and 2-methyl-2-nitrosopropane.

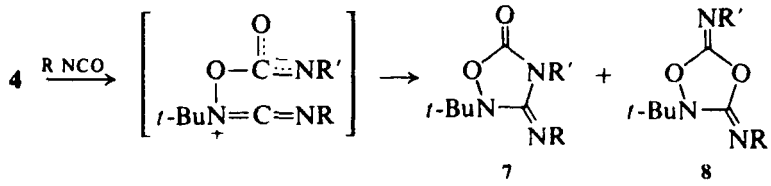


It was suggested that the condensation proceeds through the carbodiimide-*N*-oxide **4**, which undergoes ring closure to the oxaziridine imine **5**. Ring opening of **5**, perhaps to **6**, affords **3**.

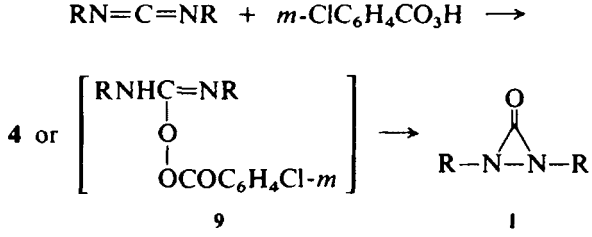
A strong indication that **4** is an intermediate was obtained by mixing together in



a 1:1:1 ratio 2-methyl-2-nitrosopropane, alkyl isocyanide, and an isocyanate. The products were **7** and **8** and, in some cases, 2-imino-1,3,4-oxadiazolidin-5-ones, which probably are derived from the isomerization of **8**.[7] Compounds **7** and **8** are considered to arise from a cycloaddition of preformed **4** with the isocyanate.

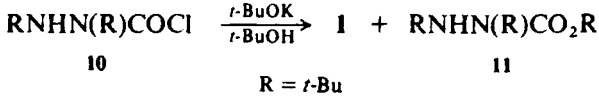


There are several other reactions, barely explored, that form diaziridinones. These include the oxidation of carbodiimides, reaction of carbazoyl chlorides with base, and photolysis of a tetrazolane. Oxidation of di-*tert*-butylcarbodiimide by *m*-chloroperbenzoic acid in methylene chloride generates **1** in 20% yield, perhaps via the intermediacy of **4** (R = *t*-Bu) or **9**.[7] Similar treatment of dicyclohexylcarbodiimide gave no diaziridinone but, instead, *N,N'*-dicyclohexylurea and di(*m*-chlorobenzoyl)peroxide.



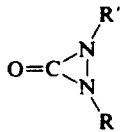
R = *t*-Bu

2,3-Di-*tert*-butylcarbazoyl chloride (**10**) reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to form **1** (R = *t*-Bu) in 45% yield and **11** in 25% yield.[1,2]



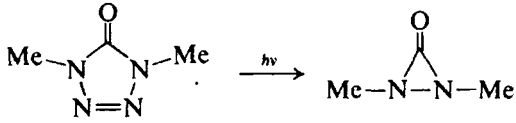
R = *t*-Bu

TABLE 1. DIAZIRIDINONES



R	R′	Mol. Formula	m.p. b.p., °C (mm)	Yield, %	Ref.
Me	Me	$C_3H_6N_2O$			8
t-Bu	*i*-Pr	$C_8H_{16}N_2O$			6
–$C(Me)_2CH_2CH_2(Me)_2C$–		$C_9H_{16}N_2O$	30	14	4
t-Bu	*t*-Bu	$C_9H_{18}N_2O$	0–1	40–80	1, 2
$EtC(Me)_2$	$EtC(Me)_2$	$C_{11}H_{22}N_2O$	66.5–67.5 (8)	75	2
t-Bu	$(Me)_3CCH_2C(Me)_2$	$C_{13}H_{26}N_2O$	50–50.5 (0.1)	71	2
t-Bu	$PhCH_2C(Me)_2$	$C_{15}H_{22}N_2O$	86–92 (0.02)	72	9
$(Me)_3CCH_2C(Me)_2$	$(Me)_3CCH_2C(Me)_2$	$C_{17}H_{34}N_2O$			2
p-$BrC_6H_4C(Me)_2$	*p*-$BrC_6H_4C(Me)_2$	$C_{19}H_{20}Br_2N_2O$	76–77	63	5
$(Me)_3CCH_2C(Me)_2$	Adamantyl	$C_{19}H_{32}N_2O$			3
$PhCH_2C(Me)_2$	$PhCH_2C(Me)_2$	$C_{21}H_{26}N_2O$	43–44		2

Irradiation of the tetrazolone **12** in $CDCl_3$ furnished 1,2-dimethyldiaziridinone **13** in unspecified yield.[8] Compound **13** represents the first example of a dialkyldiaziridinone in which the alkyl groups are not tertiary.

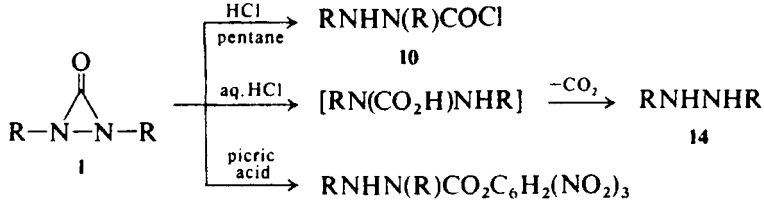


12 **13**

2. Reactions

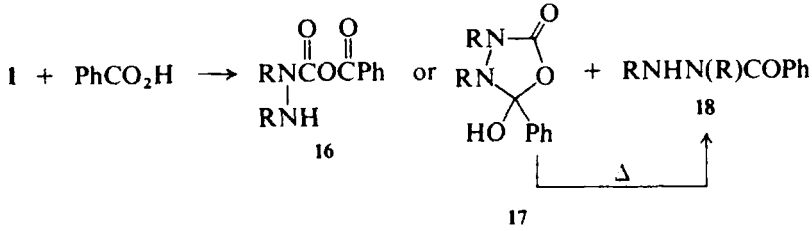
A. *Reaction of Diaziridinones with Acids*

Diaziridinones react rapidly with acids. With dry hydrogen chloride in pentane, **1** (R = *t*-Bu) forms **10** (66%), while in aqueous hydrochloric acid **1** affords the hydrazine **14** (90%).[2] Picric acid and **1** in anhydrous ether gives **15** (85.5%).



1 **10** **14** **15**

In refluxing benzene, **1** (R = *t*-Bu) and benzoic acid produces **16** or possibly its tautomer **17** (28%) and **18** (25%).[2] If the reaction time is prolonged, **18** is isolated in 87% yield. Heating converts **16** (or **17**) into **18**. Analogous reactions occur with **1** and formic acid.

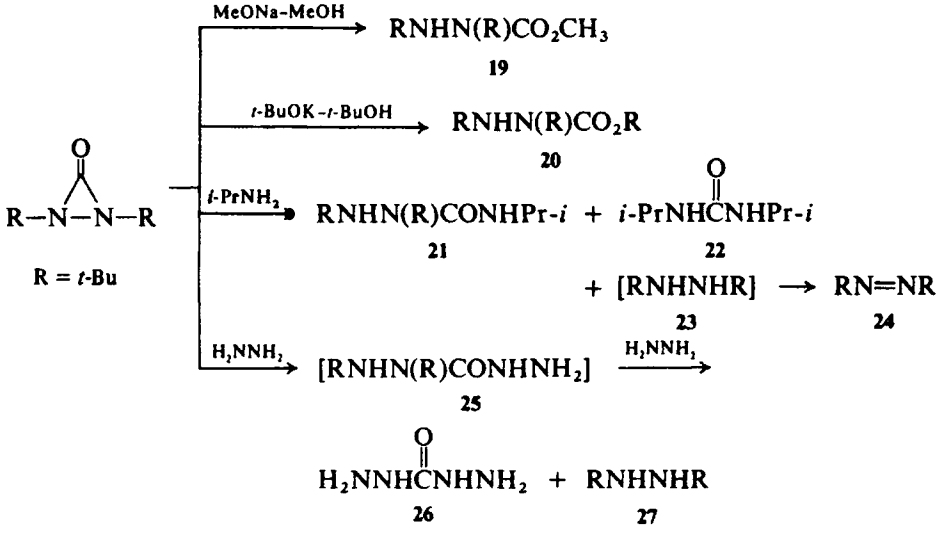


16 **17** **18**

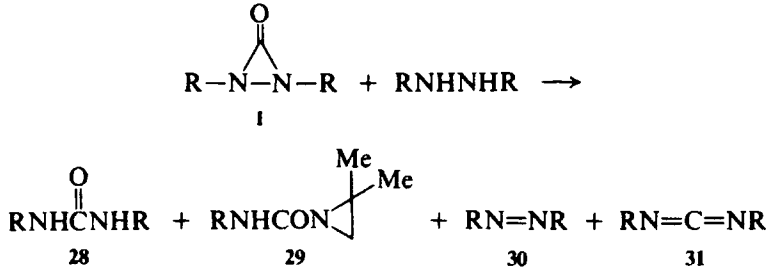
B. *Reaction of Diaziridinones with Nucleophiles*

Nucleophilic attack at the carbonyl carbon of diaziridinones has been observed with alkoxide ions, some amines, and hydrazine. For example, reaction of **1** with a refluxing solution of sodium methoxide in methanol for 40 minutes gives **19**

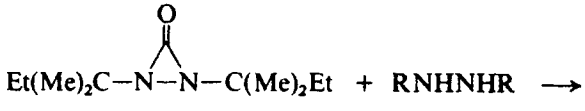
(82%).[2] A similar reaction with **1** and potassium *tert*-butoxide in refluxing *tert*-butyl alcohol forms **20**. However, only a 50% yield of **20** was obtained after 16 hours reaction time. Compound **19** forms very rapidly in methanol containing catalytic amounts of sulfuric acid. Stirring of isopropylamine with **1** at 25°C for 96 hours results in a mixture of **21** (35%), **22** (25%), and **24**, which is formed by the air oxidation of **23**.[2] Diethylamine and aniline under similar experimental conditions do not react with **1**. Treatment of **1** with a 10-fold excess of hydrazine provides **26** (93%) and **27** (72%). Apparently, **25** forms initially and subsequently reacts with additional hydrazine to produce **26** and **27**.[2]



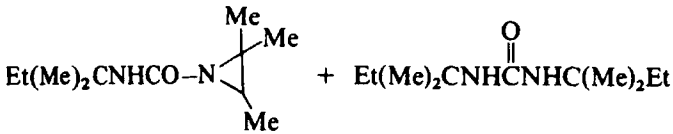
1,1-Dimethylhydrazine, hydrazobenzene, phenylhydrazine, and 1,2-di-*tert*-butylhydrazine do not attack the carbonyl carbon of diaziridinones like hydrazine itself but, instead, undergo oxidation–reduction reactions with the diaziridinone and/or cause isomerization of the diaziridinone to aziridinecarboxamides.[2,9] For example, 1,2-di-*tert*-butylhydrazine with **1** (R = *t*-Bu) in refluxing benzene for 11 days gives 1,3-di-*tert*-butylurea (**28**, 56%), *t*-(*tert*-butylcarbamyl)-2,2-dimethylaziridine (**29**, 20%), 2,2′-dimethyl-2,2′-azopropane (**30**), and a small quantity of di-*tert*-butylcarbodiimide (**31**, 7%).[9]



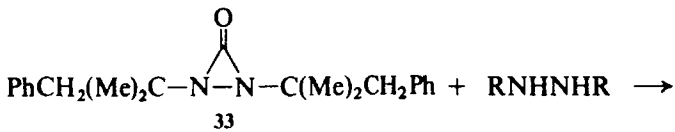
Similar reactions of 1,2-di-*tert*-butylhydrazine with di-*tert*-amyldiaziridinone (**32**) and di(2-methyl-3-phenyl-2-propyl)diaziridinone (**33**), but with much shorter reaction times, gave increasing amounts of the rearranged aziridines **34** (77%) and **35** (99%), respectively, and no carbodiimides.[9]



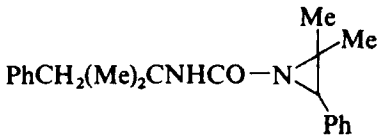
32



34



33



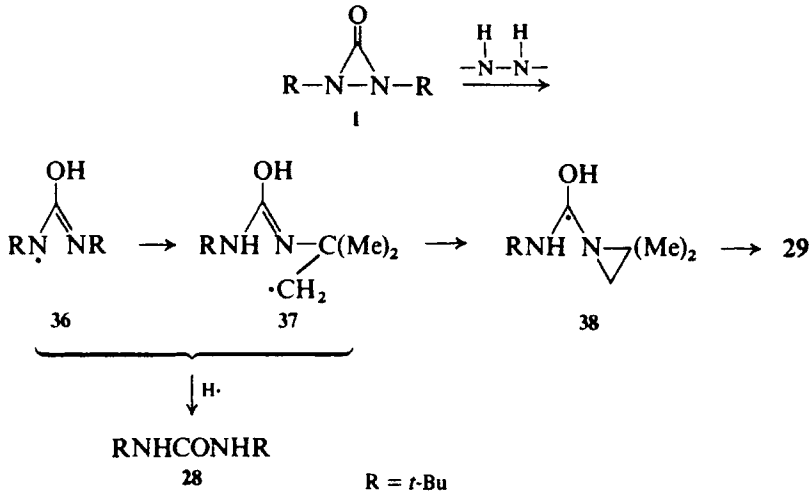
35

R = t-Bu

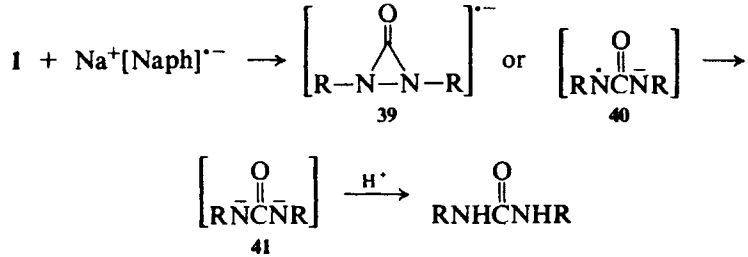
Low hydrazine concentrations favor the isomerization reaction. The ratio of oxidation–reduction product to isomerized product is dependent on the substituents on the hydrazine. Neither **1** nor **32** react with tetramethylhydrazine. Diaziridinone **33** is isomerized to the aziridine **35** by tetramethylhydrazine but at a rate 50-fold slower than with trimethylhydrazine.[9] A mechanism that accounts for the urea and aziridine products involves transfer of a hydrogen atom from the hydrazine to the diaziridinone to form **36**. Conversion of **36** to **37** by an intramolecular hydrogen abstraction and addition of a hydrogen atom to either **36** or **37** generates the urea **28**. It is also possible for **37** to isomerize to **38**, which, by loss of a hydrogen atom, affords aziridine **29**.

The reduction of **1** to 1,3-di-*tert*-butylurea is also affected by thiols, most phenols, ascorbic acid, benzhydrol, and *tert*-butylhydroxylamine.

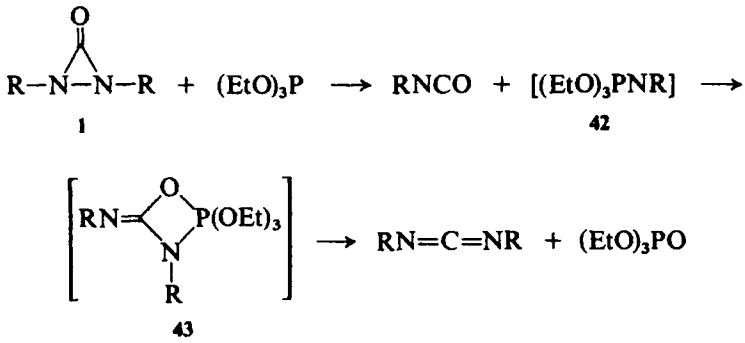
Reduction of **1** (R = *t*-Bu) to 1,3-di-*tert*-butylurea occurs electrochemically, by interaction with sodium naphthalenide, and by *tert*-butyllithium.[10] It is suggested that a radical anion, either **39** or **40** is an intermediate in both the electrochemical and the sodium naphthalenide reduction. Further electron transfer to **39** or **40** forms the dianion **41**, which reacts with a proton source to yield the urea.



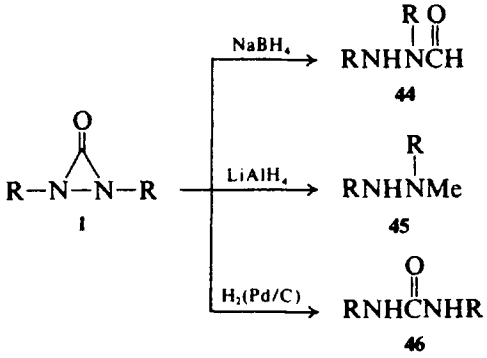
Treatment of **1** (R = *t*-Bu) with triphenylphosphine or triethyl phosphite gives di-*tert*-butylcarbodiimide (44% and 90% yields, respectively) and triphenyl phosphine oxide or triethyl phosphate.[11] In the reduction of **1** with triethyl phosphite,



a small quantity (4%) of *tert*-butyl isocyanate is produced. A shorter reaction time increases the yield of isocyanate to 20%. These observations lead to the possibility that the isocyanate and a phosphinimide (**42**) are initially formed and then recombined to produce **43**, the precursor of the carbodiimide and phosphate.

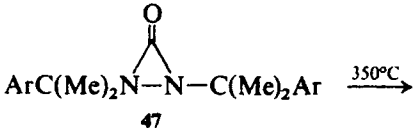


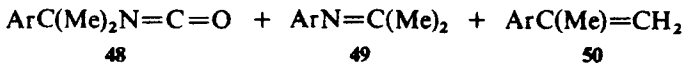
Reaction of diaziridinone **1** (R = *t*-Bu) with the conventional reducing agents sodium borohydride and lithium aluminum hydride proceeds by scission of the carbon–nitrogen bond of the ring to give **44** (60%) and **45** (85%), respectively.[1,2] Hydrogenation of **1** using palladium on carbon catalyst cleaves the nitrogen–nitrogen bond to form **46** in 96% yield.[2]



C. *Thermal Decomposition of Diaziridinones*

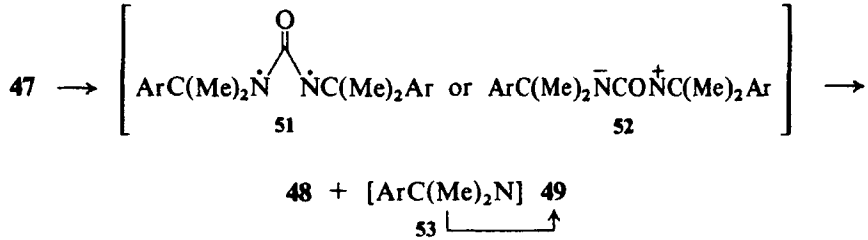
Injection of a concentrated solution of diaziridinone **47** in cyclohexane into a gas chromatograph with the injection port temperature at 350°C gave chiefly compounds **48–50**.[5]



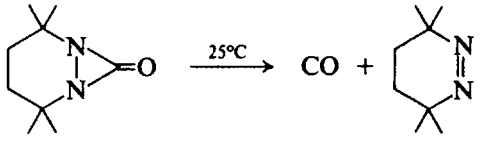


Ar = *p*-BrC_6H_4

One possible reaction pathway leading to the products **48** and **49** is the conversion of **47** to **51**, **52** or **59**. Either of these could give rise to **48** and a nitrenoid species (**53**), which by an aryl migration yields **49**.[5]



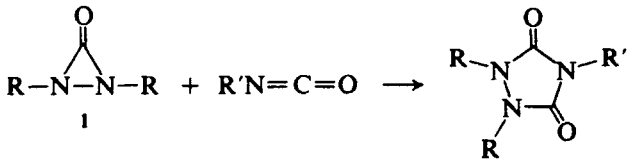
A mechanism to account for **50** envisions the decarbonylation of **47** to carbon monoxide and an azo compound that decomposes to *p*-bromocumyl radicals and nitrogen. Compound **50** is derived from the *p*-bromocumyl radicals.[5] Decarbonylations of diaziridinones to azo compounds are known. For example, **54** forms **55** at ambient temperatures.[4] Di-*tert*-butyldiaziridinones also undergo decarbonylation when heated at 180°C for several hours.[12]



54 **55**

D. *Reactions of Diaziridinones with Unsaturated Substrates*

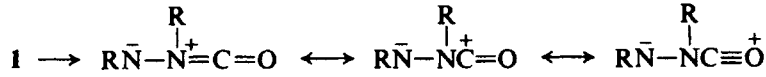
Diaziridinone **1** (R = *t*-Bu) does not react with cyclohexene, cyclopentadiene, norbornene, maleic anhydride, isocyanides, or tetracyanoethene.[2] It does react with *p*-toluenesulfonyl isocyanate,[4] *p*-nitrophenyl isocyanate,[4] and benzoyl isocyanate[13] to give adducts **56–58**, respectively. The yield of **58** is 73%. Diaziridinone **54** and *p*-nitrophenyl isocyanate form a cycloadduct analogous to **57**.[4]



1

56 R′ = *p*-$MeC_6H_4SO_2$
57 R′ = *p*-$O_2NC_6H_4$
58 R′ = PhCO

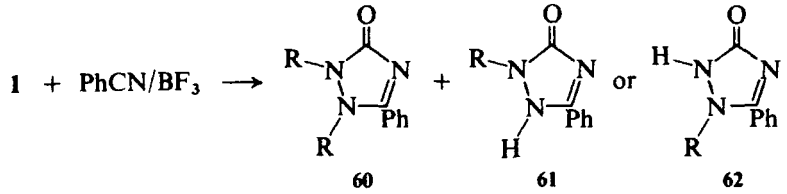
These reactions can be rationalized by presuming the conversion of **1** to dipolar species **59**, which then undergoes cycloaddition with the isocyanate. However,



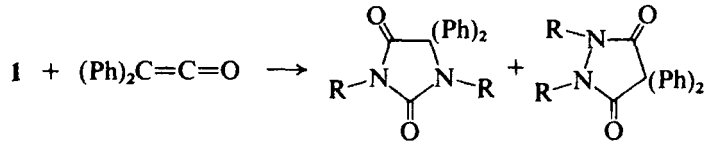
59

there is no compelling evidence for the intermediacy of **59**. The reaction of **1** with a solution of boron trifluoride etherate also results in the cleavage of the carbon–nitrogen bond of **1** to afford the cycloadduct **60** (32%) and either **61** or **62** (51%).[13] Adducts **61** or **62** are probably derived from **60**.

When **1** is heated with diphenylketene, the cycloadducts **63** (32%) and **64** (26%) are obtained. Adducts **63** and **64** are the consequence of nitrogen–nitrogen and nitrogen–carbon bond scissions of **1**.



60 61 62



63 64

3. Physical Properties

The infrared absorptions of the carbonyl group of diaziridinones in CCl_4 range from 1855 to 1882 cm^{-1}.[1,2,4,5,8] Greene has suggested that these values, which are 42 and 90 cm^{-1} higher than the carbonyl absorptions of cyclopropanone and of ureas, respectively, indicate a diminution in the delocalization of the lone pair of electrons on the nitrogens of diaziridinones.[2]

It has been established by x-ray analysis of bis(*p*-bromo-α,α-dimethylbenzyl)-diaziridinone (**47**) that the substituents attached to the nitrogen are 56° above and below the plane defined by the ring atoms and that the nitrogen–nitrogen and the nitrogen–carbonyl carbon bond lengths are 1.601 and 1.325 Å, respectively.[5] The nitrogen–nitrogen bond length of **47** is considerably longer than those of F_2NNF_2 (1.47 Å) and hydrazine (1.45 Å), while the nitrogen–carbonyl carbon bond length of **47** is similar to that in typical amide systems (1.33 Å).

4. References

1. F. D. Greene and J. C. Stowell, *J. Am. Chem. Soc.*, **86**, 3569 (1964).
2. F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).
3. F. D. Greene, U.S. Patent 3,804,829, April, 1974; *Chem. Abstr.*, **81**, 49670 (1974).
4. C. A. Renner and F. D. Greene, *J. Org. Chem.*, **41**, 2813 (1976).
5. P. E. McGann, J. T. Groves, F. D. Greene, G. M. Stack, R. J. Majeste, and L. M. Trefonas, *J. Org. Chem.*, **43**, 922 (1978).
6. F. D. Greene and F. D. Pazos, *J. Org. Chem.*, **34**, 2269 (1969).
7. C. J. Wilkerson and F. D. Greene, *J. Org. Chem.*, **40**, 3112 (1975).
8. H. Quast and L. Bieber, *Angew. Chem. Int. Ed.*, **14**, 428 (1975).
9. F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *J. Org. Chem.*, **34**, 2263 (1969).
10. A. J. Fry, W. E. Britton, R. Wilson, F. D. Greene, and J. G. Pacifici, *J. Org. Chem.*, **38**, 2620 (1973).
11. F. D. Greene, W. R. Bergmark, and J. F. Pazos, *J. Org. Chem.*, **35**, 2813 (1970).

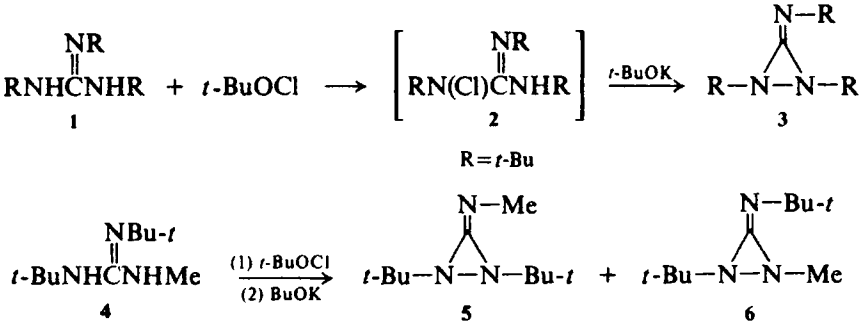
12. F. D. Greene, R. L. Camp, L. Kim, J. F. Pazos, B. Sclove, and C. J. Wilkerson, *XXIII. International Congress of Pure and Applied Chemistry*, Vol. 2, 1971, p. 325.

13. Y. Oshiro, M. Komatsu, Y. Yamamoto, K. Takaki, and T. Agawa, *Chem. Lett.*, 383 (1974).

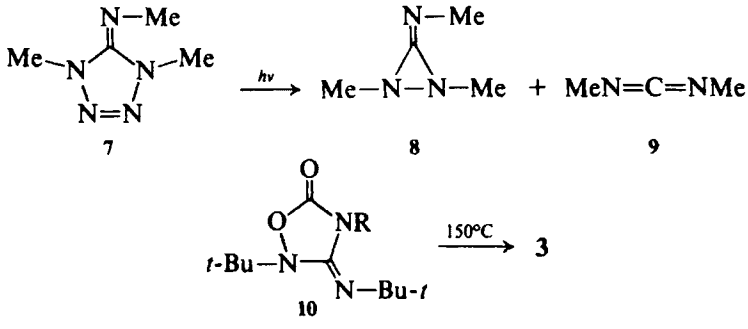
IV. DIAZIRIDINIMINES (3-IMINODIAZIRIDINES)

1. Methods of Preparation

Only a handful of diaziridinimines have been synthesized, all by H. Quast and his colleagues. In 1969 they reacted *N,N',N''*-tri-*tert*-butylguanidine (**1**) with *tert*-butyl hypochlorite in a 2 : 1 ratio in carbon tetrachloride or *n*-pentane and obtained the diaziridinimine **3** in 80–85% yields.[1,2] A better method of preparation is to treat the perchlorate salt of **1** with *tert*-butyl hypochlorite in *tert*-butyl alcohol with excess potassium *tert*-butoxide.[1,3] This reaction is analogous to that for preparing diaziridinones from ureas and *tert*-butyl hypochlorite and bases, and undoubtedly involves the intermediacy of **2**. When the procedure is extended to *N,N'*-di-*tert*-butyl-*N''*-methylguanidine (**4**), a mixture of **5** and **6** is obtained in 83% yield.[2,3]



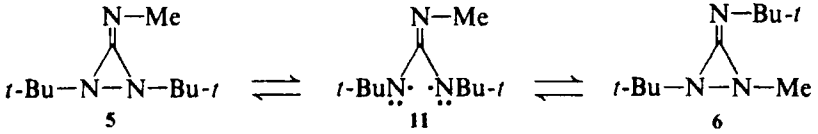
Other methods of preparation of diaziridinimines, to be further developed, include the photolysis of 2-tetrazolin-5-imines[4] and the thermolysis of 3-imino-1,2,4-oxadiazolidin-5-ones.[5] For example, photolysis of **7** forms **8** (83–86%) and **9** (14–15%), and thermolysis of **10** at 150°C gives **3**.

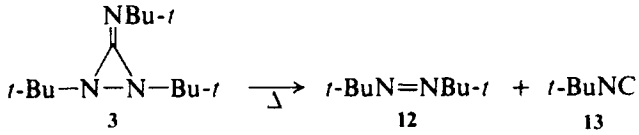


2. Reactions

A. *Diaziridinimines and Heat*

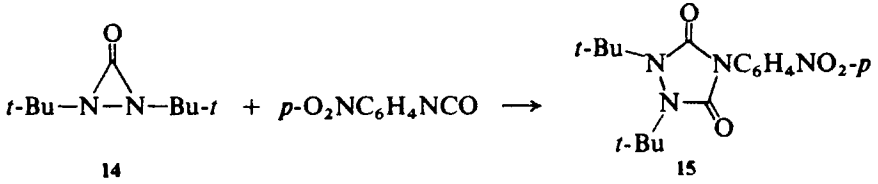
Compounds **5** and **6** rapidly equilibrate when held at 60–90°C. The equilibration may involve the intermediate **11**.[2,3] Heating diaziridinimine **3** at 150°C for one hour, however, produces the azo compound **12** and *tert*-butyl isocyanide **13** (80%).[1]

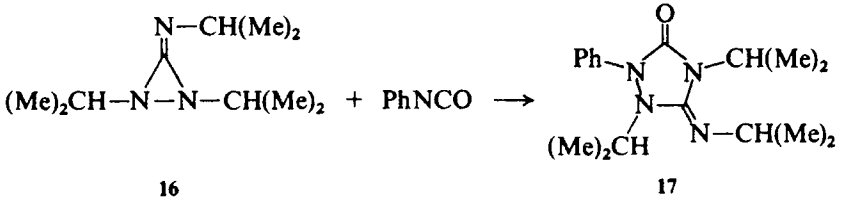




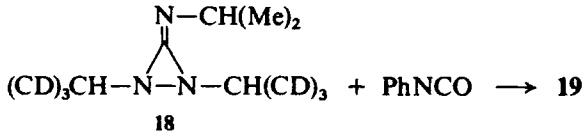
B. *Diaziridinimines and Unsaturated Substrates*

In contrast to the reaction of diaziridinone **14** with *p*-nitrophenyl isocyanate at 100°C, in which the nitrogen–carbonyl carbon bond of **14** is cleaved to give the adduct **15**,[6] diaziridinimine **16** reacts with phenyl isocyanate by scission of the nitrogen–nitrogen bond of the ring. The product **17** is formed in 82% yield.[7]



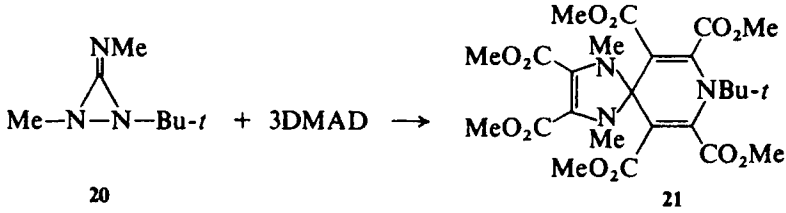


Reaction of **18** with phenyl isocyanate gives **19**, a deuterated analog of **17**. Adduct **19** had only two of the isopropyl substituents labeled, indicating that the reaction proceeds by a mechanism not requiring equilibration of the isopropyl groups. However, which of the nitrogens of **19** bear the labeled isobutyl groups remains unresolved.



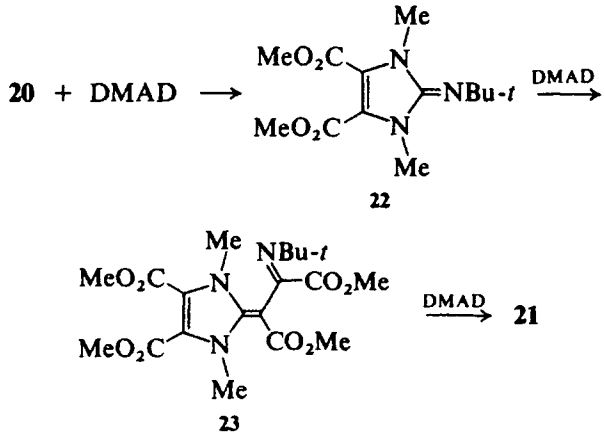
18

A novel adduct (**21**), whose structure was established by x-ray analysis, is formed when **20** is treated with excess dimethyl acetylenedicarboxylate (DMAD) in benzene/pentane at 20°C.[8]



20 21

The investigators suggest that **20** reacts with DMAD to give **22**, which, by a [2+2] cycloaddition with additional DMAD, affords an azetine. Ring opening of the azetine to **23**, followed by a [4+2] cycloaddition of **23** with DMAD, gives rise to **21**.



22 23

3. References

1. H. Quast and E. Schmitt, *Angew. Chem. Int. Ed.*, **8**, 448 (1969).
2. H. Quast and E. Schmitt, *Angew. Chem. Int. Ed.*, **8**, 449 (1969).
3. H. Quast and E. Schmitt, *Chem. Ber.*, **103**, 1234 (1970).
4. H. Quast and L. Bieber, *Angew. Chem. Int. Ed.*, **14**, 428 (1975).
5. C. J. Wilkerson and F. D. Greene, *J. Org. Chem.*, **40**, 3112 (1975).
6. C. A. Renner and F. D. Greene, *J. Org. Chem.*, **41**, 2813 (1976).
7. H. Quast and E. Spiegel, *Angew. Chem. Int. Ed.*, **16**, 109 (1977).
8. H. Quast, K.-H. Ross, E. Spiegel, K. Peters, and H. G. Von Schnering, *Angew. Chem. Int. Ed.*, **16**, 177 (1977).

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

Author Index

Numbers in parentheses are reference numbers and indicate that the author's work is referred to although his name is not mentioned in the text. Numbers in *italics* show the pages on which the complete references are listed.

Abdulla, R. F., 302(147), 303(147), 400(250), *437*
Abegg, V. P., 418(273), *441*
Abendroth, H. J., 549(1), 561(65), 566(1), 568(1), *584*
Abraham, E. P., 219(2), 220(3), *433*
Adams, W. R., 391(238,239), *440*
Adger, B. M., 109(1,2,3,4), *202*
Adickes, H. W., 415(270), *441*
Adler, K., 446(11), 448(11), *513*
Adrov, P. M., 569(85,86), 571(94,95), 597(50,51), *587*
Agawa, T., 569(88,89,90), 570(89), *587*, 624(13), *626*
Ahlgren, G., 447(19), *513*
Ahmed, F. R., 418(275), *441*
Aidakin, A. T., 22(271), *210*
Aihara, S., 260(77), 261(77), *435*
Akagi, K., 413(266), *441*
Akermark, B., 402(257), 407(261), 410(263,264), *440*, 447(19), *513*
Akhtar, M. H., 40(5), *202*
Akiyama, T., 555(43), *585*
Albanbauer, A., 90(55), *203*
Albers-Schonberg, G., 221(4), *433*
Alberts, J., 478(108), 489(108), 494(108), *515*
Albini, A., 600(61), *614*
Albrecht, F., 74(352), 75(352), 76(352), *212*
Albrecht, L., 603(85), *615*
Aldridge, M. H., 5(241), *209*
Alekseeva, N. F., 495(148,150), *516*
Allen, G. R., 91(359), *213*
Allworth, K. L., 21(5), *202*
Alper, H., 418(275), *441*
Altman, L. J., 450(30), 472(30), *513*
Altner, W., 538(48), *543*
Ames, D. E., 554(40), *585*
Amiard, G., 332(184), *438*
Amin, S. G., 260(76), 261(81,83), 271(91), *435*, *436*
Amitina, S. A., 481(124,125), *515*
Amrich, M. J., 602(66), *614*
Anderson, A. G., 12(9), 13(476), 14(10), 18(7), 38(7), 53(7), 55(7), 56(7), 63(9), 69(8,476), 71(9,11), *202*, *216*
Anderson, C. D., 475(96), *515*
Anderson, D. J., 89(11), *202*, 475(98), *515*
Anderson, D. R., 25(12,251), *202*, *209*
Anderson, J. L., 449(27), *513*
Anjaneyula, B., 361(222), *439*
Anjaneyulu, B., 254(69), 255(69), 257(69), 258(69), 260(69), *435*
Angerer, E. V., 464(65), *514*
Anselme, J-P., 591(26), 603(83), *613*
Aoki, H., 221(7), *434*
Aoki, Y., 22(242), *209*
Aoyama, H., 406(258,259), *440*
Apple, M. A., 79(13), *202*
Arbuzov, B. A., 520(13), 528(74,75,76), *542*
Arens, J. F., 238(42), *435*
Aresi, V., 33(429,430), 34(429,430), 39(430), 40(429), 63(430), 64(432), 65(429,431), *215*
Argabright, P. A., 537(105), *545*
Arison, B. H., 221(4), *433*, 560(63), 565(63), *586*
Armarego, W. L. F., 3(14), *202*
Arnett, E. M., 4(239), *209*
Arnold, D. R., 473(89), 484(135), 505(135), *514*, *516*
Arnold, P., 101(124), *205*
Arnold, R. G., 524(35), 538(35), *543*
Arnould, J. C., 22(15), *202*
Asahi, K., 79(229), *209*
Atkins, R. L., 551(25,26), *585*
Atkinson, R. F., 84(195), *208*
Au, A., 371(229), 378(229), *440*
Aubert, D., 17(146), 55(146), 56(146), 65(146), *206*
Aue, D. H., 5(16,23), 91(19), 92(19), 93(20), 94(21,22), 95(22), 105(19), *202*
Aumueller, W., 39(24), *202*
Avetisyan, E. A., 521(18), 536(18), *542*

Baba, M., 106(247), *209*
Babad, E., 38(174), *207*
Bach, H. C., 22(25), *202*

Bach, J. L., 523(33), *542*
Bachi, M. D., 242(52), 286(105), *435, 436*
Baclawski, L. M., 559(61), 560(61,63), 562(61), 565(61,63), 566(61), *586*
Baender, A., 39(24), *202*
Baird, M. S., 414(269), *441*
Baker, D., 18(382), *213*
Balchunis, R. J., 26(417), *215*, 489(143), *516*
Baldwin, J. E., 371(229), 372(230), 378(229), *440*
Balogh, G., 470(79), *514*
Balon, W. J., 522(24), *542*
Ban, Y., 358(215), *439*
Banks, R. E., 31(26,27), 62(26,27), *202*
Banthia, A. K., 68(28), *202*
Barak, S., 15(29), *202*
Bardos, T. J., 561(64), *586*
Barker, M. W., 467(71), 468(71,72), 469(72,73), 492(71), *514*, 536(104), *545*
Barlow, M. G., 31(26), 62(26), 104(30,199), 105(30), *202, 208*
Barr, D. A., 477(107), *515*
Barr, J. J., 242(53), *435*
Barton, D. H. R., 425(291), *441*
Barton, T. J., 475(94), *515*, 597(48), *614*
Baryshnikova, E. B., 549(8), 553(8), 559(8), *584*
Basselier, J., 346(203), *439*
Bassfield, R. L., 37(399), *214*
Batalova, L. G., 43(341), *212*
Battiste, M. A., 475(94), *515*
Batzer, H., 314(158), *438*
Baudour, J. L., 534(102), *544*
Baum, B. J., 78(31), *203*
Beeby, P. J., 286(106), 292(106), *436*
Behlen, F. M., 54(206), *208*
Beisiegel, E., 101(124), *205*
Bell, J. A., 457(41), *513*, 602(66), *614*
Bell, L. M., 494(145), *516*
Bellasio, E., 35(33), *203*, 340(197), 363(223), 364(224,225), *439*
Belleau, B., 283(101), *436*
Belzecki, C., 247(57,58), 248(57,58), *435*
Bender, D. R., 424(281,282,283,284), *441*
Ben Shoshan, R., 359(221), *439*
Berezin, G. H., 16(34), 34(34), 35(34), 37(34), 59(34), *203*
Bergmann, E., 471(82), *514*
Bergmark, W., 470(78), *514*
Bergmark, W. R., 531(87), 536(87), 616(2), 618(2), 619(2), 620(2,9), 621(9), 622(11), 623(2), 624(2), 625(2), *625*
Berman, H. M., 37(304), *211*
Bernath, G., 11(178), 17(178), *207*
Berneth, H., 593(29), *613*
Berning, W., 476(99), *515*
Bestian, H., 313(157), 314(157), *438*
Beyleveld, W. M., 523(33), *542*
Bhattacharya, S. K., 254(69), 255(69), 257(69), 258(69), 260(69), 361(222), *435*
Bianchi, G., 3(442), 14(442), 34(442), 35(442), 64(442), *215*
Biba, A. D., 533(98), *544*
Bieber, L., 619(8), 625(8), *625*, 626(4), *628*
Biener, H., 313(157), 314(157), *438*
Bigard, W. S., 479(7), *512*
Bigelow, L. C., 477(102), *515*
Binder, O., 459(54), 492(54), *514*
Binsch, G., 17(145), 38(145), 39(145), 41(145), 92(145), *206*
Bird, C. W., 461(57), 465(68,69,70), 479(68,116), 486(68), 489(116), 490(68), 498(68,116), 501(57,68,116), 503(116), 504(68,69,70,156,157), 505(70), *514, 515, 516*
Bird, R., 15(36), *203*
Birkofer, L., 231(27), 232(27), 341(198), *434, 439*
Bishop, D. C., 33(37), 34(37), *203*
Bjeldanes, L. F., 424(281,282), *441*
Black, D. S. C., 32(38), *203*, 429(294), *441*
Black, D. St. C., 32(40), 72(40), 81(39), *203*
Blackman, N. A., 32(38), *203*
Blade Font, A., 487(139), *516*
Blair, J. A., 557(49), *586*
Blair, J. S., 522(25), *542*
Block, F., 4(396), 5(396), *214*
Blount, J. F., 60(330), *212*, 554(41), *585*
Bödeker, J., 528(72), *544*
Boeck, L. D., 221(4), *433*
Boivin, J. L., 540(112,117), *545*
Böll, W. A., 473(87,88), 506(88), *514*
Bonati, A., 33(41), 34(426), *203, 215*
Bonfiglio, J. N., 63(42), *203*
Boni, R., 48(44), 51(44), *203*
Bonser, S. M., 556(61), 560(61), 562(61), 565(61), 566(61), *586*
Boocock, D. G. B., 481(119), *515*
Bormann, D., 90(46), 91(45,46), *203*
Borrevang, P., 550(12,14), 573(14), *585*, 601(63), *614*
Börzel, P., 503(155), *516*
Boscacci, A. B., 32(38), *203*, 429(294), *441*
Bose, A. K., 227(21), 229(24), 251(63), 253(64,65,66,67,68), 254(68,69), 255(69), 256(70,71), 257(69,71), 258(69,70,71), 260(71,75,76), 261(81,82), 263(84),

264(84,85), 267(86), 268(86,87), 271(91), 272(63), 361(222), 394(240,241), 395(243), *434, 435, 439, 440*
Bossner, P. K., 68(391), *214*
Botta, A., 14(47), 91(47), *203*
Bottini, A. T., 5(48), *203*
Bottomley, G. A., 603(78), *614*
Bouffard, F. A., 323(165), *438*
Bova, A. E., 559(59), 573(59), *586*
Bovara, M., 33(433), 34(433), 65(433), *215*
Bowers, M. T., 5(16,23), *202*
Bowie, J. H., 8(235), 9(235), *209*
Boyer, S. K., 237(37), *434*
Brace, H. N., 476(100), 510(100), 511(100), *515*
Bradbury, S., 109(1), *202*
Bradley, G. F., 551(21), 553(21), 561(21), 573(21), *585*, 589(13), 599(13), 600(13), 602(13), 603(13), 604(13), *613*
Brady, W., 227(17), 228(17), *434*
Brady, W. T., 228(22), 231(26), *434*
Braun, A., 29(57), *203*
Breckpot, R., 337(192), 338(192), *439*
Brennan, J., 424(284), *441*
Breslow, R., 555(45), 556(45), *586*
Bressel, U., 458(46), *513*
Britton, W. E., 621(10), *625*
Brogli, F., 511(167), *517*
Brooks, G., 459(55), 464(55), *514*
Brooks, W., 15(107), *205*
Brown, A. G., 221(6), *433*
Brown, A. S., 78(179), *207*
Brown, C. J., 517(5), 522(5), 534(5), *542*
Brown, D. A., 88(252), *209*
Brown, R. F. C., 81(39), *203*
Bruice, T. C., 4(131), 5(131), *206*
Brunwin, D. M., 402(256), *440*, 595(42), *613*
Bryan, D. B., 280(100), 283(100), 293(100), *436*
Bryukhova, E. V., 533(98), *544*
Buckley, T. F., III, 280(99), *436*
Buerger, H., 43(51), *203*
Buhle, E. L., 249(61), *435*
Bumgardner, C. L., 40(53,54), *203*
Burger, K., 29(57), 30(60), 90(55,56,58,59), *203*
Burgess, E. M., 100(61), 108(62), *203*
Burgner, J. W., 37(304), *211*
Burkholder, C. D., 594(30), *613*
Burns, J. M., 25(251), *209*
Buschmann, E., 425(291), *441*
Butler, B. L., 13(476), 69(476), *216*
Butler, G. B., 452(33), 453(35), *513*
Butler, W. H., 40(285), *210*
Butterworth, D., 221(6), *433*
Bystrom, S., 410(263), *440*

Cabaleiro, M. C., 223(11), 224(11), *434*
Cabani, S., 3(63), 4(63,64), *203*
Cahoon, N., 448(21), *513*
Calanda-Stiftung, 33(65), *204*
Calcagno, M. A., 6(395), *214*
Cale, A. D., 19(237), 52(237), 56(66,67), 65(66), *204*
Call, L., 488(141), *516*
Callery, P. S., 65(98), *205*
Calvo, C., 485(136), *516*
Cama, L. D., 280(97,98), *436*
Cameron, A. F., 109(67a), *204*
Cameron, D. W., 77(68), *204*
Camp, R. L., 418(273), *441*, 624(12), *626*
Campbell, J. J. A., 109(69), *204*
Cantrell, T. S., 87(70), 88(70), *204*
Caranoni, C., 4(383), *213*
Carbonnel, L., 4(383), *213*
Carboo, D., 102(264), *210*
Carlson, E. H., 509(161), *517*
Carpenter, B. K., 449(29), 450(29), 489(29), 506(29), *513*
Carrasquillo, 74(161), *206*
Carreira, L. A., 6(71,72), 8(72), *204*
Carrie, R., 28(456,457,458), 48(457), *216*
Carter, R. O., 6(71), *204*
Casey, M., 283(101), *436*
Castaigne, S. A., 17(73), *204*
Catalan, J., 6(74), 7(74), *204*
Cavalla, J. F., 33(37), 34(37), *203*
Chain, E. B., 219(2), *433*
Chambers, R., 234(31), 235(33,34), *434*
Chambers, R. D., 104(80), 105(79), 106(78), 107(77), *203, 204*
Chandrasekhar, S., 554(40), *585*
Chang, C.-C., 597(48), *614*
Chapman, O. L., 391(238,239), *440*, 448(25), *513*, 597(48), *614*
Charrier, J., 29(81), *204*
Chasle, M. F., 419(276), *441*
Chatterjee, B. G., 394(244), 397(245,246), 398(248), 400(250,251), *440*
Chatterjee, S. S., 18(83), 38(83), 52(82), 57(82), 58(82), *204*
Chawla, H. P. S., 253(68), 254(68), 263(84), 264(84,85), *435, 436*
Chedekel, M. R., 78(278), *210*, 597(48), *614*
Chen, P.-T., 45(85), 46(85), 49(85), 55(85), 56(85), *204*
Chen, T.-Y., 16(89), 30(88), 35(84,86), 36(86), 45(85,88), 46(85), 48(88), 49(85),

Chen, T.-Y. (*Continued*) 53(89), 55(85,87), 56(85,89), 57(88), *204*
Chen, W. Y., 554(41), *585*
Chiang, W., 87(483), *217*
Chib, J. S., 253(68), 254(68), *435*
Chiba, K., 358(215), *439*
Chidester, C. G., 12(421), *215*
Chien, D. H. T., 603(73), *614*
Chinone, A., 43(299), 45(300), 46(300), 48(299), 49(299), *211*, 488(142), 506(142), *516*
Chishti, N. H., 594(30), *613*
Chkheidze, I. I., 9(447), *216*
Chmielewicz, Z. F., 561(64), *586*
Choudhury, R., 400(252), *440*
Chodowska-Palicka, J., 410(264), *440*
Christensen, B. G., 271(96), 273(92,93,94), 275(92,94), 278(95,96), 279(96), 280(97,98), 323(165), *436*, *438*
Christiani, G. F., 34(435,441), 35(435), 37(435,441), 38(441), 39(435,441), *215*
Christie, M., 371(229), 372(230), 378(229), *440*
Chu, D., 283(101), *436*
Chung, S. K., 385(234), *440*
Church, R. F. R., 549(9,10), *584*, 588(3,4), 590(4,21,22), 591(23,24), 603(21), 604(3,4,21), *612*, *613*
Cignarella, G., 339(194), *439*
Cladel, N. M., 3(324b), 11(324b), 12(324b), 14(324b), 15(324b), 16(324b), 67(324b), 81(324b), *212*
Clark, J., 9(90), *204*
Clark, P., 12(308), *211*
Clark, P. A., 5(91), *204*
Clarke, H. T., 226(20), *434*
Clasen, R. A., 21(92), *204*, 470(76), 493(76), *514*
Clauss, K., 313(157), 314(157,159), 315(160), 317(160), *438*
Clemens, D. H., 457(41), *513*
Clement, R. A., 448(24), *513*
Closs, G. L., 473(87,88), 506(88), *514*
Clough, S. C., 414(267,268), *441*
Coegelman, R. T., 221(5), *433*
Coffman, D. D., 470(75), *514*
Coker, M. E., 467(71), 468(71), 492(71), *514*
Cole, M., 221(6), *433*
Colens, A., 240(45), *435*
Colonna, M., 460(56), 478(110), 478(111), *515*, 555(45), 555(45), *586*
Consonni, P., 44(364,365), 90(363), 91(363), *213*
Conti, G., 3(63), 4(63,64), *203*
Cook, A. H., 459(48), 492(48), 498(48), *514*
Cooper, R. D. G., 378(231), 380(231,232,233), 385(233), *440*
Corey, E. J., 226(15), 240(47), 249(61), 329(15), *434*, *435*
Corwin, L. M., 78(179), *207*
Cosa, J. J., 495(147), *516*
Coscia, A. T., 18(382), *213*
Coulombre, A. J., 78(95), *204*
Coulombre, J. L., 78(95), *204*
Courault, K., 528(72), *544*
Cramer, R. D., 446(14), *513*
Crawford, W. C., 306(153), 308(153), 309(153), 385(153), *438*
Creegan, F. J., 62(332), *212*
Cristiani, C., 35(33), *203*
Cristiani, G. F., 33(41), *203*, 339(194), 340(197), 364(224,225), *439*
Crockett, G. C., 25(251), *209*
Cromwell, N. H., 3(97), 6(209,211), 18(209), 20(96,114,118,119,227,266,282,375,376,377, 380,407), 38(361,376,380), 45(379), 46(379), 47(361,375,377,380), 48(361,379,380), 49(361,375,376,378,379), 51(361), 52(209), 53(207,210), 54(206,207), 56(210,211,376), *205*, *208*, *210*, *213*, *214*
Crooks, C. R., 65(98), *205*
Crowdle, J. H., 540(116), *545*
Cuingnet, E., 354(208), *439*
Culp, F. B., 57(338), 59(99,338), *205*, *212*
Cunningham, M. P., 283(101), *436*
Currie, J. D., 84(195), *208*
Curtin, D. Y., 459(52), 480(118), 495(118), *514*, *515*
Curtius, T., 444(1), *512*

Daemmgen, U., 43(51), *203*
Dall'-Asta, L., 30(100), 34(360), 37(100), *205*, *213*
Danen, W. C., 9(101), *205*
Danion, D., 28(457,458), 48(457), *216*
Danion-Bougot, R., 28(457,458), 48(457), *216*
Danisi, F., 32(303), *211*
Dardoize, F., 352(205), 354(210), *439*
Date, T., 89(216), *208*, 430(296), *441*
Davis, B. A., 242(54), *435*
Davis, C. S., 553(33), 559(33), 573(33), *585*
Davis, G. E., 78(278), *210*
Dayal, B., 253(68), 254(68), 263(84), 264(84,85), 267(86), 268(86,87), *435*, *436*
Deady, L. W., 15(102,103), 36(102), *205*
DeBoer, C. D., 594(34), 603(34), *613*
Degli Angeli, A., 34(360), *213*

De Graff, S. A. G., 6(445), *215*
Dehm, P., 78(270), *210*
Dehmlow, E. V., 571(92,93), *587*
Dehmlow, S. S., 571(93), *587*
Della Torre, A., 41(305), 55(305), 56(305), *211*
Del'tsova, D. P., 23(104), 97(105), *205*, 521(17), *542*
Delvgeard, Y., 534(102), *544*
Delyagina, N. I., 23(106), *205*
Denis, J. M., 82(184), *207*
de Ochoa, O. E., 415(270), *441*
DePerez, C., 97(163), *206*
DeRango, C., 237(39), *434*
Dergunov, Y. I., 527(65,67,68), *543*
Derkach, G. I., 521(21), 525(41), 533(98), *542*, *543*, *544*
DeSchryver, F. C., 470(79), *514*
Desphande, S. M., 353(207), *439*
DeTar, D. F., 15(107), *205*
Dev, V., 473(88), 506(88), *514*
Devaquet, A., 472(83), *514*
DeVries, L., 100(108), *205*
DeVries, M. J., 603(76), *614*
Dewar, M. J. S., 103(109), 106(110), *205*
de Wit, A. D., 85(111), *205*
Dey, P. M., 353(207), *439*
Deyrup, J. A., 30(113), *205*, 414(267,268), 476(101), *515*
Dickert, J. J., Jr., 518(9), *542*
Dietrich, R., 465(66), *514*
Ding, L. K., 244(56), *435*
Dingwall, J. G., 104(30,199), 105(30), *202*, *208*
Dipol, J., 551(26), *585*
Dobrev, A., 334(188,189), *438*
Dolbier, W. R., Jr., 472(85,86), 496(86), 506(86), *514*
Dolfini, J. E., 332(183), *438*
Dolge, P., 551(20), 553(20), 559(20), 568(20), *585*
Dollen, L. V., 13(476), 69(476), *216*
Dombi, G., 11(178), 17(178), *207*
Domelsmith, L. S., 511(166), *517*
Dominianni, S. J., 448(25), *513*
Donoghue, E. M., 448(21,23), *513*
Doomes, E., 6(211), 20(96,114,227), 56(211), *205*, *208*
Dorfman, L., 448(21,23), *513*
Dorn, H., 561(73), 562(76), *586*
Dorofeeva, O. V., 7(95,298), *204*, *211*
Doroshenko, V. A., 16(297), *211*
Dorsey, E. D., 228(22), *434*
Douglas, A. P., 564(79), *587*
Douglas, J. L., 283(101), *436*
Doyle, T., 283(101), *436*
Dubov, S. S., 477(106), 478(106), 495(106), 505(158), 506(158), *515*, *516*
Dudinskaya, A. A., 549(8), 553(8), 559(8,59), 573(59), *584*, *586*
Duhamel, L., 47(115,116), *205*
Duhamel, P., 47(115,116), *205*
Duncan, W., 234(32), *434*
Dunstan, B. T., 81(39), *203*
Dupuy, A. E., 418(274), *441*
Duran, F., 229(23), *434*
Durand, D. A., 6(281), 37(281), 63(281), 66(281), *210*
Durig, J. R., 6(71), *204*
Durst, T., 310(156), *438*
Dyatkin, B. L., 23(106), *205*, 552(29), *585*
Dybvig, D. H., 595(37), 603(37), 604(37), *613*

Eagen, M. C., 20(118,119,282), *205*, *210*
Earle, R. H., 340(196), *439*, 595(43), *613*
Eastes, J. W., 5(241), *209*
Eastman, D., 594(35), 598(35), 599(35), *613*
Eberbach, W., 511(167), *517*
Ebnöther, A., 15(121), *205*
Ebsworth, E. A. V., 477(103), 506(103), *515*
Eby, J. M., 62(122), *205*
Edie, R., 601(63), *614*
Edwards, B., 237(37), *434*
Edwards, J. A., 233(29), 234(29), 242(51), 249(29), 286(106), 292(106), *434*, *435*, *436*
Edwards, W. B., 17(397), 34(397), 38(397), *214*
Effenberger, F., 24(123), 95(123), *205*, 304(149,150), 317(162), 320(163), *438*, 457(39,40,42), *513*
Ege, G., 101(124), *205*
Ege, S. N., 424(285), *441*
Eggli, D. F., 54(206), *208*
Eichenhofer, K. W., 552(27), *585*
Eicher, T., 464(65), *514*
Eisenhardt, W., 21(353), *212*
Elberling, J. A., 47(339), 49(339), 51(339), *212*
Elgavi, A., 240(44), *435*
El-Hamamy, A. A., 21(5,203), *202*, *208*
El-Namaky, H. M., 15(125,166,168), 73(166,168), *205*, *207*
Eloy, F., 17(146), 55(146), 56(146), 65(146), *206*

Emeleus, H., 477(8), 495(8), *513*
Emori, T., 49(481), *217*
Enders, D., 40(398), 46(398), *214*
Engel, P. S., 494(146), *516*
Engelbrecht, W. J., 603(76), *614*
Engelhard, N., 459(53), 492(53), 498(53), 501(53), *514*
Englin, M. A., 446(16), 490(16), 495(148,150), *513, 516*
Entenmann, G., 529(79), *544*
Erba, C., 41(305), 55(305), 56(305), *211*
Eremina, E. I., 62(459), *216*
Ermakov, A. I., 20(260), 47(260), *210*
Erykalova, M. F., 22(271), *210*
Espie, J. C., 42(126), 44(126), 62(127), *205*
Evans, W. B. L., 551(21), 553(21), 561(21), 573(21), *585*, 589(13), 599(13), 600(13), 602(13), 603(13), 604(13), *613*
Evnin, A. B., 484(135), 505(135), *516*

Fagerburg, D. R., 56(6), *202*
Fahey, J. L., 253(65), *435*
Fahr, E., 461(59), 463(62), 478(114), 500(153), 501(62), 503(154), 506(59,62), 508(62,160), 509(160), *514, 515, 516, 517*, 520(15), 531(15), *542*
Faris, B., 78(31), *203*
Farnum, D. G., 603(83), *614*
Farrissey, W. J., 526(61), 536(61), 539(61), *543*
Fattorusso, E., 78(228), *209*
Fedor, L. R., 4(131), 5(131), *206*
Fehn, J., 90(56), *203*
Ferrari, C. F., 283(101), *436*
Feucaud, M. A., 419(276), *441*
Filatov, A. S., 446(16), 490(16,144), 495(148,150), 500(144), *513, 516*
Firestone, R. A., 273(92), 275(92), *436*
Firl, J., 446(10,12,13), 448(10), 451(10,12,13), 452(10), 454(12,36), 455(13), 497(13), 498(13,36), 510(36), *513*
Firth, W. C., 557(50), *586*
Fischer, A., 16(133), 36(133), 39(132), *206*, 530(86), *544*
Fischer, M., 100(134,135), *206*
Fischer, P., 317(162), 320(163), *438*, 526(62), 535(62), *543*
Fischer, W., 461(59), 463(62), 500(153), 501(62), 503(154), 506(59,62), 508(62), *514, 516*
Fitton, A. O., 242(49), *435*
Fleiter, R., 304(149,150), *437*
Fleming, A., 219(1), *433*
Florey, H. W., 219(2), *433*
Florey, M. E., 219(2), *433*
Florin, E., 410(263), *440*
Flowers, W. T., 530(84), *544*
Fodor, G., 15(136), 67(136), *206*
Fomochev, A. A., 6(137), *206*
Fontanella, L., 33(429,430,433,437,438), 34(429,430,433,435,441), 35(435,439), 37(435,441), 38(441), 39(430,435,441), 40(429), 63(430), 64(432), 65(429,431,433), *215*, 339(195), *439*
Ford, G. P., 103(109), *205*
Formica, J. V., 79(13), *202*
Foucaud, A., 29(81), *204*, 419(276), *441*
Fowble, J., 38(310), 55(310), *211*
Fowden, L., 49(139), 50(139), 77(140), 78(138,141,142,412,413), *206, 214*
Fowler, F. W., 27(143), 63(42), *203, 206*, 472(84), *514*
Franich, R. A., 595(41), 596(41), 602(41), *613*
Frank, S., 595(39), *613*
Franklin, R., 530(84), *544*
Franzblau, C., 78(31,179), *203, 207*
Fraser, P. S., 47(339), 49(339), 51(339,340), *212*
Fredrich, A., 521(19), *542*
Freeman, J. P., 14(144), 17(145), 38(145), 39(145), 40(53,54), 41(145), 92(145), *203, 206*
Freer, A. A., 109(67), *204*
Freer, P. C., 480(117), *515*
Frehel, D., 17(146), 55(146), 56(146), 65(146), *206*
Frentzel, W., 524(34), *542*
Frey, H. M., 589(12), 590(16), 603(12,16,74,75,87), 604(12,87,96), *612, 613, 614, 615*
Freyermuth, H. B., 525(39), 533(94), 540(115), *543, 545*
Fried, J. H., 286(106), 292(106), *436*
Friedrich, H. J., 320(164), *438*
Fritchie, C. J., Jr., 483(131), *516*
Frost, J. R., 242(49), *435*
Fry, A. J., 621(10), *625*
Fuchs, J. J., 590(20), *613*
Fuhr, K. H., 302(147), 303(147), *437*
Fujii, T., 16(313), 38(313), 48(313), 50(313), *211*
Fukomoto, F., 260(77), 261(77), *435*
Fuks, R., 95(147), *206*
Funayama, S., 79(230), *209*
Funke, W., 56(149), *206*
Furey, R. L., 470(80), *514*, 520(16), *542*
Furrer, H., 89(150), *206*

Furuta, T., 554(39), *585*
Fu-Taichen, A., 449(28), *513*

Gaertner, V. R., 15(153), 17(152,155,156), 18(152,153), 53(152,154,158), 54(158), 55(154), 56(154), 65(151), 66(153,157), *206*
Gagnon, John G., 595(38), *613*
Gai, B. J., 19(159), *206*
Gaillard, R. A., 35(236), *209*
Gale, D. M., 599(56), 603(56), *614*
Gallarate, V., 41(305), 55(305), 56(305), *211*
Galle, J. E., 82(198), 83(198), *208*
Gallegos, E. J., 8(160), *206*
Galperin, V. A., 527(65), *543*
Gambaryan, N. P., 23(104,487), 24(486), 97(105), *205, 217,* 359(217,218,219,220), *439,* 521(17,18), 536(18), *542,* 597(53), 599(53), *614*
Gardner, R. J., 557(49), *586*
Gassman, P. G., 74(161), *206,* 489(143), *516*
Gatti, E., 33(41), 34(426), *203, 215*
Gaudemar, M., 352(205), 354(210), *439*
Gaule, A., 555(45), 556(45), *586*
Gaylord, N. G., 540(116), *545*
Gehlen, H., 525(40), 538(40), *543*
Gelhaus, J., 458(46), *513*
Gella, I. M., 6(137), 8(259), 9(259), 81(258), *206, 209, 210*
Georgian, V., 237(37), *434*
Gerega, V. F., 527(67,68), *543*
Gerlock, J. L., 477(104), 495(149), 511(149), *515, 516*
Ghosez, L., 91(295), 97(163), *206, 211,* 229(23), 240(45), *434, 435*
Ghosh-Mazumdar, B. N., 395(243), *440*
Gilbert, K. E., 481(122), 491(122), 494(122), 506(122), 511(165), *515*
Giles, R. G. F., 77(68), *204*
Gilmore, C. J., 109(67), *204*
Ginsburg, V. A., 477(106), 478(106), 495(106), *515*
Girman, H., 346(202), *439*
Giulbault, L. J., 453(35), *513*
Glasbey, T. O., 107(163), *206*
Glaze, A., 564(79), *587*
Glazer, E., 416(271,272), *441*
Gleason, J. G., 280(99,100), 283(100), 293(100), *436*
Gleiter, R., 457(42), *513*
Glidewell, C., 43(164), *206*
Goebel, P., 314(159), *438*
Goehausen, H. J., 40(288), *210*
Goethals, E. J., 5(165), 68(28,165,391,392, 393), *202, 207, 214*
Gogte, V. N., 14(167), 15(166,168,444), 73(166,168,444), *207, 215*
Gold, E. H., 20(173,175), 21(169,170), 34(170,171), 37(170), 38(174), 46(175), 47(173,175), 49(175), 52(170), 57(170), 58(170), *207*
Gompper, R., 107(177,403), *207, 214,* 537(106), *545*
Gondos, G., 11(178), 17(178), *207*
Goodman, L., 550(15), 573(15), *585*
Gordetsov, A. S., 527(65,67,68), *543*
Gorelik, V. P., 65(350), *212*
Gorman, M., 221(4), *433*
Gorrie, T. H., 483(130), *516*
Gottardi, W., 537(54,59), *543*
Graf, R., 304(148), 323(148), *437*
Graham, W. H., 588(9), 592(27,28), 593(9), 594(9,36), 603(27), 604(27), *612, 613*
Grammaticakis, P., 484(133), *516,* 558(53), *586*
Grant, M. M., 78(179), *207*
Grasso, J. A., 78(31), *203*
Grayston, M. W., 603(79), *614*
Grechkin, N. P., 43(180,181,182), *207*
Greene, F. D., 418(273), *441,* 481(122), 491(122), 494(122), 506(122), *515,* 531(87), 532(90), 536(87), *544,* 616(1-6), 618(1,2,7), 619(2), 620(2,9), 622(11), 623(1,2,5), 624(2,4,5,12), 625(1,2,4,5), 626(5), 627(5), *625, 626, 628*
Greenwald, R. B., 483(128,132), 486(128), 501(132), *516*
Greiner, D., 7(95), *204*
Grob, C. A., 11(183), 15(184), 62(183), 66(183), *207*
Gross, A., 461(58), *514*
Groves, J. T., 616(5), 623(5), 624(5), 625(5), *625*
Gruber, G. W., 474(92), *515*
Gruber, R., 21(353), 74(354), 75(355), *212, 213*
Gründemann, C., 551(22), 559(22), 560(22), 561(22,69), 562(22), 566(22), *585, 586,* 590(18), 601(18), 602(18), *613*
Gsponer, H. E., 495(147), *516*
Gubnitskaja, E. S., 525(41), *543*
Guddal, E., 550(14), 573(14), *585*
Guermont, J. P., 49(362), *213*
Guillemin, J. C., 82(184), *207*
Gumenyuk, A. V., 526(47), *543*
Gupta, P. K., 261(78), 268(88,89), 269(88,89), *435, 436*
Gusel'nikov, L. E., 62(459), *216*
Guthikonda, R. N., 280(98), *436*

Gutman, I., 107(185), *207*
Guzman, A., 286(106), 292(106), *436*

Haas, A., 538(57,111), *543, 545*
Haber, S. B., 371(229), 372(230), 378(229), *440*
Habisch, D., 551(22,23), 559(22,23), 560(22,23), 561(22), 562(22), 566(22,81), 567(81), 568(81), 572(81), 573(81), *585, 587*
Haddadin, M. J., 83(196), *208*
Häfliger, F., 487(138), *516*
Hagan, W. V., 30(113), *205*
Häkli, H., 572(97), *587*
Hale, W. J., 517(6), 529(80), *542, 544*
Haley, N. F., 483(130), *516*
Hall, H. K., 65(186), *207*
Hall, J. H., 457(43,44), 459(49), 479(7), 492(49), 493(49), 498(152), 499(152), *512, 513, 514, 516*
Hall, R. F., 280(100), 283(100), 293(100), *436*
Halliwell, P., 109(69), *204*
Hamada, T., 87(483), *217*
Hamelin, J., 28(457,458), 48(457), *216*
Hamill, R. L., 221(4), *433*
Han, S. Y., 523(30), 523(31), *542*
Hanscomb, G., 221(6), *433*
Hansen, H., 39(132), *206*
Hansen, J. F., 90(356), *213*
Harada, K., 394(242), *440*
Hardy, E. E., 540(114), *545*
Hargrove, W. W., 19(188,189,190), 53(189), 57(189), 58(189), *207*
Harkema, S., 85(111,360), *205,213*
Harnisch, J., 82(191), 83(191), *207*
Harris, S., 560(63), 565(63), *586*
Hartke, K., 521(20), *542*
Hartough, H. D., 518(8,9), *542*
Hartzler, H. D., 24(194), 97(192,193), *207, 208*
Hasan, I., 63(42), *203*
Hasegawa, Y., 37(416), 41(416), 42(416), 55(414), *214, 215,* 406(258,259), *440*
Haselbach, E., 511(167), *517*
Hashimoto, M., 5(484), *217,* 293(107), 380(107), *436*
Hashimoto, S., 68(482), 242(55), 244(55), *435*
Hassner, A., 82(197,198), 83(196,197,198), 84(195), 89(11), *202, 208,* 304(148), 317(148), *437,* 445(9), 448(9), 451(9), 456(9), 475(98), 501(9), 506(9), 510(9), *513, 515*
Haszeldine, J., 31(26), 62(26), *202*
Haszeldine, R. N., 31(27), 62(27), 104(30,199), 105(30), *202, 208,* 477(107), *515,* 530(84), *544*
Hata, Y., 65(200), 69(201), *208*
Hatch, C. E., 424(286), *441*
Hatch, C. E. III, 424(287,288), 425(289,290), *441*
Haug, T., 314(158), *438*
Häuser, H., 458(46), *513*
Hausler, J., 425(291), *441*
Hayes, R. A., 494(146), *516*
Heatley, N. G., 219(2), *433*
Heilbronner, E., 511(167), *517*
Heine, H. W., 551(24), 558(54), 559(55,61), 560(24,61,63), 561(24,71), 562(54,61), 564(24,78,79), 565(54,61,63,71), 566(24,54,61), 568(24,54), *585, 586, 587*
Heinrichs, G., 475(95), *515*
Heitz, L., 551(24), 560(24), 561(24), 564(24,78), 566(24), 568(24), *585, 587*
Helfert, H., 520(15), 531(15), *542*
Hendlin, D., 221(4), *433*
Hendrickson, J. B., 14(203), 36(203), *208*
Henery-Logan, K. R., 330(181,182), 331(182), *438*
Henke, D., 553(37), *585*
HengSuen, M., 353(206), *439*
Henn, D., 537(54), 539(54), *543*
Henrich, G., 549(1), 566(1), 568(1), *584*
Henrie, R., 551(24), 560(24), 561(24), 564(24), 566(24), 568(24), *585*
Hernandez, L., 234(30), 235(33,34), *434*
Hernandez, L., Jr., 234(31), *434*
Hernandez, S., 221(4,5), *433*
Hesabi, M. M., 21(203a), *208*
Hesbi, M. M., 21(5a), *202*
Hess, B. A., 107(204,205), *208*
Hess, D., 445(9), 448(9), 451(9), 456(9), 501(9), 506(9), 510(9), *513*
Hess, O., 444(2), *512*
Hesson, D., 371(229), 378(229), *440*
Heymes, A., 17(146), 55(146), 56(146), 65(146), *206*
Heymes, R., 332(184), *438*
Heyn, H., 313(157), 314(157), *438,* 473(88), 506(88), *514*
Higgens, C. E., 221(4), *433*
Higgins, R. H., 6(209,211), 18(209), 20(119), 26(253), 52(209), 53(207,210), 54(206,207), 56(210,211), 82(253), *205, 208, 209*
Hiiragi, M., 239(43), 240(43), *435*
Hill, J., 9(90), 21(5,203,212,213,214), *202, 204, 208*
Hiltmann, R., 35(479), *217*

Hinchliffe, M. D., 559(60), *586*
Hino, J., 68(482), *217*
Hirai, K., 391(237), *440*
Hirai, Y., 89(216), *208*, 430(295,296), *441*
Hiramatsu, Y., 55(414), 65(451), *214*, *216*
Hiramitsu, T., 554(39), *585*
Hirokami, S., 430(295,296), *441*
Hirokami, S-i., 89(216), *208*
Hjort, J., 601(63), *614*
Hlasta, D. J., 386(236), *440*
Hoberg, H., 533(95), *544*
Hoch, J., 6(274), *210*
Hodgkin, D. C., 220(3), *433*
Hodgson, P. K. G., 489(143), *516*
Hoehn, M. M., 221(4), *433*
Hoehne, E., 559(58), *586*
Hoerig, C., 561(69), *586*
Hoffmann, H., 6(401), 58(402), 59(401), *214*
Hoffman, R., 308(154), *438*
Hoffman, R. W., 458(46), 470(74), 497(74), 509(74), *513*, *514*
Hoffman, W. A. III, 253(67), *435*
Hofmann, A. W., 517(3), 522(3), 538(109), *542*, *545*
Hofmann, R., 526(60), *543*
Holden, K. G., 280(99,100), 283(100), 293(100), *436*
Holly, A. D., 226(19), *434*
Holly, R. H., 226(19), *434*
Holton, W. F., 57(326), 59(326), *212*
Holtschmidt, H., 522(26), *542*
Holzapfel, C. W., 425(291), *441*
Hölzer, 517(1), *542*
Holyoke, C. W., 107(205), *208*
Hood, J. D., 221(6), *433*
Hoppe, D., 337(191), *438*
Hoppe, I., 99(217), *208*, 232(28), 233(28), 249(28), *434*
Hõrig, C., 590(18), 601(18,62,64), 602(18), *613*, *614*
Horkema, S., 42(360), 86(360), *213*
Hornby, R. B., 450(30), 472(30), *513*
Horner, L., 461(58), 498(151), 499(151), 501(151), *516*
Hornung, V., 511(167), *517*
Horovitz, D., 479(6), 506(6), *512*
Horrom, B. W., 13(218,219), *208*
Hortmann, A. G., 56(220,221), *208*
Horvitz, D., 39(374), *213*
Hosoda, J., 221(7), *434*
Houghton, P. G., 242(49), *435*
Houk, K. N., 5(316,387), *211*, 511(166), *517*
Howard, K. A., 25(251), *209*
Howard, K. H., 25(254), *209*
Hoye, R. C., 561(71), 565(71), *586*
Hoye, T. R., 558(54), 561(71), 562(54), 565(54,71), 566(54), 568(54), *586*
Huck, G., 566(80), 567(80), 568(80), *587*
Huebner, C. F., 448(21,23), *513*
Huffman, W. F., 280(99,100), 283(100), 293(100), *436*
Huisgen, R., 242(54), *435*, 464(63), 506(63), *514*
Hull, F. Jr., 227(17), 228(17), *434*
Hull, R., 227(18), 228, *434*, 527(66), *543*
Hung, M.-H., 45(85), 46(85), 49(85), 55(85), 56(85), *204*
Hünig, S., 476(99), *515*, 593(29), *613*
Hurst, D. T., 340(196), *439*, 595(43), *613*
Hurst, G. L., 477(8,103), 495(8), 506(103), *513*, *515*
Huseya, Y., 488(142), 506(142), *516*
Hutchinson, C. R., 78(278), *210*
Hutchinson, R. E. J., 15(103), 16(133), 36(133), *205*, *206*
Hutchison, A. J., 253(67), *435*
Hyatt, J. A., 25(223), 26(418), *208*, *215*
Hynes, J. B., 477(102), *515*

Ichikawa, Y., 71(232), 72(232), *209*
Iguchi, E., 221(7), *434*
Ikeda, H., 68(388), *214*
Ikeda, M., 102(225), *208*
Ikoku, C., 482(127), 500(127), *516*
Imanaka, H., 221(7), *434*
Imbach, J.-L., 20(227), *208*
Impellizzeri, G., 78(228), *209*
Inaba, S., 355(211), 357(211,212,213), 358(213), *439*
Ingold, C. K., 459(47), 462(47), 480(47), 498(47), 503(47), *514*, 520(16), *542*
Ingold, K. U., 603(84), *614*
Ip, P. C., 483(129), 485(129,136), 486(129), *516*
Irwin, W. J., 244(56), *435*
Isakova, O. V., 19(228), *209*
Isensee, G., 525(46), *543*
Ishibashi, H., 102(225), *208*
Ishihara, T., 16(313), 38(313), 48(313), 50(313), *211*
Ishitoku, T., 430(297), *441*
Isida, T., 555(43), *585*
Isono, K., 79(229,230), *209*
Ivanov, C., 334(188,189), *438*
Ivanov, N. A., 528(71), *544*
Iwakura, Y., 39(233,234), 71(232,234), 72(232), 73(234), *209*, 550(17), 561(17), 566(17), 573(17), *585*
Iwano, Y., 391(237), *440*

Izumi, A., 65(451), *216*
Izydore, R. A., 556(46), 566(46), *586*
Izzo, P. I., 412(265), *441*

Jackson, M., 221(4), *433*
Jackson, M. B., 8(235), 9(235), *209*
Jacob, R. M., 35(236), *209*
Jaffrain, M., 6(274), *210*
Jahn, U., 487(140), *516*
Jalandoni, C. C., 310(155), *438*
Janssen, E., 518(10), *542*
Janzen, E. G., 477(104), 495(149), 511(149), *516*
Jean, Y., 472(83), *514*
Jelagin, S., 224(13), *434*
Jelinek, A. G., 530(86), *544*
Jen, S. J., 364(247), *440*
Jenkins, H., 19(237), 52(237), 56(67), *204*, *209*
Jennings, B. M., 602(65,68), 603(65), *614*
Jennings, M. A., 219(2), *433*
Jensen, H., 45(311,312), *211*
Johansson, N. G., 402(257), 407(261), 409(262), 410(263), *440*
Johnson, P. Y., 424(286,287,288), 425(289,290), *441*
Johnson, R., 286(106), 292(106), *436*
Johnston, D. B. R., 323(165), *438*
Jomilenko, E. I., 558(52), *586*
Jonas, V., 510(162), *517*
Jones, D. G., 459(48), 492(48), 498(48), *514*
Jones, F. M., 4(239), *209*
Jones, R. H., 468(72), 469(72), *514*, 536(104), *545*
Jones, W. E., 594(30), *613*
Joop, N., 398(249), *440*
Jose, F., 378(231), 380(231,232), *440*
Joullie, M. M., 237(35), *434*
Jucker, E., 15(121), *205*
Jung, A., 463(62), 501(62), 506(62), 508(62), *514*
Jung, M. E., 597(48), *614*
Just, G., 283(102,103,104), 286(104), *436*
Just, M., 525(40), 538(40), *543*

Kabbe, H. J., 398(249), *440*
Kaczmar, M. W., 465(70), 504(70), 505(70), *514*
Kagan, H. B., 237(38,39,40,41), 238(38), 346(203), 349(204), 353(206), *434*, *439*
Kagan, H. M., 78(31), *203*
Kahan, F. M., 221(5), *433*
Kahan, J. S., 221(5), *433*
Kahr, E., 464(64), *514*
Kaji, K., 553(38), *585*
Kakihana, T., 33(357), 90(356), 92(357), 108(357), *213*
Kametani, T., 239(43), 240(43), 260(77), 261(77), *435*
Kaminsky, L. S., 32(240), *209*
Kamiya, T., 293(107), 380(107), *436*
Kamlet, M. J., 5(241), *209*
Kan, R. O., 470(80), *514*, 520(16), *542*
Kane, M. P., 12(421a), *215*
Kaneko, T., 17(347), 18(347), 34(347), 53(347), 55(347), 56(347), *212*
Kao, F.-T., 78(367), *213*
Kapoor, A. L., 354(209), *439*
Kapur, J. C., 253(66), 260(75), 267(86), 268(86,87), *435*, *436*
Karnischky, L. A., 484(135), 505(135), *516*
Kartsev, V. V., 19(228), *209*
Kashima, C., 22(242), *209*
Kato, H., 16(89), 30(88), 35(86), 36(86), 45(88), 48(88), 53(89), 55(87), 56(89), 57(88), 65(89), *204*, 590(19), *613*
Katritzki, A. R., 478(113), *515*
Kauer, J. C., 446(15), 494(15), *513*
Kausch, E., 533(96), *544*
Kawamura, M., 553(38), *585*
Kawanisi, M., 555(43), *585*
Kawasaki, T., 569(87), *587*
Kealy, T. J., 448(24), *513*
Keating, K., 109(3), *202*
Keating, M., 109(1,2), *202*
Keefer, L., 51(284), *210*
Keifer, G., 317(162), *438*
Keifer, L., 494(146), *516*
Kellog, R., 459(49), 492(49), 493(49), *514*
Kelly, J. F., 33(357,358), 73(358), 92(357), 108(357), *213*, 305(152), *438*
Kende, A. S., 549(9), *584*
Kensler, T. T., 9(101), *205*
Keogh, J., 445(9), 448(9), 451(9), 456(9), 501(9), 506(9), 510(9), *513*
Kerber, R. C., 459(50,51), 461(50), 462(50), 463(50), 468(50,51), 492(50), 493(50), 506(50), *514*
Kerwsin, J. F., Jr., 385(235), 386(235), *440*
Keschmann, E., 39(243), *209*
Kessel, C. R., 476(100), 510(100), 511(100), *515*
Ketschmer, G., 95(467), *216*
Keute, J. S., 25(12,251), *202*, *209*
Khafizov, Kh., 8(259), 9(259), 20(260), 47(260), 81(258), *209*, *210*
Khamitov, R. N., 43(181,182), *207*
Khmelnitski, L. I., 549(8), 553(8), 559(8,59), 573(59), *584*, *486*

Kiefer, G., 457(42), *513*
Kigosawa, K., 239(43), 240(43), *435*
Kiguchi, T., 554(42), *585*
Kim, B., 87(483), *217*, 445(9), 448(9,22), 451(9,22), 456(9), 501(9), 506(9), 510(9), *513*
Kim, L., 624(12), *626*
Kimura, Y., 68(387,388), *214*
Kinoshita, S., 49(481), *217*
Kinugasa, M., 242(55), 244(55), *435*
Kirk, K. L., 4(131), 5(131), *205*
Kirsanova, N. A., 533(98), *544*
Kirste, K., 5(244), 39(245), 41(244,245), *209*
Kisch, H., 600(61), *614*
Kiser, R. W., 8(160), *206*
Kishi, Y., 366(227), 367(227), 369(227), 370(228), 371(228), *440*
Kitamura, T., 555(43), *585*
Kitaura, Y., 102(246), *209*
Klar, G., 503(155), *516*
Kleinberg, G., 224(12), 264(12), *434*
Klever, H. W., 223(9,10), 302(9), 329(180), *434*, *438*
Klimenko, O. I., 16(297), *211*
Klindukhova, T. K., 561(72), 562(74), 565(72), *586*
Klonowski, R. S., 14(455), 17(455), 37(455), 38(455), *216*
Kluge, A. F., 233(29), 234(29), 242(51), 249(29), *434*, *435*
Knapp, D. R., 424(281), 424(282), *441*
Knipe, A. C., 15(36), *203*
Knoth, W. H., 470(75), *514*
Knowles, J. R., 589(14,15), 592(15), 602(14,15), 604(15), *613*
Knunyants, I. L., 23(106,487), 24(486), *205*, *217*, 359(217,218,219,220), *439*, 521(17), *542*, 552(29), *585*, 597(53), 599(53), *614*
Kobayashi, S., 68(387,388), *214*
Kobayashi, Y., 106(247), *209*
Kober, P., 223(10), 329(180), *434*, *438*
Kobor, J., 15(249), 64(248), *209*
Koch, J., 302(146), *437*
Koch, T. A., 88(252), *209*
Koch, T. H., 25(12,251,254,255), 26(253,381), 82(253), *202*, *209*, *213*
Kodama, T., 550(17), 561(17), 566(17), 573(17), *585*
Koenig, K. H., 530(86), *544*
Koeppe, H., 65(256), *209*
Koerner von Gustorf, E., 445(9), 448(9,22), 451(9,22), 456(9), 501(9), 506(9), 510(9), *513*
Koft, E., 518(8), *542*
Kohsaka, M., 221(7), *434*
Kolb, B., 510(162), *517*
Kolb, R., 529(81), *544*
Kole, J., 597(48), *614*
Kolshorn, H., 100(257), *209*
Komatsu, M., 569(88,89,90), 570(89), *587*, 624(13), *626*
Kondrat'eva, K. A., 22(271), *210*
Konomi, T., 221(7), *433*
Koopmann, H., 511(164), *517*
Koppel, G. A., 378(231), 380(231,232,233), 385(233), *440*
Korff, J., 533(95), *544*
Korger, G., 39(24), *202*
Koroleva, L. B., 569(85), 571(95), 572(96), *587*, 597(49,51), *614*
Koshar, R. J., 595(37), 603(37), 604(37), *613*
Kostyanovskii, R. G., 6(137), 8(259), 9(259), 15(389), 20(260), 23(389), 41(261), 47(260), 81(258), *206*, *209*, *210*, *214*, 552(28), 561(66,68), 572(28,68,98,99), *585*, *586*
Koul, V. K., 28(338), *212*
Kovvali, S. R., 551(24), 560(24), 561(24), 564(24), 566(24), 568(24), *585*
Koyama, H., 562(77), 566(77), *587*
Kozhushko, B. N., 526(47), *543*
Kozlov, N. S., 528(71), *544*
Kraatz, U., 529(78), *544*
Kraemer, R., 465(67), *514*
Krapf, H., 475(95), *515*
Krapivin, A. M., 43(419), *215*
Krasnobajew, V., 11(183), 62(183), 66(183), *207*
Krawczyk, Z., 247(57,58), 248(57,58), *435*
Kreeger, R. L., 597(48), *614*
Kremlev, M. M., 533(98), *544*
Krespan, C. G., 555(44), *585*, 599(56), 603(56), *614*
Kresze, G., 224(14), *434*
Kretscher, G., 240(48), 241(48), *435*
Kreymborg, J. H., 54(206), *208*
Krishan, K., 242(50), *435*
Krishnamachari, N., 485(136), *516*
Kristensen, I., 50(262), 78(262,263), *210*
Kristinsson, H., 400(253), *440*
Krohn, K., 102(264), *210*
Krohn, W., 98(478), *216*
Kroneberg, G., 35(479), *217*
Kruse, L. I., 372(230), *440*
Kubo, Y., 430(297), *441*
Kubochi, Y., 221(7), *434*
Kugajevsky, I., 227(21), *434*
Kuhn, N., 524(37), 534(37), *543*
Kulkarni, S. B., 14(167), 15(167), 20(266,282), *207*, *210*
Kumadaki, I., 106(247), *209*

Kummer, W., 65(256), *209*
Kunert, D., 234(31), 235(33), *434*
Kunz, W., 400(253), *440*
Kurita, J., 475(97), *515*, 554(42), *585*
Kurita, K., 59(99), *205*
Kurtev, B., 334(187), 341(199), *438*, *439*
Kurz, J., 228(22), *434*
Kutz, M., 525(43), *543*
Kuzuya, M., 554(39), *585*

LaBerge, J. M., 551(25), *585*
Lablache-Combier, A., 82(184), *207*
Lacadie, J. A., 385(234), *440*
Lagerlund, I., 410(263,264), *440*
Laguchcva, E. S., 518(7), *542*
Lahiri, S. K., 400(250), *440*
Lal, B., 260(76), *435*
Lambert, J. B., 6(268,269), *210*
Lamchen, M., 32(240), *209*
Landis, M. E., 478(109), 479(115), 489(115), 494(145), 508(115), 510(115), 511(115), *515*, *516*
Lane, J. M., 78(270), *210*
Lang, K. L., 11(178), 17(178), *207*
Lange, N. A., 529(80), *544*
Lapshin, N. M., 22(271), *210*
Larsen, P. O., 50(262), 78(262,263), *210*
Latajka, Z., 103(272), *210*
Lattrell, R., 317(161), *438*
Lau, A., 599(58), 603(86), 604(129), *614*, *615*
Laubach, G. D., 249(61,62), *435*
Lauria, F., 41(305), 55(305), 56(305), *211*
Laurina, L. G., 12(421), *215*
Lazilotti, A. E., 550(15), 573(15), *585*
Leary, G. J., 5(273), 15(102), 36(102), *205*
Le Brumant, J., 6(274), *210*
LeClef, B., 240(44), *435*
Ledina, L. E., 43(341,419), *212*
Lee, D. Y., 523(30,31), *542*
Lee, K. Y., 40(285), *210*
Lee, R. E., 13(472), 216, 269(90), *436*
Leete, E., 78(276,277,278), *210*
Lehman, L. S., 560(63), 564(79), 565(63), *586*, *587*
Lehn, J. M., 6(279,280), *210*
Leigh, W. J., 473(89), *514*
Leitich, J., 445(9), 448(9), 451(9), 456(9), 501(9), 506(9), 510(9), *513*
Lemal, D. M., 478(108), 489(108), 494(108), 511(167), *515*, 603(79), *614*
Leonard, N. J., 6(281), 37(281), 63(281), 66(281), *210*
Lepori, L., 3(63), 4(63,64), *203*
Lesuisse, D., 91(295), *211*
Leung, H.-K., 20(282), *210*
Levenberg, B., 78(411), *214*
Levin, A. A., 39(373), *213*
Levin, S. G., 76(466), *216*
Levy, A. B., 82(197,198), 83(196,197,198), *208*
Lewis, B. A., 591(25), 604(25), *613*
Li, J. C. W., 600(59), *614*
Lijinsky, W., 40(285,286), 51(284), *210*
Lik'yanov, O. A., 65(350), *212*
Lim, G., 283(101), *436*
Linke, K. H., 40(288), *210*
Lippert, E., 5(289,291), 6(290), *210*, *211*
Lipshutz, B. H., 20(470), 49(470), 52(468,469,470), *216*, 431(298,299,300), *441*
Lipsky, J. A., 478(108), 489(108), 494(108), *515*
Liu, M. T. H., 588(10), 594(30), 600(59,60), 602(65,68,69,70), 603(65,69,71,72,73,75, 77,80), *614*
Liv, T., 332(186), *438*
Lockhart, I. M., 33(37), 34(37), *203*
Lohse, C., 88(292), *211*
Lohse, F., 314(158), *438*
Lok, R., 18(7), 38(7), 53(7), 55(7), 56(6,7), *202*
Loo, J., 51(284), *210*
Lookwood, W. H., 522(27), *542*
Lora-Tamayo, M., 448(26), 497(26), *513*
Lord, R. C., 6(72), 8(72), *204*
Lowe, G., 401(255), 402(256), 419(277), 421(277,278,279), *440*, *441*, 595(40,41,42), 596(41), 602(41), *613*
Lowe, J. A., 597(48), *614*
Lown, J. W., 570(91), *587*
Lozinskii, M. O., 534(99,100), *544*
Luche, J., 237(38,39,40,41), 238(38), 346(203), 349(204), *434*, *439*
Luettke, W., 39(245), 41(245), *209*
Luh, B. Y., 283(101), *436*
Lyon, J. M., 523(29), *542*
Lysenko, Z., 237(35), *434*

McBrady, J. J., 595(38), *613*
McCallum, K. S., 40(54), *203*
McCullagh, L., 100(61), *203*
McElhinney, R. S., 14(455), 17(455), 37(455), 38(455), *216*
McEntire, E. E., 82(198), 83(198), *208*
McEwan, R., 474(93), *515*
McGandy, E. L., 37(304), *211*
McGann, P. E., 616(5), 623(5), 624(5), 625(5), *625*

McGillivray, G., 17(475), 38(475), *216*
Maciegewicz, N. S., 273(92), 275(92), *436*
Maciel, G. E., 6(293), 38(293), *211*
McIver, R. T., 5(16), *202*
McKean, D. R., 424(281), *441*
McLean, S., 556(46), 566(46), *586*
McLoughlin, V. C. R., 477(102), *515*
McShane, L., 378(231), 380(231,232), *440*
Madan, P. B., 554(41), *585*
Madhauarao, M., 358(214), *439*
Madoux, D. C., 494(145), *516*
Maeda, Y., 603(84), *614*
Maffii, G., 3(442), 14(442), 33(437), 34(442), 35(442), 64(442), *215*
Maffrand, J. P., 17(146), 55(146), 56(146), 65(146), *206*
Magno, S., 78(228), *209*
Maier, G., 104(294), *211*
Maier, R., 24(123), 95(123), *205*, 457(40), *513*
Majeste, R. J., 616(5), 623(5), 624(5), 625(5), *625*
Makarov, K. N., 552(29), *585*
Makarov, S. P., 446(17), 490(17,144), 500(144), *513*, *516*
Maki, Y., 553(38), 554(39), *585*
Maleike, R. R., 588(3), 604(3), *612*
Mallory, D., 551(25), *585*
Mangiafico, S., 78(228), *209*
Manhas, M. S., 229(24), 251(63), 253(64,65,66,67,68), 254(68,69), 255(69), 256(70,71), 257(69,71), 258(69,70,71), 260(69,75,76), 261(81,82), 264(85), 267(86), 268(86,87), 271(91), 272(63), 361(222), 364(247), 394(243), *434*, *435*, *436*, *439*, *440*
Manley, P. W., 107(163), 109(69), *204*, *206*
Mannschreck, A., 463(62), 501(62), 506(62), 508(62,160), 509(160), 510(162), *514*, *517*, 561(67), 572(67,97), *586*, *587*
Manz, F., 29(57), 90(55), *203*
Marascia, F. J., 59(327), 62(332), *212*
Marchand-Brynaert, J., 91(295), *211*
Margerison, R., 448(21), *513*
Mariani, L., 33(438), 34(435,441), 35(435,439), 37(435), 38(441), 39(435,441), 64(438), *215*, 363(223), *439*
Markert, J., 478(114), *515*
Markov, V. I., 6(137), 8(259), 9(259), 16(297), 20(260), 41(261), 47(260), *206*, *210*, *211*, 552(28), 561(68), 572(28,68), *585*, *586*
Markovskij, L. N., 533(97), *544*
Marten, D. F., 358(214), *439*
Martens, F., 559(55), *586*
Martin, J. C., 590(17), 604(17), *613*
Martin, K. J., 40(53), *203*
Martynova, L. L., 477(106), 478(106), 495(106), *515*
Maruyama, K., 430(297), *441*
Maslakiewicz, J. R., 106(78), 107(77), *203*, *204*
Maslen, E. N., 220(3), *433*
Mastryukov, V. S., 7(95,298), *204*, *211*
Masuda, K., 17(347), 18(347), 34(347), 43(299), 45(300), 46(300), 48(299), 49(299), 52(337), 53(347), 54(348), 55(347), 56(347), 57(347), 58(337), *211*, *212*
Mata, J. M., 221(4), *433*
Matiskella, J. D., 3(324), 11(324), 12(324), 14(324), 15(324), 16(324), 67(324), 81(324), *212*
Matsugashita, S., 102(225), *208*
Matsui, K., 341(200), *439*
Matsuura, T., 102(246), *209*
Matthews, V., 31(27), 62(27), *202*
Mattingly, P. C., 385(235), 386(235), *440*
Mazumdar, B. N. G., 397(245), *440*
Mazzocchi, P. H., 17(336), 32(302,303), 34(336), 38(336), 74(302), *211*, *212*, 304(151), *438*
Medeiros, R. W., 59(327), 62(332), *212*
Medvedev, A. N., 477(106), 478(106), 495(106), *515*
Meier, H., 100(257), *209*, 596(45,46), *613*
Meinwald, J., 4(131), 5(131), *206*
Meisel, S. L., 518(8), *542*
Meisert, E., 538(48), *543*
Melillo, D. G., 332(186), *438*
Melloni, P., 41(305), 55(305), 56(305), *211*
Melton, T., 12(308), *211*
Menard, M., 283(101), *436*
Mercer, F., 234(31), 235(33), 365(226), *434*, *439*
Metzger, C., 228(22), *434*
Metzger, K., 314(158), *438*
Meyers, A. I., 15(307), *211*
Middleton, R., 104(80), 105(79), *204*
Middleton, W. J., 555(44), *585*, 599(56), 603(56), *614*
Miller, A. K., 221(4), *433*
Miller, D., 12(308), *211*
Miller, D. D., 38(310), 55(310), *211*
Miller, J., 559(60), 561(70), *586*
Miller, M. J., 385(235), 386(235), *440*
Miller, T. W., 221(4), *433*
Millward, B. B., 14(455), 17(455), 37(455), 38(455), *216*
Milun, M., 107(185), *207*

Min, T. J., 523(30), *542*
Minasyan, R. B., 24(486), *217*, 597(53), 599(53), *614*
Minesinger, R. R., 5(241), *209*
Mishchenko, A. I., 552(28), 572(28), *585*
Mitchell, J. C., 478(109), 494(145), *515*, *516*
Mitote, T., 413(266), *441*
Mitsch, R. A., 558(51), 588(8,11), 594(11), 595(11,37), 599(55), *586*, 603(8,37,81,82), 604(8,37), *612*, *613*
Mittelback, H., 261(79), *436*
Mitzlaff, M., 45(311,312), *211*
Miura, I., 237(35), *434*
Miyasaka, K., 55(414), *214*
Miyashi, T., 596(47), 602(47), *613*
Miyoshi, M., 16(313), 38(313), 48(313), 50(313), *211*
Mizsak, S. A., 302(145), *437*
Mizuguchi, R., 525(44,45), *543*
Mladenova, M., 341(199), *439*
Mo, O., 6(74), 7(74), *204*
Moffett, R. B., 35(315), *211*
Mohan, S., 354(209), *439*
Moll, F., 595(44), *613*
Mollere, P. D., 5(316), *211*
Mondron, P. J., 14(144), *206*
Monti, A., 478(112), *515*
Montzka, T. A., 3(324), 11(324), 12(324), 14(324), 15(324), 16(324), 67(324), 81(324), *212*
Moore, C. B. 602(67), *614*
Moore, D. R., 19(159), *206*
Moore, D. W., 482(127), 500(127), *516*, 551(25, 26), *585*
Moore, H. W., 234(30,31,32), 235(33,34), *434*
Moore, J. A., 3(324), 11(324), 12(324), 14(324), 15(324), 16(324), 57(326,338), 59(99,326,327,328,329,333,338), 60(330,385), 62(122,329,332), 67(324), 81(324), 99(443), *205*, *212*, *214*, *215*, 226(16), *434*, 444(3), 452(3), *512*, 553(34), 568(34), *585*
Moosmüller, F., 526(60), *543*
Mora-Portuguez, M., 91(295), *211*
Moreau, J. L., 352(205), 354(210), *439*
Moreton, J. E., 65(98), *205*
Mori, M., 358(215), *439*
Moriarty, R. M., 4(335), *212*
Moriconi, E. F., 304(151), 305(152), 306(153), 308(153), 309(153), 385(153), *438*
Moriconi, E. J., 17(336), 34(336), 38(336), *212*, 310(155), *438*
Morikawa, M., 242(54), *435*
Morimoto, A., 52(337), 57(337), 58(337), *212*
Morishima, I., 5(484), *217*
Morris, L. R., 283(101), *436*
Mosely, R. H., 25(12), *202*
Moss, R. A., 594(32), *613*
Motoi, M., 341(200), *439*
Moyer, C. E., Jr., 538(110), *545*
Moza, P. N., 395(244), 397(246), *440*
Mrotzek, H., 24(394), 94(394), 95(394), *214*, 237(36), *434*
Mueller, E., 90(56,59), *203*
Mukai, T., 596(47), 602(47), *613*
Mukerjee, A. K., 353(207), 359(216), *439*
Mukhedkar, V. A., 15(168), 73(168), *207*
Mukkavill, L., 271(91), *436*
Müller, E., 540(119), *545*, 555(45), 556(45), *586*
Müller, R., 540(119), *545*
Müller, U., 553(37), *585*
Murray, S. J., 474(90), *514*
Musierowicz, S., 478(113), *515*
Myers, M. D., 595(39), *613*

Nabeya, A., 39(233,234), 57(338), 59(338), 71(232,234), 72(232,234), *209*, *212*, 562(77), 566(77), *587*
Nadir, U. P., 28(338), *212*
Nagarajan, R., 221(4), *433*
Nagasawa, H. T., 47(339), 49(339), 51(339,340), *212*
Nagata, M., 89(216), *208*, 430(295,296), *441*
Nair, V., 588(1), *612*
Nakaguchi, O., 293(107), 380(107), *436*
Nakajo, T., 596(47), 602(47), *613*
Nakatsuka, S., 366(227), 367(227), 369(227), 370(228), 371(228), *440*
Nametkin, N. S., 43(341,419), 62(459), *212*, *215*, *216*, 562(75), *586*
Narayanan, C. S., 229(24), *434*
Narbut, A. V., 521(21), *542*
Nash, C. P., 5(48), *203*
Navarro, P., 448(26), 497(26), *513*
Neidlein, R., 525(63), *543*
Nelson, D. A., 229(25), 230(25), 261(80), *434*, *436*
Nelson, J. A., 524(35), 538(35), *543*
Nelson, S. F., 476(100), 479(115), 489(115), 508(115), 510(100,115), 511(100,115), *515*
Nerdel, F., 45(343), 55(343), *212*
Neumann, F., 503(155), *516*
Neumann, W., 526(62), 535(62), *543*
Neuvar, E. W., 595(37), 603(37,82), 604(37), *613*, *614*

Nevestveit, O., 85(111), *205*
Newton, G. G. F., 220(3), *433*
Nicolaus, B. J. R., 363(223), *439*
Nielsen, A. T., 551(25,26), *585*
Niklas, H., 446(11), 448(11), *513*
Ning, R. Y., 554(41), *585*
Nishiguchi, T., 39(233,234), 71(232,234), 72(232,234), *209*
Nishikaze, N., 569(89), 570(89), *587*
Noguchi, M., 78(344,345), *212*
Noma, M., 78(344,345), *212*
Nomine, G., 332(184,185), *438*
Noreau, A., 353(206), *439*
Normant, M. H., 419(276), *441*
Novak, C. J., 448(23), *513*
Novikov, S. S., 549(8), 553(8), 559(8,59), 573(59), *584, 586*
Nunn, E. E., 446(18), 449(18), 450(18), 491(18), *513*
Nyberg, G. L., 603(78), *614*
Nyss, N. L., 400(251), *440*

Oberdier, J., 32(384), *214*
O'Brian, J. L., 457(41), *513*
Oe, K., 27(449,450), *216*, 486(137), *516*
Oehlschlager, A. C., 40(5), *202*
Oertel, G., 522(26), *542*
Ogata, Y., 104(346), *212*
Ogden, P. H., 470(77), 484(134), *514, 516*, 603(81), *614*
Ohkawa, K.-H., 39(234), 71(234), 73(234), *209*
Ohme, R., 549(7), 550(18,19), 551(7,20,21), 553(7,20,21,31,32), 559(7,20,56,57,68), 561(21,68), 572(68), 573(21), *584, 585, 586*, 588(2,6,7), 590(2,6,7), 597(52,54), 603(85,86), 604(129), *612, 614, 615, 616*
Ohsawa, A., 106(247), *209*
Ohshiro, Y., 569(88,89,90), 570(89), *587*
Ohta, M., 12(448), 16(89), 30(88), 35(86), 36(86), 43(299), 45(85,88,300), 46(85,300), 48(88,299), 49(85,299), 53(89), 55(85,87), 56(85,89), 57(88), 65(89), *204, 211, 216*, 488(142), 506(142), *516*, 590(19), *613*
Ojima, I., 355(211), 357(211,212,213), 358(213), *439*
Okada, H., 49(481), *217*
Okamoto, H., 553(38), *585*
Okawara, T., 394(242), *440*
Okay, G., 85(360), *213*
Okazaki, M., 406(259), *440*
Okita, M., 358(215), *439*
Oku, T., 293(107), 380(107), *436*
Okutani, T., 17(347), 18(347), 34(347), 52(337), 53(347), 54(348), 55(347,348), 56(347,348), 57(337), 58(337), *212*
Oliver, W. L., 6(268,269), *210*
Olofson, R. A., 240(46), *435*
Omote, Y., 22(242), *209*, 406(258,259), *440*
Onishchenko, A. A., 65(350), *212*
Oonway, T. T., 283(101), *436*
Opitz, G., 302(146), *437*
Orakhovats, A., 14(408), *214*
Oriente, G., 78(228), *209*
Orville-Thomas, W. J., 103(272), *210*
Oshiro, Y., 624(13), *626*
Osman, R., 6(351), *212*
Ostermayer, F., 15(184), *207*
O'Sullivan, M. J., 310(156), *438*
Otsuka, M., 569(87), *587*
Ottlinger, R., 90(58), *203*
Otto, A., 562(76), *586*
Ourisson, G., 30(390), *214*
Overberger, C. G., 591(26), 603(83), *613, 614*
Owens, R.A., 231(26), *434*

Pacifici, J. G., 620(9), 621(9,10), *625*
Packard, B. S., 6(268,269), *210*
Paddon-row, M. N., 95(467), *216*
Padwa, A., 21(353), 74(352,354), 75(352,355), 76(352), *212, 213*, 470(78), *514*, 594(35), 598(35), 599(35), *613*
Paek, U. H., 523(31), *542*
Pagani, G., 33(41), 34(426), *203, 215*, 363(223), *439*
Paget, C. J., 553(33), 559(33), 573(33), *585*
Pak, V. D., 528(71), *544*
Paliichuk, Y. A., 526(47), *543*
Pandit, U. K., 6(445), *215*
Pandya, L. J., 59(328), *212*
Paquette, L. A., 33(357,358), 73(358), 90(356), 91(359), 92(357), 108(357), *213*
Parcell, R. F., 33(359), *213*
Parker, J., 401(255), 402(256), *440*, 595(40,41,42), 596(41), 602(41), *613*
Parry, E. H., III, 228(22), *434*
Pashayan, D., 21(353), *212*, 470(78), *514*
Passerini, N., 41(305), 55(305), 56(305), *211*
Pasto, D. J., 449(28), *513*
Patil, P. N., 38(310), 55(310), *211*
Paudler, W. W., 6(209), 18(209), 52(209), *208*
Paulsen, S. R., 549(2), 560(62), 566(80), 567(80), 568(80), *584, 586, 587*, 588(2), 590(2), *612*
Pazos, F. D., 616(6), *625*
Pazos, J. F., 622(11), 624(12), *625*

Peacock, V. E., 479(115), 489(115), 508(115), 510(115), 511(115), *515*
Pedrazzoli, A., 30(100), 34(360), 37(100), *205, 213*
Pelizza, G., 90(363), 91(363), *213*
Pelkis, P. S., 534(99,100), *544*
Penland, A. D., 43(410), *214*
Pennings, M. L. M., 42(360), 85(111,360), 86(360c), *205, 213*
Perchenko, V.N., 43(341,419), 62(459), *212, 215, 216,* 562(75), *586*
Perelman, M., 302(145), *437*
Pererd, C. P., 418(275), *441*
Perry, R. J., 530(84), *544*
Person, H., 29(81), *204*
Perumal, S., 469(73), *514*
Pete, J. P., 22(15), *202*
Peters, K., 628(8), *628*
Petrizilka, T., 334(190), 336(190), 400(254), *438, 440*
Petrov, K. D., 518(7), *542*
Petrova, I. D., 549(8), 553(8), 559(8), *584*
Pfister, R., 487(138), *516*
Philips, J. C., 90(356), *213*
Phillips, B., 3(97), *205*
Phillips, B. A., 38(361), 47(361), 48(361), 49(361), 51(361), *213*
Phung, N. L., 49(362), *213*
Piatelli, M., 78(228), *209*
Pichat, L., 49(362), *213*
Pickett, L. W., 5(91), *204*
Pierson, G. O., 418(273), *441*
Pifferi, G., 44(364,365), 90(363), 91(363), *213*
Piggott, H. A., 520(16), *542*
Pimental, G. C., 602(67), *614*
Piwinski, J. J., 63(42), *203*
Plekhanov, V. G., 8(259), 9(259), *210*
Pliess, M. G., 553(34), 568(34), *585*
Podkhalyuzin, A. T., 477(105), *515*
Polyakov, A. E., 561(68), 572(68,98), *586, 587*
Pomerantz, M., 474(92), *515*
Pommier, J. C., 13(386), *214*
Porter, J., 13(476), 69(476), *216*
Poulain, D., 354(208), *439*
Prasad, K. K., 334(190), 336(190), 400(254), *438, 440*
Prigge, H., 5(289,291), 6(290), *210, 211*
Prockop, D. J., 78(270,422), *210, 215*
Prosell, G., 317(162), 320(163), *438*
Prosyanik, A. V., 20(260), 41(261), 47(260), *210*
Pucci, D. G., 17(145), 38(145), 39(145), 41(145), 92(145), *206*
Puchalski, C. B., 541(113), *545*
Puck, T. T., 78(367), *213*
Pukhova, V. I., 518(7), *542*
Putnam, R. E., 449(27), *513*
Puttfarcken, U., 102(264), *210*

Quarterman, L. A., 4(396), 5(396), *214*
Quast, H., 619(8), 625(8), *625,* 626(1,2,3,4e), 627(1,2,3,7), 628(8), *628*
Quiring, B., 540(119), *545*

Raban, M., 509(161), *517*
Rachman, A., 223(11), 224(11), *434*
Radau, M., 521(20), *542*
Radeglia, R., 561(67), 572(67), *586*
Rademacher, P., 39(245), 41(245), *209,* 511(163,164), *517*
Rai, M., 242(50), *435*
Raiford, L. C., 525(39), 532(92), 533(94), 540(115), *543, 544, 545*
Ram, B., 253(67), 261(81), 271(91), *435, 436*
Ramakrishnan, K., 483(129), 485(129), 486(129), *516,* 602(69), 603(69,80), *614*
Ramasseul, R., 42(126), 44(126), *205*
Rankin, D. W. H., 43(164), *206*
Rao, V. V., 397(245), 398(248), *440*
Rapala, R. T., 601(63), *614*
Rapoport, H., 424(281, 282, 283, 284), *441*
Rasmussen, J., 304(148), 317(148), *437*
Rassat, A., 42(126), 44(126), 62(127), *205*
Ratajczak, E., 103(272), *210*
Ratajczak, H., 103(272), *210*
Ratcliffe, R. W., 271(96), 273(92,93,94), 275(92,94), 278(95,96), 279(96), *436*
Raude, E., 337(191), *438*
Rausch, D. J., 103(477), 104(477), *216*
Raudenbusch, W., 15(184), *207*
Reading, C., 221(6), *433*
Rebertus, R. L., 595(38), *613*
Rebman, R. P., 20(227), *208*
Rees, C. W., 109(1–4,368–371), *202, 213*
Reichen, W., 525(43), *543*
Reichle, A., 526(60), *543*
Reid, A. A., 474(90,91), 496(91), 510(91), *514, 515*
Reinhoudt, D. N., 85(111,360), 98(372), *205, 213*
Reissig, H.-U., 464(63), 506(63), *514*
Renger, B., 40(398), 46(398), *214*
Renner, C. A., 616(4), 624(4), 625(4), *625,* 627(6)
Resetova, O. S., 65(350), *212*
Riccardi, R. J., 526(61), 536(61), 539(61), *543*

Richmond, M. H., 78(142), *206*
Richter, R., 520(14), 521(14), 524(38), 525(42), 528(70), 530(14), 534(103), 537(107,108), *542, 543, 544, 545*
Richter, S. B., 39(373), *213*
Ridley, D. D., 419(277), 421(277,278), *441*
Rieber, N., 478(108), 489(108), 494(108), *515*
Ried, W., 464(64), 465(66,67), *514*
Rinck, R., 82(421), 83(421), *215*
Risaliti, A., 460(56), 478(110,111,112), *514, 515*, 555(45), 556(45), *586*
Riseman, S., 559(55), *586*
Rissmann, G., 508(160), 509(160), *517*
Ritchie, J. P., 103(109), *205*
Rivest, P., 283(101), *436*
Robert, J. G., 35(236), *209*
Roberts, I. M., 39(374), *213*
Robertson, D. A., 56(220,221), *208*
Robinson, J. R., 226(20), *434*
Robinson, R., 226(20), *434*
Robson, P., 477(102), *515*
Rodebaugh, R. M., 20(375,376,377,380), 38(376,380), 45(379), 46(377,379,380), 47(375,377,380), 48(379,380), 49(375,376,378,379), 56(376), *210, 213*, 237(35), *434*
Rodehorst, R. M., 25(251,255), 26(381), *209, 213*
Rodkin, S. A., 446(17), 490(17), *513*
Roesky, H. W., 518(10), *542*
Rohlfing, W., 508(160), 509(160), *517*
Rohr, W., 39(132), *206*
Rokholin, E. M., 597(53), 599(53), *614*
Rolland, F., 17(146), 55(146), 56(146), 65(146), *206*
Rosenblum, M., 358(214), *439*
Ross, A. E., 40(286), *210*
Ross, J. H., 18(382), *213*
Ross, K.-H., 628(8), *628*
Rossbach, F., 521(20), *542*
Rossi, A., 41(305), 55(305), 56(305), *211*
Rosso, J. C., 4(383), *213*
Rosso, P. D., 32(384), *214*
Rothenberger, O. S., 60(385), *214*
Rothfield, M., 242(52), *435*
Roubineau, A., 13(386), *214*
Roy, S.K., 395(244), *440*
Rozeboom, M. D., 5(387), *214*
Rubinova, N. R., 528(76), *544*
Rudtchenko, V. F., 561(66), 572(99), *586, 587*
Ruff, J. F., 477(104), 495(149), 511(149), *515, 516*
Ruppert, L., 521(22), *542*
Rusanov, G. N., 528(74), *544*
Ryan, J. J., 249(59,60,61), *435*
Ryan, K., 332(186), *438*
Ryan, T. J., 459(50,51), 461(50), 462(50), 463(50), 468(50,51), 492(50), 493(50), 506(50), *514*
Rynbrandt, R. H., 456(38), 497(38), *513*
Rytslin, E. E., 359(219,220), *439*
Rzepa, H. S., 103(109), *205*

Sachko, G. P., 16(297), *211*
Saegusa, T., 68(387,388), *214*
Saito, J., 562(77), 566(77), *586*
Sakai, H., 221(7), *434*, 525(45), *543*
Sakamoto, M., 569(89), 570(89), *587*
Salama, M. A., 15(125,166,168), 73(166,168), *205, 207*
Sami Khan, M., 223(11), 224(11), *434*
Samoilova, Z. E., 15(389), 23(389), *214*
Sanchez, J. P., 33(359), 108(62), *203, 213*
Sanders, A. G., 219(2), *433*
Sandriss, C., 30(390), *214*
Sanjiki, T., 16(89), 30(88), 45(88), 48(88), 53(89), 56(89), 57(88), 65(89), *204*
Sanquer, M., 534(102), *544*
Santacroce, C., 78(228), *209*
Saprin, A. N., 6(137), *206*
Sarel, S., 359(221), *439*
Sassiver, M. L., 591(25), 604(25), *613*
Sato, T., 106(247), *209*
Saver, J., 475(95), *515*
Saver, L., 463(62), 501(62), 506(62), 508(62), *514*
Saver, R. J., 552(30), *585*
Saunders, J. H., 540(114), *545*
Savitsky, G. B., 6(293), 38(293), *211*
Sawada, S., 68(387), *214*
Sayigh, A. A. R., 519(12), 526(12,61), 527(12,64), 529(82), 532(88,89,91), 536(12,61), 539(61), *542, 544*
Scahill, T. A., 12(421), *215*
Schaad, L. J., 107(204,205), *208*
Schaap, A. P., 509(161), *517*
Schacht, E. H., 5(165), 68(28,165,391,392,393), *202, 207, 214*
Schaefer, U., 104(294), *211*
Schäfer, W., 470(74), 497(74), 509(74), *514*
Schatz, F., 487(140), *516*
Schaumann, E., 24(394), 94(394), 95(394), *214*, 237(36), *434*, 533(96), *544*
Schenck, G. O., 459(53), 492(53), 498(53), 501(53), *514*
Schickaneder, H., 30(60), *203*
Schiff, H., 517(2), *542*

Schlenk, W., 471(82), *514*
Schliebs, R., 552(27), *585*
Schmidt, A., 524(37), 534(37), *543*
Schmidt, E., 526(60), *543*
Schmidt, J. M., 494(145), *516*
Schmidt, R.-D., 553(32), *585*
Schmitz, E., 549(3–7), 550(16,18,19), 551(7,20,21,22,23), 553(7,20,21,31,32), 559(7,20,22,23,56,57), 560(22,23), 561(21,22,69), 562(22), 566(3,5,17,22,81), 567(5,81), 568(3,16,20,81,83), 572(81), 573(17,21,81), *584, 585, 586, 587,* 588(2,6,7), 589(6,7), 590(2,18), 597(52,54), 599(57), 601(18,62,64), 602(18), 603(85), 604(129), *612, 613, 614, 615, 616,* 626(1,2,3), 627(1,2,3), *628*
Schmitt, S. M., 323(165), *438*
Schmuff, N. R., 424(287), 425(290), *441*
Schneider, A. K., 446(15), 494(15), *513*
Schöllkopf, U., 99(217), *208*
Schollkopf, V., 232(28), 233(28), 249(28), *434*
Schönefeld, J., 571(92), *587*
Schott, P., 538(111), *545*
Schramm, J., 231(27), 232(27), 341(198), *434, 439*
Schramm, S., 550(18,19), *585*
Schröder, B., 475(95), *515*
Schubert, U., 450(32), *513*
Schulz, M., 553(35,36,37), 562(35), 566(35), 568(82), *585, 587*
Schupp, O. E., 35(463), 63(463), *216*
Schuppiser, J.-L., 554(42), *585*
Schuster, H. F., 26(253), 82(253), *209*
Schwaller, J.-C., 554(42), *585*
Schwartz, J., 332(183), *438*
Schwarz, W., 524(37), 534(37), *543*
Schweizer, E. E., 6(395), *214*
Schwenker, G., 529(81), *544*
Sciuto, S., 78(228), *209*
Sclove, B., 624(12), *626*
Scopes, D. I. C., 233(29), 234(29), 242(51), 249(29), *434, 435*
Scott, A. I., 385(234), *440*
Searles, S., 4(396), 5(387,396), 21(92), *204, 214*
Searles, S., Jr., 338(193), 339(193), *439,* 470(76), 493(76), *514*
Secor, H. V., 17(397), 34(397), 37(399), 38(397), *214*
Seebach, D., 40(398), 46(398), *214*
Seeman, J. I., 37(399), *214*
Segre, A., 34(400), *214*
Seitz, G., 6(401), 58(402), 59(401), *214*
Seybold, G., 107(403), *214*
Seitz, H., 572(97), *587*
Seitz, W., 508(160), 509(160), *517*
Sellstedt, J. H., 528(77), *544*
Semin, G. K., 533(98), *544*
Semmelhack, M. F., 450(30), 472(30), *513*
Sen, P. K., 407(260), *440*
Senier, A., 528(73), *544*
Sethi, P. S., 354(209), *439*
Seybold, J., 107(177), *207*
Seyedrezai, S. E., 5(387), *214*
Seyferth, D., 556(47,48), *586*
Shah, M. A., 459(55), 464(55), *514*
Sharkey, W. H., 449(27), *513*
Sharma, S. D., 260(75), 261(78), 268(88,89), 269(88,89), *435, 436*
Sharp, J. H., 475(96), *515*
Sharp, J. T., 474(90,91,93), 496(91), 510(91), *514, 515*
Shechter, H., 597(48), *614*
Sheehan, J. C., 38(404), 52(404), *214,* 226(15), 249(59,60,61,62), 329(15), 330(182), 394(240,241), 412(265), *434, 435, 438, 440, 441*
Shelton, R. J., 532(92), *544*
Shephard, F. G., 528(73), *544*
Shepherd, R. G., 591(25), 604(25), *613*
Sheradsky, T., 426(292,293), *441*
Shick, J. W., 518(8,9), *542*
Shieh, W.-C., 594(32), *613*
Shih, H., 556(47,48), *586*
Shinkai, I., 332(186), *438*
Shiratori, Y., 260(77), 261(77), *435*
Shivanyuk, A. F., 534(99,100), *544*
Shoeb, A., 52(82), 57(82), 58(82), *204*
Shoradsky, T., 425(291), *441*
Shustov, G. B., 552(28), 572(28), *585*
Shustov, G. V., 561(68), 572(68,98,99), *586, 587*
Shvo, Y., 6(351), *212*
Sica, D., 78(228), *209*
Siefken, V., 82(421), 83(421), *215*
Siefken, W., 540(118), *545*
Simonyan, L. A., 23(487), 24(486), *217*
Simova, E., 334(187), 341(199), *438, 439*
Simpson, R., 554(40), *585*
Sing, A., 234(30), *434*
Singh, A., 242(50), *435*
Singh, G., 261(78), *435*
Singh, H., 15(307), *211*
Singh, P., 74(352), 75(352), 76(352), *212,* 481(119,120), 488(120), 491(120), *515,* 540(112,117), *545*
Sipyagin, A. M., 19(228), *209*

Siret, P., 47(115,116), *205*
Sirotenkova, N. F., 446(16), 490(16), *513*
Sjoberg, B., 402(257), *440*
Skaletzky, L., 35(315), *211*
Skraup, S., 459(54), 492(54), *514*
Skoglund, M., 597(48), *614*
Sletzinger, M., 332(186), *438*
Sliwa, W., 32(405), *214*
Sluski, R. J., 25(251), *209*
Smith, G. E. P., 522(25), *542*
Smith, J. G., 471(81), *514*
Smith, J. L., 221(4), *433*
Smith, N. P., 594(31,33), 603(33), *613*
Smith, R. A. G., 589(14,15), 592(15), 602(14,15), 604(15), *613*
Snape, H. L., 522(23), *542*
Snieckus, V., 554(42), *585*
Soerensen, H., 78(263), *210*
Solomon, D. M., 20(175), 46(175), 47(175), 49(175), *207*
Somanathan, R., 109(369), *213*
Sommer, S., 446(10,12,13), 450(31,32), 451(10,12,13), 452(10), 454(12,36), 455(13), 462(60,61), 464(61), 497(13), 498(13,36), 510(36), *513*
Sood, H. R., 474(91), 496(91), 510(91), *515*
Soto, J. L., 448(26), 497(26), *513*
Speeter, M. A., 346(202), *439*
Spencer, J. A., 479(115), 489(115), 494(145), 508(115), 510(115), 511(115), *515, 516*
Spiegel, E., 627(7), 628(8), *628*
Spiegelman, G., 251(63), 253(64), 256(70), 258(70), 272(63), *435*
Spietschka, E., 461(58), 498(151), 499(151), 501(151), *514, 516*
Spotswood, T. M., 8(235), 9(235), *209*
Springer, J. P., 560(63), 565(63), *586*
Srivastava, K. C., 106(78), *204*
Srivastava, R. C., 359(216), *439*
Stack, G. M., 616(5), 623(5), 624(5), 625(5), *625*
Staehle, H., 65(256), *209*
Stallmann, O., 522(24), *542*
Staninets, V. I., 558(52), *586*
Stapley, E. O., 221(4,5), *433*
Staricco, E. H., 495(147), *516*
Stark, A., 601(64), *614*
Stark, W. M., 221(4), *433*
Staskun, B., 59(329), 60(330), 62(329), *212*
Staudinger, H., 223(8,9), 224(13), 302(9), 329(180), *434, 438*, 444(4), 452(4), 458(4), *512*, 517(4), 522(4), *542*, 555(45), 556(45), *586*
Stefaniuk, E., 475(96), *515*
Steigel, A., 475(95), *515*
Steinberg, N. G., 278(95), *436*
Steinfeld, A. S., 84(195), *208*
Steinheimer, T. F., 82(480), *217*
Stekoll, L. H., 418(274), *441*
Stephens, M., 33(37), 34(37), *203*
Sternhell, S., 81(39), *203*
Stetter, J., 537(106), *545*
Stevens, I. D. R., 551(21), 553(21), 561(21), 573(21), *585*, 589(12,13), 590(16), 594(31,33), 599(13), 600(13), 602(13), 603(12,13,16,33,74,87), 604(12,13,87,96), *612, 613, 614, 615*
Stevens, M. F., 20(407), *214*
Stevens, T. E., 594(36), *613*
Stirling, C. J. M., 15(36), *203*
Stoepel, K., 35(479), *217*
Stoilova, V., 14(408), *214*
Stookalo, E. A., 533(97), *544*
Stork, G., 421(280), 423(280), *441*
Storr, A., 43(409,410), *214*
Storr, R. C., 107(163), 109(1–4,369–371), *202, 206, 213, 214*, 242(53), *435*
Stournas, S., 240(46), *435*
Stowell, J. C., 480(5), 500(5), 506(5), *512*, 531(87), 536(87), *544*, 616(1,2,3), 618(1,2), 619(2), 620(2), 623(1,2), 624(2), 625(1,2), *625*
Strachan, P. L., 448(21), *513*
Strathdee, R. S., 475(96), *515*
Streith, J., 240(47), *435*, 554(42), *585*
Strom, E., 484(135), 505(135), *516*
Strube, R. E., 35(315), *211*
Strukov, O. G., 505(158), 506(158), *516*
Su, E. F. W., 78(411), *214*
Sufrin, J. R., 14(203), 36(203), *208*
Sugano, H., 16(313), 38(313), 48(313), 50(313), *211*
Sugi, H., 239(43), 240(43), *435*
Suhadolnik, R. J., 79(230), *209*
Sulima, V. V., 43(419), *215*
Sullivan, D. F., 233(29), 234(29), 249(29), *434*
Sung, M.-L., 78(412,413), *214*
Sunita, 268(89), 269(89), *436*
Suschitzky, H., 242(49), *435*, 527(66), *543*
Suzuki, S., 79(229), *209*
Suzuki, M., 553(38), 554(39), *585*
Suzuki, Y., 37(416), 41(416), 42(416), 55(414), 65(451), *214, 215, 216*
Swenton, J. S., 25(223), 26(417,418), 32(384), *208, 213, 215*
Sytov, G. A., 43(419), *215*
Szajewski, R. P., 421(280), 423(280), *441*

Szantay, C., 561(64), 568(83), *586, 587*
Szecsi, P., 482(127), 500(127), *516*
Szeghy, A., 11(178), 17(178), *207*
Szeimies, G., 82(191,421), 83(191,420,421), *207, 215*
Szilagyi, S., 494(146), 511(166), *516, 517*
Szmuszkovicz, J., 12(421), *215*

Tabusa, F., 102(225), *208*
Takagi, K., 104(346), *212*
Takaki, K., 624(13), *626*
Takayaki, H., 68(482), *217*
Takeno, H., 293(107), 380(107), *436*
Takeuchi, T., 78(422), *215*
Talaty, E. R., 418(274), *441*
Tamaki, E., 78(345), *212*
Tamres, M., 4(396), 5(396), *214*
Tamura, Y., 102(225), *208*, 550(17), 561(17), 566(17), 573(17), *585*
Tang, D. Y., 445(9), 448(9), 451(9), 456(9), 501(9), 506(9), 510(9), *513*
Tanigawa, K., 239(43), 240(43), *435*
Tanino, H., 366(227), 367(227), 369(227), 370(228), 371(228), *440*
Taniyama, H., 16(423), *215*
Tartakovskii, V. A., 65(350), *212*
Tarterat-Adalberon, M., 354(208), *439*
Tarwater, O. R., 33(473), *216*
Tashiro, M., 27(449,450), *216*, 486(137), *516*
Tate, F. E. G., 522(28), *542*
Taylor, D. A., 425(291), *441*
Taylor, E. C., 483(128,132), 486(128), 501(132), *516*
Taylor, G. A., 459(55), 464(55), *514*
Ter Gabrielyan, E. G., 23(487), *217*
Testa, E., 3(442), 14(442), 33(41,429,430,433,437,438), 34(426,429,430,433,435,441,442), 35(435,439,442), 37(435,441), 38(441), 39(430,435,441), 40(429), 44(364), 63(430), 64(432,438,442), 65(429,431,433), 90(363), 91(363), *203, 213, 215*, 339(194,195), 363(223), 364(224,225), *439*
Tetelbaum, B. I., 477(106), 478(106), 495(106), *515*
Thenn, W., 30(60), 90(59), *203*
Thever, W. J., 99(443), *215*
Thiedmann, R., 508(160), 509(160), *517*
Thomas, B. S., 43(409,410), *214*
Thomas, D., 91(19), 92(19), 93(20), 94(21,22), 95(22), 105(19), *202*
Thomas, J., 32(303), *211*
Thomas, J. J., 32(302), 74(302), *211*
Thomson, R.H., 523(29), *542*
Thun, J., 444(1), *512*
Thurman, D. E., 538(110), *545*
Tikhonova, L. A., 481(123,124,125,126), 482(123), 496(123), 502(126), *515, 516*
Tilak, B. D., 14(167), 15(166,167,168,444), 73(166,167,168,444), *207, 215*
Tilley, J. N., 532(88), *544*
Timberlake, J. W., 494(146), 511(166), *516*
Toda, F., 413(266), *441*
Tollens, 517(1), *542*
Tomatis, L., 40(285), *210*
Tommasini, R., 41(305), 55(305), 56(305), *211*
Topsom, R. D., 5(273), 15(102,103), 16(133), 36(102,103), *205, 206, 210*
Toriyama, K., 603(72,77), *614*
Torres, J. M., 487(139), *516*
Tourwe, D., 6(445), *215*
Townend, J., 21(212,213,214), *208*
Toxler, R. F., 78(31), *203*
Trede, A., 224(14), *434*
Trefonas, L. M., 616(5), 623(5), 624(5), 625(5), *625*
Tremper, A. W., 20(470), 49(470), 52(470), *216*, 386(326), 432(301), *440, 441*
Trifonov, L. S., 14(408), *214*
Trofimov, V. I., 9(447), *216*
Triggle, D. J., 18(83), 38(83), *204*
Trinajstic, N., 106(110), 107(185), *205, 207*
Tristram, E. W., 480(118), 495(118), *515*
Troll, T., 475(95), *515*
Trompenaars, W. P., 85(111), *205*
Tronich, W., 556(48), *586*
Troxler, R. F., 78(179), *207*
Tseng, S. S., 488(141), *516*
Tsoucaris, G., 237(39), *434*
Tsuboyama, S., 12(448), *216*
Tsuchiya, T., 475(97), *515*, 554(42), *585*
Tsuge, O., 27(449,450), *216*, 486(137), *516*, 525(44,45), *543*
Tsukamoto, K., 37(416), 41(416), 42(416), 55(414), 65(451), *214, 215, 216*
Tucker, B., 519(12), 526(12), 527(12,64), 529(82), 536(12), *542, 543, 544*
Tucker, H., 65(452), *216*
Tulis, R. W., 38(404), 52(404), *214*
Tumey, M. L., 597(48), *614*
Turner, S. R., 452(33), 453(35), *513*
Tveten, J. L., 459(52), *514*
Twibell, T. D., 465(69), 504(69), *514*

Uebel, J. J., 590(17), 604(17), *613*
Ullman, E. F., 481(119,120,121), 488(120), 491(120), *515*

Ulman, E. F., 488(141), *516*
Ulrich, H., 519(11,12), 523(32), 524(38), 525(42), 526(12), 527(12,64), 529(82), 532(88,89,91), 534(103), 536(12,38), 537(107), *542, 543, 544, 545*
Urry, W. J., 482(127), 500(127), *516*
Utermoehlen, C. M., 418(274), *441*

Valint, P. L., 55(454), *216*
Vallana, C. A., 495(147), *516*
Van Binst, G., 6(445), *215*
VandenHeuvel, W. J. A., 560(63), 565(63), *586*
VanderMeer, R. K., 240(46), *435*
Van Etten, R. L., 37(304), *211*
VanLevsen, A. M., 238(42), *435*
van Hummel, G. J., 42(360), 85(360), 86(360), *213*
Vasil'eva, E. S., 562(75), *586*
Vasileva, M. N., 477(106), 478(106), 495(106), *515*
Vaughan, J., 15(102,103), 36(102), *205*
Vaughan, W. R., 14(455), 17(455), 37(455), 38(455), *216*
Vaultier, M., 28(456,457,458), 48(457), *216*
Vaya, J., 286(105), *436*
Veal, C. J., 407(260), *440*
Vederas, J. C., 450(30), 472(30), *513*
Vega, E., 74(352), 75(352), 76(352), *212*
Verbanc, J. J., 524(35), 538(35), *543*
Verdini, A. S., 48(44), 51(44), *203*
Vereshchinskii, I. V., 477(105), *515*
Versak, U., 107(403), *214*
Vestling, M. M., 30(113), *205*
Vdovin, G. P., 558(52), *586*
Vgolini, A., 283(104), 286(104), *436*
Viehe, H. G., 95(147), *206*
Viehe, H. G., 240(44), *435*
Vigevani, A., 44(365), *213*, 340(197), *439*
Vilkow, L. V., 7(298), *211*
Vincent, J. E., 271(91), *436*
Viney, M., 340(196), *439*, 595(43), *613*
Viterbo, R., 34(400), *214*
Voigt, E., 596(45,46), *613*
Volkova, V. V., 62(459), *216*
Volodaskii, C. B., 481(123,124,125,126), 482(123), 496(123), 502(126), *515, 516*
Vollrath, R., 530(83,85), 533(83), *544*
Von Schnering, H. G., 628(8), *628*
Vostokov, I. A., 527(65,67,68), *543*

Wachob, G., 556(61), 560(61), 562(61), 565(61), 566(61), *586*
Wadsworth, D. H., 13(461,462), 35(463), 36(461), 38(461,462), 63(463), *216*
Wagener, K. B., 452(33), *513*
Wagner, F., 100(135), *206*
Wagner, H., 39(24), *202*
Wagner, H.-V., 107(464), *216*
Wagner, J., 6(279,280), *210*
Wagner, K., 540(119), *545*
Wagner-Jauregg, T., 487(140), *516*
Wakisaka, K., 239(43), 240(43), *435*
Walround, R. E., 527(66), *543*
Walter, K., 561(73), *586*
Wani, M. C., 76(466), *216*
Wann, R. E., 338(193), 339(193), *439*
Warkentin, J., 483(129), 485(129,136), 486(129), *516*
Warning, K., 45(311,312), *211*
Warren, W. H., 533(93), *544*
Warrener, R., 240(48), 241(48), *435*
Warrener, R. N., 95(467), *216*, 446(18), 449(18), 450(18), 491(18), *513*
Wasserman, H., 52(468), *216*
Wasserman, H. H., 20(470), 49(470), 52(469,470), *216*, 386(236), 414, 414(269), 415(270), 416(271,272), 431(298,299,300), 432(301), *440, 441*
Wasson, J. S., 594(30), *613*
Watabe, M., 406(258), *440*
Watanabe, T., 37(416), 41(416), 42(416), 65(200), 69(201), *208, 215*
Watson, K. G., 32(40), 72(40), *203*
Weaver, S. D., 459(47), 462(47), 480(47), 498(47), 503(47), *514*
Webb, H. M., 5(16,23), *202*
Weber, H., 39(24), *202*
Wells, J. L., 483(131), *516*
Wells, J. N., 13(472,473), *216*
Wells, N. J., 269(90), *436*
Wenkert, E., 448(21,23), *513*
Weinstein, B., 63(42), *203*
Weisenborn, F., 332(183), *438*
Weisman, G. R., 479(115), 489(115), 508(115), 510(115), 511(115), *515*
Weiss, M. J., 549(9,10), *584*, 588(3,4), 590(21,22), 591(23,24), 603(21), 604(4,21), *612, 613*
West, G., 553(35,36,37), 562(35), 566(35), 568(82), *585, 587*
Weyer, R., 39(24), *202*
Weyerstahl, P., 45(343), 55(343), *212*
Weyler, W., 234(32), *434*
Whidby, J. F., 37(399), *214*
White, D. V., 445(9), 448(9), 451(9), 456(9), 501(9), 506(9), 510(9), *513*, 532(90), *544*

White, J., 17(475), 38(475), *216*
Whitney, J. G., 221(4), *433*
Whittle, P. J., 109(370,371), *213*
Wierengo, C. J., 469(73), *514*
Wild, H. J., 522(28), *542*
Wildi, E. A., 449(29), 450(29), 489(29), 506(29), *513*
Wiley, D. H., 603(83), *614*
Wilkerson, C. J., 618(7), 624(12), *625*, 626(5), *628*
Williams, M. T., 109(1), *202*
Williams, W. M., 472(85,86), 496(86), 506(86), *514*
Williard, P. G., 558(54), 561(71), 562(54), 565(54,71), 566(54), 568(54), *586*
Wills, I. E., 13(476), 69(476), *216*
Wills, M. T., 12(9), 13(476), 14(10), 63(9), 69(8,476), 71(9,11), *202*, *216*
Wilms, H., 35(479), *217*
Wilson, F. E., 533(93), *544*
Wilson, R., 621(10), *625*
Wilzbach, K. E., 103(477), 104(477), *216*
Wimmer, T., 261(79), *436*
Winder, C. V., 33(37), 34(37), *203*
Wineholt, R. L., 59(327), 62(332), *212*
Winterfeldt, E., 98(478), *216*
Wittgens, A., 3(442), 14(442), 34(442), 35(442), 64(442), *215*
Wittig, G., 503(155), *516*
Wittle, E. L., 57(326), 59(326), *212*
Wojciechowska, M., 457(43,44), *513*
Wollweber, H., 35(479), *217*
Wong, A., 33(37), 34(37), *203*
Wong, C. K., 465(70), 504(70), 505(70), *514*
Wong, P. K., 358(214), *439*
Woo, K. K., 78(278), *210*
Woodruff, H. B., 221(4), *433*
Woodward, R. B., 308(154), 341(201), *438*, *439*
Woolf, C., 523(33), *542*
Woolhouse, A. D., 109(369), *213*
Wright, C. D., 518(10), *542*
Wright, G. J., 15(103), 16(133), 36(133), *205*, *206*
Wright, J., 65(98), *205*
Wright, M., 33(37), 34(37), *203*
Wu, J. S., 20(470), 49(470), 52(469,470), *216*, 386(236), *440*
Wu, L., 280(99), *436*
Wulfman, D. S., 82(480), *217*
Wyvratt, M. J., 91(359), *213*

Yakubovich, A. Y., 446(17), 477(106), 478(106), 490(17,144), 495(106), 500(144), *513*, *515*, *516*
Yamada, Y., 49(481), *217*
Yamaguchi, H., 569(87), *587*
Yamamoto, I., 600(60), *614*
Yamamoto, Y., 624(13), *626*
Yamashita, T., 68(482), *217*
Yamauchi, T., 59(333), *212*
Yamazaki, T., 89(216), *208*, 430(295), 430(296), *441*
Yanagita, M., 12(448), *216*
Yandovski, V. N., 561(72), 562(74), 565(72), 569(85,86), 571(94,95), 572(96), *586*, *587*, 597(49,50,51), *614*
Yanez, M., 6(74), 7(74), *204*
Yang, N. C., 87(483), *217*
Yaroslavsky, C., 555(45), 556(45), *586*
Yaroslavsky, S., 555(45), 556(45), *586*
Yasui, B., 16(423), *215*
Yates, P., 603(83), *614*
Yeung, H. W., 421(279), *441*
Yokohama, S., 260(77), 261(77), *435*
Yoneda, N., 16(313), 38(313), 48(313), 50(313), *211*
Yoo, S. E., 385(234), *440*
Yoshida, K., 355(211), 357(211), *439*
Yoshikawa, K., 5(484), *217*
Young, D. W., 407(260), *440*
Yukimura, S., 569(87), *587*
Yun, H. Y., 30(113), *205*
Yuzon, D. L., 51(340), *212*

Zabel, K., 45(343), 55(343), *212*
Zaikin, V. G., 62(459), *216*
Zakharov, K. S., 561(66,68), 572(68), *586*
Zamboni, R., 283(102,103,104), 286(104), *436*
Zamorina, I. A., 569(86), *587*
Zaripova, M., 561(66), *586*
Zbaida, D., 426(292,293), *441*
Zbiral, E., 39(243), *209*
Zeeh, B., 530(86), *544*
Zeifman, Yu. V., 15(389), 23(389,487), 24(486), *214*, *217*, 521(17), *542*
Zeifman, Z. V., 597(53), 599(53), *614*
Zeisberg, R., 571(93), *587*
Zelwer, C., 237(39), *434*
Zetzsche, F., 521(19), *542*
Ziegler, E., 224(12), 261(79), 264(12), *434*, *436*
Zinner, G., 525(46), 530(83,85), 533(83), *543*, *544*
Zobova, N. N., 520(13), 528(74,75,76), *542*, *544*
Zollinger, J. L., 518(10), *542*
Zon, I. A., 6(137), 20(260), 47(260), *206*, *210*

Chemistry of Heterocyclic Compounds, Volume 42
Edited by Alfred Hassner
Copyright © 1983 by John Wiley & Sons, Ltd.

Subject Index

Acid halides, reaction of, with azomethine substrates, 248–301
Acids, reaction of diaziridinones with, 619
2-Acyl and 2-alkylideneazetidines, 47
Acyl anhydrides, reaction of diaziridines with, 569
Acylated diaziridines, 559–560
N-Acylation, and carbamylation, 38–39
Alkenes, and azo compounds, 445–450
2-Alkoxyazetidines, 45
2-Alkyl- and 2-alkylideneazetidines, 44
N-Alkyl-2-aryl-3-acylazetidines, 20
N-Alkylation, 34–36
N-Alkylazetidine-2-carboxylates, 19–20
N-Alkylazetidines, 12–14
N-Alkyl-3-azetidinols, 17–19
N-Alkyldiaziridines, 559
3-Alkylideneazetidines, 58–59
Allenes, 458–470
Amidines, halogenation of, 593–594
β-Amino acids, cyclization of, 329–337
3-Aminoazetidines, 55
β-Amino carbonyl derivatives, cyclization of, 355–359
  Grignard- and aluminum-catalyzed condensations, 337–346
  Reformatsky reaction, 346–355
N-Arylation, 36
N-Arylazetidines, 15
N-Arylsulfonyldiaziridines, 560
1-Azabicyclo [1.1.0] butanes, 3-substituted azetidines from, 56–57
Azaprismanes, 103–106
Azetes, 106–109
Azetidine-2-alkanols, 45–46
Azetidine-2-carboxamides, 48–49
Azetidine-2-carboxylates, 47–48
Azetidine-2-carboxylic acid, 49–52
L-Azetidine-2-carboxylic acid, 77–79
Azetidines:
  azetes and benzazetes, 106–109
  azetines (dihydroazetes), 80–106
    2-alkoxy- and alkylthio-, amino-1-azetines, 90–95
    1-azetines, 81–90
    2-azetines, 95–100
    benzazetines, 100–103
    dewar pyridines, azaprismanes, and benzvalenes, 103–106
  introduction, 3–4
  naturally occurring, 77–80
    L-azetidine-2-carboxylic acid, 77–79
    polyoximic acid, 79–80
  oxidation (synthesis of β-lactam function), 431–433
  physical properties, 4–9
    diffraction data and molecular structure, 7–8
    ESR spectra, 9
    infrared and raman data, 5–6
    mass spectra, 8–9
    NMR spectra, 6
    thermodynamic data and basicity, 1–2
    vacuum ultraviolet and photoelectron spectra, 5
  ring-opening and rearrangement reactions, 62–77
    with nucleophiles, 64–67
    photochemistry, 74–77
    polymerization, 68–69
    rearrangements, 69–74
    thermal cleavage, 62–64
  substituents, 32–62
    at C_2, 44–52
    at C_3, 52–62
    at N_1, 33–43
    reduction of 2-azetidinones and malonimides, 33
  synthesis of the ring, 10–32
    C_2—C_3 bond, 21–22
    cycloaddition, 22–30
    N—C_2 bond, 10–20
  tables, 110–201
Azetidine synthesis, 10–32
  C_2—C_3 bond, 21–22
    other methods, 22
    photochemical cyclization, 21–22
  cycloaddition, 22–30
    [3+1] cycloaddition, 28–30
    formation from other ring systems, 30–32
    photochemical, 25–27
    thermal, 23–24

Azetidine synthesis (*Continued*)
N—C_2 bond, 10–20
N-alkyl-2-aryl-3-acylazetidines, 20
N-alkylazetidine-2-carboxylates, 19–20
N-alkylazetidines, 12–14
N-alkyl-3-azetidinols and azetidinones, 17–19
N-arylazetidines, 15
quarternary azetidinium compounds, 14–15
secondary azetidines, 11
N-sulfonylazetidines, 16–17
3-Azetidinols, 52–53
Azetidinone formation:
via photochemical cyclizations, 401–407
via transition metal carbenes, 407–412
Azetidinones, 17–19
2-Azetidinones, reduction of, 33
3-Azetidinones, 57–58
Azo compounds:
alkenes and, 445–450
electron-rich, 450–458
Azomethine substrates, reaction of acid halides, 248–301

Benzazetes, 109–110
Benzazetines, 100–103
Benzvalenes, 103–106

Carbamylation, *N*-acylation and, 38–39
Carbodiimides, cycloaddition of isocyanates to, 526–528
Chloral adducts of diaziridines, 559
3-Cyano- and 3-carboxyazetidines, 56
Cyclization methods, azetines (dihydroazetes), 81
Cycloadditions:
1,2-diazetines and 1,2 diazetidines, 445–478
alkenes and azo compounds, 445–450
[3+1] cycloadditions, 476
dimerization of imines, 470–471
electron-rich alkenes and azo compounds, 450–458
intramolecular [2+2], 471–476
ketenes, ketenimines, and allenes, 458–470
miscellaneous, 476–478
[2+2], 445–476
dihydroazetes (azetines):
2-alkoxy- and alkylthio-, amino-1-azetines, 90–95
2-azetines, 95–98
intramolecular, 88–90
[1+3], 90
[2+2], 86–87
isocyanates to carbodiimides, 526–528
isocyanates to imines, 528–529
leading to azetidines, 22–30
examples of [3+1], 28–30
photochemical, 25–27
thermal, 23–24
Cyclopropyl azides, rearrangement of, 82–84

Dewar pyridines, 103–106
1-(Dialkylaminomethyl) diaziridines, 559
1,2-Diazabicyclo [3.2.0] heptanones, 59–62
1,3-Diazetidines, 517–545
methods of preparation:
cycloaddition of isocyanates to carbodiimides, 526–528
cycloaddition to isocyanates to imines, 528–529
dimerization of imines, 520–522
dimerization of isocyanates, 522–526
miscellaneous synthesis of 1,3-diazetidines, 532–534
ring-closure reactions, 530–532
miscellaneous methods of synthesis, 532–534
reactions:
fragmentation, 535–536
nucleophylic ring-opening reactions, 538–541
ring expansion to six-membered-ring heterocycles, 536–537
1,2-Diazetines and 1,2-diazetidines:
cycloaddition reactions, 445–478
alkenes and azo compounds, 445–450
[2+2] cycloadditions, 445–476
[3+1] cycloadditions, 476
dimerization of imines, 470–471
electron-rich alkenes and azo compounds, 450–458
intramolecular [2+2], 471–476
ketenes, ketenimines, and allenes, 458–470
miscellaneous cycloadditions, 476–478
introduction, 444–445
methods of preparation, 445–488
cycloaddition reactions, 445–478
ring-closure reactions involving HX abstraction, 478–484
ring contractions, 484–488
reactions, 489–505
retention of the heterocycle, 489–491
ring-opening, 492–502

ring opening by chemical agents, 497–502
thermal and photochemical fragmentation, 492–497
structure and spectral properties, 506–512
1-Diaziridinecarboxamides, 561
1,2-Diaziridinedicarboxamides, 561
Diaziridines (1,2-diazacyclopropanes), 549–588
introduction, 549
isolable invertomers and optical antipodes, 572
methods of preparation, 549–558
3-alkyl- and 3-aryldiaziridines from acid hydrolysis of 1,3,5-triazabicyclo-[3.1.0]hexanes (Method D), 551
diaziridines from diazirines (Method F), 553
3,3-disubstituted and 1,3,3-trisubstituted diaziridines from *N*-haloketimines and ketoxime-*O*-sulfonates (Method E), 552–553
miscellaneous, 557–558
photochemical synthesis of diaziridines, 553–555
reactions of aminals with sodium hypochlorite (Method C), 551
reactions of azodicarbonyl compounds with aliphatic diazo and organomercury substrates, 555–557
reaction of imines with NH_2Cl and RNHCl (Method A) and H_2NOS_3H and $RNHOSO_3H$ (Method B), 549–550
of pharmacological interest, 573
physical properties, 572–573
preparation utilizing other diaziridines, 558–562
acylated diaziridines, 559–560
adducts with Michael-type substrates, 561–562
N-alkyldiaziridines, 559
N-arylsulfonyldiaziridines, 560
chloral adducts of diaziridines, 559
1-(dialkylaminomethyl)diaziridines, 559
1-diaziridinecarboxamides and 1,2-diaziridinedicarboxamides, 561
diaziridinyl phosphinyl derivatives, 561
1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines, 558
N-(2-hydroxyalkyl)diaziridines, 559
N-silyldiaziridines, 562
ring-opening reactions, 562–572
azomethine imine intermediates, 562–566
1,2-dialkyl- and 1,2,3-trialkyldiaziridines with ketones and isocyanates, 569–570
with diphenylcyclopropenone, 570–571
hydrolysis of diaziridines, 568–569
with lead tetraacetate, 571–572
nitrogen–nitrogen bond breaking, 566–568
reaction of diaziridines with acyl anhydrides, 569
tables, 574–588
Diaziridinimines (3-iminodiaziridines), 626–628
methods of preparation, 626
reactions:
and heat, 627
and unsaturated substrates, 627–628
Diaziridinones, 616–626
methods of preparation, 616–619
physical properties, 625
reactions, 619–624
with acids, 619
with nucleophiles, 619–623
thermal decomposition, 623–624
with unsaturated substrates, 624
Diaziridinyl phosphinyl derivatives, 561
3H-Diazirines (1-diazirines), 588–616
introduction, 588
methods of preparation, 589–598
dehydrogenation of 1,2-unsubstituted diaziridines, 589–591
halogenation of amidines, 593–594
miscellaneous, 597
photochemical isomerization of diazo compounds, 595–597
reaction of imines with dichloro- and difluoro-amines, 592–593
reductive deflorinative cyclization, 594–595
of pharmacological interest, 604
physical properties, 603–604
reactions, 598–603
and electrophiles, 599–601
and nucleophilic reagents, 598–599
thermal and photolytic decomposition, 602–603
tables, 605–612
Diazo compounds, photochemical isomerization, 595–597
Dichloro- and difluoroamines, reaction with imines, 592–593

Dihydroazetes (azetines), 80–106
2-alkoxy- and alkylthio-, amino-1-azetines, 90–95
cycloaddition, 93–95
oxidation, 92–93
thermal stability and valence isomerization, 91–92
1-azetines, 81–90
azetine-1-oxides from nitroalkenes and ynamines, 85–86
cyclization methods, 81
[1+3] cycloaddition, 90
[2+2] cycloaddition, 86–88
elimination methods, 81–82
intramolecular cycloaddition, 88–90
rearrangement of cyclopropyl azides, 82–84
ring expansion of trichloromethylaziridines, 84
2-azetines, 95–100
cycloaddition, 95–98
elimination, 95
enolic azetidinones and imines, 99–100
intramolecular cycloaddition, 98–99
benzazetines, 100–103
dewar pyridines, azaprismanes, and benzvalenes, 103–106
1-(2,4-Dinitrophenyl), 558
Diphenylcyclopropenone, reaction of diaziridines, 570–571

Electron-rich alkenes, azo compounds and, 450–458
Electrophiles, 3H-diazirines and, 599–601
Elimination methods, azetines (dihydroazetes), 81–82
2-azetines, 95
Enolic azetidinones (or imines), 99–100
ESR spectra, of azetidines, 9–10

Four-membered rings (containing two nitrogen heteroatoms):
1,3-diazetidines, 517–545
introduction, 517–520
methods of preparation, 520–534
physical and spectral properties, 534–535
reactions, 535–541
1,2-diazetines and 1,2-diazetidines, 444–517
introduction, 444–445
methods of preparation, 445–488
reactions, 489–505
structure and spectral properties, 506–512

2-Halocarboxylic amides, cyclization of, 394–401
3-Halocysteinylamides, cyclization of, 366–385
Halogenation of amidines, 593–594
3-Halopropionamides, cyclization of, 359–366
Heat, diaziridinimines and, 627
Hydrazides, 48–49
Hydrolysis of diaziridines, 568
Hydroxamic acids, cyclization of, 385–386
N-(2-Hydroxyalkyl) diaziridines, 559

Imines, enolic azetidinones, 99–100
cycloaddition of isocyanates, 528–529
dimerization, 470–471
1,3-diazetidines, 520–522
reaction with dichloro- and difluoroamines, 592–593
Infrared data, azetidines, 5–6
Intramolecular cycloaddition:
2-azetines, 98–99
leading to 1-azetine system, 88–90
Isocyanates:
cycloaddition reaction, 302–328
cycloaddition to carbodiimides, 526–528
cycloaddition to imines, 528–529
dimerization of, 522–526
reaction of 1,2-dialkyl- and 1,2,3-trialkyldiaziridines with, 569–570

Ketene-azomethine cycloadditions, 223–248
Ketenes:
and ketenimines, 458–470
reaction of 1,2-dialkyl- and 1,2,3-trialkyldiaziridines with, 569–570

β-Lactam function, synthesis of:
cycloaddition reactions, 223–328
acid halides with azomethine substrates, 248–301
[2+2] cycloaddition reaction of isocyanates and olefins, 302–328
ketene-azomethine cycloadditions, 223–248
formation of C_3—C_4 bond, 394–412
formation of N—C_4 bond, 359–394
oxidation of azetidines, 431–433
ring-closure reactions, 329–359
formation of C_3—C_4 bond, 394–412
formation of N—C_2 bond, 329–359
formation of N—C_4 bond, 359–394
ring-contraction reactions, 419–431
ring-expansion reactions, 412–418

Lead tetraacetate, reaction of diaziridines with, 571–572

Malonimides, reduction of, 33
Mass spectra, of azetidines, 8–9
Michael-type substrates, adducts of diaziridines, 561

Nitriles, 48–49
Nitroalkenes, azetine-1-oxides from, 85–86
Nmr spectra, azetidines, 6
Nucleophiles, reaction of diaziridinones with, 619
Nucleophilic reagents, 3H-diazirines, 598–599
Nucleophilic ring-opening reactions, 538–541
Nucleophilic substitution, mechanistic considerations, 53–55

Olefins, cycloaddition reaction, 302–328

Photochemical cyclizations:
  azetidines by closure of C—C bond, 21–22
  azetidinone formation, 401–407
Photochemical [2+2] cycloaddition, 25–27
Photochemical isomerization, diazo compounds, 595–597
Photoelectron spectra, azetidines, 5
Photolytic decomposition, 3H-diazirines, 602–603
Polyoximic acid, 79–80

Quaternary azetidinium compounds, 14–15

Raman data, azetidines, 5–6
Reductive deflorinative cyclization, 594–595
Ring-closure reactions, β-lactam function, 329–359
  1,3-diazetidines, 530–532
  formation of C_3—C_4 bond, 394–412
    azetidinone formation via photochemical cyclizations, 401–407
    azetidinone formation via transition metal carbenes, 407–412
    cyclization of α-halocarboxylic amides, 394–401
  formation of N—C_2 bond, 329–359
    β-amino acids, 329–337
    β-amino carbonyl derivatives, 355–359
    β-amino esters (Grignard- and aluminum-catalyzed condensations), 337–346
    β-amino esters (Reformatsky reaction), 346–355
  formation of N—C_4 bond, 359–394
    3-halocysteinylamides, 366–385
    3-halopropionamides, 355–366
    hydroxamic acids, 385–386
    miscellaneous N—C_4 cyclizations, 386–394
Ring-opening reactions, diaziridines (1,2-diazacyclopropanes), 562–572
  with acyl anhydrides, 569
  azomethine imine intermediates, 562–566
  1,2-dialkyl- and 1,2,3-trialkyldiaziridines with ketones and isocyanates, 569–570
  with diphenylcyclopropenone, 570–571
  hydrolysis, 568–569
  with lead tetraacetate, 571–572
  nitrogen–nitrogen bond breaking, 566–568
Ring-opening and rearrangement reactions (of azetidines), 62–77
  with nucleophiles, 64–67
  photochemistry, 74–77
  polymerization, 68–69
  rearrangements, 69–74
  thermal cleavage, 62–64

Secondary azetidines, 11
N-Silyldiaziridines, 562
Substituents, azetidine and ring-substituted azetidines, 32–62
  at C_2, 44–52
    2-acyl- and 2-alkylideneazetidines, 47
    2-alkoxyazetidines, 45
    2-alkyl- and 2-alkylideneazetidines, 44
    azetidine-2-alkanols and -amines, 45–46
    azetidine-2-carboxamides, hydrazides, and nitriles, 48–49
    azetidine-2-carboxylates, 48–50
    azetidine-2-carboxylic acid, 49–52
  at C_3, 52–62
    3-alkylideneazetidines, 58–59
    3-amino-, alkoxy- and alkylthioazetidines, 55
    3-azetidinols and derivatives, 52–53
    3-azetidinones, 57–58
    3-cyano- and 3-carboxyazetidines, 56
    1,2-diazabicyclo[3.2.0]heptanones, 59–62
    mechanistic considerations in nucleophilic substitution, 53–55
    3-substituted azetidines from 1-azabicyclo[1.1.0]butanes, 56–57
  at N_1, 33–43
    N-acylation and carbamylation, 38–39
    N-alkylation, 34–36
    N-arylation, 36

Substituents, azetidine and ring-substituted azetidines (*Continued*)
at N_1 (*Continued*)
nitrogen substituents, 39–41
other elements, 43
oxygen substituents, 41–42
quaternization, 36–37
removal of groups, 37–38
reduction of 2-azetidiones and malonimides, 33
N-Sulfonylazetidines, 16–17

Thermal [2+2] cycloaddition, 23–24
Thermodynamic data, azetidines, 4–5
Trichloromethylaziridines, ring expansion of, 84
1-(2,4,6-Trinirophenyl) diaziridines, 588

Unsaturated substrates, reactions and diaziridinimines (3-iminodiaziridines), 627–628
diaziridinones, 624
1,2-Unsubstituted diaziridines, dehydrogenation of, 589–591

Vacuum ultraviolet, azetidines, 5

Ynamines, azetine-1-oxides from, 85–86