AZEPINES
Part 2

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AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS
NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

An Interscience® Publication
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Library of Congress Cataloging in Publication Data:

Azepines.

(Chemistry of heterocyclic compounds, ISSN 0069-3154; v. 43)

Pt. 1: authors, Burt Renfroe, Clinton Harrington, George R. Proctor; pt. 2: authors, Jeffrey W.H. Watthey, James Stanton, Norton P. Peet.

"An Interscience publication."

Includes bibliographies and indexes.

1. Azepines. I. Renfroe, Burt. 2. Watthey, Jeffrey, W.H. III. Rosowsky, Andre. IV. Series.

QD401.A97 1984 547'.593 83-3497

ISBN 0-471-01878-3 (v. 1)

ISBN 0-471-89592-X (v. 2)

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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This is the forty-third volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

Editors

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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.

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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.

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Preface

Heterocyclic systems with seven atoms, once considered chemical oddities, are today just as easily obtained as their five- and six-membered cousins, thanks to the very substantial advances in synthetic art that have been made in this field over the past 20 years. In a previous volume of the *Heterocyclic Compounds* (Volume 26), seven-membered oxygen ring systems (oxepins) and sulfur ring systems (thiepins) were reviewed. The present two-part volume extends this coverage to the seven-membered nitrogen heterocycles (azepines).

As with the oxepins and thiepins, interest in the azepines encompasses a broad spectrum of theoretical and applied disciplines. At the theoretical level, chemists are fascinated by these compounds from the molecular orbital standpoint. Of particular importance in this regard are the azulenoid cyclopentazepine ring systems, the bridgehead nitrogen benz[*a*]azepinium cation, the bridged annulene system 11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene (''1,6-azirino[10]annulene''), and the still unknown cycl[4.4.3]azine. At the ''applied'' end of the spectrum, one hardly need be reminded of the enormous amount of research that has been conducted in pharmaceutical laboratories since the early 1960s on tranquilizers, antidepressants, and other psychotropic drugs of the benzodiazepine and dibenzazepine class. Probably more than any other factor, the vast commercial success of these medicinal agents and their benefit to society have caused the chemistry of condensed azepines to evolve into a major area of research in heterocyclic chemistry. One of the consequences of this effort has been the appearance, on the chemical scene, of a host of new ring systems which collectively form a dazzling array of structural types. It is the purpose of this two-part volume to give an account of the current state of knowledge concerning the synthesis, chemical reactions, and physical properties of some—though by no means all—of these systems, with particular emphasis on those facets that pertain to the ''seven-memberedness'' of the azepine ring.

Part 1 consists of two chapters. Chapter I (Renfroe and Harrington) is devoted to tricyclic systems containing an azepine ring along with two other other rings that can be either carbocyclic or heterocyclic. This category includes no fewer than 150 different heterocyclic systems, ranging from oxireno[*d*][2]benzazepines (a 3,6,7-system) to benzo[*e*]cyclooct[*b*]azepines (a, 6,7,8-system). The largest single family, the dibenz [*b,f*]azepines, has as its most famous members the antidepressant imipramine and its congeners, such as carbamazepine. Other dibenzazepines of pharmaceutical interest are the dibenz[*c,e*]azepines, a number of which possess hypotensive activity. Certain tricyclic azepine ring systems are also noteworthy because they appear in natural products. Here may be cited certain alkaloids of the rheadan family (1,3-dioxolo[4,5-*h*][3]benzazepines) and at least three groups of indole

alkaloids, the erythroidine and tuberostemonine family (azepino[3,2,1-*hi*]indoles), the naucladerine family (azepino[4,5-*b*]indoles), and the ergot family (azepino[5,4,3-*cd*]indoles). Additionally, fused tricyclic azepine systems have been generated from tricyclic terpene ketones (e.g., santonin) via ring enlargement. The identification and characterization of the products from these reactions have played an important role in increasing our understanding of the mechanism of the Schmidt and Beckmann rearrangements and in providing model systems for the synthesis of ring-enlarged azasteroid analogues.

Chapter II (Proctor) presents a review of the chemistry of bicyclic, as opposed to tricyclic, azepine derivatives. Here again a substantial number of fused, bridged, and spiran systems are covered, with emphasis being placed again on the seven-membered ring. Among these compounds the 1-, 2-, and 3-benzazepines are of interest because of their potential psychopharmacologic activity. A novel class of antiviral agents also cited in this chapter consists of compounds belonging to the bridged 1,6-azirino[10]annulene ring system. The development of these compounds represents an intriguing blend of "pure" and "applied" heterocyclic chemistry.

Part 2 also consists of two chapters. Chapter I (Watthey and Stanton) covers the tricyclic diazepine systems, a number of which have attracted attention because of the pharmaceutical importance of some of their members. Here may be cited anxiolytic agents such as benzazepam, oxazolam, and triazolam; antidepressants such as dibenzopin; and antipsychotic agents such as clozapine. All these tricyclic azepine derivatives have contributed in a major way to the modern treatment of mental illness. Another example of a biologically important class of tricyclic azepine derivatives is provided by the anthramycin antibiotics (pyrrolo[2,1-*c*][1,4]benzodiazepines), which have shown impressive activity as antineoplastic agents.

The practical importance of azepine derivatives is by no means limited to medical applications. For example, among the ring systems discussed in Chapter II (Peet) are the 1,2,5-triazepines, some of which have found use in the agricultural field as pesticidal plant protectants. Other triazepines, of the 1,3,5-type with *N*-nitro substituents, have been investigated as high explosives.

In summary, the two-part volume for which this Preface is written bears witness to the fact that seven-membered heterocyclic compounds are no longer the esoteric species they were once considered to be. Quite to the contrary, the pace of research and development in this area is accelerating, and there seems to be virtually no limit to the number of interesting ring systems that can be created in the laboratory by a combination of ingenuity and perseverance. The future should bring rich rewards not only in terms of new academic knowledge but also in terms of practical applications that will benefit us all, chemists and nonchemists alike. I wish to gratefully thank the several authors who have joined me in preparing this review. Their thoroughness and limitless patience cannot be sufficiently praised. Thanks

are due, as well, to Drs. Arnold Weissberger and Edward C. Taylor for their encouragement and support of the project, and to the capable staff at John Wiley & Sons for their expeditious handling of these chapters.

ANDRE ROSOWSKY

Boston, Massachusetts
January 1984

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