

---

---

# THE PYRAZINES

## Supplement I

**D. J. Brown**

Research School of Chemistry  
Australian National University  
Canberra



---

---

AN INTERSCIENCE<sup>®</sup> PUBLICATION  
**JOHN WILEY & SONS INC.**

---

---



**THE PYRAZINES**

**Supplement I**

*This is the Fifty-Eighth Volume in the Series*

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

---

---

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

A SERIES OF MONOGRAPHS

**EDWARD C. TAYLOR** and **PETER WIPF**, *Editors*

**ARNOLD WEISSBERGER**, *Founding Editor*

---

---

---

---

# THE PYRAZINES

## Supplement I

**D. J. Brown**

Research School of Chemistry  
Australian National University  
Canberra



---

---

AN INTERSCIENCE<sup>®</sup> PUBLICATION  
**JOHN WILEY & SONS INC.**

---

---

This book is printed on acid-free paper. ©

Copyright © 2002 by John Wiley & Sons, Inc., New York. All rights reserved.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except as permitted under Sections 107 or 108 of the 1976 United States Copyright Act, without either the prior written permissions of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4744. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, (212) 850-6011, fax (212) 850-6008, E-Mail: PERMREQ@WILEY.COM.

For ordering and customer service, call 1-800-CALL-WILEY.

*Library of Congress Cataloging in Publication Data is available.*

Brown, D. J.

The Pyrazines: Supplement I

ISBN 0-471-40382-2

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

*To*  
*Professor Emeritus Felix Bergmann<sup>†</sup>*  
*(heterocyclic chemist and pharmacologist)*  
*now in his ninety-fifth year*

<sup>†</sup>Felix Bergmann was born in Frankfurt an der Oder in 1908 and graduated with doctorates in chemistry and medicine from Berlin in 1933. He then joined his brother Ernst at the Weizmann Institute, Rehovot, until he was elected in 1950 to the chair of Pharmacology within the Hebrew University of Jerusalem. During retirement, he has remained active in research until quite recently.





## The Chemistry of Heterocyclic Compounds Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

*The Chemistry of Heterocyclic Compounds*, has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

It is a major challenge to keep our coverage of this immense field up to date. One strategy is to publish Supplements or new Parts when merited by the amount of new material, as has been done, *Inter alia*, with pyridines, purines, pyrimidines, quinazolines and isoxazoles. This strategy was also the case recently with *Pyrazines*, (published in 2000) which had last been covered in this series in 1982. We acknowledge once again the extraordinary contributions of Dr. D. J. Brown, whose previous classics in heterocyclic chemistry in this series (*The Pyrimidines*, *The Pyrimidines Supplement I*, *The Pyrimidines Supplement II*, *Pteridines*, *Quinazolines Supplement I*, *The Pyrazines, Supplement I*) are now joined by the present exhaustive treatment of the last twenty years of pyrazine chemistry.

We extend once again our congratulations and our thanks to Dr. Brown for a further outstanding contribution to the literature of heterocyclic chemistry.

*Department of Chemistry  
Princeton University  
Princeton, New Jersey*

EDWARD C. TAYLOR

*Department of Chemistry  
University of Pittsburgh  
Pittsburgh, Pennsylvania*

PETER WIPF

## Preface

This supplement seeks to build on the solid foundation established by Dr. G. B. Barlin's original volume, *The Pyrazines*, that appeared within this series in 1982. That original book presented the first comprehensive review of pyrazines, embracing a mass of important historical material as well as a modern systematic treatment of pyrazine chemistry. Not surprisingly, it stimulated a great deal of research in all aspects of the field, resulting in the need for a supplementary volume to cover literature published between 1979 and 2000, inclusive.

In undertaking this task, the present author thought it wise to make certain changes in format to conform with recent trends. Thus pyrazine *N*-oxides and reduced pyrazines are no longer separated out from regular pyrazine derivatives; primary syntheses are now divided between two chapters, one involving aliphatic or carbocyclic substrates and the other involving heterocyclic substrates; and the many classified tables of pyrazine derivatives are replaced by a single alphabetical table of simple pyrazines that aims to list *all* such pyrazines (including those in the earlier tables). In view of these and other necessary changes, the essential status of the present volume as a *supplement* has been maintained by many sectional cross-references (e.g., *H* 28) to pages in the original volume (*Hauptwerk*), where earlier relevant information may be found; such cross-references are used also in the Table of Simple Pyrazines.

Chemical nomenclature used in this supplement follows current IUPAC recommendations [*Nomenclature of Organic Chemistry, Sections A–F, H* (eds. J. Rigaudy and S. P. Klesney, Pergamon Press, Oxford, 1970)] with one important exception: in order to keep “pyrazine” as the principal part of each name, those groups that would normally qualify as principal suffixes, but that are not attached directly to the nucleus, are rendered as prefixes. For example, 3-carboxymethyl-2 (1*H*)-pyrazinone is used instead of 2-(3-oxo-3, 4-dihydropyrazin-2-yl) acetic acid. Secondary and tertiary amino groups are rendered as prefixes. Ring systems are named according to Chemical Abstracts Service recommendations [*Ring Systems Handbook* (eds. anon., American Chemical Society, Columbus OH, 1998 edition)]. Many trivial names for pyrazines are listed in Section 5.6. In preparing this supplement, the patent literature has been largely ignored in the belief that useful factual information therein usually appears subsequently in the regular literature.

I am greatly indebted to my good friend and author of the original volume, Dr. Gordon Barlin, for invaluable consultation and advice; to the Dean of the Research School of Chemistry, Professor Denis Evans, for the provision of postretirement facilities within the School; to the branch Librarian, Mrs Joan Smith, for continual assistance in library matters; and to my wife, Jan, for much needed encouragement and her mighty help during indexing, proofreading, and the like.

Research School of Chemistry  
Australian National University, Canberra

DES BROWN



## Contents

<b>CHAPTER 1</b>	<b>PRIMARY SYNTHESSES FROM ALIPHATIC OR CARBOCYCLIC SYNTHONS</b>	<b>1</b>
1.1	From a Single Six-Atom Synthons	1
1.1.1	By Completion of the N—C2 Bond	1
1.1.1.1	From Appropriate $\omega$ -Unsaturated Azaalkylamines	1
1.1.1.2	From Appropriate $\omega$ -Halogeno(azaalkylamines)	2
1.1.1.3	From Appropriate $\alpha,\omega$ -Diamino(azaalkanes)	2
1.1.1.4	From Appropriate $\omega$ -Amino(azaalkanols)	3
1.1.1.5	From Appropriate $\omega$ -Amino(azaalkanals)	3
1.1.1.6	From Appropriate $\omega$ -Amino(azaalkanones)	4
1.1.1.7	From Appropriate $\omega$ -Amino(azaalkanoic Acids)	6
1.1.1.8	From Appropriate $\omega$ -Amino(azaalkanoic Esters)	6
1.1.1.9	From Appropriate $\omega$ -Amino(azaalkanamides)	8
1.1.1.10	From Appropriate $\omega$ -Amino(azaalkanenitriles)	8
1.1.2	By Completion of the C2—C3 Bond	9
1.2	From Two Synthons	10
1.2.1	By Using a One-Atom and a Five-Atom Synthons	11
1.2.1.1	Where the One-Atom Synthons Supplies N1	11
1.2.1.2	Where the One-Atom Synthons Supplies C2	14
1.2.2	By Using a Two-Atom and a Four-Atom Synthons	15
1.2.2.1	Where the Two-Atom Synthons Supplies N1 + C2	15
1.2.2.2	Where the Two-Atom Synthons Supplies C2 + C3	16
1.2.3	By Using Two Three-Atom Synthons	29
1.2.3.1	Where Identical Synthons Provide N1 + C2 + C3 and N4 + C5 + C6	29
1.2.3.2	Where Different Synthons Provide N1 + C2 + C3 and N4 + C5 + C6	34
1.2.3.3	Where the Synthons Provide N1 + C2 + C6 and C3 + N4 + C5	37
1.3	From Three Synthons	39
1.4	From Four or More Synthons	39
1.4.1	Where Synthons Provide N1, C2 + C3, N4, C5 + C6	40
1.4.2	Where Synthons Provide N1 + C2, C3 + N4, C5, C6	41
1.4.3	Where Synthons Provide N1 + C2, C3, N4 + C5, C6	42
1.5	Appendix: Glance Index to Typical Pyrazine Derivatives Available from Aliphatic or Carbocyclic Synthons	42

<b>CHAPTER 2</b>	<b>PRIMARY SYNTHESSES FROM OTHER</b>	
	<b>HETEROCYCLIC SYSTEMS</b>	<b>47</b>
2.1	Pyrazines from Other Heteromonocyclic Systems	47
2.1.1	Azepines as Substrates	47
2.1.2	Azetes as Substrates	48
2.1.3	Azirines as Substrates	48
2.1.4	Azocines as Substrates	51
2.1.5	1,2-Diazepines as Substrates	52
2.1.6	1,4-Diazepines as Substrates	52
2.1.7	Furans as Substrates	52
2.1.8	Imidazoles as Substrates	53
2.1.9	Isoxazoles as Substrates	55
2.1.10	Oxazoles as Substrates	56
2.1.11	Oxirenes as Substrates	56
2.1.12	Pyridazines as Substrates	57
2.1.13	Pyridines as Substrates	57
2.1.14	Pyrroles as Substrates	58
2.1.15	1,2,5-Selenadiazoles as Substrates	58
2.1.16	1,2,5-Thiadiazoles as Substrates	59
2.1.17	Thiirenes as Substrates	59
2.2	Pyrazines from Heterobicyclic Systems	59
2.2.1	1, 2-Diazabicyclo[2.2.0]hexanes as Substrates	60
2.2.2	2,4,-Diazabicyclo[3.1.0]hexanes as Substrates	60
2.2.3	2,3-Dioxa-5,7-diazabicyclo- [2.2.2]octanes as Substrates	60
2.2.4	Furo[2,3- <i>b</i> ]pyrazines as Substrates	60
2.2.5	Imidazo[1,2- <i>a</i> ]pyrazines as Substrates	61
2.2.6	Indoles as Substrates	61
2.2.7	Isoxazolo[2,3- <i>a</i> ]pyrazines as Substrates	62
2.2.8	Isoxazolo[4,5- <i>b</i> ]pyrazines as Substrates	63
2.2.9	Pteridines as Substrates	63
2.2.10	Pyrazino[2,3- <i>d</i> ][1,3]oxazines as Substrates	66
2.2.11	Pyrazino[2,3- <i>e</i> ][1,3,4]thiadiazines as Substrates	66
2.2.12	Quinoxalines as Substrates	66
2.2.13	4-Thia-1-azabicyclo[3.2.0]heptanes as Substrates	67
2.2.14	[1,2,5]Thiadiazolo[3,4- <i>b</i> ]pyrazines as Substrates	68
2.2.15	Thiazolo[3,2- <i>a</i> ]pyrazines as Substrates	68
2.2.16	Thiazolo[3,4- <i>a</i> ]pyrazines as Substrates	69
2.3	Pyrazines from Heterotricyclic Systems	69
2.4	Pyrazines from Spiro Heterocycles	70
2.5	Appendix: Glance Index to Typical Pyrazine Derivatives Available from Other Heterocyclic Systems	71

<b>CHAPTER 3</b>	<b>PYRAZINE, ALKYL PYRAZINES, AND ARYL PYRAZINES</b>	<b>75</b>
3.1	Pyrazine	76
3.1.1	Preparation of Pyrazine	76
3.1.2	Properties of Pyrazine	76
3.1.3	Reactions of Pyrazine	77
3.2	<i>C</i> -Alkyl- and <i>C</i> -Arylpyrazines	79
3.2.1	Preparation of <i>C</i> -Alkyl- and <i>C</i> -Arylpyrazines	80
3.2.1.1	By Direct <i>C</i> -Alkylation	80
3.2.1.1.1	General Procedures for <i>C</i> -Alkylation	80
3.2.1.1.2	<i>C</i> -Alkylation in the Schöllkopf Synthesis	86
3.2.1.2	By Replacement of Halogeno Substituents	93
3.2.1.3	By Replacement of Alkoxy, Cyano, Nitro, or Oxo Substituents	100
3.2.1.4	By Interconversion of Simple Alkyl Substituents	101
3.2.1.5	By Elimination of Functionality from Existing Substituents	102
3.2.1.6	By <i>Ips</i> o-Substitution of Trimethylsilyloxycarbonyl Substituents	105
3.2.2	Preparation of <i>N</i> -Alkyl- and <i>N</i> -Arylpiperazines	105
3.2.2.1	By <i>N</i> -Alkylation Processes	106
3.2.2.2	By Reduction of <i>N</i> -Acyl or <i>N</i> -Alkoxycarbonylpiperazines	112
3.2.2.3	By Miscellaneous Routes	113
3.2.3	Properties of Alkyl- and Arylpyrazines	114
3.2.4	Reactions of Alkyl- and Arylpyrazines	117
3.2.4.1	Oxidative Reactions	117
3.2.4.2	Reductive Reactions	119
3.2.4.3	Extranuclear Halogenation	120
3.2.4.4	Extranuclear Alkylation	122
3.2.4.5	Extranuclear Alkylidenation	123
3.2.4.6	Extranuclear Acylation or Carboxylation	125
3.2.4.7	Cyclization	126
3.2.4.8	“Amoxidation” of Methyl to Cyano Groups	128
3.2.4.9	Addition Reactions at Alkenyl or Alkynyl Substituents	128
3.2.4.10	Miscellaneous Reactions	130
3.3	<i>N</i> -Alkylpyrazinium Salts and Related Ylides	131
3.3.1	Preparation of <i>N</i> -Alkylpyrazinium Salts	131
3.3.2	Reactions of <i>N</i> -Alkylpyrazinium Salts	132
<b>CHAPTER 4</b>	<b>HALOGENOPYRAZINES</b>	<b>137</b>
4.1	Preparation of Nuclear Halogenopyrazines	137
4.1.1	Nuclear Halogenopyrazines from Pyrazinones	137

4.1.2	Nuclear Halogenopyrazines by Direct Halogenation	141
4.1.3	Nuclear Halogenopyrazines by Deoxidative Halogenation of Pyrazine <i>N</i> -Oxides	145
4.1.4	Nuclear Halogenopyrazines from Pyrazinamines	146
4.1.5	Nuclear Halogenopyrazines by Transhalogenation	148
4.1.6	Nuclear Halogenopyrazines via Trimethylsiloxy-pyrazines	149
4.2	Reactions of Nuclear Halogenopyrazines	149
4.2.1	Aminolysis of Nuclear Halogenopyrazines	150
4.2.2	Hydrolysis of Nuclear Halogenopyrazines	158
4.2.3	Alcoholysis or Phenolysis of Nuclear Halogenopyrazines	159
4.2.4	Thiolysis of Nuclear Halogenopyrazines	164
4.2.5	Alkanethiolysis or Arenethiolysis of Nuclear Halogenopyrazines	166
4.2.6	Azidolysis of Nuclear Halogenopyrazines	170
4.2.7	Hydrogenolysis of Nuclear Halogenopyrazines	171
4.2.8	Cyanolysis of Nuclear Halogenopyrazines	173
4.2.9	Miscellaneous Displacement Reactions of Nuclear Halogenopyrazines	174
4.2.10	Fission, Rearrangement, or Cyclocondensation of Nuclear Halogenopyrazines	176
4.3	Preparation of Extranuclear Halogenopyrazines	178
4.3.1	Extranuclear Halogenopyrazines from Corresponding Hydroxypyrazines	178
4.3.2	Extranuclear Halogenopyrazines by Minor Procedures	180
4.4	Reactions of Extranuclear Halogenopyrazines	181
<b>CHAPTER 5 OXYPYRAZINES</b>		<b>191</b>
5.1	Tautomeric Pyrazinones	191
5.1.1	Preparation of Tautomeric Pyrazinones	191
5.1.2	Reactions of Tautomeric Pyrazinones	196
5.1.2.1	Conversion into Pyrazinethiones	196
5.1.2.2	Conversion into <i>O</i> - and/or <i>N</i> - Alkylated Derivatives	198
5.1.2.3	Conversion into <i>O</i> - and/or <i>N</i> -Acylated Derivatives	203
5.1.2.4	Miscellaneous Reactions	205
5.2	Extranuclear Hydroxypyrazines	208
5.2.1	Preparation of Extranuclear Hydroxypyrazines	208
5.2.2	Reactions of Extranuclear Hydroxypyrazines	212
5.3	Nuclear and Extranuclear Alkoxy- or Aryloxy-pyrazines	217
5.3.1	Preparation of Alkoxy- or Aryloxy-pyrazines	217
5.3.2	Reactions of Alkoxy- or Aryloxy-pyrazines	219
5.4	Nontautomeric Pyrazinones and <i>N</i> -Alkylpyraziniumolates	221



5.4.1	Preparation of Nontautomeric Pyrazinones	221
5.4.2	Reactions of Nontautomeric Pyrazinones	222
5.5	Pyrazine <i>N</i> -Oxides	225
5.5.1	Preparation of Pyrazine <i>N</i> -Oxides	226
5.5.1.1	From <i>N</i> -Alkoxy pyrazinones	226
5.5.1.2	By Direct <i>N</i> -Oxidation	226
5.5.2	Reactions of Pyrazine <i>N</i> -Oxides	230
5.5.2.1	Deoxygenation	231
5.5.2.2	<i>O</i> -Alkylation or <i>O</i> -Acylation	233
5.5.2.3	Conversion into <i>C</i> -Acyloxy pyrazines	234
5.5.2.4	Conversion into <i>C</i> -Amino-, <i>C</i> -Azido-, <i>C</i> -Cyano-, or <i>C</i> -Alkylthiopyrazines	237
5.5.2.5	Miscellaneous Reactions	238
5.6	Appendix: Trivial Names for Pyrazine Derivatives	240
<b>CHAPTER 6 THIOPYRAZINES</b>		<b>245</b>
6.1	Pyrazinethiones and Pyrazinethiols	245
6.1.1	Preparation of Pyrazinethiones and Pyrazinethiols	245
6.1.2	Reactions of Pyrazinethiones and Pyrazinethiols	248
6.2	Alkylthiopyrazines and Dipyrazinyl Sulfides	251
6.2.1	Preparation of Alkylthiopyrazines	251
6.2.2	Reactions of Alkylthiopyrazines	252
6.2.2.1	Oxidation to Sulfoxides or Sulfones	252
6.2.2.2	Miscellaneous Reactions	254
6.3	Dipyrazinyl Disulfides and Pyrazinesulfonic Acid Derivatives	255
6.4	Pyrazine Sulfoxides and Sulfones	255
<b>CHAPTER 7 NITRO-, AMINO-, AND RELATED PYRAZINES</b>		<b>259</b>
7.1	Nitropyrazines	259
7.1.1	Preparation of Nitropyrazines	259
7.1.2	Reactions of Nitropyrazines	261
7.2	Nitrosopyrazines	262
7.2.1	<i>C</i> -Nitrosopyrazines	262
7.2.2	<i>N</i> -Nitrosopiperazines and Related Compounds	262
7.3	Regular Aminopyrazines	265
7.3.1	Preparation of Regular Aminopyrazines	265
7.3.2	Reactions of Regular Aminopyrazines	273
7.3.2.1	<i>N</i> -Acylation of Aminopyrazines and Subsequent Cyclizations	273
7.3.2.2	<i>N</i> -Alkylidenation of Aminopyrazines and Subsequent Cyclizations	277
7.3.2.3	<i>N</i> -Alkylation of Aminopyrazines and Subsequent Cyclizations	280

7.3.2.4	Conversion into Ureidopyrazines or Related Products	282
7.3.2.5	Conversion into Trialkylsilylamino-, Triphenylphosphoranylideneamino-, or Dimethylsulfimidopyrazines	285
7.3.2.6	Miscellaneous Minor Reactions	287
7.4	Preparation and Reactions of Hydrazinopyrazines	290
7.5	Preparation, Structure, and Reactions of Azidopyrazines	294
7.6	Nontautomeric Iminopyrazines	297
7.7	Arylazopyrazines	298
<b>CHAPTER 8 PYRAZINECARBOXYLIC ACIDS AND RELATED DERIVATIVES</b>		<b>299</b>
8.1	Pyrazinecarboxylic Acids	299
8.1.1	Preparation of Pyrazinecarboxylic Acids	299
8.1.2	Reactions of Pyrazinecarboxylic Acids	302
8.2	Pyrazinecarboxylic Esters	308
8.2.1	Preparation of Pyrazinecarboxylic Esters	308
8.2.2	Reactions of Pyrazinecarboxylic Esters	311
8.3	Pyrazinecarbonyl Halides	317
8.3.1	Preparation of Pyrazinecarbonyl Halides	317
8.3.2	Reactions of Pyrazinecarbonyl Halides	318
8.4	Pyrazinecarboxamides, Pyrazinecarboxamidines, and Related Derivatives	321
8.4.1	Preparation of Pyrazinecarboxamides and the Like	321
8.4.2	Reactions of Pyrazinecarboxamides and the Like	324
8.5	Pyrazinecarbohydrazides and Pyrazinecarbonyl Azides	328
8.6	Pyrazinecarbonitriles	330
8.6.1	Preparation of Pyrazinecarbonitriles	330
8.6.2	Reactions of Pyrazinecarbonitriles	331
8.7	Pyrazinecarbaldehydes	336
8.7.1	Preparation of Pyrazinecarbaldehydes	336
8.7.2	Reactions of Pyrazinecarbaldehydes	338
8.8	Pyrazine Ketones	340
8.8.1	Preparation of Pyrazine Ketones	341
8.8.2	Reactions of Pyrazine Ketones	343
8.9	Pyrazine Cyanates, Isocyanates, Thiocyanates, Isothiocyanates, and Carbonitrile Oxides	346
APPENDIX : Table of Simple Pyrazines		349
REFERENCES		461
INDEX		515

## CHAPTER 1

# Primary Syntheses from Aliphatic or Carbocyclic Synthons

Primary synthetic routes to pyrazines or hydroypyrazines from aliphatic or carbocyclic synthons are so numerous and diverse that any system of classification cannot be satisfactory in all respects. The approach adopted here is based on the ways in which the six ring atoms of pyrazine can be supplied by synthons, as indicated in the Contents headings.

In each subsection, any examples of syntheses that lead directly to pyrazines usually precede any that afford di-, tetra-, or hexahydropyrazines (piperazines) in that order. Examples of any pre-1978 syntheses in each broad category may be located from the cross-references (e.g., *H* 49) to appropriate subsections in Barlin's parent volume.<sup>1686</sup> Less comprehensive reviews of primary syntheses in the pyrazine series have appeared in recent years.<sup>743, 1287, 1426, 1677</sup>

### 1.1. FROM A SINGLE SIX-ATOM SYNTHON

Because of symmetry in the pyrazine ring, there are only two ways in which a pyrazine can be formed from a six-atom synthon: by completion of the N1—C2 bond or the C2—C3 bond. In most examples, the synthon has been isolated but not necessarily characterized prior to ring closure.

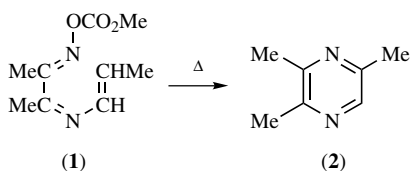
#### 1.1.1. By Completion of the N1—C2 Bond

The cyclization of an N—C—C—N—C—C synthon has been used widely to make pyrazines and hydroypyrazines. Because the terminal nitrogen atom is usually an amino or related group, examples are classified according to the substituent (or unsaturation) at the terminal carbon atom of the synthon: The nature of the synthon naturally determines the degree of aromaticity in the product.

##### 1.1.1.1. From Appropriate $\omega$ -Unsaturated Azaalkylamines (*H* 358)

This unusual synthesis is exemplified by the cyclization of methyl [1-methyl-2-(prop-2-enylimino)propylideneamino]carbonate (**1**) to 2,3,5-trimethylpyrazine

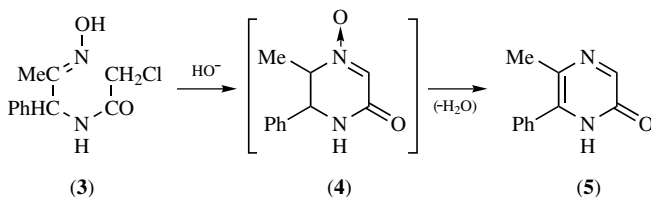
(2) in 63% yield by brief thermolysis in toluene at 300°C,<sup>839</sup> several analogues were prepared from comparable substrates.<sup>839, 1534</sup>



### 1.1.1.2. From Appropriate $\omega$ -Halogeno(azaalkylamines)

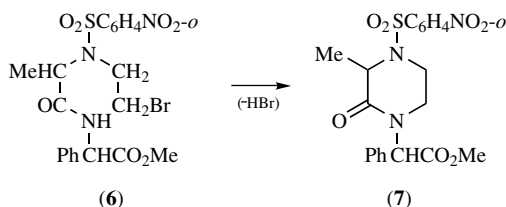
Such cyclizations are illustrated in the following examples:

1-(2-Chloroacetamido)-1-phenylacetone oxime (3) gave 5-methyl-6-phenyl-2 (1*H*)-pyrazinone (5) via the *N*-oxide (4) (NaOH, dioxane, 20°C, 20 h: 86%); several analogues of (4) and (5) were made similarly.<sup>544</sup>



Methyl 2-{2-[*N*-(2-bromoethyl)-*o*-nitrobenzenesulfonamido]propionamido}-2-phenylacetate (6) gave 1-( $\alpha$ -methoxycarbonylbenzyl)-3-methyl-4-*o*-nitrobenzenesulfonyl-3.4.5.6-tetrahydro-2(1*H*)-pyrazinone (7) [1,8-diazabicyclo [5,4,0]undec-7-ene, tetrahydrofuran(THF): > 95%].<sup>1622</sup>

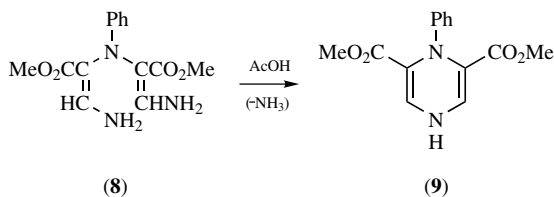
Also other examples.<sup>863, 1493, 1772</sup>



### 1.1.1.3. From Appropriate $\alpha, \omega$ -Diamino(azaalkanes)

This rare synthesis has been used to advantage in the conversion of *N,N*-bis(2-amino-1-methoxycarbonylvinyl)aniline (8) into dimethyl 1-phenyl-1,4-dihydro-

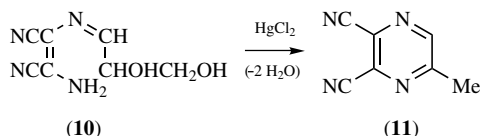
2,6-pyrazinedicarboxylate (**9**) (74%) by simply boiling in acetic acid for 20 min; analogues were made similarly.<sup>810</sup> Related examples have been reported.<sup>1767</sup>



#### 1.1.1.4. From Appropriate $\omega$ -Amino(azaalkanol)s (H 372)

This synthesis usually gives hydropyrazines but appropriate substituents in the substrate can ensure autooxidation to pyrazines, as illustrated in the first of the following examples:

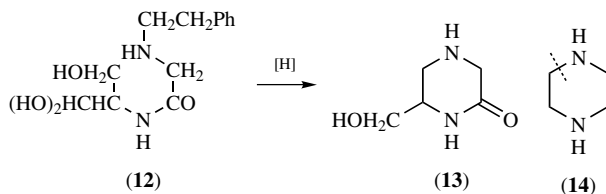
2-Amino-3-(2,3-dihydroxypropylideneamino)maleonitrile (**10**) gave 5-methyl-2,3-pyrazinedicarbonitrile (**11**) ( $\text{HgCl}_2$ ,  $\text{Me}_2\text{SO}$ ,  $25^\circ\text{C}$ , 3 h: 60%).<sup>76</sup>



2-[2-(Benzoyloxycarbonylamino)acetamido]-3-hydroxypropionaldehyde hydrate (**12**) gave 6-hydroxymethyl-3,4,5,6-tetrahydro-2 (1*H*)-pyrazinone (**13**) ( $\text{Pd/C}$ ,  $\text{MeOH}$ ,  $\text{H}_2$ , 50 atm,  $20^\circ\text{C}$ , 24 h: 96%).<sup>1061</sup>

2-(2-Aminoethylamino)ethanol gave piperazine (**14**) ( $\text{Cu}-\text{Al}_2\text{O}_3$  catalyst, continuous flow,  $200^\circ\text{C}$ : 95%).<sup>1064</sup>

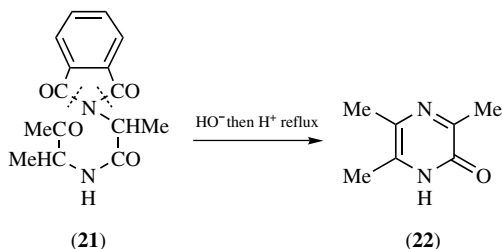
Also other examples.<sup>1330, 1641</sup>



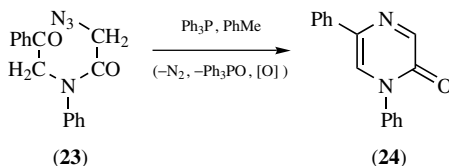
#### 1.1.1.5. From Appropriate $\omega$ -Amino(azaalkanol)s (H 49)

In this type of synthesis, the substrate's aldehyde group is usually present as an acetal and its amino group may sometimes form part of a terminal amido group. Such possibilities are illustrated in some of the following examples:

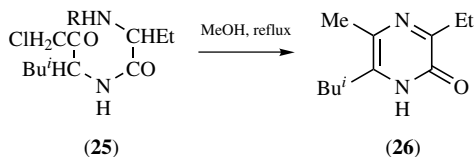




2-Azido-*N*-phenacyl-*N*-phenylacetamide (**23**) gave 1,5-diphenyl-2(1*H*)-pyrazinone (**24**) ( $\text{Ph}_3\text{P}$ ,  $\text{PhMe}$ ,  $20^\circ\text{C}$ , 20 h: 35%; the evident oxidation was not aerial); analogues likewise.<sup>555</sup>

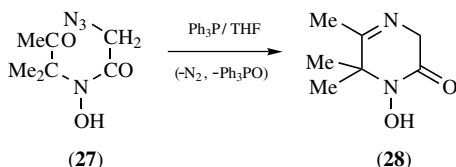


2-Amino-*N*-(1-chloroacetyl-3-methylbutyl)butyramide (**25**,  $\text{R} = \text{H}$ ), prepared *in situ* as hydrochloride by treatment of its *N*-*tert*-butoxycarbonyl derivative (**25**,  $\text{R} = \text{CO}_2\text{Bu}^t$ ) in  $\text{HCl}$ -dioxane, gave 3-ethyl-6-isobutyl-5-methyl-2(1*H*)-pyrazinone (**26**) ( $\text{MeOH}$ , reflux, 2 h: 90%);<sup>389</sup> many analogues were made similarly.<sup>118, 121, 175, 389, 1452, 1491</sup>



*N*-(1-Acetyl-1-methylethyl)-2-azido-*N*-hydroxyacetamide (**27**) gave 1-hydroxy-5,6,6-trimethyl-3,6-dihydro-2(1*H*)-pyrazinone (**28**) ( $\text{Ph}_3\text{P}$ ,  $\text{THF}$ ,  $20^\circ\text{C}$ , 24 h: 79%).<sup>424</sup>

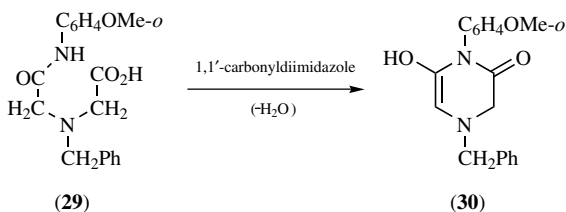
Also other examples.<sup>416, 1031, 1101, 1386, 1628, 1743</sup>



### 1.1.1.7. From Appropriate $\omega$ -Amino(azaalkanoic) Acids

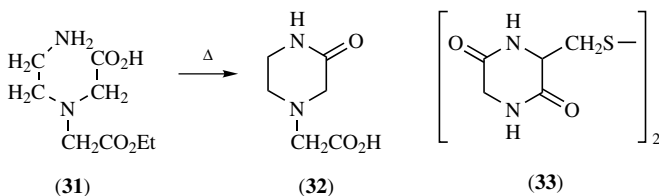
Such substrates have been used occasionally, as illustrated in the following examples:

*N*-Benzyl-*N*-[(*N*-*o*-methoxyphenylcarbamoyl)methyl]glycine (**29**) underwent dehydrative cyclization to 4-benzyl-6-hydroxy-1-*o*-methoxyphenyl-3,4-dihydro-2(1*H*)-pyrazinone (**30**) (1,1'-carbonyldiimidazole, THF,  $-30 \rightarrow 65^\circ\text{C}$ , 17 h: 83%; other reagents gave lower yields).<sup>487</sup>



*N*-(2-Aminoethyl)-*N*-carboxymethylglycine (**31**) gave 4-carboxymethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrazinone (**32**) ( $\text{Me}_2\text{NCHO}$ , reflux: ?%).<sup>820</sup>

Also the formation of bis(3,6-dioxopiperazin-2-ylmethyl)disulfide (**33**)<sup>1440</sup> and other examples.<sup>671, 1748, 1759, 1770</sup>

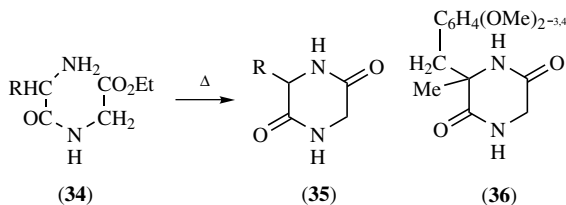


### 1.1.1.8. From Appropriate $\omega$ -Amino (azaalkanoic) Esters (H 363, 369)

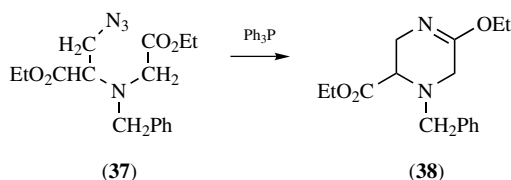
Such cyclizations have been used extensively, especially to prepare hydropyrazines. The amino group of the substrate may be replaced by an azido group or it may be used (especially for chiral syntheses) in a protected form: In the latter case, deprotection is usually done prior to cyclization albeit in a one-pot sequence; the ester group of the substrate may be replaced by a terminal lactonic grouping.<sup>813</sup> The following examples illustrate some such possibilities:

Ethyl *N*-(2-amino-3-methylbutyryl)glycinate (**34**,  $\text{R} = \text{Pr}^i$ ) gave 3-isopropyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**35**,  $\text{R} = \text{Pr}^i$ ) (PhMe, reflux, 24 h: 79%);<sup>1351</sup> similar procedures afforded the 3-isobutyl homologue (**35**,  $\text{R} = \text{Bu}^i$ ) (71%)<sup>193</sup> and 3-(3,4-dimethoxybenzyl)-3-methyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**36**) (81%).<sup>188</sup>

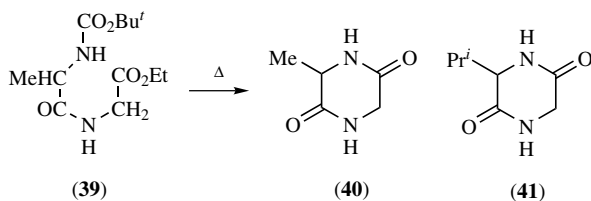




Ethyl *N*-(2-azido-1-ethoxycarbonyl-ethyl)-*N*-benzylglycinate (**37**) gave ethyl 1-benzyl-5-ethoxy-1,2,3,6-tetrahydro-2-pyrazinecarboxylate (**38**) (Ph<sub>3</sub>P, PhMe, 100°C, 9 h: 58%).<sup>1468</sup>

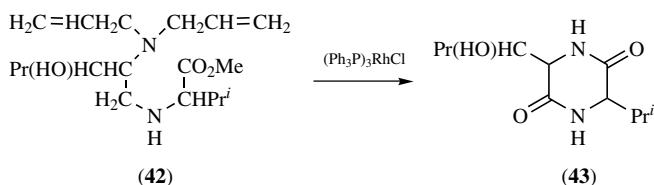


Ethyl *N*-[2-(*tert*-butoxycarbonylamino)propionyl]glycinate (**39**) gave 3-methyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**40**) (200°C, A, 30 min: > 95%; mechanism?),<sup>1616</sup> an homologous product, 3-isopropyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**41**) was made somewhat similarly but in two stages (Pd/C, MeOH—CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>, 24 h; then PhMe, reflux, 12 h: 65%).<sup>50</sup>



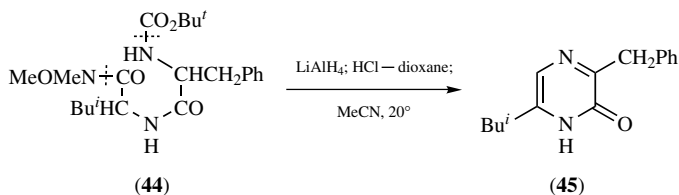
Methyl *N*-(2-diallylamino-3-hydroxyhexyl)-2-isopropylglycinate (**42**) gave 6-(1-hydroxybutyl)-3-isopropyl-3,4,5,6-tetrahydro-2(1*H*)-pyrazinone (**43**) [(Ph<sub>3</sub>P)<sub>3</sub>RhCl, MeCN—H<sub>2</sub>O, distillation (see original for details), 5 h: 47%].<sup>404</sup>

Also other examples.<sup>182, 189, 229, 703, 813, 843, 1347, 1465, 1495, 1498, 1535, 1750</sup>



### 1.1.1.9. From Appropriate $\omega$ -Amino(azaalkanamides)

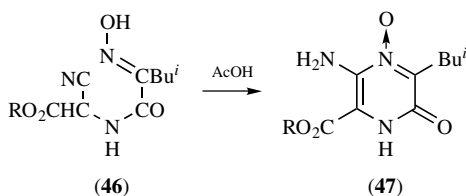
Such substrates are seldom used but *tert*-butyl {1-[1-(*N*-methoxy-*N*-methylcarbamoyl)-3-methylbutyl]carbamoyl -2-phenylethyl}aminoformate (**44**) gave 3-benzyl-6-isobutyl-2(1*H*)-pyrazinone (**45**) (21%) by two deprotections ( $\text{LiAlH}_4$ ; and  $\text{HCl}$ —dioxane) and a final cyclization in acetonitrile during 13 h.<sup>1510</sup>



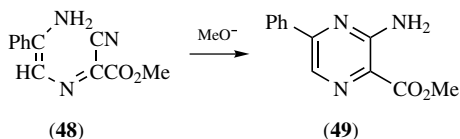
### 1.1.1.10. From Appropriate $\omega$ -Amino(azaalkanenitriles) (H 49, 344)

These nitriles are usually employed to afford aromatic pyrazinamines but they can be used to produce hydroypyrazinamines, chloropyrazinamines, or even pyrazines without an amino substituent. The following cyclizations illustrate some of these uses:

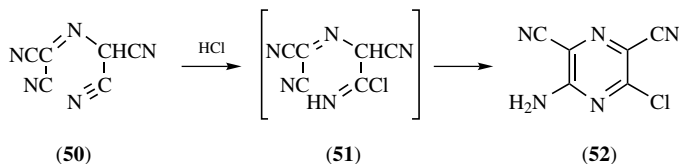
Methyl 2-cyano-*N*-(2-hydroxyimino-4-methylvaleryl)glycinate (**46**, R = Me) gave methyl 3-amino-5-isobutyl-6-oxo-1, 6-dihydro-2-pyrazinecarboxylate 4-oxide (**47**, R = Me) ( $\text{AcOH}$ , 70°C, 3 h: > 32%),<sup>337</sup> the ethyl ester (**47**, R = Et) (> 62%) was made similarly.<sup>848</sup>



Methyl 2-( $\beta$ -aminostyrylimino)-2-cyanoacetate (**48**) gave methyl 3-amino-5-phenyl-2-pyrazinecarboxylate (**49**) ( $\text{MeONa}$ ,  $\text{MeOH}$ — $\text{CH}_2\text{Cl}_2$ , 20°C, 15 min: 70%).<sup>941</sup>

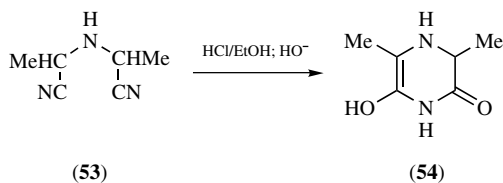


$\alpha$ -(Dicyanomethyleneamino)malononitrile (**50**) underwent addition of hydrogen chloride to afford the unisolated iminonitrile (**51**) and thence 3-amino-5-chloro-2,6-pyrazinedicarbonitrile (**52**) (HCl—AcMe, reflux, 10 min: 43%).<sup>447</sup>



2,2'-Iminodipropiononitrile (**53**) gave 6-hydroxy-3,5-dimethyl-3,4-dihydro-2(1*H*)-pyrazinone (**54**) (HCl/EtOH, 0°C, 12 h; then Na<sub>2</sub>CO<sub>3</sub>—H<sub>2</sub>O: 18%; by a yet unconfirmed mechanism).<sup>577</sup>

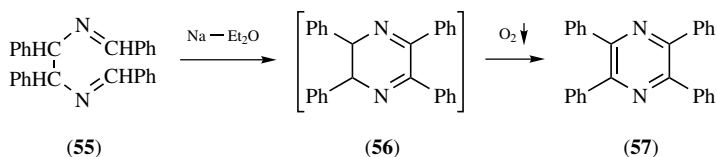
Also other examples.<sup>436, 747, 749, 1180, 1284</sup>



### 1.1.2. By Completion of the C2-C3 Bond

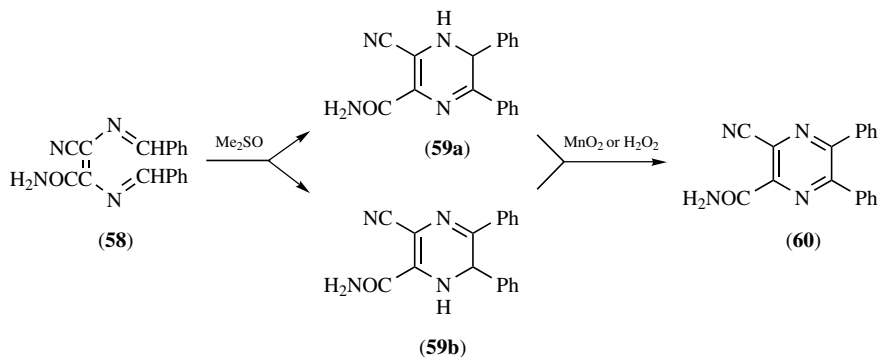
Not unnaturally, the synthesis of a pyrazine or hydroypyrazine from a single C—N—C—C—N—C synthon is rare. However, the cyclization of *N,N'*-dibenzylidene or *N,N'*-diacyl derivatives of ethylenediamines has proven possible, as indicated in the following examples:

1,2-Bis (benzylideneamino)-1,2-diphenylethane (**55**) gave 2,3,5,6-tetraphenylpyrazine (**57**), via the unisolated 2,3-dihydro derivative (**56**) (Na—Et<sub>2</sub>O, reflux, N<sub>2</sub>, 6 h; then O<sub>2</sub> ↓, 20°C, 10 min: 90%).<sup>138</sup>

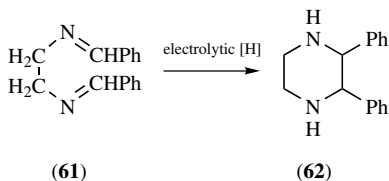


2,3-Bis(benzylideneamino)-2-cyanoacrylamide (**58**) gave a separable mixture of 3-cyano-5,6-diphenyl-4,5-dihydro- (**59a**) and 3-cyano-5,6-diphenyl-1,6-dihydro-2-pyrazinecarboxamide (**59b**) (Me<sub>2</sub>SO, 80°C, 10 min: 10 and 68%, respectively);

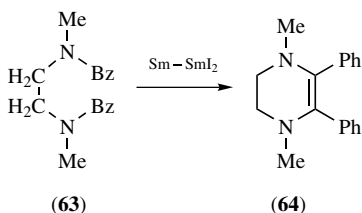
oxidation of either product gave 3-cyano-5,6-diphenyl-2-pyrazinecarboxamide (**60**) ( $\text{MnO}_2$ ,  $\text{Me}_2\text{NCHO}$ ,  $60^\circ\text{C}$ , 12 h: 80%; or  $\text{H}_2\text{O}_2$ ,  $\text{MeOH}$ ,  $55^\circ\text{C}$ , 8 h: 30%); several substituted-phenyl derivatives were made likewise.<sup>752</sup>



1,2-Bis(benzylideneamino)ethane (**61**) afforded 2,3-diphenylpiperazine (**62**) ( $\text{TsONeEt}_4$ ,  $\text{MsOH}$ ,  $\text{Me}_2\text{NCHO}$ , Pb cathode, 0.5 amp: 95%); analogues likewise.<sup>845</sup>



1,2-Bis(*N*-methylbenzamido)ethane (**63**) gave 1,4-dimethyl-2,3-diphenyl-1,4,5,6-tetrahydropyrazine (**64**) ( $\text{Sm}-\text{SmI}_2$ , THF,  $67^\circ\text{C}$ , 3 h: 62%).<sup>463</sup>



## 1.2. FROM TWO SYNTHONS

Most of the primary syntheses from aliphatic or carbocyclic substrates fall into this category, which is subdivided successively according to the number and the type of ring atoms supplied by each synthon.

### 1.2.1. By Using a One-Atom and a Five-Atom Synthon

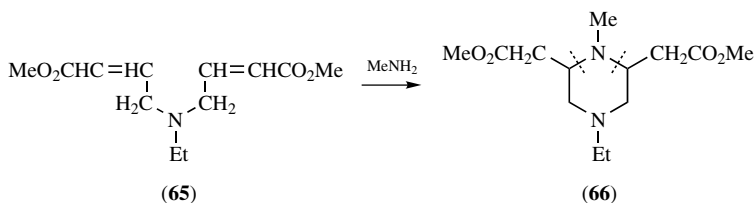
The one-atom synthon may supply either N1 or C2 but nearly all known examples fall into the first of these subcategories.

#### 1.2.1.1. Where the One-Atom Synthon Supplies N1 (H 49)

Such one-atom synthons are normally ammonia or a primary or secondary amine. The following examples are therefore classified according to the type of five-atom cosynthon used:

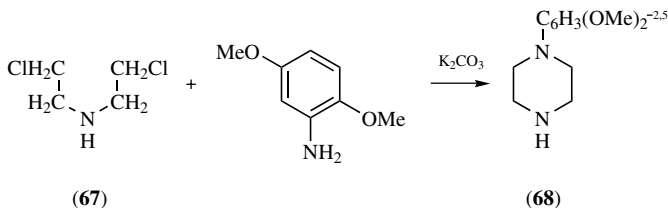
##### With 1,5-Dialkylidene-3-azapentanes

*N*-Ethyl-*N,N*-bis(3-methoxycarbonylallyl)amine (**65**) gave 1-ethyl-3,5-bis(methoxycarbonylmethyl)-4-methylpiperazine (**66**) (MeNH<sub>2</sub>, MeOH, 0 → 25°C, ? h: 69%); homologues likewise.<sup>1494</sup>



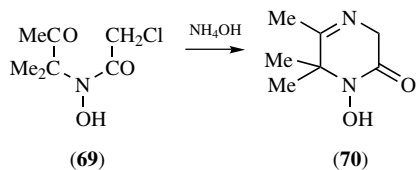
##### With 1,5-Dihalogeno-3-azapentanes

Bis(2-chloroethyl)amine (**67**) and 2,5-dimethoxyaniline gave 1-(2,5-dimethoxyphenyl)piperazine (**68**) ( $\text{K}_2\text{CO}_3$ ,  $\text{MeOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OMe}$ , reflux, 48 h: 62%).<sup>610</sup>



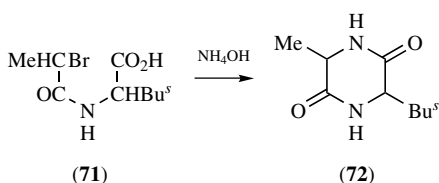
##### With 5-Halogeno-3-azapentanyl Ketones or Aldehydes

*N*-(1-Acetyl-1-methylethyl)-2-chloro-*N*-hydroxyacetamide (**69**) gave 1-hydroxy-5,6,6-trimethyl-3,6-dihydro-2(1*H*)-pyrazinone (**70**) ( $\text{NH}_4\text{OH}$ — $\text{EtOH}$ —dioxane, 20°C, 3 days: 8%); likewise one homologue.<sup>424</sup> Aldehydes gave better results under reductive conditions.<sup>1768</sup>



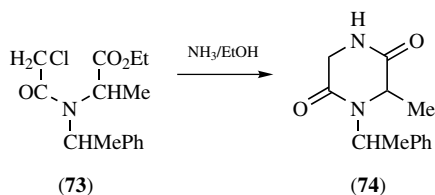
### With 5-Halogeno-3-azapentanoic Acids or Esters

2-(2-Bromopropionamido)-3-methylvaleric acid (**71**) gave 3-*sec*-butyl-6-methyl-3,6-dihydro-2,5 (1*H*,4*H*)-pyrazinedione (**72**) ( $\text{NH}_4\text{OH}$ ,  $20^\circ\text{C}$ , 7 days, volatiles  $\uparrow$ ;  $\text{PhOH}$ ,  $145^\circ\text{C}$ , 2 h: 73%).<sup>317</sup>



Ethyl 2-[2-chloro-*N*-(1-phenylethyl)acetamido]propionamide (**73**) gave 3-methyl-4-(1-phenylethyl)-3,6-dihydro-2,5 (1*H*,4*H*)-pyrazinedione (**74**) (7 M  $\text{NH}_3/\text{EtOH}$ ,  $20^\circ\text{C}$ , 24 h: ?%).<sup>1349</sup>

Also other examples.<sup>890</sup>



### With 3-Aza-1,5-pentanediois

A neat mixture of diethanolamine hydrochloride and aniline hydrochloride gave 1-phenylpiperazine (**75**) (microwave irradiation, Dean–Stark, 12 min: 50%);<sup>1197</sup> also related examples.<sup>1066, 1197</sup>

Diethanolamine and *m*-(trifluoromethylthio)aniline gave 1-[*m*-(trifluoromethylthio)phenyl]piperazine (**76**) ( $\text{HCl}$  gas  $\downarrow$ ,  $\sim 190^\circ\text{C}$ , 1 h; then  $240^\circ\text{C}$ , 90 min: 33%); analogues likewise.<sup>592</sup>

Also other examples.<sup>814, 894</sup>

*Note:* It seems relevant that aqueous solutions of *N*-methyldiethanolamine (**77**), employed to remove  $\text{H}_2\text{S}$  from hydrocarbon gases, gradually accumulate *inter alia* 1,4-dimethyl-, 1-(2-hydroxyethyl)-4-methyl-, and 1,4-bis(2-hydroxyethyl)piperazine.<sup>1583</sup>