Studies in the Pyrazole Series

by

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A THESIS

SUBMITTED TO THE FACULTY
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
Master of Arts

Houston, Texas
May 1950
Acknowledgment

It is with sincere appreciation that I express my gratitude to Professor G. H. Richter, who conceived the problem and patiently guided its solution. I also wish to thank Dr. F. S. Lewis for a number of timely and valuable suggestions.

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I. Introduction
Introduction

The remarkable analogy between the reactions undergone by aromatic compounds and those exhibited by a large number of heterocyclic systems constitutes one of the important generalizations of organic chemistry. Among the reactions of the aromatic substitution type, one of the most valuable from a synthetic viewpoint, that of chloromethylation, has been applied to a wide variety of aromatic compounds; however, since its discovery in 1893, the chloromethylation reaction has been extended only to that heterocyclic nucleus which bears the closest resemblance to benzene, namely, thiophene (1,2). An investigation of the applicability of the reaction to other heterocyclic series would therefore be of some importance.

Although numerous heterocyclic systems invite attention, the choice of a particular series for the study of chloromethylation should be governed by two factors. The primary requirement is one of stability of the nucleus under the conditions of the reaction. A second consideration involves the nature of the highly reactive $\text{CH}_2\text{Cl}$ group which is the product of chloromethylation; inasmuch as this group is the requisite structure for a number of important condensation reactions, it would be most prudent to investigate the chloromethylation of a ring system which has not yet been coupled with such common intermediates as malonic ester. Both of the above requirements are met by the members of the pyrazole series.\(^1\) Especially characteristic of the pyrazole nucleus (I) is its

\(^1\) Since the present investigation was undertaken, a number of amino acids containing the pyrazole ring have been described (3).
stability and the case with which it undergoes the typical aromatic re-
actions of halogenation, nitration, and sulfonation in the 4-position.
Accordingly, the present investigation had as its immediate objective
the study of chloroethylation in the pyrazole series and the prepara-
tion of chloroethylpyrazoles as synthetic intermediates.

The essential features of the chloroethylation of aromatic
compounds are described in the general equation

\[ \text{ArH} + \text{HCHO} + \text{HCl} \rightarrow \text{ArCH}_2\text{Cl} + \text{H}_2\text{O} \]

Although numerous modifications of the procedure for chloroethylation
have been developed,\(^2\) the minimum requirement is a source of formalde-
hyde and hydrogen chloride. These reactants can be employed in a number
of forms, and a variety of general acid catalysts of the Friedel-Crafts
type can be used. The reaction is subject to the usual reactivity and
orientation effects which are characteristic of aromatic substitution.
Chloroethylation is frequently accompanied by an important side reac-
tion which results in the formation of diarylmethane derivatives. A
familiar example of such a reaction in heterocyclic systems is the for-
mation of dipyrrylmethanes from pyrroles and formaldehyde in the presence
of mineral acid; and in the chloroethylation of thiophene, the produc-
tion of di-α-thiophenemethane is just as extensive as is that of α-
-thiophenemethyl chloride (1). Finally, mention should be made of the use
of higher homologs of formaldehyde in effecting correspondingly higher
chloroalkylations.

\(^2\) The chloroethylation of aromatic compounds has been reviewed (4).
The investigation described here had its origin in the work of Landua (5) on the chloromethylation of 3,5-dimethyl-pyrazole (II). Landua studied the reaction of this compound with paraformaldehyde in

![Structures I and II](image)

the presence of concentrated hydrochloric acid under the five conditions summarized in Table I. By successive extraction of the basic reaction mixtures with ether and alcohol, Landua obtained three products, to which he assigned the structures

![Structures III, IV, and V](image)

<table>
<thead>
<tr>
<th>Mole ratio of pyrazole:HCHO:HCl</th>
<th>temp. °C</th>
<th>time hours</th>
<th>1-carbinol</th>
<th>1,4-dicarbinol</th>
<th>4-carbinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1.37 : 19.2</td>
<td>30</td>
<td>13</td>
<td>33.2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1 : 1.37 : 22.2</td>
<td>30</td>
<td>23</td>
<td>43.6</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>1 : 2.74 : 21.6</td>
<td>30</td>
<td>23</td>
<td>43.0</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>1 : 3.00 : 31.2</td>
<td>30</td>
<td>65</td>
<td>31.3</td>
<td>33</td>
<td>--</td>
</tr>
<tr>
<td>1 : 3.60 : 53.0</td>
<td>75</td>
<td>4</td>
<td>19.1</td>
<td>--</td>
<td>56</td>
</tr>
</tbody>
</table>

Table I
All three products were found not to contain chlorine and to react vigorously with acetyl chloride. Since these observations suggested that the compounds were alcohols, Landau decided to identify the individual structures by oxidation to the corresponding acids. The ether-soluble 3,5-dimethyl-pyrazole-1-carbinol (III) was oxidized by permanganate to an acid the melting point of which coincided with that reported for 3,5-dimethyl-pyrazole-1-carboxylic acid (VI). The ether-insoluble 1,4-dicarbinol (IV), which decomposed on standing to the 4-carbinol, was converted by oxidation to a compound which possessed a neutral equivalent corresponding to that of the previously unreported diacid (VII). The ether-insoluble 3,5-dimethyl-pyrazole-4-carbinol (V) when oxidized yielded the corresponding acid (VIII), which was characterized by its melting point and neutral equivalent. No combustion analyses were obtained.

Although Landau's work did not progress to such an extent that the structures III, IV, and V could be regarded as established with certainty, these will be assumed to be correct, and are employed throughout the discussion which follows.

With the above results on the chloromethylation of 3,5-dimethyl-pyrazole as a point of departure, the work described in the
following sections was concerned with a systematic study of aldehyde condensation in the pyrazole series. The structural investigations related to the various condensation products are separately considered. Since the original goal of the direct synthesis of chloromethylated pyrazoles was not achieved, several indirect attacks on the problem are also described. Finally, a number of side reactions which occur during the synthesis of various pyrazole derivatives seem to merit individual treatment, and are discussed in the last section.
II. Aldohyde Condensation in the Pyrazole Series
Aldol Condensation in the Pyrazole Series

In view of the fact that the products obtained by Landua in the attempted chloromethylation of 3,5-dimethyl-pyrazole were alcohols, the problem of the function of the HCl in the reaction arises. Two interpretations are immediately suggested: the carbinols either resulted from hydrolysis of the chloromethyl derivatives or were intermediates in the formation of chloromethyl compounds. The problem was therefore attacked by an investigation of the reaction of 3,5-dimethyl-pyrazole with formaldehyde in the absence of HCl.

The reaction between equimolar proportions of 3,5-dimethyl-pyrazole and 35% formalin at room temperature was found to result in a 71% yield of a compound shown by mixed-melting point tests to be identical with Landua's 3,5-dimethyl-pyrazole-1-carbinol. An attempt was made to obtain higher condensation products by the use of an excess of formalin, but the only product which could be isolated was the 1-carbinol, obtained in a yield of 62%.

The effect of a higher temperature on the reaction was studied by allowing a molten mixture of equivalent amounts of 3,5-dimethyl-pyrazole and paraformaldehyde to react at 110-120°. The 1-carbinol was again obtained, this time in a yield of 90%. An excess of paraformaldehyde gave identical results, the gaseous unchanged material having escaped from the reaction mixture. A study of the melting point of the solidified product obtained from the molten mixture as a function of the reaction period (page 7) indicated that the reaction is essentially complete in one-half hour. The high-temperature reaction was found to be the most convenient method for the preparation of the 1-carbinol.
Since no product other than the 1-carbinol could be obtained from the pyrazole and formaldehyde alone, the effect of HCL on the reaction was determined. Inasmuch as the 1-carbinol is formed both in the presence and in the absence of HCL, it was decided to carry out a reaction between 3,5-dimethyl-pyrazole-1-carbinol, paraformaldehyde, and hydrochloric acid. From these reactants there was obtained 3,5-dimethyl-pyrazole-1,4-dicarbinol in a maximum yield of 24%.

Several experiments in which 3,5-dimethyl-pyrazole, paraformaldehyde, and HCL were allowed to react at room temperature were carried out. The mixture of products consisted predominantly of the 1-carbinol; smaller amounts of the 1,4-dicarbinol were formed, and only traces of the 4-carbinol could be isolated.

A number of attempts were made to prepare 3,5-dimethyl-pyrazole-4-carbinol, which is a necessary intermediate in further synthetic work. Since the maximum yield of this substance obtained by Landau resulted from a high-temperature reaction, a series of reactions between the pyrazole, formaldehyde, and HCL were studied at temperatures between 75 and 100°. The immediate products of these reactions were always polymeric materials from which no definite compounds could be isolated. However, a white semi-crystalline substance which melted over the range 209-250° was obtained by repeated application of purification techniques to the tarry products. This material was very soluble in alcohol and difficultly soluble in hot water. It might reasonably be considered impure di-(3,5-dimethyl-pyrazoly1-4)-methane (IX), which is reported (6) to have a melting point of 200° and to possess the same solubility properties as those of the substance obtained in this investigation.
An effort was made to obtain the 4-carbinol by the use of milder conditions, but even a molten mixture of 3,5-dimethyl-pyrazole hydrochloride and paraformaldehyde resulted in an intractable tar.

The nature of the formaldehyde condensation in a strongly acidic medium was then investigated. From the reaction in dioxane solution between 3,5-dimethyl-pyrazole and paraformaldehyde in the presence of zinc chloride and anhydrous HCl there was obtained a gummy substance. Purification of this product yielded only a solid material of indefinite composition.

At this stage of the investigation it had been found that 3,5-dimethyl-pyrazole condenses with formaldehyde in the 1-position in neutral media and in both the 1- and 4-positions in acidic media. A study of the course of the reaction in strongly basic solution was therefore in order. Especially noteworthy in this connection are the well-known side-chain formaldehyde condensations undergone by α- and γ-methylpyridines. Since these reactions are base-catalyzed, the formation of an analogous product (X) from the dimethylpyrazole and formaldehyde in basic solution was considered a strong possibility. Accordingly, the reaction in methanol solution between 3,5-dimethylpyrazole, paraformaldehyde, and sodium methoxide at room temperature was studied. Again the product was a viscous mass, from which a small amount of unchaged dimethylpyrazole was the only isolable compound.
The reaction of formaldehyde with 3,5-dimethyl-pyrazole was explored no further. It seemed appropriate at this point to extend the investigation to other members of the pyrazole series, in particular to those containing a substituent in the 1-position. The readily accessible 1-phenyl-pyrazole (XI) and 1-phenyl-3,5-dimethyl-pyrazole (XII) were chosen for this work.

It is conceivable that in these compounds formaldehyde condensation can occur either in the heterocyclic ring or in the aromatic ring. Isomeric condensation products of the 1-phenyl-pyrazoles are readily distinguishable, however, by oxidation to the corresponding acids, most of which are described in the literature. In the case of 1-phenyl-pyrazole, those acids in which the carboxyl group is located in the 3,4, and 5-positions of the pyrazole ring and in the ortho- and para-positions of the benzoic ring have been well-characterized and possess widely separated melting points.
The immediate product of the reaction between 1-phenyl-pyrazole, paraformaldehyde, and hydrochloric acid at room temperature was a tarry material, from which a small amount of a white crystalline compound melting at 172-173° was obtained. Oxidation of the remainder of the tar by permanganate resulted in an 8% yield of 1-phenyl-pyrazole-4-carboxylic acid (XIV). From the reaction mixture 35% of the unchanged 1-phenyl-pyrazole was also recovered. The intermediate compound may well have been 1-phenyl-pyrazole-4-carbinol (XIII).

![Chemical structures XIII and XIV](image)

The possibility of reaction of the 1-phenyl-pyrazole with paraformaldehyde in the absence of acid was investigated by maintaining the mixture at 120-140° for fifteen minutes. Depolymerization of the paraformaldehyde was all that occurred, and 90% of the 1-phenyl-pyrazole was recovered. When the two reactants were heated in the presence of sulfuric acid, however, there was obtained a viscous tar, which furnished the 4-carboxylic acid in 13% yield when oxidized.

A similar reaction of 1-phenyl-3,5-dimethyl-pyrazole with paraformaldehyde in hydrochloric acid solution yielded a white crystalline substance melting at 121-122°. This compound, assumed to be di-(1-phenyl-3,5-dimethyl-pyrazoly1-4)-methane (XV), was obtained in a yield of 20%; 43% of unchanged pyrazole derivative was also recovered.
From the information on the reactions between formaldehyde and various pyrazoles discussed above, there emerges one important conclusion: although formaldehyde adds to the 1-position of the pyrazole nucleus in both neutral and acidic media, condensation in the 4-position occurs only in the presence of acid. This observation suggests that the reactions at the two positions follow different courses. Reaction in the 1-position probably occurs by a carbonyl-addition type mechanism:

\[
\begin{align*}
\text{H-C}^+ + \text{N} &\rightarrow \text{H-C}^- + \text{N} \\
\text{H} &\rightarrow \text{H}
\end{align*}
\]

Condensation in the 4-position, on the other hand, can be regarded as involving an electrophilic attack by the conjugate acid of formaldehyde on the pyrazole nucleus:

\[
\begin{align*}
\text{CH} + \text{N}^- &\rightarrow \text{C}^- + \text{N}^- \\
\text{H} &\rightarrow \text{H} \\
\text{H} &\rightarrow \text{H}
\end{align*}
\]

This interpretation is based on the fact that pyrazole undergoes the usual aromatic substitutions in the 4-position.
In view of the manner in which chloromethylation can be extended to higher chloroalkylation by the use of the homologs of formaldehyde, the reaction between the pyrazole nucleus and higher aldehydes was of interest. A mixture of 3,5-dimethyl-pyrazole and paraaldehyde in the presence of hydrochloric acid, however, yielded no product other than the original reactants. Substitution of monomeric acetaldehyde also resulted in no reaction.

A final study of pyrazole-aldehyde condensation was made with benzaldehyde. From several reactions of 3,5-dimethyl-pyrazole with benzaldehyde in both the presence and absence of HCl there were obtained small amounts of a well-defined crystalline compound which melts at 203-204°. Although several structures for the product of this reaction might be considered, the most reasonable on the basis of the limited information obtained in this investigation is phenyl-di-(3,5-dimethyl-pyrazolyl-1)-methane (XVI).

![Chemical structure](image)
Experimental Part

Preparation of 3,5-dimethyl-pyrazole:

The procedure of Khorr and Rosengarten (7) was followed in the preparation of 3,5-dimethyl-pyrazole from acetylaceton and hydrazine:

$$\text{CH}_3\text{C}-\text{CH}_2\text{C}-\text{CH}_3 + \text{H}_2\text{N}-\text{NH}_2 \rightarrow \text{H}-\text{C}-\text{C}-\text{CH}_3 + 2\text{H}_2\text{O}$$

Acetylaceton was prepared by a Claisen condensation between ethyl acetate and acetone according to the procedure described in Organic Syntheses (8). A maximum yield of 27% of a product boiling at 131-135° was obtained. The diketone was converted to the pyrazole, n.p. 105-107°, in 80% yield.

Reaction of 3,5-dimethyl-pyrazole with formalin:

To a solution of 3.27 g. (0.034 mole) of 3,5-dimethyl-pyrazole in 53 ml. of water and 5 ml. of ethanol, 3.00 ml. (0.037 mole) of 35% formalin (d$_4^{21}$ 1.003) was added. After standing at 30° for forty-two hours, the mixture was extracted with three 25-ml. portions of chloroform, and the solvent from the combined extracts evaporated on the steam bath. Recrystallization of the residue from benzene yielded 3.03 g. (71%) of 3,5-dimethyl-pyrazole-1-carbinol, n.p. 103-109°.

The same procedure was repeated with the use of a ten-fold excess of formalin, and the identical 1-carbinol was obtained in a yield of 62%.
Reaction of 3,5-dimethyl-pyrazole with paraformaldehyde:

A mixture of 0.951 g. (0.01 mole) of 3,5-dimethyl-pyrazole and 0.300 g. (0.01 mole) of paraformaldehyde (Eastman trioxyethylcane) was immersed for twenty minutes in an oil bath maintained at 110-120°. The mixture was then cooled to 30°, and the solidified melt recrystallized from benzene. The benzene solution furnished 1.13 g. (90%) of 3,5-dimethyl-pyrazole-1-carbinol.

The same procedure was repeated with a 2:1 mole ratio of paraformaldehyde, and again a 90% yield of the 1-carbinol was obtained.

Reaction between 3,5-dimethyl-pyrazole-1-carbinol, paraformaldehyde, and HC1:

A mixture of 1.2 g. (0.01 mole) of 3,5-dimethyl-pyrazole-1-carbinol and 0.4 g. (0.013 mole) of paraformaldehyde was dissolved in 8.5 ml. (0.10 mole) of conc. HC1. The solution was left standing at 30° for one week. In order to remove the bulk of the HC1, the mixture was transferred to a Claissen flask and subjected to distillation at the water pump until 4 ml. of distillate had been collected. The residue was then carefully neutralized with K2CO3, and the HC1 removed by filtration. After addition of 15 ml. of ethanol to the filtrate, the solution was saturated with K2CO3, and the upper alcoholic layer separated. Evaporation of the alcohol at room temperature in the hood left a solid residue which was contaminated with inorganic material. The organic product was most readily purified by recrystallization from n-propyl alcohol. The yield of purified 3,5-dimethyl-pyrazole-1,4-dicarbinol, m.p. 133-140°, was 0.35 g. (24%).
Reaction between 3,5-dimethyl-pyrazole, paraformaldehyde, and HCl:

A solution of 3.27 g. (0.034 mole) of 3,5-dimethyl-pyrazole and 3.05 g. (0.102 mole) of paraformaldehyde in 85 ml. (1.02 moles) of conc. HCl was left standing at room temperature for five days. The mixture was then cooled in an ice-bath and made basic to litmus by careful addition of 50% NaOH. After removal of the precipitated NaCl, the basic solution was extracted twice with 50 ml. portions of ether, and the combined ether extracts evaporated on the steam-bath; the residue was a white crystalline substance. Recrystallization of this product from benzene yielded 0.85 g. (21%) of 3,5-dimethyl-pyrazole-1-carbinol.

The aqueous layer from the ether extraction was then treated with 100 ml. of ethanol, whereupon more NaCl was precipitated. Saturation of the decanted aqueous solution with $\text{K}_2\text{CO}_3$ resulted in an upper alcoholic layer, from which the solvent was evaporated in the hood at room temperature. The residue was a white solid with a yellow discoloration, and consisted largely of inorganic matter. It was warmed with 20 ml. of ethanol, and the yellow alcoholic solution decolorized with Norite. Evaporation of the alcohol in the hood left a sticky white residue, which yielded after recrystallization from an ethanol-benzene mixture 0.30 g. (15%) of 3,5-dimethyl-pyrazole-1,4-dicarbinol.

That portion of the residue from the alcoholic solution which was insoluble in ethanol-benzene was treated with warm water. From the aqueous solution there were obtained a few crystals of 3,5-dimethyl-pyrazole-4-carbinol, m.p. 174-176°.
Reaction of 1-phenyl-pyrazole with paraformaldehyde in the presence of acid:

1-phenyl-pyrazole was prepared from epichlorohydrin (Eastman) and phenylhydrazine according to the procedure of Balbiano (9):

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} + \text{H}_2\text{N} = \text{N}-\text{H}_2 \rightarrow \text{H-C} = \text{C-H} + \text{HCl} + \text{H}_2 + \text{H}_2\text{O}
\]

The 1-phenyl-pyrazole was obtained as a pale-yellow oil, b.p. 244-248°, in a yield of 31%.

A solution of 7.20 g. (0.05 mole) of 1-phenyl-pyrazole and 1.65 g. (0.05 mole) of paraformaldehyde in 8.5 ml. (0.10 mole) of conc. HCl was allowed to stand at 30° for one week. The mixture was then cooled in an ice-bath and carefully neutralized with a saturated solution of Na_2CO_3. When the mixture became basic, an upper oily layer separated. An equal volume of ether was added, whereupon the mixture separated into three phases: a lower, colorless aqueous layer, an intermediate, black tarry phase, and an upper, yellow ether solution.

Evaporation of the solvent from the ether layer left a yellow oily residue. Cooling of this residue in an ice-salt bath resulted in precipitation of 0.090 g. of a substance which crystallized from ethanol in the form of glistening white platelets, m.p. 172-173°. This product was considered to be 1-phenyl-pyrazole-4-carbinol. Distillation of the liquid portion of the residue yielded 2.5 g. (35%) of unchanged 1-phenyl-pyrazole.
The terry middle layer was oxidized with a cold, saturated solution of \( \text{KMnO}_4 \). Removal of the \( \text{MnO}_2 \) was effected by bubbling \( \text{SO}_2 \) through the mixture. Addition of 50% \( \text{H}_2\text{SO}_4 \) resulted in precipitation of a cream-colored solid material, which was removed by filtration. The precipitate was redissolved in 20% \( \text{NaOH} \), the basic solution filtered, and the filtrate acidified with \( \text{H}_2\text{SO}_4 \). Recrystallization of the precipitated acid from dilute alcohol yielded white needle-like crystals which melted at 221-222° with partial sublimation; these properties are exhibited by 1-phenyl-pyrazolo-4-carboxylic acid (10). The weight of pure acid obtained was 0.7 g. (6%).

Application of essentially the same purification techniques to the product of the reaction of 1-phenyl-pyrazole with paraformaldehyde in the presence of \( \text{H}_2\text{SO}_4 \), carried out at 120-140° for ten minutes, furnished the 4-carboxylic acid in 13% yield.

Reaction between 1-phenyl-3,5-dimethyl-pyrazole, paraformaldehyde, and \( \text{HCl} \):

1-phenyl-3,5-dimethyl-pyrazole was prepared from acetylacetone and phenylhydrazine by a modified procedure of Combes (11):

\[
\text{CH}_3\text{C=CH}_2\text{C=CH}_3 + \text{H}_2\text{NNH}_2 \rightarrow \text{H-C-CH}_3 + 2\text{H}_2\text{O}
\]

The pyrazole was obtained in 75% yield as a yellow oil boiling at 269-271°.
A solution of 8.50 g. (0.05 mole) of 1-phenyl-3,5-dimethyl-pyrazole and 1.65 g. (0.05 mole) of paraformaldehyde in 8.5 ml. (0.10 mole) of conc. HCl was allowed to stand at 30° for six weeks. The mixture was made basic with saturated Na₂CO₃ solution, whereupon two layers were formed. Evaporation of the solvent from the ether extracts of both the upper aqueous solution and the lower oily layer left only 4 g. (45%) of unchanged ether-soluble pyrazole. After standing for several days the oily layer crystallized almost completely. Recrystallization of the solidified product from water containing a little alcohol yielded 1.8 g. (20%) of a compound which took the form of acen-white needles melting at 121-122°. This substance was assumed to be di-(1-phenyl-3,5-dimethyl-pyrazolyl-4)-methane.

Reaction of 3,5-dimethyl-pyrazole with benzaldehyde:

A solution of 0.400 g. (0.0042 mole) of 3,5-dimethyl-pyrazole and 1.15 g. (0.011 mole) of freshly purified benzaldehyde in 2 ml. of benzene was refluxed for one hour. The bulk of the benzene was removed by distillation, and the residue was heated on the steam bath with 10 ml. of 3% H₂O₂ and 5 ml. of 10% NaOH until all of the unchanged benzaldehyde was oxidized. The aqueous solution, after standing at room temperature for two days, developed a cluster of white needle-like crystals. These were removed by filtration and recrystallized from dilute alcohol. The purified product, assumed to be phenyl-di-(3,5-dimethyl-pyrazolyl-1)-methane, melted at 203-204°. From this reaction there was obtained 0.120 g. (21%) of the compound.
III. Structure Determination of Aldehyde Condensation Products
Structure Determination of Aldehyde Condensation Products

The structures employed in the preceding section for the various aldehyde condensation products were arrived at through the investigations described below.

3,5-dimethyl-pyrazolo-1-carbinol:

The presence of the alcoholic group in this compound was verified by combustion analysis:

<table>
<thead>
<tr>
<th>Calculated for $C_{10}H_{10}O_N$</th>
<th>Found:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$ = 57.12</td>
<td>$C$ = 57.18</td>
</tr>
<tr>
<td>$H$ = 7.99</td>
<td>$H$ = 7.78</td>
</tr>
</tbody>
</table>

Inasmuch as the three isomers III, V, and X satisfy the requirements of the analysis, it was necessary to determine with certainty the position of the carbinol group. Landua had tentatively identified the compound by its oxidation to the 1-carboxylic acid (VI), reported to melt with decomposition at 90° (12). Since the carboxyl group of this acid is directly attached to a nitrogen atom, however, its stability is somewhat questionable in view of the ease with which carbonic acids decarboxylate. This expected instability is supported by the fact that N-carboxylic esters of both the indazole and pyrazole series lose carbon dioxide when distilled at atmospheric pressure. Furthermore, treatment of 1-carboxethoxy-3,5-dimethyl-pyrazole (XVII) with cold, dilute sodium bicarbonate yields 3,5-dimethyl-pyrazole (13). The acid described in the literature, however, is reported to have been prepared by alkaline hydrolysis of the same ester. It was therefore attempted to obtain the 1) All micro-combustion analyses reported here were performed by the Clark Microanalytical Laboratory, Urbana, Illinois.
1-carboxylic acid by an independent route involving the reaction of 3,5-dimethyl-pyrazole-1-carboxamide (XVIII) with nitrous acid at 0-5°. Repeated efforts in this direction, however, resulted only in nearly quantitative formation of 3,5-dimethyl-pyrazole.

The inconclusive results concerning the stability of the 1-carboxylic acid called for a different series of attacks on the problem of the structure of the carbinol. The first of these was dependent upon the product of the reaction of paraformaldehyde with 1-acetyl-3,5-dimethyl-pyrazole (XIX), in which condensation can occur either in the 4-position or on the side chain, but not in the 1-position. Removal of the acetyl group from the condensation product by hydrolysis would yield either the 4-carbinol or the side-chain carbinol, which in turn could be compared with the products obtained from the unsubstituted pyrazole. A number of reactions between the two compounds were carried out at 110-140°, but the product was always a viscous mass which apparent-
ly resisted all attempts at both acid and basic hydrolysis. Substitution of the formyl pyrazole XX for the acetyl derivative might have offered more promising results, because of the ease with which formyl derivatives are hydrolyzed (14); similarly, the phthalyl derivative XXI, which contains a free carboxyl group, should readily undergo alkaline hydrolysis. Neither of these two intermediates could be prepared, however. Attempted formation of XX from 3,5-dimethyl-pyrazole and formic acid (15) resulted in no reaction, while the synthesis of XXI from the pyrazole and phthalic anhydride (15) yielded a substance which melted at 87-88° and possessed a neutral equivalent of 133, that of the desired compound being 244.

The distinction between the 1-carbinol and its isomers could have been made by application of the iodoform test to the product of the condensation of acetaldehyde with 3,5-dimethyl-pyrazole. Of the three possible products XXII, XXIII, and XXIV, the first should give a negative iodoform test, while the other two would be expected to show positive tests. The information thus obtained could be transferred to the case of the formaldehyde products, provided the assumption that both aldehydes react in the same position under the same conditions were valid. It was stated in the preceding section, however, that no acetaldehyde product could be prepared.
Perhaps the most obvious method of distinguishing the 1-car- 
binal from its isomers is an active-hydrogen determination, since the 
1-carbinol possesses only one active hydrogen atom, while each of the 
other two alcohols contains two. It was decided to determine the ac-
tive-hydrogen content of the 1-carbinol by a quantitative acetylation 
procedure (17,18) in which the compound to be analyzed is heated with 
an acetic anhydride-pyridine mixture, the hot, unchanged acylating re-
agent hydrolyzed to acetic acid, and the free acid titrated with meth-
anesolic sodium hydroxide. Preliminary tests on 3,5-dimethyl-pyrazole 
itself, however, gave erratically low results for the >N-N content of 
this compound. From the reaction mixtures 72% of the unsubstituted 
dimethylpyrazole was recovered. The low values obtained in this pro-
cedure were therefore attributed to partial hydrolysis of the acetyl-
ated pyrazole, in view of the fact that 1-acetyl-3,5-dimethyl-pyrazole 
is readily hydrolyzed by hot water (12). Quantitative acetylation of 
the 1-carbinol was not attempted.

Conclusive information regarding the structure of the 1-car-
binal was finally obtained by taking advantage of the case with which 
the pyrazole ring undergoes halogonation in the 4-position. It was 
found that 4-bromo-3,5-dimethyl-pyrazole (XXV), m.p. 117-118°, reacts 
with formalin at room temperature to give a product which melts at 133-
134°. By direct bromination of 3,5-dimethyl-pyrazole-1-carbinol (III), 
m.p. 108-109°, there was obtained a compound which also melts at 133-
134°. The products of these two reactions were shown to be identical 
by a mixed-melting point test. Combustion analysis of the compound in-
dicated that it is a bromo-dimethyl-pyrazole-carbinol. The carbinol
group is definitely excluded from the 4-position because of the presence of the bromine atom; it is therefore located either in the 1-position or on the side chain.

The distinction between the latter two possibilities was based upon a characteristic property of pyrazoles which contain an unsubstituted imino hydrogen atom - the formation of a nitric acid-soluble precipitate with silver nitrate solution. Table II summarizes the results obtained in testing alcoholic solutions of the four compounds with alcoholic silver nitrate. Since all of the precipitates were completely soluble in dilute nitric acid, they did not contain silver bromide. The slow formation of the precipitates by the two carbinols suggests that the alcoholic group is located in the 1-position and not on the side chain, and that the precipitates probably resulted from displacement of formaldehyde by silver ion. This explanation is supported by the fact that 3,5-dimethyl-pyrazole-1-carbinol on treatment with amniacal silver nitrate slowly formed both a precipitate and a silver mirror. Posner (20) has observed that 3,5-dimethyl-pyrazole-1-carbinamide also gives a precipitate with silver nitrate. It follows, therefore, that the compound of melting point 133-134° is 4-bromo-3,5-dimethyl-pyrazole-1-carbinol (XXVI), and that it was formed according to the equations

Table II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Precipitate Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,5-dimethyl-pyrazole</td>
<td>ppt. formed immediately</td>
</tr>
<tr>
<td>3,5-dimethyl-pyrazole-1-carbinol</td>
<td>ppt. formed after fifteen seconds</td>
</tr>
<tr>
<td>4-bromo-3,5-dimethyl-pyrazole</td>
<td>ppt. formed immediately</td>
</tr>
<tr>
<td>4-bromo-3,5-dimethyl-pyrazole-1-</td>
<td>ppt. formed after thirty seconds</td>
</tr>
<tr>
<td>carbinol</td>
<td></td>
</tr>
</tbody>
</table>
The ultraviolet absorption spectrum of 3,5-dimethyl-pyrazole-1-carbinol (page 25) was observed to be identical with that of 3,5-dimethyl-pyrazole. This relationship is consistent with the structure assigned to the carbinol.

3,5-dimethyl-pyrazole-1,4-dicarbinol:

Combustion analysis of this compound confirmed the presence of two carbinol groups:

Calculated for C$_7$H$_{12}$O$_2$H$_2$:  
\[ C = 53.82 \quad H = 7.74 \]

Found:  
\[ C = 52.49 \quad H = 7.30 \]

3,5-dimethyl-pyrazole-4-carbinol:

This compound was shown by combustion analysis to be isostructural with the 1-carbinol:

Calculated for C$_6$H$_{10}$OH$_2$:  
\[ C = 57.12 \quad H = 7.99 \]

Found:  
\[ C = 57.40 \quad H = 7.79 \]
The 4-carbinol was prepared independently of formaldehyde condensation by reduction of 4-carbethoxy-3,5-dimethyl-pyrazole (XXVII) with lithium aluminum hydride. The product thus obtained was shown by a mixed-melting point test to be identical with the compound which resulted from formaldehyde condensation.

![Structure](image)

**XXVII**

di-(1-phenyl-3,5-dimethyl-pyrazolyl-4)-methane:

The product of the reaction of 1-phenyl-3,5-dimethyl-pyrazole with paraformaldehyde in hydrochloric acid solution did not react with acetyl chloride, nor could it readily be oxidized by permanganate; it was therefore concluded that the compound is not an alcohol. The only obvious alternative structure is the dipyrazolymethane derivative, which has a molecular weight of 355. Although a fast determination of the molecular weight of the unknown compound gave the value 255, it should be pointed out that the hot camphor solution of the substance exhibited a distinct yellow color. This observation suggests that the active methylene group of the dipyrazolymethane may have reacted with the carbonyl group of the camphor, so that the apparent molecular weight was too low. The above structure was therefore retained.
phenyl-di-(3,5-dimethyl-pyrazolyl-1)-methane:

The molecular weight of the product of the reaction of 3,5-dimethyl-pyrazole with benzaldehyde was found by the Rest method to be 296. This value excludes from consideration structures derived from a one-to-one mole ratio of the reactants. Compounds isomeric with XVI, however, have a molecular weight of 280. The product of the present investigation was therefore considered to be a benzal pyrazole, a conclusion strengthened by the fact that benzaldehyde forms similar condensation products with members of the pyrrole series (19). It remained to determine which position of the pyrazole ring was the center of reaction. Since an alcoholic solution of the compound did not give a precipitate with silver nitrate solution, the structure XVI, in which both of the imino hydrogen atoms have been replaced, was considered the most reasonable. This interpretation is supported by the observation that the compound is formed in both the absence and presence of HCl.
Experimental Part

Preparation of intermediates used in structural studies:

3,5-dimethyl-pyrazole-1-carboxamide was prepared from acetylacetone and semicarbazide according to the procedure of Posner (20):

\[
\text{CH}_3\text{C}==\text{CH}_2\text{C}=\text{O} + \text{H}_2\text{N}=\text{NH}-\text{C}=\text{NH}_2 \rightarrow \text{CH}_3\text{C}==\text{C}==\text{CH}_3 + 2\text{H}_2\text{O}
\]

A product melting at 113-114° was obtained in 23% yield.

1-acetyl-3,5-dimethyl-pyrazole was prepared from the unsubstituted pyrazole and acetyl chloride by the method of Seidel et al. (21). The acetyl derivative, b.p. 70° (12 mm), was obtained in a yield of 50%.

4-bromo-3,5-dimethyl-pyrazole was prepared by direct bromination of 3,5-dimethyl-pyrazole. The procedure of Morgan and Ackerman (22) was first employed, but the product obtained by this method contained objectionable quantities of perbromides. Slight modification of the original procedure gave the bromopyrazole, m.p. 117-118°, in a yield of 85%.

4-carbethoxy-3,5-dimethyl-pyrazole was prepared from ethyl diacetylacetate and hydrazine:

\[
\text{CH}_3\text{C}=\text{CH}_2\text{OC}=\text{O} + \text{H}_2\text{N}-\text{NH}_2 \rightarrow \text{C}=\text{O} + \text{H}_2\text{O}
\]

\[
\text{CH}_3\text{C}==\text{CH}_2\text{CH}=\text{CO}_2\text{H} + \text{H}_2\text{N}-\text{NH}_2 \rightarrow \text{CH}_3\text{C}==\text{C}==\text{CH}_3 + 2\text{H}_2\text{O}
\]
Ethyl diacetylacetate was prepared from acetic acid and acetyl chloride by the procedure given in Organic Syntheses (23). A product boiling at 92-93° (12 mm) was obtained in a yield of 37%. The conversion of the diketonic ester to the pyrazole derivative according to the method of Enorr and Rosengarten (7) was attempted, but the pyrazole ester was obtained in a yield of only 0.6%. The following modification, however, represents a distinct improvement in the original procedure.

To a well-stirred solution of 5.9 g. (0.1 mole) of 85% hydrazine hydrate in 10 ml. of water, cooled in an ice-bath, 17.2 g. (0.1 mole) of ethyl diacetylacetate was added dropwise. After precipitation appeared to be complete, the solid material, a by-product, was removed by filtration. The filtrate, which consisted of an aqueous layer and a lower oily layer, was placed in the refrigerator; after five hours the mixture became a thick suspension. The solid material was again separated by filtration, and the second filtrate discarded.

Treatment of the crude solid with 30 ml. of water on the steam-bath resulted in an aqueous solution and a lower oily layer. The red upper layer was decanted from the oil and allowed to cool in an ice-bath. The crystalline precipitate of the dihydrate of 4-carbethoxy-3,5-dimethylpyrazole thus formed was collected on a filter; it melted at 59-60°. After standing in a vacuum desiccator for three weeks, the compound lost its water of crystallization. The yield of the anhydrous compound, m.p. 95-95°, was 0.87 g. (5.2%).
Preparation of 4-bromo-3,5-dimethyl-pyrazole-1-carbinol:

a). A solution of 1.15 g. (0.0066 mole) of 4-bromo-3,5-dimethyl-pyrazole and 5.7 ml. (0.016 mole) of 35% formalin in 5 ml. of water and 3 ml. of ethanol was allowed to stand at room temperature for four weeks. The mixture was extracted with three 3-ml. portions of chloroform, and the solvent from the combined extracts evaporated in the hood. After two recrystallizations from water the yellow amorphous residue furnished 0.68 g. (65%) of 4-bromo-3,5-dimethyl-pyrazole-1-carbinol, n.p. 133-134°.

b). A mixture of 0.50 g. (0.004 mole) of 3,5-dimethyl-pyrazole-1-carbinol and 1.00 g. (0.003 mole) of sodium acetate was dissolved in 10 ml. of water. Dropwise addition of 0.5 ml. (0.009 mole) of bromine to the well-stirred solution resulted in precipitation of a pale-yellow solid material. After the excess bromine had been removed by heating on the steam-bath, the white suspension was filtered, and the precipitate recrystallized from water. The weight of the white crystalline product, n.p. 133-134°, was 0.70 g. (85%).

Analysis:

Calculated for C₆H₉O₃Br:

C = 35.14  H = 4.42

Found:

C = 34.94  H = 4.33

Reduction of 4-carbethoxy-3,5-dimethyl-pyrazole to 3,5-dimethyl-pyrazole-4-carbinol:

A solution of 0.98 g. (0.0053 mole) of 4-carbethoxy-3,5-dimethyl-pyrazole in 40 ml. of anhydrous ether was placed in a three-necked flask fitted with a dropping funnel, reflux condenser, and mercury-sealed stirrer. To the stirred solution of the ester, 40 ml. of an
ether solution of 0.32 g. (0.0024 mole) of lithium aluminum hydride was added over a period of one-half hour. The mixture was stirred for another hour, and the excess hydride decomposed with 3 ml. of water. After removal of the ether by distillation from a steam-bath, the white residue was extracted with 30 ml. of warm ethanol. Evaporation of the filtered alcoholic solution left a crystalline residue. Recrystallization of the crude product from ethanol yielded 0.47 g. (64%) of 3,5-dimethyl-pyrazole-4-carbinol, m.p. 179-180°.
IV. Preparation of Chloromethylpyrazoles by Indirect Methods
Preparation of Chloromethylpyrazoles by Indirect Methods

The original goal of the present investigation involving the preparation of chloromethylated pyrazoles from the parent heterocycle, formaldehyde, and hydrochloric acid was not realized. Although the various reactions which were employed yielded several pyrazole alcohols, which in turn can readily be converted to the chloromethyl derivatives, the amount of the synthetically important 3,5-dimethyl-pyrazole-4-carbinol thus formed was impractically small. The initial objective of the problem was therefore approached from a number of other directions.

A variation of the standard chloromethylation technique which makes use of chloromethyl ether and the catalyst stannic chloride (4) was first attempted. Treatment of 3,5-dimethyl-pyrazole with these reagents, however, resulted in no reaction. Substitution of zinc chloride as the catalyst apparently caused the reaction to proceed too far; the product was a polymeric substance from which no definite compound could be isolated.

One of the routes other than chloromethylation which leads to the synthesis of chloromethylated aromatic compounds is based upon bromination of side-chain methyl groups with N-bromosuccinimide. Since this reagent is capable of effecting both nuclear and side-chain bromination in aromatic compounds (24,25), the nature of its reaction with 3,5-dimethyl-pyrazole, which contains both side chains and an unsubstituted hydrogen in the 4-position, was determined. It was found that equimolar proportions of the two compounds react to give a nearly quantitative yield of 4-bromo-3,5-dimethyl-pyrazole without the formation of polybromides. This reaction therefore represents a distinct improvement
over the rather troublesome procedure of direct bromination for the
synthesis of such compounds.

The effect of a second mole of the brominating reagent was
observed by carrying out a reaction between 4-bromo-3,5-dimethyl-pyrazole
and an equivalent quantity of N-bromosuccinimide. The immediate product
of the reaction was a brown viscous mass with a sharp odor, a substance
which may well have been polymeric 4-bromo-3(5)-bromomethyl-5(3)-methyl-
pyrazole (XXVIII), since the highly reactive bromomethyl group would
be expected to condense with the basic part of the molecule. By re-
peated application of purification techniques to this tarry material a
little 4-bromo-3,5-dimethyl-pyrazole was recovered, and in addition a
small amount of a crystalline compound melting at 154-155° was isolated.
If side-chain bromination occurred during the reaction, this product
probably has the structure XXIX. The preparation of bromomethylpyraz-
ol-es with N-bromosuccinimide was not studied beyond this point.

Further attempts to prepare chloromethylpyrazoles were based
on the use of the corresponding alcohols as intermediates, so that the
problem at hand involved the synthesis of the desired pyrazole carbinols.
Attention was directed to the preparation of 3,5-dimethyl-pyrazole-4-
carbonil. Inasmuch as this compound was obtained in excellent yield by
reduction of the corresponding ester with lithium aluminum hydride, the method of attack seemed clear. Since the carbethoxy compound could not be used because of the great difficulty encountered in its preparation, it was decided to employ some other derivative, such as the aldehyde, which might be more readily accessible. The high yield obtained by Taggart in the synthesis of 2-pyrrole-aldehyde from pyrrole by the Reinor-Tiemann reaction (25) suggested that the same method might be used for preparing 3,5-dimethyl-pyrazole-4-aldehyde. Application of Taggart's procedure to 3,5-dimethyl-pyrazole, however, resulted in no reaction.
Experimental Part

Reaction of 3,5-dimethyl-pyrazole with N-bromosuccinimide:

The procedure of Ziegler (24) was followed in the preparation of N-bromosuccinimide. The yield of pure product was 52%.

From the reaction in carbon tetrachloride solution between 1.92 g. (0.02 mole) of 3,5-dimethyl-pyrazole and 3.56 g. (0.02 mole) of N-bromosuccinimide, carried out by the method of Ziegler (24), there was obtained 3.32 g. (95%) of 4-bromo-3,5-dimethyl-pyrazole.

The same procedure was employed in a reaction between 2.02 g. (0.0115 mole) of 4-bromo-3,5-dimethyl-pyrazole and 2.05 g. (0.0115 mole) of N-bromosuccinimide. The initial product, a brown viscous material with a sharp odor, was boiled with 50 ml. of 10% alcoholic KOH for one-half hour. Removal of the remaining insoluble material by filtration left a brown filtrate, to which 20 ml. of water was added. The off-white precipitate thus formed was collected on a filter and decolorized with Norite in glacial acetic acid solution. Evaporation of the solvent from the acid solution left a white residue, which after recrystallization from dilute alcohol yielded 0.1 g. of a compound melting at 164-165°.
V. Side Reactions in the Synthesis of Pyrazoles
Side Reactions in the Synthesis of Pyrazoles

The investigations discussed in the preceding sections required the preparation of several intermediate pyrazole derivatives for which synthetic procedures have previously been reported in the literature. Although most of these early syntheses were successfully repeated in the course of the present study, some were found to yield only very small amounts of the desired product, and others to furnish none at all. In a number of cases it was possible to ascribe the poor yields to side reactions which are of sufficient importance to receive separate discussion.

The greatest difficulty was encountered in the preparation of pyrazoles containing a carboxethoxy group in the 4-position from ethyl diacetylacetate and the requisite hydrazine derivative. It has already been pointed out that a repetition of the procedure of Knorr and Rosengarten (7) for the synthesis of 4-carboxethoxy-3,5-dimethyl-pyrazole resulted in an exceedingly small yield of this compound. There were obtained instead large amounts of 3-methyl-pyrazolone, m.p. 215°, and a compound of unknown structure melting at 243°. Even the modified procedure described above, which furnishes the ester in 5% yield, results primarily in the formation of the other two compounds. Although Knorr and Rosengarten called attention to these two "by-products," they made no mention of the yield of the pyrazole ester obtained. In the light of the observations recorded here, the formation of the carboxethoxy compound must be considered the side reaction, and that of the other products the main reaction.
An attempted synthesis of 4-carbethoxy-1-phenyl-3,5-dimethyl-pyrazole (XXX) from ethyl diacetylacetate and phenylhydrazine yielded none of the desired compound; the main product was instead 1-acetyl-2-phenylhydrazine (XXXI). The occurrence of this side reaction has been discussed by Knorr (27). In addition to the acetylated hydra-

![Chemical structure](attachment:chemical_structure.png)

zine there was obtained a small amount of a compound which crystallized from alcohol in orange-red needles melting at 152-153°. The structure of this substance was not investigated.

Another series of reactions involving the preparation of 3,5-dimethyl-pyrazoles containing a functional group in the 1-position from acetylacetone and the corresponding hydrazines was found to be accompanied by an interesting side reaction which appears to be somewhat general. In connection with the structural studies discussed earlier, it was intended to compare 3,5-dimethyl-pyrazole-1-carbinol with the product of the reduction of 1-carbethoxy-3,5-dimethyl-pyrazole (XVII) with lithium aluminum hydride. An attempt was therefore made to prepare the necessary intermediate from acetylacetone and ethyl hydrazine carboxylate according to the equation
Von Auwers and Daniel (13) prepared the ester by carrying out the above reaction in the presence of sodium acetate and acetic acid. In the present study, however, the buffer mixture was first omitted, and aqueous solutions of the reactants mixed in the manner employed for the synthesis of dimethylpyrazole itself. As a result, none of the desired compound, n.p. 37-38°, was obtained. Instead there was formed a large amount of a white solid material which melted with decomposition at 199-200° after recrystallization from dilute alcohol. Since this substance might have been a carbethoxy hydrazone of acetylacetone, it was decided to observe its behavior in the presence of acetic acid. The original compound was recovered from its acetic acid solution, however, no ring closure having occurred.

A second attempt to prepare the pyrazole ester was based upon the exact procedure used by von Auwers and Daniel. From the aqueous solution of acetylacetone, ethyl hydrazino carboxylato hydrochloride, sodium acetate, and acetic acid, again no carbethoxy-pyrazole could be isolated. After standing at room temperature for two weeks, the reaction mixture deposited a cluster of white needle-like crystals with a melting point of 133-134°. Smaller amounts of 3,5-dimethyl-pyrazole and unchanged acetylacetone were also recovered.

Since the crystalline substance was obviously the main prod-
uct of the reaction, its structure was investigated. The compound was observed to be quite stable to prolonged heating above its melting point; when heated on a platinum foil, it melted but did not burn. Elementary analysis showed that it contained nitrogen. The substance was found to be soluble in water and ether and neutral to litmus. An unsaturation test with bromine in carbon tetrachloride was negative. The compound did not form a 2,4-dinitrophenylhydrazone, nor did it give a positive iodoform test. It reduced Tollens' reagent in the cold, however, and Fehling's solution when heated. Two fast determinations of the molecular weight of the compound gave the values 204 and 193.

**Analysis:**

*Found:*

\[
\begin{align*}
C &= 40.85 \\
H &= 6.73 \\
N &= 15.53
\end{align*}
\]

The only reasonable empirical formula consistent with this percentage composition is \( C_6H_{12}O_4N_2 \), which has a molecular weight of 176.

*Calculated for \( C_6H_{12}O_4N_2 \):*

\[
\begin{align*}
C &= 40.90 \\
H &= 6.87 \\
N &= 15.90
\end{align*}
\]

A search of the literature revealed that \( \alpha,\beta \)-dicarboethoxyhydrazine (XXXII) has all of the properties described above for the unknown substance. This compound has previously been prepared only by Curtius and Heidenreich (20), who obtained it by the action of ethyl chlorocarbonate on hydrazine hydrate. Its formation in the experiment described above must have resulted from the reaction of two molecules of ethyl hydrazine carboxylate according to the equation

\[
2 \text{C}_2\text{H}_2\text{N}-\text{N}-\text{C}-\text{OC}_2\text{H}_5 \longrightarrow \text{C}_2\text{H}_5\text{O}-\text{C}-\text{N}-\text{N}-\text{C}-\text{OC}_2\text{H}_5 + \text{H}_2\text{N}-\text{NH}_2
\]

XXXII
Inasmuch as the acetylacetone used in the reaction does not enter into this equation and was indeed largely recovered, an experiment was conducted to determine whether the formation of the hydrazine diester was a result of the particular reaction medium employed. From an aqueous solution of ethyl hydrazine carboxylate hydrochloride, sodium acetate, and acetic acid, prepared exactly as in the first case, none of the diester could be obtained. The above reaction can be somewhat better understood, however, by assuming that it is reversible, and that the production of the diester is facilitated because of the removal of hydrazine by acetylacetone to form 3,5-dimethyl-pyrazole. The fact that some of the pyrazole was isolated from the reaction mixture supports this assumption.

An analogous situation was encountered in connection with the preparation of 3,5-dimethyl-pyrazole-1-carbonamide from acetylacetone and anilicarbazide hydrochloride. When these two reactants were mixed in an aqueous solution containing sodium acetate and acetic acid in a manner similar to that which yielded the hydrazine diester of the preceding experiment, there was obtained in addition to the desired pyrazole derivative a smaller amount of a substance which melted with decomposition at 255-257°C and reduced Tollens' reagent in the cold. This compound was observed to have properties similar to those reported by Thiele (29) for hydrazino-α,β-dicarbonamide (XXXIII). Its formation can be described by the equation

\[ 2 \text{H}_2\text{N}-\text{NH}-\overset{0}{\text{C}}-\overset{0}{\text{NH}}_2 \rightarrow \text{H}_2\text{N}-\overset{0}{\text{C}}-\overset{0}{\text{NH}}-\overset{0}{\text{C}}-\overset{0}{\text{NH}}_2 + \text{H}_2\text{N}-\overset{0}{\text{NH}}_2 \]

XXXIII
A considerable amount of 3,5-dimethyl-pyrazole was again isolated from the reaction mixture. The formation of the above dione has previously been reported in relation to the reaction of semicarbazide with itself (23) and with a number of ketones, including the synthesis of a pyrazole (30,31).

In an attempt to synthesize 1,4-dicarbethoxy-3,5-dimethyl-pyrazole (XXXIV), ether solutions of ethyl diacetylacetate and ethyl hydrazine carboxylate were allowed to react. There was obtained a large amount of white needle-like crystals which melted at 55-55° after recrystallization from dilute alcohol. This compound was recovered unchanged after treatment with an excess of lithium aluminum hydride, so it was not the desired pyrazole diester. Its structure was not investigated.

\[
\begin{align*}
\text{XXXIV}
\end{align*}
\]

The synthesis of pyrazoles from 1,3-diketones and primary hydrazines might be expected to result also in the formation of the corresponding dihydrazones. Compounds of this type are readily formed by 1,2- and 1,4-diketones. Furthermore, acetylacetone, when added to an excess of hydroxylamine, reacts to give the dioxime (32). Numerous
Attempts to prepare dihydrazones from 1,3-diketones, however, have always failed (33,20). Even hydrazines of the type \textit{H}_2\textit{N}-\textit{NR'} \textit{H}, which cannot give cyclic derivatives, do not yield 1,3-dihydrazones (34). Similar efforts in this direction were made during the course of the investigation described here, and in no case could a dihydrazono be obtained.
Experimental Part

Formation of $\alpha,\beta$-dicarbethoxy-hydrazine from ethyl hydrazino carboxylate:

Ethyl hydrazine carboxylate was prepared from diethyl carbonate and hydrazine hydrate according to the procedure of Diels (35). A product melting at 45° was obtained in a yield of 100%.

To a solution of 4.62 g. (0.033 mole) of ethyl hydrazine carboxylate hydrochloride (prepared by passing ECl gas through an ether solution of the free base) and 4.48 g. (0.033 mole) of sodium acetate in 10 ml. of H$_2$O was added a solution of 3.29 g. (0.033 mole) of acetylacetone in 2 ml. of glacial acetic acid. The mixture immediately became warm and cloudy. After standing at room temperature for two weeks, it developed a cluster of white needle-like crystals. These were collected on a filter and shown to consist of 1.92 g. of pure $\alpha,\beta$-dicarbethoxy-hydrazine, m.p. 133-134°.

The filtrate contained an upper oily layer which was separated and found to be approximately 2 g. of unchanged acetylacetone. Addition of a cold, saturated solution of Na$_2$CO$_3$ to the aqueous layer until the mixture was alkaline resulted in precipitation of a white amorphous solid. This substance was removed by filtration, and after recrystallization from water yielded 0.92 g. more of $\alpha,\beta$-dicarbethoxy-hydrazine. The total weight of the hydrazino diester was 2.84 g. (97%).

Finally, the basic aqueous filtrate was extracted several times with ether. Evaporation of the solvent from the combined extracts left a white solid residue, which after recrystallization from water consisted of 0.3 g. of 3,5-dimethyl-pyrazole.
Formation of hydrazino-α,β-dicarbonamide from semicarbazide:

A reaction between semicarbazide hydrochloride and acetylacetone in the presence of sodium acetate and acetic acid was carried out in a manner similar to that described above. As soon as the reactants were mixed, however, the mixture became warm and immediately deposited a white crystalline precipitate. This product was collected on a filter and recrystallized from water. It was found to consist of a 30% yield of 3,5-dimethyl-pyrazole-1-carbonamide. Cooling of the aqueous filtrate in an ice-bath resulted in precipitation of white granular crystals of hydrazino-α,β-dicarbonamide, m.p. 255-257° (with decomposition), obtained in a yield of 8%. Neutralization of the remaining filtrate with Na₂CO₃ followed by extraction with ether gave a 10% yield of unsubstituted 3,5-dimethyl-pyrazole.
VI. Summary
Summary

A study of the reaction of several representative pyrazoles with formaldehyde has shown that those compounds in which the 1-position of the heterocyclic ring is unsubstituted react in both neutral and acidic media to give the corresponding 1-carbinols. Furthermore, the same nuclei react with formaldehyde in acid medium to form alcohols resulting from condensation in the 4-position. Pyrazoles containing a substituent in the 1-position undergo no reaction in neutral solution, but condense with the aldehyde in the presence of acid to yield the 4-carbinols. No product of the condensation of formaldehyde with a side-chain methyl group could be obtained, even in basic solution. Although acetaldehyde undergoes no reaction with 3,5-dimethyl-pyrazole, benzaldehyde gives a product which appears to result from reaction in the 1-position.

Attempts to prepare the synthetic intermediate 3,5-dimethyl-pyrazole-4-carbinol by various modifications of the chloromethylation reaction were unsuccessful. Reduction of the corresponding ester with lithium aluminum hydride was found to give an excellent yield of the 4-carbinol, but the inaccessibility of the requisite ester and the analogous acid and aldehyde prevents this method from being of synthetic value.

Finally, a number of side reactions which accompany the synthesis of pyrazole derivatives have been encountered, one of which appears to be general. In addition, preparative methods superior to those previously reported in the literature were discovered for several pyrazoles.
The following new compounds were prepared:

3,5-dimethyl-pyrazole-1-carbinol*

3,5-dimethyl-pyrazole-1,4-dicarbinol*

3,5-dimethyl-pyrazole-4-carbinol*

4-bromo-3,5-dimethyl-pyrazole-1-carbinol

4-bromo-5(3)-methyl-pyrazole-3(5)-carbinol

1-phenyl-pyrazole-4-carbinol

di-(1-phenyl-3,5-dimethyl-pyrazoly1-4)-methane

phenyl-di-(3,5-dimethyl-pyrazoly1-1)-methane

* First prepared by Landua (5), but structure verified in present investigation.
VII. References
References

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