PYRAZOLES, PYRAZOLINES, 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

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This is the twenty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Editor*

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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.

Research Laboratories
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Rochester, New York

Arnold Weissberger

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PREFACE

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

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Part 1

PYRAZOLES

Raffaello Fusco

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

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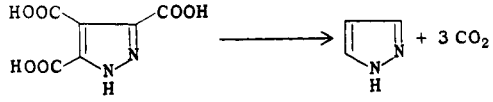
CHAPTER 1

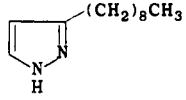
INTRODUCTION

Pyrazole was first described by Buchner[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[556,572] and



1

in early studies of the problem of the structure of benzene.[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.[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[593] who isolated 3-n-nonylpyrazole (**2**) from Houttuynia Cordata (a plant of the "piperaceae" family from tropical Asia) and observed its antimicrobal activity. A pyrazolic amino acid: *levo*-β-(1-pyrazolyl)alanine (**3**) has been isolated from watermelon seeds (Citrullus Vulgaris).[395,792,986] 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.



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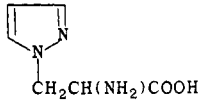

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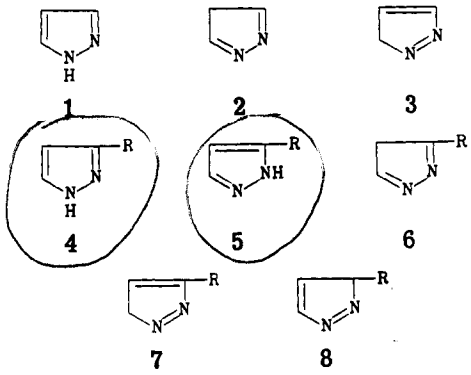
CHAPTER 2

TAUTOMERISM AND ISOMERISM

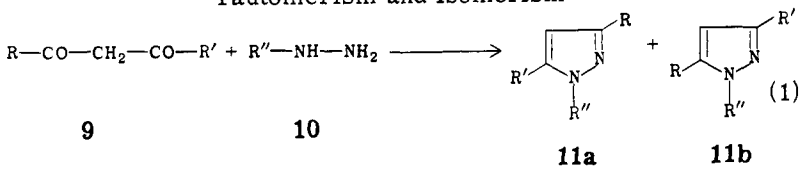
The pyrazole ring, like other nitrogen containing heterocycles, can be represented by different tautomeric structures. Three tautomeric forms can be written for unsubstituted pyrazole (**1, 2, 3**) and five (**4, 5, 6, 7, 8**) for compounds in which the two carbon atoms adjacent to nitrogens carry different 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.[29,53,498,502] 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.

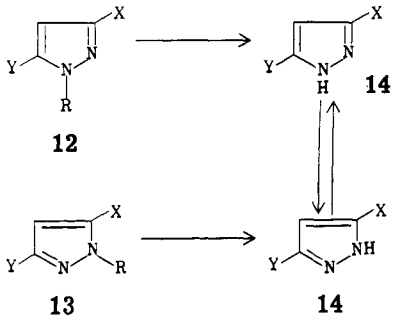
Hypotheses for the existence of tautomerism between **4** and **5** are based on the following experimental evidence:

1. One of the more general synthetic approaches to the pyrazole nucleus is the reaction between a hydrazine (**10**) and a β-dicarbonyl compound (**9**). When the β-dicarbonyl compound is unsymmetrical (**9**, $R \neq R'$) two isomeric pyrazole derivatives (**11a** and **11b**) are usually formed if a substituted hydrazine (**10**, $R'' \neq H$) is used. Only a single compound is obtained from hydrazine itself (**10**, $R'' = H$).[53,63,547,581,787,846]



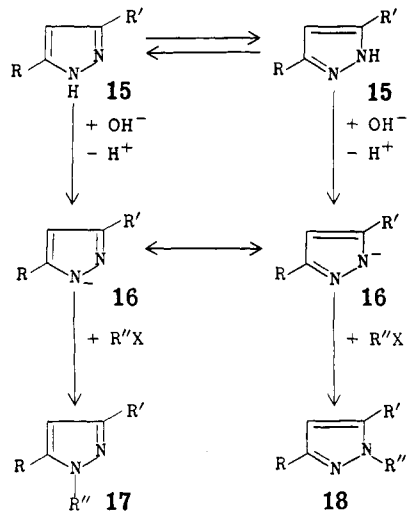
9 10 11a 11b (1)

2. Two isomeric pyrazoles carrying the same substituent R on two different nitrogen atoms (**12** and **13**) are converted to the same compound (**14**) on elimination of the substituent R.[87,88]



12 **14** **13** **14**

3. Alkylation or arylation of an unsymmetrically substituted pyrazole (**15**) yields normally two isomeric products (**17** and **18**).[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.



15 **15** **16** **16** **17** **18**

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[69]. 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.[395,1158-1161]

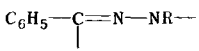
The tautomerism encountered in unsubstituted pyrazoles has a counterpart in the isomerism of substituted pyrazoles. There are four positions (three in pyrazolium salts) that can undergo substitution to give various isomeric possibilities. Among these, the isomerism exclusively dependent on position of 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 alkylating 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,

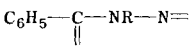
TABLE 1

Exaltation of molecular refraction in pyrazoles

3-aryl structures:



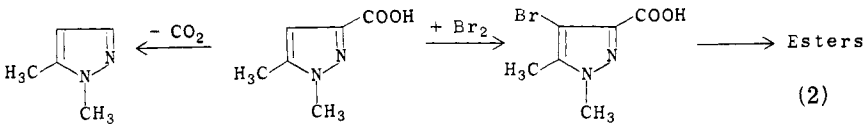
5-aryl structures:

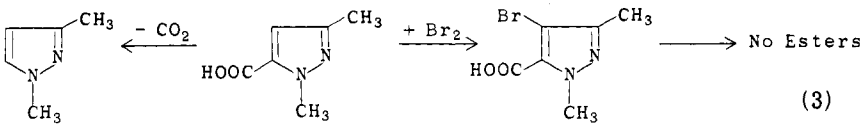


	Pyrazole	Exaltation		Pyrazole	Exaltation
A	1-methyl-3-phenyl-5-carbethoxy	47			
B	3(5)-phenyl-5(3)-carbethoxy	39	G	1-methyl-3-carbethoxy-5-phenyl	14
C	1, 5-dimethyl-3-phenyl	35			
D	3(5)-methyl-5(3)-phenyl	30	H	1, 3-dimethyl-5-phenyl	23
E	1-methyl-3-phenyl	36			
F	3(5)-phenyl	31	J	1-methyl-5-phenyl	19

as will be illustrated in the chapter describing general synthetic procedures for the pyrazole ring, these "reactivity series" are of questionable 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 pyrazole 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 comparison 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 carboxylic acids **22** and **21**. The acids in turn were identified through bromination 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.[71,884] If a substituent is already 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.[62] Similar observations can be made about rates of hydrolysis of the corresponding esters.[72]

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

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.[69,70] Regardless of the nature of substituents on other positions 5-phenyl-3-alkylpyrazolines can be easily distinguished from 3-phenyl-5-alkylpyrazolines. 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.[1064] The 1,5-isomers show less intense ($\epsilon = 1.46-1.53 \times 10^4$) absorption bands at lower wavelengths ($\lambda = 241-255$ mμ) than do the 1,3-isomers ($\epsilon = 1.66-2.25 \times 10^4$; $\lambda = 257-262$ mμ). 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.[395,1158-1161]

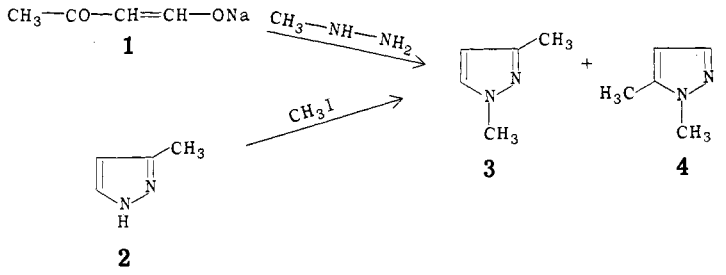
CHAPTER 3

SYNTHESES OF THE PYRAZOLE RING

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).

The synthesis of pyrazoles from β-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 β-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.

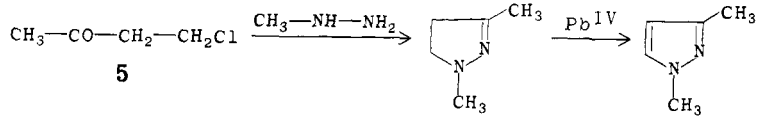
The reaction of methylhydrazine with the sodium salt of formylacetone (**1**) gives a mixture of two isomeric pyrazoles (**3** and **4**) (Eq. 4).[559,868]



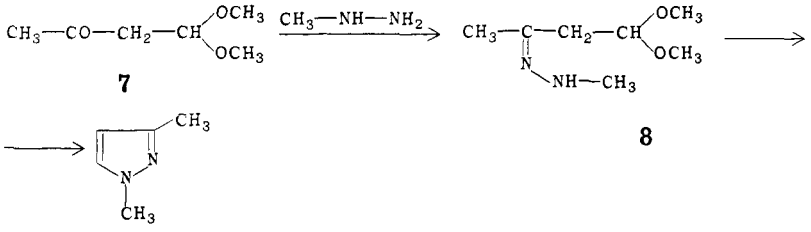
(4)

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°

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 Auwers[70] assigned structure (**3**) to the isomer corresponding to the lower-melting picrate on the ground that the same product was obtained by oxidation with Pb^{IV} 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 Burness[238] who, from the reaction of methylhydrazine with acetylacetaldehydedimethylacetal (**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.

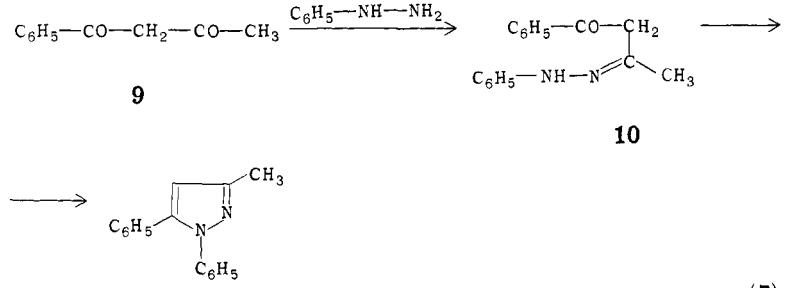


5 **6** **3** (5)



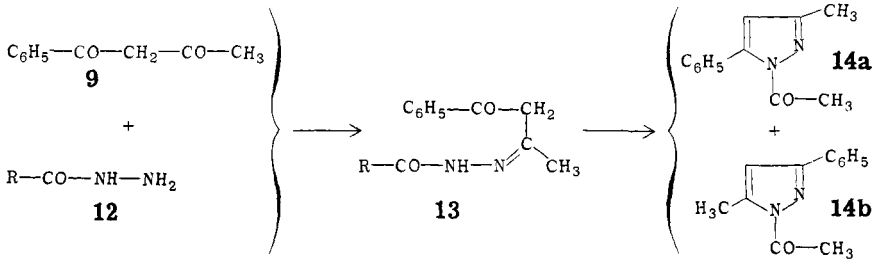
7 **8** **3** (6)

Benzoylacetone (**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 established[92,390,391] as that of 3-methyl-1, 5-diphenylpyrazole (**11**) (see page 12).



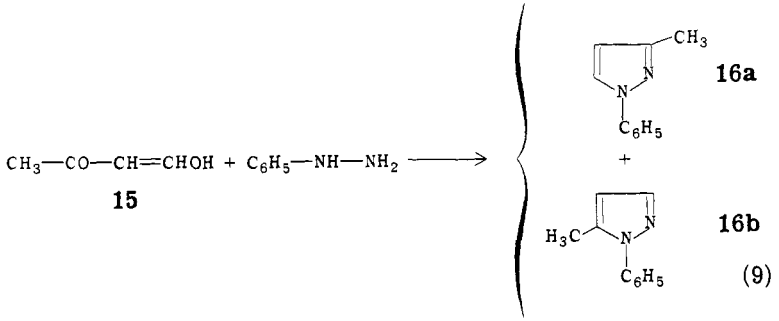
9 **10** **11** (7)

Other simple arylhydrazines (*p*-chlorophenylhydrazine,[127] *o*-, *m*-, and *p*-nitrophenylhydrazine[130]) 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[387] 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.[92] 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 (**14**a, b).[67] Sometimes even at low temperatures the latter substance is obtained directly.



(8)

The reaction of hydrazines with β-ketoaldehydes (α-hydroxymethyleneketones) appears to be more complex than the reaction with β-diketones. Hydroxymethyleneacetone (**15**) and phenylhydrazine yield, in acetic acid solution, both of the two possible isomeric pyrazoles: 1-phenyl-3-methyl (**16**a) and 1-phenyl-5-methyl (**16**b).[271,274] (Eq. 9.) From the reaction of hydroxymethyleneacetophenone with phenylhydrazine two phenylhydrazones have been isolated and on cyclization



(9)

these have been converted into the corresponding pyrazoles in different proportions according to reaction conditions;[81,91] *p*-nitrophenylhydrazine yielded instead a single *p*-nitrophenylhydrazone (**17**) and