PYRAZOLONES, PYRAZOLIDONES, AND DERIVATIVES

Richard H. Wiley
University of Louisville, Louisville, Kentucky

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This is the twentieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting 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.

ARNOLD WEISSBERGER

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Preface

Perhaps one of the most unusual facets of pyrazole chemistry is the extensive literature on the pyrazolin-5-ones. Although this will probably come as no surprise to those who have had any interest in this class of compounds, the basic chemical reasons underlying this extensive literature, and the man-hours of chemical research which have gone into producing it, deserve careful consideration. There are very real practical and theoretical bases for the situation.

Historically, dyes and pharmaceuticals derived from pyrazolin-5-ones were among the first successful commercial synthetic organic chemicals in which interest has continued actively until the present. Ludwig Knorr's discovery in 1883 of antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) and Ziegler's discovery in 1884 of the yellow dyestuff tartrazine: 4-(4-sulfophenylazo)-1-(4-sulfophenyl)-5-oxo-2-pyrazolin-3-carboxylic acid gave useful compounds before their structures were known. The value of these materials was immediately recognized and both are still in use. Much of the voluminous literature has resulted from studies directed toward modification of these structures to enhance their useful characteristics. A group of widely used pharmaceuticals including aminopyrine (4-dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one); dipyrone (2,3-dimethyl-1-phenyl-5-oxo-2-pyrazolin-4-methylaminomethanesulfonic acid sodium salt); and sulfamipyrine (a dipyrone analog) were developed. This research has recently culminated in the discovery of the useful anti-inflammatory properties of phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidinedione). In spite of the problems encountered in the undesirable side-reactions, principally agranulocytosis, produced by these drugs, interest in them has never abated and one feels confident in predicting the discovery of additional useful and improved drugs in this structural classification.

The development of new and improved dyes based on pyrazolinone structures has likewise led to modern developments of no inconsiderable magnitude. The use of tartrazine as an approved color for foodstuffs is of significance. The development of pyrazolinone dyes for use as magenta couplers and sensitizers in color photography and in metal chelate dye structures has established a renewed, modern interest in these dyes. The chelating characteristics, which will be of continuing theoretical structure interest in coordination chemistry, have been used in developing picrolonates (salts of 3-methyl-4-nitro-1-*p*-nitrophenyl-2-pyrazolin-5-one) of possible utility in analytical procedures.

The overwhelming deluge of chemical research arising from these utilitarian values has probably obscured the possibilities for fundamental research with these compounds. For the most part the structural problems that have been encountered are not complex. This is probably due in part to the fact that modern organic reaction techniques, such as radiation-induced transformations, modern structural concepts, such as molecular orbital theory and conformational analysis, and modern physical instrumentation, such as n.m.r., have not as yet been applied to the possibilities inherent in the chemistry of these compounds. It is also perhaps unusual that no pyrazolinone has been found to occur in nature. With the discovery in 1959 of β-(1-pyrazolyl)alanine in the seeds of *Citrullus vulgaris*, it would now appear probable that a pyrazolinone may likewise be found in some living tissue. This would certainly provide a new type of fundamental interest in the bio-organic chemistry of these materials. It might lead ultimately to a clue as to the mode of action of the pharmaceuticals—a problem about which there appears to be little or no current available information.

With the hope that the availability of the information on pyrazolinones presented in this volume might be of value in the furtherance of both fundamental and applied studies, the publishers and authors have considered it best to present this material as promptly as possible in the present volume rather than as part of the pyrazole volume for which it was originally intended. The authors are appreciative of this cooperation on the part of the publishers and it is hoped that users of this book will be aware that the immensity and sheer bulk of the literature has posed an unusual, but altogether interesting, challenge to all concerned in the preparation of this volume. The authors also wish especially to thank Miss Ollidene Weaver who did much of the typing of the manuscript in her spare time.

Richard H. Wiley
Paul Wiley

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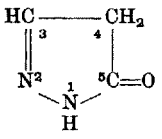
CHEMISTRY

CHAPTER I

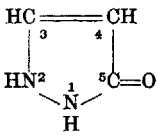
General

1. Introduction

Pyrazolinones and pyrazolidinones are oxo derivatives of pyrazolines and pyrazolidines, respectively, and are so named in *Chemical Abstracts* at present. However, the usual method of naming in the earlier literature is the pyrazolone–pyrazolidone system. Although a large number of tautomeric structures are possible for pyrazolinones, the usual assignment of ring structures is as shown in (I), (II) and (III). The *Chemical Abstracts* names for these are: (I) 2-pyrazolin-5-one, (II)



(I)



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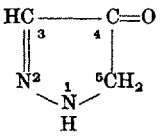
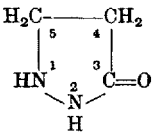


(III)

3-pyrazolin-5-one and (III) 2-pyrazolin-4-one. The names most frequently used in the literature for (I) and (II) are 5-pyrazolone and 3-pyrazolone, respectively. In many cases there has been no certain identification of a compound as a 2-pyrazolin-5-one or a 3-pyrazolin-5-one. Because of this it will be assumed that all pyrazolin-5-ones having no substituent at N–2 are 2-pyrazolin-5-ones unless this has been definitely shown to be incorrect. The basic ring structures for pyrazolidinones are (IV) and (V) but no compounds of type (V) have been



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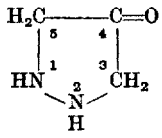


(V)

reported. Compounds of type (IV) are usually called pyrazolidones in the literature.

The nomenclature used in this discussion will generally be in accordance with *Chemical Abstracts*, although some trivial names will be used since these are very common among pyrazolinones and are frequently well known. Examples of such names are antipyrine, pyrazole blue and aminopyrine. The numbering is as shown in formulas (I)–(V).

As an aid to classification all compounds in which the tautomerism

$$>CH-\overset{|}{C}=X \rightleftharpoons >C=\overset{|}{C}-XH$$

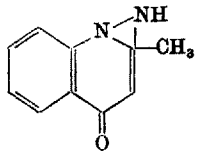
can theoretically exist will be considered as $>CH-\overset{|}{C}=X$ compounds (X = O, S, Se, Te, NH, NR or NCOR). It is recognized that this will frequently be in disagreement with the actual structure which, if known, will be indicated in the discussion.

This review will cover all pyrazolinones and pyrazolidinones reported up to and including the 1956 *Chemical Abstracts* and will cover the more important publications which have appeared since. However, a number of publications dealing with applications, biological activities and analysis were omitted as they were regarded as being of insufficient significance for coverage. A rather extensive list of the compounds of these types which have been reported is included, although here again there are many omissions. A number of dyes were not included as their structure was uncertain. Some very complex dyes which would require considerable space for inclusion are omitted and a reference to them is given. In general, the large number of salts reported were not included and in particular all picrolonates were omitted. However, many of the complexes which pyrazolin-5-ones form so readily are discussed, although in some cases these may be of a salt-like nature. Compounds in which the oxo substituents are replaced by such groups as imino, thiono and seleno are considered in this review. The early literature, which is available from standard sources (Beilstein, Meyer-Jacobson) has not been exhaustively compiled.

2. Historical

The well-known German chemist, Ludwig Knorr, reported the preparation of the first pyrazolinone in 1883.[805] This compound was 3-methyl-1-phenyl-2-pyrazolin-5-one prepared by the reaction of ethyl acetoacetate with phenylhydrazine. In the first publication no structure was proposed, but in a later publication[806] structure (VI) was suggested.

In this same article synthesis of the widely used analgesic and antipyretic, antipyrine, was reported. This was one of the first synthetic

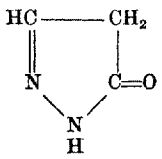


(VI)

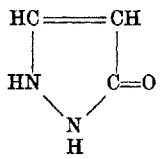
organic drugs. It was marketed and used before the correct structure for pyrazolinones was suggested by Knorr[809] in 1887 and the name by Ruhemann.[1230]

3. Structure

A short time after the discovery of pyrazolin-5-ones Knorr[809] proposed the 2-pyrazolin-5-one and the 3-pyrazolin-5-one structures on the basis of analyses, methods of preparation and reactions. These structures in the main approximate the correct ones and in some cases are correct. However, a large number of structures are theoretically possible for most pyrazolin-5-ones and in many cases no one structure can be said to fit completely. The tautomeric isomers (VII)–(XIII) are possible for unsubstituted pyrazolin-5-ones:



(VII)



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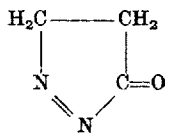

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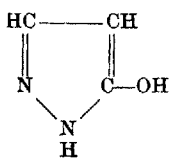
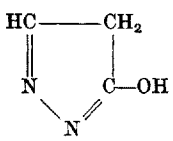


(X)



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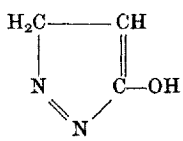

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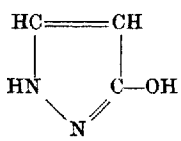
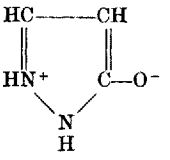


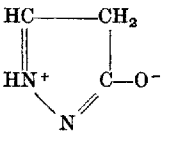
(XIII)

In addition a number of ionic tautomeric isomers can be envisaged which could make very important contributions to the over-all structure. These are (XIV)–(XVIII). Substitutions at N–1, N–2 and disubstitution at C–4 substantially alter the possibilities for various tautomeric

and resonance forms. Of the possible tautomeric forms shown, only (VII), (VIII) and (X) appear to exist to any extent although Valyashko



(XIV)



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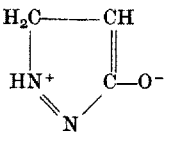
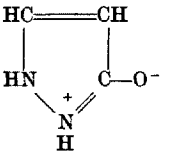
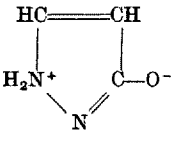


(XVI)



(XVII)



(XVIII)

and Bliznykov[1510] report diazo structures as present on the basis of rather complex ultraviolet absorption spectra. There is extensive evidence, both chemical and physical for these three structures. The presence of enolic forms is shown by the fact that one of the most common tests for 2-pyrazolin-5-ones is the use of ferric chloride to form a colored complex[809,1551] and by the ready formation of 5-alkoxypyrazoles from pyrazolinones.[655,811] Dmowska and St. Weil[376] have claimed the isolation of the keto and enol forms of 4,4′-(3-nitrobenzylidene)bis(3-methyl-1-phenyl-2-pyrazolin-5-one) and keto and enol forms of similar compounds have been isolated.[1134,1135] Existence of the form (VIII) is shown by alkylation of 3-phenyl-2-pyrazolin-5-one to give 2-methyl-3-phenyl-3-pyrazolin-5-one.[54]

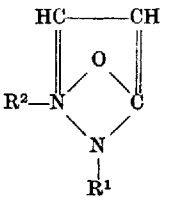
The structures of pyrazolin-5-ones have been very extensively studied using ultraviolet and infrared absorption spectra and such techniques have established unequivocally that (VII), (VIII) and (X) are the chief tautomeric contributors. Most of the workers in this field have emphasized the complexity of ultraviolet spectra due to the existence of tautomeric mixtures. Gomez[584] has stated that no deduction can be drawn from the ultraviolet spectra of 1-methyl-3-phenyl-2-pyrazolin-5-one, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and its 4-dimethylamino analog because of the tautomeric equilibria present. The existence of an equilibrium between 2-pyrazolin-5-one and 3-pyrazolin-5-one structures has been proposed by Biquard and Grammaticakis[95] for 3-alkyl-1-aryl- and 1-aryl-3,4-dialkyl-2-pyrazolin-5-ones on the basis of ultraviolet absorptions. Gagnon and co-workers[503,505]

have been most active in this field and have drawn several conclusions from ultraviolet studies, some of which were in disagreement with infrared absorption spectra interpretations. These workers have found that pyrazolin-5-ones absorb ultraviolet light either in the neighborhood of 240–260 mμ with a log ε value of 4.0–4.4 or at 295–325 mμ with a log ε value of 3.3–4.0, or in both regions. The shorter wave length absorption is believed to be due to >C=C< absorption while the longer is due to >C=N—. Thus type (VII) would show the longer wave length absorption, type (VIII) the shorter, and type (X) both, or a mixture of any two would show absorption at both wave lengths. 4-Alkyl-3-aryl-2-pyrazolin-5-ones absorb at the lower wave length only, indicating that they possess only structure (VIII). However, this conclusion was in disagreement with the finding that these compounds exhibited absorption in the infrared at 1600 cm.$^{-1}$ due to >C=N— and at 3300 cm.$^{-1}$ [505] and showed no absorption attributable to carbonyl. Thus they must actually be of type (X). From the ultraviolet spectra 4-alkyl-1,3-diaryl-2-pyrazolin-5-ones were concluded to be a mixture of types, but the infrared spectra very clearly showed them to be type (VII) as there was only carbonyl and >C=N— absorption. It would appear that the 1-arylpyrazolin-5-ones with no N–2 substituent are usually of type (VII), since Glauert and Mann[578] found no imino or hydroxyl absorption in the infrared spectra of 1,4-diaryl-2-pyrazolin-5-ones. Recently[366a] the infrared spectra of 3-methyl-, 3-trifluoromethyl-, 1,3-dimethyl-, 1-methyl-3-trifluoromethyl- and 1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one have been studied. The presence of absorption bands at 2400–2700 cm.$^{-1}$ believed due to zwitterionic forms indicated that these compounds exist largely as form (XIV).

The effect of substitution on the structure of pyrazolinones is a very important one, because certain of the tautomeric forms then become impossible. For example, substitution at N–1 allows only structures (VII), (VIII) and (X). Substitution at N–2 would make (VIII) and (XIII) the only possible tautomers. A combination of N–1 and N–2 substitution leaves (VIII) as the only possibility. If there is substitution at N–1 and disubstitution at C–4, then only isomer (VII) is possible. There has been little investigation of the possibilities for tautomeric structures of N–2 substituted pyrazolinones. However, Kitamura[788] has suggested that such compounds exist as a mixture of forms (VIII) and (XIII).

There has been considerable discussion of the situation in regard to the ionic structures. About fifty years ago Michaelis[978,983,984,1002,1003] proposed (XIX) as the structure for 1,2-disubstituted pyrazolinones. In modern terminology this could correspond to structure (XIV).

Komada[844-846] recently has used this structure to explain the structure of the tetrabromides of this type of pyrazolinones. Kitamura[788]



(XIX)

has used rather inconclusive chemical evidence in support of the exis tence of 3-pyrazolin-5-ones in form (XVII). Somewhat better evidence for the structural contributions of these resonance forms has been given in the form of dipole moments, ultraviolet data and bond lengths. Jensen and Friedinger[715] and Brown *et al.*[245] have found abnormally high dipole moments for 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and its thiono analog. This was considered to be due to contributions by forms (XIV) and (XVII) to the extent of about 35 per cent. A structure analogous to (XVII) has been proposed for 2-pyrazolin-5-thiones also on the basis of dipole moments.[934] Valyashko and Bliznykov[1509] have found that 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones have ultraviolet spectra very similar to that of 5-chloro-3-methyl-1-phenyl-pyrazole methochloride, indicating a considerable contribution by form (XIV). Krohs[860] has demonstrated a considerable contribution from the carbonyl form, as shown by infrared absorption in the carbonyl region. This has been confirmed by other infrared studies, and it has been proposed on the basis of this that form (VIII) is the predominating one in some cases.[366a] Romain[1208] has studied the bond lengths in 4-bromo-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. These bond lengths indicate a resonance hybrid structure composed of forms (VIII) and (XIV) with some contribution from (XVII).

Chattaway and co-workers[287-290,294] have synthesized a number of 1-aryl-2-pyrazolin-4-ones which, as a rule, have been considered to have the 4-hydroxypyrazole structures. However, some of these must have the 2-pyrazolin-4-one structure due to disubstitution at C–5. Emerson and Beegle[425] have synthesized some 2-pyrazolin-4-ones unsubstituted at N–1 permitting more possibilities for isomerism. These will be discussed later.

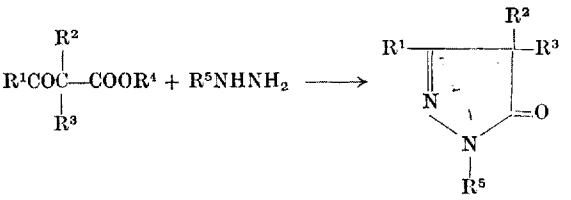
The pyrazolidinones (IV) present a number of possibilities for structural isomerism, but very little study of their structure has been made. It is generally assumed that they have the classical form (IV).

Certainly they would not be expected to have the tendency of 2-pyrazolin-5-ones to enolize, since they could not achieve an aromatic-like structure.

4. Synthesis

Only a few of the principal synthetic methods for pyrazolinones and pyrazolidinones will be discussed at this point. Other methods will be mentioned in connection with various classes of compounds. The procedures mentioned here will be discussed in greater detail at the appropriate places.

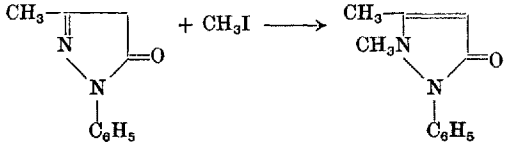
By far the most widely used synthesis for 2-pyrazolin-5-ones is the condensation of a β-ketoester with a hydrazine (eq. 1).[6,11,64,269,303,805]



(1)

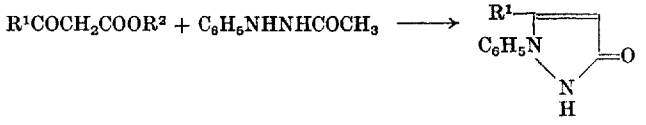
The R groups in this reaction can be almost anything, H, alkyl, aralkyl, aryl, heterocyclic and many others. Modifications of this procedure have employed β-thionoesters,[1006,1008] β-oximinoesters[1555] and β-ketoamides.[99,197,1276]

Perhaps the most common procedure for preparing 3-pyrazolin-5-ones is alkylation of a 2-pyrazolin-5-one at N–2 as shown for the synthesis of antipyrine (eq. 2).[806] Other alkylating agents such as dimethyl



(2)

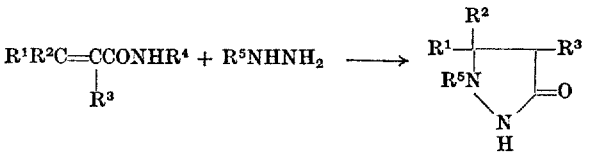
sulfate[781] can be used, and almost any 2-pyrazolin-5-one can be alkylated, although frequently *O*-alkylation occurs and also alkylation at N–1 if it has no substituent. Another useful synthesis of 3-pyrazolin-5-ones is the condensation of a β-ketoester with acetylphenylhydrazine (eq. 3). The acetyl group is lost and the phenyl group appears at



(3)

N–2.[984,988,993] A modification of this consists of using a symmetrically substituted hydrazine to give 1,2-disubstituted-3-pyrazolin-5-ones.[54]

The synthesis of pyrazolidinones is readily achieved by condensation of an α,β-unsaturated acid,[1550] ester[1209,1569] or amide[758] with a hydrazine. In eq. 4 is shown the reaction for an amide.



(4)

The reaction of a malonic ester or chloride with hydrazines gives 3,5-pyrazolidinediones (eq. 5).[188,222,248,252,1234]

(5)

5. Physical Properties

Most pyrazolinones and pyrazolidinones are solids, although many, some very complex, can be distilled as high-boiling liquids. 2-Pyrazolin-5-one is a liquid boiling at 163°. Reduction of the >C=N— lowers this to 132°. Substitution on N–1 and N–2 gives a low-melting solid. However, substitution at C–3 or C–4 has a more pronounced effect, as for example in 3-methyl-2-pyrazolin-5-one, which melts at 215°. Alkyl substitution in pyrazolidinones does not have such a marked effect but does raise boiling and melting points. Almost all aryl substituted pyrazolinones and pyrazolidinones are solids, but many can be distilled.

The solubility of pyrazolinones and pyrazolidinones is so varied as to make generalizations of little value. The simpler ones, of lower molecular weight, are soluble in hot water and a few are even soluble in cold water. Almost all are soluble in polar organic solvents and many are soluble in ether and benzene. However, most are insoluble in petroleum ether.

Ultraviolet and infrared spectra have been considered in some detail in the section dealing with structure. Concerning the ultraviolet spectra it can be stated that, while there is considerable absorption by pryazolinones and some pyrazolidinones, these absorptions are so complex, owing to tautomerism, that little can be deduced from them.

The infrared spectra are as would be expected. In some cases there are clear bands due to carbonyl and >C=N— and in others the carbonyl band is missing but hydroxyl bands are present. Raman spectra of antipyrine and aminopyrine have been investigated.[273,1167]

Dipole moments have already been discussed in the section dealing with structure. They have been found to be quite high for the few 3-pyrazolin-5-ones studied. The only value reported for a 2-pyrazolin-5-one is considerably lower, being 2.54 for 3-methyl-2-pyrazolin-5-one.

A number of miscellaneous physical properties of antipyrine and a few of its derivatives have been studied. These are listed with references in Table I.

TABLE I. Physical Properties of Antipyrine Investigated

Physical Property	Reference
Crystal Form	844
Dielectric Constant	367
Dielectric Coefficient	367
Heat Capacity	1466
Latent Heat	668
Phase Diagram	669
Surface Activity	561

6. Chemical Properties

Only a few of the more important chemical properties of pyrazolinones and pyrazolidinones will be discussed in this section, since these will be covered more thoroughly in connection with the different classes.

The pyrazolinones are in general weak acids[805] and many can be titrated with strong bases. The 2-pyrazolin-5-ones are stronger acids than the 3-pyrazolin-5-ones[1523] which are very weak. Most pyrazolinones are readily soluble in bases. The pyrazolidinones are not acidic, unless some special feature makes them so. The most extensive data on basicity have been provided by Veibel and co-workers[1521,1522,1525] who have titrated a number of pyrazolinones with perchloric acid in acetic acid. The pK_b values range from 10.3 to 12.3, except for 4,4-disubstituted and 4-halogen substituted 2-pyrazolin-5-ones. The 4,4-disubstituted 2-pyrazolin-5-ones are so weak that they are essentially neutral, while the halogenated compounds have pK_b values of about 13.2.

Both 2-pyrazolin-5-ones and 3-pyrazolin-5-ones undergo substitution at C–4 in an aromatic fashion. Halogenation, nitration and coupling with diazonium salts occur readily. In 2-pyrazolin-5-ones such reactions

as condensation with aldehydes and ketones and alkylations occur readily at C–4. The pyrazolinone and pyrazolidinone rings do not have aromatic stability, although in many cases they can assume an aromatic-like structure. The ring is readily destroyed by acid or base hydrolysis and by oxidation. Pyrazolidinones react very much as do aliphatic hydrazides.