# SPECIAL TOPICS IN HETEROCYCLIC CHEMISTRY

Edited by

Arnold Weissberger Edward C. Taylor

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AN INTERSCIENCE®PUBLICATION

JOHN WILEY & SONS
NEW YORK - LONDON - SYDNEY - TORONTO

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11 10

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Library of Congress Cataloging in Publication Datas

(The Chemistry of heterocyclic compounds; v. 30)

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An Interscience ® Publication

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#### Library of Congress Cataloging in Publication Data:

Main entry under title:

Special topics in heterocyclic chemistry.

(The Chemistry of heterocyclic compounds; v. 30)

"An Interscience publication."

Bibliography: p.

1. Heterocyclic compounds—Addresses, essays, lectures.

I. Weissberger, Arnold, 1898-. II. Taylor, Edward Baylon Angel Baylon Angel Market Mar

Curtis, 1923-

QD400.S512 547'.59 76-10672

ISBN 0-471-67253-X

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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#### 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.

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#### Concerning Special Topics in Heterocyclic Chemistry

This volume is the first in the series "The Chemistry of Heterocyclic Compounds" to contain collected treatments of topics not necessarily related to each other and not comprising sufficient pages to be issued individually. Since the series' inception about 25 years ago, volumes have contained exhaustive discussions of syntheses, reactions, properties, structure, physical chemistry, and so on, of compounds belonging to a specific ring system (such as pyridines, thiophenes, pyrimidines, and indoles). This series has become the basic reference collection for information on heterocyclic compounds.

The series "General Heterocyclic Chemistry," initiated in 1971, is devoted to those disciplines of heterocyclic chemistry that are of general significance and application, and that are of interest to all organic chemists as well as to those whose particular concern is heterocyclic chemistry. Each volume in this series surveys the entire field of heterocyc-

lic chemistry rather than a particular ring system.

We have long felt a need for an additional forum for discussions of topics of more limited scope whose treatment in a separate monograph might not be appropriate. We hope that readers and research workers in the field will comment on the usefulness of this new forum, we welcome suggestions for improvements and contributions to future volumes.

ARNOLD WEISSBERGER EDWARD C. TAYLOR

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#### CHAPTER I

## 5,5-Systems with a Bridgehead Nitrogen Atom

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#### I. Introduction

The systems we discuss in this chapter are those 5,5 fused ring systems with a bridgehead nitrogen atom which have  $\pi$ -electrons in mutual cyclic

1.2 4-triazole (12)

2. Boekefhelde and Federu

from 1-alkyl imidazoles (13)

conjugation or for which the tautomeric potential for this condition exists. These systems contain  $10 \pi$ -electrons and as the bridgehead nitrogen atoms of such molecules contribute two  $\pi$ -electrons, the systems will of necessity be anions (e.g., 1) or contain one or two other heteroatoms that can contribute two  $\pi$ -electrons. The introduction of one other heteroafom contributing two  $\pi$ -electrons (e.g., 2) gives a neutral molecule and the introduction of a second heteroatom contributing two π-electrons gives a cation (e.g., 3). Polycyclic systems containing these 5,5 groupings will also be considered. Cyclazines, in which the nitrogen

atom is common to three rings, and mesoionic systems are discussed in other chapters.

No preference is given to any one definition of aromaticity, 2a,b and the term is used in its broadest sense.

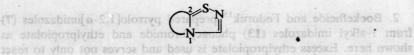
The term pyridine type nitrogen refers to a ring nitrogen atom contributing one  $\pi$ -electron to the system, and a pyrrole type nitrogen is one that contributes two  $\pi$ -electrons to the system.

Chemical Abstracts has been covered through December, 1972; later selected references are also included.

#### II. Synthesis

The formation of fused ring systems with bridgehead nitrogen atoms usually involves the building of one ring onto an existing ring, although there are examples in which both rings are formed during the course of the reaction. We deal with the former type first, discussing those ring closures that produced 5,5 systems.

For convenience, the following notation is used in designating systems. The bridgehead nitrogen is "1" and the other bridgehead atom "2" and nitrogen is given preference in nomenclature. The example shown would be a [1,4,3]thiadiazole.



#### A. Pyrroles nitrogen atoms of such molecules contribute two melectrons, the systems

exists.1 These systems contain

1. The reaction of a 2-alkyl system (4) with an  $\alpha$ -halo carbonyl compound gives a quaternary salt (5) which cyclizes, in base, to a pyrrole ring (6). Sodium bicarbonate, 3-6 sodium carbonate, 7.8 sodium ethoxide, 9,10 and triethylamine 11 and sodium acetate-acetic anhydride have all been used as bases.

$$R = H, \text{ alkyl, aryl or } N - C - C_6H_5$$

$$R' = \text{alkyl or aryl}$$

$$R'' = H \text{ or alkyl}$$

$$R'' = H \text{ or alkyl}$$

This procedure has been used extensively for the preparation pyrrolo-[1,2-a]imidazoles<sup>3,5</sup> (7), pyrrolo[1,2-a]benzimidazoles (8),<sup>3,4,7,8,10</sup> pyrrolo[2,1-b]thiazoles (9),<sup>11,12,14</sup> pyrrolo[2,1-b]benzothiazoles (10),<sup>13,14</sup> 7H-naptho[2,1-d]pyrrolo[1,2-a]imidazoles (11)9 and pyrrolo[1,2-b]-1,2,4-triazole (12)°.

H. Synthes

2. Boekelheide and Fedoruk<sup>15</sup> prepared pyrrolo[1,2-a]imidazoles (7) from 1-alkyl imidazoles (13) phenacylbromide and ethylpropiolate as shown here. Excess ethylpropiolate is used and serves not only to react with the ylid (15) but also to dehydrogenate the apparent intermediate (16).

3. Dimethylacetylene dicarboxylate reacts with compounds with pyridine type nitrogens. Thiazole and benzothiazole (18) reacted with two moles of diethylacetylene dicarboxylate to give the corresponding triester

(19). The benzothiazole was obtained in better yield (40%) than pyrrolo[2,1-b]thiazole (8.5%). While these workers did not obtain any pyrrolothiazole when a 2-alkyl thiazole was used (they did however obtain some other interesting compounds), Acheson and Tully<sup>17</sup> were able to obtain a pyrrolo[2,1-b]benzimidazole (21) (among other products) from the reaction of 2-ethyl-1-methylbenzimidazole (20) and diethylacetylene dicarboxylate. Such a result indicates that the 2-carbon (and alkyl substituent, if any) is one of the two carbon atoms lost in this process.

4. The intramolecular alkylation of benzylhalide of type 22 (followed by abstraction of HX with base) gives fused pyrroles of type 23. This procedure was used by Babichev and Kibirev<sup>18</sup> for the preparation of isoindolo[1,2-b]benzothiazole (24), and by a group at Merck<sup>19</sup> for the preparation of derivatives of imidazo[2,1-a]isoindole (25).

$$\begin{array}{c}
 & \begin{array}{c}
 & \begin{array}{c}
 & 1)\Delta \\
 & 2) \text{ base}
\end{array} \\
 & X \\
 & 22 \\
 & X = \text{Cl or Br}
\end{array}$$

5. Manjunath<sup>20</sup> obtained a substance which he called "8,9-(1,2-cyclohexyl)tetrahydrocarbazole" from the interaction of 9-nitroso-1,2,3,4-tetrahydrocarbazole (26; R=H), cyclohexanone, zinc, and acetic

T .(VE) muibods

acid. Lions and Ritchie<sup>21</sup> pointed out that Manjunath had reported an incorrect structural formula. They designated structure 27, a normal product of the Fisher indole synthesis, as being the correct structure.

NO 
$$Z_{n-HOAc}$$
  $Z_{n-HOAc}$   $Z_{n-HOAc}$ 

[They prepared a 6-methyl derivative (27; R=CH<sub>3</sub>) using the same approach.] 8-Methyl-9-nitrosocarbazole (28); in which the ortho position is blocked, failed to give a similar substance, which is to be expected if structure 27 is correct.

Manjunath<sup>20</sup> also prepared the hydrazone (29) but was unable to effect a Fisher ring closure with it. Preston and Tucker<sup>22</sup> accomplished this by treating this hydrazone with dry HCl in tetralin at 160° and obtained the tetrahydro indolo[3,2,1-i,l]carbozole (30).

6. The Pschorr reaction was used by Preston and Tucker<sup>22</sup> to prepare indolo[3,2,1-i,k]carbazole (22) from 1-amino-9-phenyl carbazole (31).

7. Kovtinenko and Babichev<sup>23</sup> alkylated 1-alkyl-2-methyl benzimidazoles (33) with an alkyl halide having the halogen atom on a methylene group, to give quaternary salts of type 34. Treatment of these salts with anhydrides gave pyrrolo[1,2-a]benzimidazoles of type 35.

8. In their study on diynes, Muller and Zountsas<sup>24</sup> prepared fused pyrroloindoles. Tris(triphenylphosphine)rhodium chloride acted on the

$$CH_{2}-C \equiv C-Ph$$

$$Rh(PPh_{3})CI$$

$$Rh-Cl$$

$$Ph$$

$$Rh-Cl$$

$$Ph$$

$$R-C=C-R$$

$$Ph$$

$$R = Ph \text{ or } COOC_{2}H$$

$$R$$

$$R = Ph \text{ or } COOC_{2}H$$

diacetylenic benzimidazole (36) to give chloro 1H-pyrrolo[1,2-a]-benzimidazole-2,3-diylidenbis (phenylmethylidyne)bistriphenylphosphine rhodium (37). Treatment of this rhodium compound with selenium gave 1,3-diphenyl-10H-seleno[3',4':3,4]pyrrolo[1,2-a]benzimidazole (38). The rhodium compound (37) reacted with disubstituted aceytenes to form

the 11H-isoindolo[2,1/a]benzimidazole (39). (These compounds are written in the "methylene" form but the potential for tautomerism to the N-H form exists—see tautomerism.)

9 Likhitskaya and Babichev<sup>25</sup> used the reaction of 2-(2-hydroxymethylphenyl)benzoselenazole (40) and phosphorous tribromide to prepare isoindolo[1,2-b]benzoselenazole as the hydrobromide salt (41). Treat-

(445)

ment of this salt with sodium hydroxide gives the free base 42. Pyrido-[2,3-c]benzoselenazolo-[3,2-a]pyrrole (43).

10. Quarternary salts of heterocyclic systems having an active Nmethylene group and an open carbon  $\alpha$  to the nitrogen (e.g., 44) react with picryl chloride (45) to form a pyrrole ring.

$$\begin{array}{c} CH_3 \\ NO_2 \\ NO_2 \\ \hline P \cdot Br - C_6H_4 - C = O \\ \hline \end{array}$$

$$\begin{array}{c} CH_3 \\ NO_2 \\ \hline \\ VCH_2 \\ \hline \\ VCH_2 \\ \hline \\ VCH_2 \\ \hline \\ VCH_2 \\ \hline \\ VCH_3 \\ \hline \\ VCH_3 \\ \hline \\ VCH_3 \\ \hline \\ VCH_3 \\ \hline \\ VCH_4 \\ \hline \\ VCH_3 \\ \hline \\ VCH_4 \\ \hline \\ VCH_5 \\ \hline \\ VCH_5$$

Reuschling and Krohnke<sup>86</sup> used this reaction to prepare the 1,3-dinitro-5-methyl-11-(4-bromobenzoyl)-5H-benzimidazo[2,1-a]isoindole (46) which was debenzoylated in sulfuric acid (giving 47). In like manner, 6,8-dinitrothiazolo[2,3-a]isoindole (48) was prepared. The electron withdrawing effect of the third nitro group of picryl chloride can be simulated by a fused benzene ring as 1-chloro-2,4-dinitronaphthalone was used to prepare 5-nitro-7-methyl-7H-benzimidazo[2,1-a]benz[e]isoindole (49).

#### **B.** Pyrazoles

ment of this salt with sodium

es the free base 42. Pyrido-.

1. Becker and Bottcher<sup>26</sup> used the Wolff reaction to effect the ring contraction of **50** to a pyrazole (**51**).

2. Claramunt, Fabrega, and Elguero<sup>27</sup> reported that 3,4-diaminotriazole (52) reacts with ethylacetoacetate to give the diazepinone (53). Treatment of this compound in hot acetic anhydride gave the acetyl