PYRAZOLES, PYRAZOLIDINES, INDAZOLES AND CONDENSED RINGS

Edited by Richard H. Wiley
Hunter College, The City University of New York, New York

Authors
Lyell C. Behr
College of Arts and Sciences, State College, Mississippi

Raffaello Fusco
Institute of Industrial Chemistry, University of Milan, Milan, Italy

C. H. Jarboe
Department of Pharmacology, University of Louisville, Louisville, Kentucky

1967
INTERSCIENCE PUBLISHERS
a division of John Wiley & Sons
New York - London - Sydney
PYRAZOLES, PYRAZOLINES, PYRAZOLIDINES, INDAZOLES AND CONDENSED RINGS

This is the twenty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
PYRAZOLES, PYRAZOLINES, 
PYRAZOLIDINES, INDAZOLE 
AND CONDENSED RINGS 
Edited by Richard H. Wiley 
Hunter College, The City University of New York, New York 

Authors 
Lyell C. Behr 
College of Arts and Sciences, State College, Mississippi 

Raffaello Fusco 
Institute of Industrial Chemistry, University of Milan, Milan, Italy 

C. H. Jarboe 
Department of Pharmacology, University of Louisville, Louisville, Kentucky 

1967 
INTERSCIENCE PUBLISHERS 
a division of John Wiley & Sons 
New York - London - Sydney
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.

Research Laboratories
Eastman Kodak Company
Rochester, New York

Arnold Weissberger
There have been some notable advances in recent years in the chemistry of the pyrazole types of heterocycles. These have added to the venerable background of available information on this heterocyclic system and establish a position of considerable magnitude deserving careful consideration. Recent reviews have had and will continue to have an important role in presenting and correlating current developments and are regarded as properly supplemental to the purposes of this volume. It is hoped that volumes such as this one and its companion in this series (Volume 20) on Pyrazolones and Pyrazolidones will serve their respective roles by collating the total background in the field in reasonably modern terms. Accordingly, the objective of the authors and assistant editor in compiling and evaluating the material to be included in this volume has been to strive for completion rather than for either up-to-the-minute inclusion of recent developments, which are to-day readily available through the very highly efficient Chemical Abstracts Service, or for critical elimination of reports thought to be less significant at present. The user of the literature on heterocycles has to-day available and therefore needs not so much another timely compilation nor a critique of current activity as he needs a treatment of the total literature for the period covering the transition from the classical period (1890-1920) through the development of the modern period (1905-1960). It is this need which it is hoped the present volume will help fill.

Richard H. Wiley
This Page Intentionally Left Blank
# CONTENTS

## PART 1 PYRAZOLEs

By Raffaello Fusco

1. **Introduction** ........................................... 3

2. **Tautomerism and Isomerism** .......................... 4

3. **Syntheses of the Pyrazole Ring** ....................... 10

   I. Syntheses from β-Dicarbonyl Compounds and their Functional Derivatives (Ethers, Enol-ethers, Acetals, Enamines, etc.) with Hydrazine and its Derivatives (Eq. 1, Ch. 2) ...... 10

   II. Syntheses from Acetylenic Carbonyl Compounds with Hydrazine and its Derivatives ...................... 16

   III. Syntheses by Ring Closure at the 4, 5-Position .... 19

   IV. Syntheses from 1, 2, 3-Tricarbonyl Compounds and their Functional Derivatives with Hydrazine and its Derivatives .................................................. 20

   V. Syntheses from α-Halocarbonyl Compounds with Mono- and Dithiocarbohydrazides .......................... 20

   VI. Syntheses from Aldehyde Arylhydrazones with β-Ketoesters .................................................. 23

   VII. Syntheses from Aliphatic Diazo Compounds ........... 26

      A. From Aliphatic Diazo Compounds with Acetylene Derivatives .............................................. 26

      B. From Aliphatic Diazo Compounds with Halo- or Nitro-vinyl Derivatives ................................ 28

      C. From Aliphatic Diazo Compounds with Malonic Derivatives .................................................. 32

   VIII. Syntheses from Diazoketones, Ethyl Diazoacetate, or Diazodiketones with Ketomethylene Compounds ... 33

   IX. Syntheses from Aromatic Diazo Compounds with Compounds Carrying a Carbonyl Group β to a Carbon Capable of Diazo Coupling ........................................ 34
X. Syntheses from Hydrazonic Halides . . . 35
   A. With Alkaline Salts of Compounds Containing Activated Methylene Groups . . . . 35
   B. With Enamines . . . . . . 40
   C. With Organomagnesium Derivatives of Acetylenic Compounds . . . . 41

XI. Syntheses from Pyrazolines by Oxidation or Other Reactions . . . . . . . . . . 41

XII. Syntheses from Isopyrazoles . . . . . . 49

XIII. Syntheses by Rearrangement of 4,4- or 5,5-Di-substituted Pyrazolines . . . . . . 52

XIV. Syntheses from Various Heterocyclic Compounds with Hydrazine and its Derivatives . . . . . . 53

XV. Syntheses from Epoxides and from Ethylene Imine Derivatives . . . . . . . . . . 57

XVI. Syntheses from Sydnones with Acetylene Derivatives . . . . . . . . . . . . 59

XVII. Syntheses from Pyrazoles and Pyrazolethiones . . . . . . . . . . . . . . . . 62

4. General Reactions of Pyrazole Compounds . . . . . . . . . . . . . 65
   I. Oxidation Reactions . . . . . . . . . . . . 65
   II. Reduction of the Pyrazole Ring . . . . . . . . . . . . . . 67
   III. Cleavage of the Pyrazole Ring . . . . . . . . . . 70
   IV. Alkylation and Dealkylation Reactions of the Pyrazole Ring . . . . . . . . . . . . 71

5. Chemistry of Pyrazole Compounds . . . . . . . . . . . . . . . . . 81
   I. Pyrazole . . . . . . . . . . . . . . . . . . 81
   II. Alkyl- and Arylpyrazoles . . . . . . . . . . . . . . 82
   III. Halogenopyrazoles . . . . . . . . . . . . . . 84
   IV. Nitroso- and Nitropyrazoles . . . . . . . . . . . . . . 91

x
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Azo- and Hydrazopyrazoles</td>
<td>98</td>
</tr>
<tr>
<td>A. Azopyrazoles</td>
<td>98</td>
</tr>
<tr>
<td>B. 3-Azopyrazoles</td>
<td>98</td>
</tr>
<tr>
<td>C. 4-Azopyrazoles</td>
<td>99</td>
</tr>
<tr>
<td>D. 5-Azopyrazoles</td>
<td>101</td>
</tr>
<tr>
<td>E. Chemical Properties of Azopyrazoles</td>
<td>101</td>
</tr>
<tr>
<td>F. Hydrazopyrazoles</td>
<td>102</td>
</tr>
<tr>
<td>VI. Aminopyrazoles</td>
<td>102</td>
</tr>
<tr>
<td>VII. Pyrazolecarboxylic Acids</td>
<td>106</td>
</tr>
<tr>
<td>A. Pyrazole-3-carboxylic Acids</td>
<td>106</td>
</tr>
<tr>
<td>B. Pyrazole-4-carboxylic Acids</td>
<td>107</td>
</tr>
<tr>
<td>C. Pyrazole-5-carboxylic Acids</td>
<td>109</td>
</tr>
<tr>
<td>D. Pyrazole-3, 4-dicarboxylic Acids</td>
<td>109</td>
</tr>
<tr>
<td>E. Pyrazole-4, 5-dicarboxylic Acids</td>
<td>110</td>
</tr>
<tr>
<td>F. Pyrazole-3, 5-dicarboxylic Acids</td>
<td>111</td>
</tr>
<tr>
<td>G. Pyrazole-3, 4, 5-tricarboxylic Acids</td>
<td>112</td>
</tr>
<tr>
<td>H. Pyrazole-1-carboxylic Acids and their Derivatives</td>
<td>113</td>
</tr>
<tr>
<td>I. Reactions of Pyrazolecarboxylic Acids</td>
<td>114</td>
</tr>
<tr>
<td>VIII. Carbonyl Derivatives of Pyrazoles</td>
<td>117</td>
</tr>
<tr>
<td>A. 3-Acylpyrazoles</td>
<td>117</td>
</tr>
<tr>
<td>B. 4-Acylpyrazoles</td>
<td>121</td>
</tr>
<tr>
<td>C. 5-Acylpyrazoles</td>
<td>123</td>
</tr>
<tr>
<td>D. Polyacylpyrazoles</td>
<td>124</td>
</tr>
<tr>
<td>E. Reactions of the Acylpyrazoles</td>
<td>125</td>
</tr>
<tr>
<td>IX. Hydroxypyrazoles</td>
<td>126</td>
</tr>
<tr>
<td>A. 4-Hydroxypyrazoles</td>
<td>126</td>
</tr>
<tr>
<td>B. Acyloxypyrazoles</td>
<td>128</td>
</tr>
<tr>
<td>C. Alkyl- and Aryl-oxypyrazoles</td>
<td>130</td>
</tr>
<tr>
<td>X. Pyrazoles with Sulfur and Selenium Substituents</td>
<td>132</td>
</tr>
<tr>
<td>A. Acylthiopyrazoles</td>
<td>132</td>
</tr>
<tr>
<td>B. Alkylthiopyrazoles</td>
<td>132</td>
</tr>
<tr>
<td>C. Dipryrazolesulfides, Disulfides, and Trisulfides</td>
<td>134</td>
</tr>
<tr>
<td>D. Pyrazole Sulfoxides and Sulfones</td>
<td>135</td>
</tr>
</tbody>
</table>
E. Pyrazolesulfonic and Sulfinic Acids .......................... 135
F. Selenium Derivatives ............................................ 137

XI. N-acylpyrazoles .................................................. 137

References

PART 2 PYRAZOLINES AND PYRAZOLIDINES
By C. H. Jarboe

6. Introduction ...................................................... 177

7. Pyrazoline Syntheses ............................................. 180
   I. Hydrazine Based Reactions ..................................... 180
      A. Arylhydrazines ................................................. 180
         1. Condensations with \( \alpha, \beta \)-unsaturated carbonyl compounds .. 181
         2. Additions to \( \alpha, \beta \)-unsaturated nitriles .................. 185
         3. Condensations with \( \beta \)-substituted ketones ................. 185
         4. Condensations with oxiranes and aziridines .................. 186
         5. Anomalies to arylhydrazine reactions ...................... 187
      B. Hydrazine and its Aliphatic Derivatives .................... 189
         1. Condensations with \( \alpha, \beta \)-unsaturated carbonyl compounds .. 189
         2. Condensations with \( \beta \)-substituted ketones and \( \alpha \)-epoxy-ketones . 190
         3. Additions to \( \alpha, \beta \)-unsaturated nitriles ................ 191
         4. Anomalies to hydrazine reactions ............................ 191
      C. Cyclization Based Syntheses .................................. 192
      D. Miscellaneous Hydrazine Based Syntheses ..................... 193
      E. Synthesis of 3-Pyrazolines .................................. 194

II. Aliphatic Diazo Compound Based Syntheses ..................... 195
   A. Addition of Diazooalkanes to Carbon–carbon Double Bonds .. 195
   B. Azomethine Imine Additions to Acetylenes .................... 205

III. Miscellaneous Pyrazoline Syntheses ........................... 206
8. Chemistry of the Pyrazolines . . . . . . 209
   I. Pyrolysis Reactions . . . . . . 209
   II. Tautomerism . . . . . . 214
   III. Oxidation Reactions . . . . . . 215
   IV. Reduction with Cleavage . . . . . . 221
   V. Reactions at Position One . . . . . . 221
   VI. Reactions at Position Three . . . . . . 222
   VII. Spectra . . . . . . 223
   VIII. Uses . . . . . . 225

TABLES
1. Group Migration in Pyrazole Formation from 1-Phenyl-5-Hydroxy-2-Pyrazolines . . . . . . 218
2. 3-Pyrazolines . . . . . . 226
3. 1-Pyrazolines . . . . . . 227
4. 3-Substituted-2-Pyrazolines . . . . . . 230
5. 4-Substituted-2-Pyrazolines . . . . . . 231
6. 5-Substituted-2-Pyrazolines . . . . . . 231
7. 3,4-Disubstituted-2-Pyrazolines . . . . . . 232
8. 3,5-Disubstituted-2-Pyrazolines . . . . . . 233
9. 4,5-Disubstituted-2-Pyrazolines . . . . . . 234
10. 5,5-Disubstituted-2-Pyrazolines . . . . . . 235
11. 3,4,5-Trisubstituted-2-Pyrazolines . . . . . . 236
12. 4,4,5-Trisubstituted-2-Pyrazolines . . . . . . 237
13. 3,5,5-Trisubstituted-2-Pyrazolines . . . . . . 237
14. 4,5,5-Trisubstituted-2-Pyrazolines . . . . . . 238
15. 3,4,4-Trisubstituted-2-Pyrazolines . . . . . . 238
16. 4,4,5-Trisubstituted-2-Pyrazolines . . . . . . 238
17. 3,4,4,5-Tetrasubstituted-2-Pyrazolines . . . . . . 239
18. 3,4,5,5-Tetrasubstituted-2-Pyrazolines . . . . . . 240
19. 4,4,5,5-Tetrasubstituted-2-Pyrazolines . . . . . . 241
20. 1-Substituted-2-Pyrazolines . . . . . . 241
21. 1,3-Disubstituted-2-Pyrazolines . . . . . . 242
References

9. Pyrazolidine Chemistry
   I. Introduction
   II. Pyrazolidine Syntheses
      A. Fused Ring Syntheses
1. Diels–Alder type reactions . . . 279
2. Other cycloaddition reactions . . . 280
3. Azomethine–imine reactions . . . 280

B. Reductions . . . . . . . . . . . 281
1. Reductive cyclizations . . . 281
2. Reduction of heterocyclic compounds . 281

C. Oxidative Cyclization . . . . . . 282

D. Cyclizations Involving Halogenated Compounds . 282
1. Reactions based on hydrazine . . . 282
2. Malonitrile fluorination . . . . 283

III. Pyrazolidine Chemistry . . . . . . 283

References . . . . . . . . . . . 285

PART 3 INDAZOLES AND CONDENSED TYPES
By Lyell C. Behr

10. Indazoles and Condensed Types . . . . . . . . . 289

I. Introduction . . . . . . . . . . . 289

II. The Structure of the Indazole Nucleus . . . . . 289

III. Nomenclature . . . . . . . . . . . 293

IV. Synthesis of the Ring System . . . . . . . . . 294
A. Type A Syntheses . . . . . . . . 295
B. Type B Syntheses . . . . . . . . 303
C. Type C Syntheses . . . . . . . . 304

V. Substitution in the Indazole Nucleus . . . . . . 305
A. Halogenation . . . . . . . . . . 305
B. Nitration . . . . . . . . . . . 308
C. Sulfonation . . . . . . . . . . 309
D. Alkylation . . . . . . . . . . 309
E. Acylation . . . . . . . . . . . 315
F. Other Substitutions . . . . . . . 317

VI. Indazole and its Alkyl and Aryl Derivatives . . . 317

VII. Haloindazoles . . . . . . . . . . 324
<table>
<thead>
<tr>
<th>VIII.</th>
<th>Nitroindazoles</th>
<th>328</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX.</td>
<td>Hydroxyindazoles</td>
<td>335</td>
</tr>
<tr>
<td>X.</td>
<td>Indazolecarboxylic Acids</td>
<td>340</td>
</tr>
<tr>
<td>XI.</td>
<td>Aminoindazoles</td>
<td>344</td>
</tr>
<tr>
<td>XII.</td>
<td>Indazolesulfonic Acids</td>
<td>351</td>
</tr>
<tr>
<td>XIII.</td>
<td>Indazoles of Biochemical Interest</td>
<td>352</td>
</tr>
<tr>
<td>XIV.</td>
<td>Indazole-1-oxides</td>
<td>353</td>
</tr>
<tr>
<td>XV.</td>
<td>3H-Indazoles (Ring Index 1211)</td>
<td>355</td>
</tr>
<tr>
<td>XVI.</td>
<td>Indazolones</td>
<td>356</td>
</tr>
<tr>
<td>XVII.</td>
<td>Reduced Indazoles</td>
<td>362</td>
</tr>
</tbody>
</table>

References 366

**PART 4 TABLES**

By Raffaello Fusco

| Foreword to the Tables Section | 385 |
| Key to the Preparation Methods | 387 |
| **Subject Index** | 881 |
Part 1

**PYRAZOLES**

Raffaello Fusco

*Institute of Industrial Chemistry, University of Milan, Milan, Italy*
CHAPTER 1

INTRODUCTION

Pyrazole was first described by Buchner\textsuperscript{207} who obtained it by decarboxylation of pyrazole-3,4,5-tricarboxylic acid (1). Much of the basic information about the chemistry of the pyrazole nucleus was developed as a result of the interest in comparing the aromatic properties of the pyrazoles with those of benzene derivatives\textsuperscript{556,572} and

\[
\begin{align*}
\text{HOOC-} & \text{N} \text{COOH} \\
\text{HOOC-} & \text{N} \text{H} \\
\end{align*}
\rightarrow
\begin{align*}
\text{N} \text{H} \\
\text{N} \text{H} \\
\end{align*} + 3 \text{CO}_2
\]

in early studies of the problem of the structure of benzene.\textsuperscript{207a} Since then the studies of the pyrazoles have centered principally about structural problems arising from the tautomerism existing in the \(N\)-unsubstituted types and the isomerism of the \(N\)-substituted derivatives.\textsuperscript{54} Until recently the pyrazole ring was believed to be unknown in nature. In 1954, however, the first natural pyrazole derivative was isolated by Japanese workers\textsuperscript{593} who isolated 3-n-nonylpyrazole (2) from \textit{Houttuynia Cordata} (a plant of the "piperaceae" family from tropical Asia) and observed its antimicrobial activity. A pyrazolic amino acid: \textit{levoratrix} (1-pyrazolyl)alanine (3) has been isolated from watermelon seeds (\textit{Citrullus Vulgaris}).\textsuperscript{595,792,986} These are the only naturally occurring pyrazole derivatives known at present and it is interesting to compare their rarity with the widespread occurrence in nature of derivatives of the isomeric imidazole ring.

\[
\begin{align*}
2 & \text{N} \text{CH}_2 \text{CH}_3 \\
3 & \text{CCH}_2 \text{CH} \text{(NH}_2\text{)} \text{COOH}
\end{align*}
\]
The pyrazole ring, like other nitrogen containing heterocycles, can be represented by different tautomeric structures. Three tautomeric forms can be written for unsubstituted pyrazole (1, 2, 3) and five (4, 5, 6, 7, 8) for compounds in which the two carbon atoms adjacent to nitrogen carry different substituents.

Existence of forms 4 and 5 has been proved but evidence for the isopyrazole form (2, 6) and for the pyrazolenine form (3, 7, 8) is lacking. They are apparently capable of existence only for those derivatives carrying substituents in place of all four hydrogen atoms of the nucleus. Such compounds often show a tendency to rearrange to yield true pyrazoles. This indicates that the isopyrazoles and the pyrazolenines are less stable than the pyrazoles. The common and important tautomerism encountered with pyrazoles is that between the two pyrazole forms 4 and 5 and it is this which will be considered in this chapter.

Hypotheses for the existence of tautomerism between 4 and 5 are based on the following experimental evidence:

1. One of the more general synthetic approaches to the pyrazole nucleus is the reaction between a hydrazine (10) and a \( \beta \)-dicarbonyl compound (9). When the \( \beta \)-dicarbonyl compound is unsymmetrical (9, \( R \neq R' \)) two isomeric pyrazole derivatives (11a and 11b) are usually formed if a substituted hydrazine (10, \( R'' = H \)) is used. Only a single compound is obtained from hydrazine itself (10, \( R'' = H \)).
2. Two isomeric pyrazoles carrying the same substituent R on two
   different nitrogen atoms (12 and 13) are converted to the same com-
   pound (14) on elimination of the substituent R.\textsuperscript{87,88}

3. Alkylation or arylation of an unsymmetrically substituted pyrazole
   (15) yields normally two isomeric products (17 and 18).\textsuperscript{53,72,74,89,205}
   This establishes that the hydrogen atom can be bound to either nitrogen
   atom in the parent molecule. Actually, when alkylation is carried out in
   presence of a strong base, intermediate formation of a resonance
   stabilized anion (16) can be hypothesized.

4. Further evidence for the existence of tautomeric forms, which is of
   value in establishing the predominant form for a given compound, is
obtained from data on the exaltation of molecular refractions. This method is useful only in special cases. It has been employed successfully for tautomeric pyrazoles with a phenyl substituent on the carbon atom adjacent to nitrogen (position 3 or 5). The principle underlying the method can be clearly understood from the illustrative data in Table 1. Exaltation of the molecular refraction of three pairs of isomeric 1,3,5-tri-substituted pyrazoles are compared with the values of the three corresponding tautomeric pyrazoles with no substituent on position 1. The three compounds with a phenyl group at position 3 (compounds A, C, and E) show greater exaltation than the corresponding 5-phenyl-substituted compounds (G, H, and J). The conjugation of the benzene ring with the nitrogen-carbon double bond creates a greater exaltation than is present in the corresponding 5-phenyl-substituted structure (G, H, and J). The conjugation of the benzene ring with the carbon-nitrogen double bond creates a greater exaltation of the molecular refraction than does conjugation with the carbon-carbon double bond. As for pyrazoles B, D, and F in which, through tautomerism, the phenyl ring can be either 3 or 5-substituted, exaltation of the molecular refraction is nearer that of compounds B, C, and E (3-phenyl-substituted) than it is to that of G, H, and J (5-phenyl-substituted). Thus, in the tautomeric equilibrium, 3-phenyl-substituted forms appear to predominate.

It appears also that nuclear magnetic resonance studies of pyrazole structures will establish the relative amounts of the tautomers present under different conditions.

The tautomerism encountered in unsubstituted pyrazoles has a counterpart in the isomerism of substituted pyrazoles. There are four positions (three in pyrazolium salts) that can undergo substitution to give various isomeric possibilities. Among these, the isomerism exclusively dependent on position of a nitrogen-bound substituent (17 and 18 corresponding to tautomers 4 and 5) is of particular interest. Such isomeric pairs are formed on alkylation of tautomeric pyrazoles and in many of the reactions leading to the pyrazole ring. It is to be noted that, for a great many of the known pyrazoles formed in these reactions, isomeric structural assignments for the product or products are uncertain and that for many others, for which the literature arbitrarily assigns one isomeric structure, definitive structural evidence is unavailable for such an assignment.

The pairs of isomeric pyrazoles (17 and 18) obtained on alkylation of tautomeric pyrazoles are often formed at different rates. The relative rates of formation of the two products depend on the nature of the parent compound, the alkylation agent, and the experimental conditions. There seems to be no general rule for establishing which isomer is formed preferentially. Many attempts have been made to assign structures to the products obtained by the action of a hydrazine on an unsymmetrical β-diketone in terms of a difference in "reactivity" of the two carbonyl groups. Reactivity was evaluated through such reactions as tendency to enolize and kinetics of oxime formation. Unfortunately,
<table>
<thead>
<tr>
<th>Pyrazole</th>
<th>Exaltation</th>
<th>Pyrazole</th>
<th>Exaltation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1-methyl-3-phenyl-5-carbethoxy</td>
<td>47</td>
<td>G 1-methyl-3-carbethoxy-5-phenyl</td>
<td>14</td>
</tr>
<tr>
<td>B 3(5)-phenyl-5(3)-carbethoxy</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1,5-dimethyl-3-phenyl</td>
<td>35</td>
<td>H 1,3-dimethyl-5-phenyl</td>
<td>23</td>
</tr>
<tr>
<td>D 3(5)-methyl-5(3)-phenyl</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E 1-methyl-3-phenyl</td>
<td>36</td>
<td>J 1-methyl-5-phenyl</td>
<td>19</td>
</tr>
<tr>
<td>F 3(5)-phenyl</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 2

as will be illustrated in the chapter describing general synthetic pro-
cedures for the pyrazole ring, these "reactivity series" are of ques-
tionable value. Other factors involved in pyrazole formation such as
the nature of the hydrazine substituent and the experimental conditions
often determine which isomer is formed. Other procedures for pyra-
zole synthesis, such as the reaction of aliphatic diazo compounds with
unsymmetrical acetylene derivatives and the thermal decomposition
of pyrazolium salts, are similarly unreliable as bases for assignment of
alternative isomeric structures.

A brief survey of the methods that can be employed to assign correct
structures to isomeric pyrazoles obtained by these above procedures
appears therefore to be of great importance. A very useful method for
structural determination of isomeric alkyl- and acyl-pyrazoles is
based on decarboxylation of isomeric pyrazolecarboxylic acids.

The structures of these acids and esters can be deduced from compari-
sion of esterification and hydrolysis rates. Differences in these rates
originate in different steric hindrance at the carboxylic functions of the
two isomeric molecules. As an example the isomeric pair: 1, 3- and
1,5-dimethylpyrazoles (20 and 19) will be considered. The structure of
these two compounds was established by their formation from carboxy-
lric acids 22 and 21. The acids in turn were identified through bromina-
tion at position 4 and comparisons of the esterification behavior of the
bromo acids 24 and 23. Only isomer 21 yielded a bromo acid (23) that
could be esterified. Bromo acid 24 did not furnish the corresponding
esters due to the hindrance that the two adjacent substituents (methyl
and bromo) exert on the carboxylic group.\(^7,8,^{44}\) If a substituent is al-
ready present on position 4, as is the case for 1, 4, 5-trimethylpyrazole-
3-carboxylic acid and 1, 3, 4-trimethylpyrazole-5-carboxylic acid,
bromination is unnecessary and a comparison of the esterification
rates of the two acids can directly be made.\(^6,2\) Similar observations can
be made about rates of hydrolysis of the corresponding esters.\(^7,2\)

An alternative method available for structural determinations of this
kind is based on the conversion of pyrazolines of established struc-
Tautomerism and Isomerism

ture into pyrazoles by oxidation. Pyrazolines substituted by a phenyl
group on position 3 or 5 are specially suited for this reaction since
differences of exaltation of molecular refraction values between the pairs of isomers are even greater than in the pyrazole series.\textsuperscript{69, 70}

Regardless of the nature of substituents on other positions 5-phenyl-3-alkylpyrazolines can be easily distinguished from 3-phenyl-5-alkyl-pyrazolines. Only mild oxidizing treatment is required to convert pyrazolines into the corresponding pyrazoles and this apparently eliminates the possibility of concurrent isomerization. The reverse procedure—reduction of pyrazoles of uncertain structure to pyrazolines whose structures can be established by molar refraction—usually requires such a drastic treatment that simultaneous isomerization reactions are unavoidable.

Ultraviolet absorption characteristics have been used to assign isomeric structures. 1,5-Diarylpyrazoles have been distinguished from their 1,3-isomers through examination of their u.v. absorption spectra.\textsuperscript{1064} The 1,5-isomers show less intense ($\epsilon = 1.46-1.53 \times 10^4$) absorption bands at lower wavelengths ($\lambda = 241-255 \text{ m}{\mu}$) than do the 1,3-isomers ($\epsilon = 1.66-2.25 \times 10^4; \lambda = 257-262 \text{ m}{\mu}$). This behavior is probably related to steric hindrance which prevents coplanarity of the phenyl groups in the 1,5-derivatives.

The application of other physical methods of structure assignment will undoubtedly clarify many of the unsolved problems of structure assignment in these 1,3- and 1,5-isomeric structures. Certainly nuclear magnetic resonance analyses and diffraction techniques, both x-ray and electron, provide powerful tools for such studies, and examples of the use of NMR techniques have been reported.\textsuperscript{385, 1158-1161}
CHAPTER 3

SYNTHESES OF THE PYRAZOLE RING

I. SYNTHESSES FROM \( \beta \)-DICARBONYL COMPOUNDS AND THEIR FUNCTIONAL DERIVATIVES (ETHERS, ENOL-ETHERS, ACETALS, ENAMINES ETC.) WITH HYDRAZINE AND ITS DERIVATIVES (EQ. 1, CH. 2).

The synthesis of pyrazoles from \( \beta \)-dicarbonyl compounds and hydrazines is the most widely used and the most general method for pyrazole synthesis. A single pyrazole is obtained with a symmetrical \( \beta \)-dicarbonyl compound or with hydrazine itself. With other reactants two isomeric pyrazoles can theoretically arise and sometimes both can be isolated from the reaction mixture. Many structural and experimental factors are involved in selective formation of one of the two isomeric compounds but at present the controlling influence of such factors is not fully understood. The formation of the pyrazole compound may take place via different routes which only in some instances have been clearly established. A further difficulty arises in the assignment of the correct structure to the pyrazoles obtained. In many experiments the structure of the products has not been established (e.g., refs. 148, 601, 963); in some cases it has been assigned without definitive experimental evidence or on the strength of simple analogies;\(^{26,48,67,787}\) and in a few examples it has been established on the ground of more or less rigorous experimental evidence.\(^{48,63,67,72,92,250,254,377,384,385,862}\) The data from those studies in which definitive structural assignments have been made will be considered in the following paragraphs.

The reaction of methylhydrazine with the sodium salt of formylacetone (1) gives a mixture of two isomeric pyrazoles (3 and 4) (Eq. 4).\(^{559,868}\)

\[
\text{CH}_3\text{CO-CH=CH-ONa} + \text{CH}_3\text{NH-NH}_2 \rightarrow \begin{array}{c}
\text{CH}_3 \\text{N}\text{CH}_3 \\
\text{3} \\
\text{CH}_3 \text{N}\text{CH}_3 \\
\text{4}
\end{array}
\text{CH}_3\text{I}
\]

These are the same products which arise from methylation of 3-methylpyrazole (2) by methyl iodide under various conditions.\(^{72,548}\) Both the dimethylpyrazoles are liquids at room temperature (b.p. 136°)
Syntheses of the Pyrazole Ring

and 150°) but they can easily be identified from their different boiling points and from the melting points of the corresponding picrates (137°, 170°). Von Auwers70 assigned structure (3) to the isomer corresponding to the lower-melting picrate on the ground that the same product was obtained by oxidation with PbIV of the pyrazoline (6), produced in turn by reacting methylhydrazine with β-chloroethylmethylketone (5) (Eq. 5). This conclusion is also in agreement with the data obtained from studies of the esterification rates of the carboxylic acids (see "isomerism"). This evidence has been questioned by Burness238 who, from the reaction of methylhydrazine with acetylacetaldheydemethylacetal (7), obtained the corresponding hydrazone (8). This was subsequently cyclized in acidic medium to yield a dimethylpyrazole corresponding to the high-melting picrate (Eq. 6). Further study will be required to clarify this contradictory evidence.

Benzoylaceton (9) reacts with phenylhydrazine to give a monophenylhydrazone (10) (Eq. 7). As with other β-diketones no bis-phenylhydrazone is obtained. On heating or by treatment with acids or with hydrogen chloride in pyridine, the phenylhydrazone is converted to a single product the structure of which has been clearly established92,390,391 as that of 3-methyl-1,5-diphenylpyrazole (11) (see page 12).
Other simple arylhydrazines (p-chlorophenylhydrazine, q-, m-, and p-nitrophenylhydrazine) also give a single pyrazole. 2,4-Dinitrophenylhydrazine yields, however, a mixture of the two isomeric pyrazoles which were separated and whose structure has been established on the ground of the identity of one of them with the cyclization product from phenyl propargyl ketone phenylhydrazone. Methylhydrazine with benzoylacetone also yields two isomeric pyrazoles which have been separated and their structures established. Acyl substituted hydrazines (12) with benzoylacetone usually yield an open-chain hydrazone (13) which can be subsequently cyclized by phosphorus oxychloride at 0°C. with formation (Eq. 8) of a 1-acyl substituted pyrazole (14a, b). Sometimes even at low temperatures the latter substance is obtained directly.

\[
\begin{align*}
C_6H_5-CO-CH_2-CO-CH_3 + &\quad R-CO-NH-NH_2 \\
\text{9} &\quad \text{12} \\
\rightarrow &\quad R-CO-NH-C=N\text{CH}_3 \\
&\quad \text{13a} \\
&\quad \text{13b}
\end{align*}
\]

The reaction of hydrazines with \(\beta\)-ketoaldehydes (\(\alpha\)-hydroxymethyleneketones) appears to be more complex than the reaction with \(\beta\)-diketones. Hydroxymethyleneacetone (15) and phenylhydrazine yield, in acetic acid solution, both of the two possible isomeric pyrazoles: 1-phenyl-3-methyl (16a) and 1-phenyl-5-methyl (16b). From the reaction of hydroxymethyleneacetophenone with phenylhydrazone two phenylhydrazones have been isolated and on cyclization

\[
\begin{align*}
\text{CH}_3-CO-CH=CHOH + C_6H_5-NH-NH_2 &\rightarrow \\
\text{15} &\quad \text{16a} \\
&\quad \text{16b}
\end{align*}
\]

these have been converted into the corresponding pyrazoles in different proportions according to reaction conditions; \(p\)-nitrophenylhydrazine yielded instead a single \(p\)-nitrophenylhydrazone (17) and...