1-ORTHO-TOLYL-3-ETHYL-4-METHYL-5-PYRAZOLONE

Thesis for the Degree of M. S.
MICHIGAN STATE COLLEGE
Albert E. Timreck
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R. L. Huston

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A Thesis

Submitted to the Faculty

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In partial fulfillment of the

requirements for the degree of Master

of Science.

By

Albert E. Timrock

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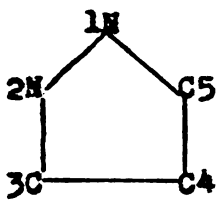
It is with appreciation that I take this opportunity to express my thanks to Dr. R. C. Huston for his assistance and encouragement in carrying out this work.

A.E.T.

REVIEW OF THE LITERATURE

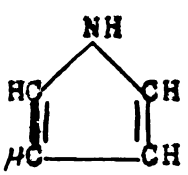
I. Constitution of the Pyrazole Group

The pyrazole group is made up of those compounds having a five-membered cyclic system of two nitrogen and three carbon atoms arranged as follows:

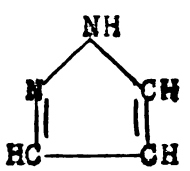


Pyrazole itself is a 1,2-diazole. The structure of the pyrazole ring has been definitely established by the investigations of many workers. Outstanding was the work done by L. Knorr and his coworkers (1,2,3,4).

Pyrazole may be regarded as a derivative of pyrrole in which one of the methine groups adjacent to the NH group has been replaced by nitrogen.

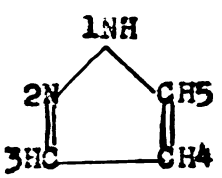


Pyrrole

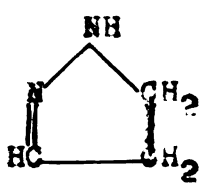


Pyrazole

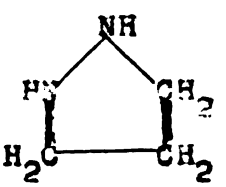
Because of this structural relation, Knorr suggested the use of the same nomenclature for derivatives of pyrazole as are used for pyrrole derivatives. The dihydropyrazoles then are known as the pyrazolines and the tetrahydro-derivatives as the pyrazolidines.



Pyrazole



Pyrazoline

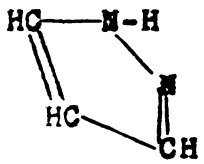


Pyrazolidine

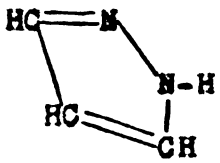
The positions of substituent groups are indicated by numbering the members of the ring starting with the imino nitrogen atom , as shown above, thus giving the hetero-atoms the lowest possible numbers.

Knorr suggested the formula for pyrazole shown above based on his work with 1-phenyl pyrazole (5). Later Knorr and coworkers showed that 1-phenyl-3-methyl pyrazole and 1-phenyl-5-methyl pyrazole gave the same methyl pyrazole and concluded that in pyrazole itself the three and five position are equivalent. The 3(5)-methyl pyrazole then is a mixture of the two desmotropic forms.

Knorr assumed that the 1-hydrogen is not permanently linked to one nitrogen atom, but may alternate to the other nitrogen with a readjustment of the double bond.



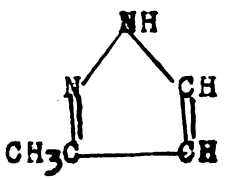
I.



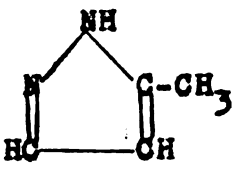
II.

According to the modern conception, the rearrangement is not a simple tautomeric shift of the hydrogen atom. Actually the rearrangement is the same as that encountered in the formation of pyrrolidine from pyrrole and involves the splitting off of a proton followed by shift of the electron pair and addition of a proton.

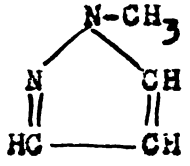
There cannot be then two methyl pyrazoles with the formulas:



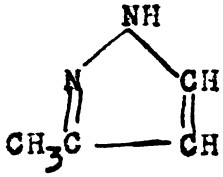
and



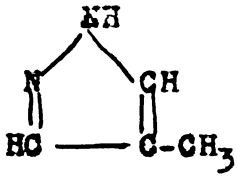
There are only three possible isomeric methyl pyrazoles:



1-methyl pyrazole

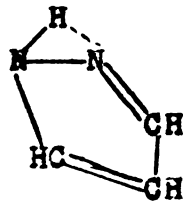


3(5)-methyl pyrazole



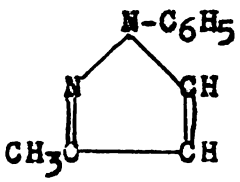
4-methyl pyrazole

For these reasons Knorr suggested the structural formula of the 3(5)-pyrazole to be:

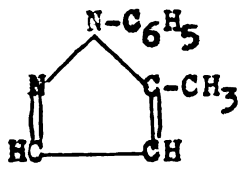


His conclusion has been confirmed by the fact that methyl pyrazole can act as either a 3- or 5-methyl pyrazole.

From the above discussion it can be seen that replacement of the imino hydrogen atom by a substituent group makes the 3- and 5-positions no longer equivalent.



1-phenyl-3-methyl pyrazole



1-phenyl-5-methyl pyrazole

Claisen and Roosen obtained these isomeric pyrazole derivatives by condensing phenyl hydrazine with oxymethylene acetone (6,7).

Although pyrazole and pyrrole are similar in their structural formulas, they are quite different in their chemical properties. Pyrazole is much more stable and has a more basic character than pyrrole. In its chemical properties, it resem-

bles the pyridine bases.

Pyrazole is a weak secondary base which has a definite aromatic character. Knorr has listed a number of properties which show its aromatic nature.

1. It is sulfonated by fuming sulfuric acid to pyrazole sulfonic acid.

2. In its halogen derivatives, the halogen atom is held even more firmly than in benzene derivatives.

3. Pyrazole is nitrated readily with concentrated nitric acid. As with aromatic nitro compounds, 4-nitro pyrazole and its derivatives can be reduced to the corresponding amino compounds (9,21).

4. Amino pyrazole resembles the aromatic bases in its behavior. It gives a color reaction with a solution of bleaching powder, and it is readily diazotized.

5. Diazo pyrazoles couple with phenols to give azo-dyes. Their salts are more stable than those of the aromatic diazonium compounds in aqueous solution, giving off nitrogen only after prolonged heating at higher temperatures. The diazo pyrazoles do not, however, give the usual "diazo-reactions."

6. Pyrazoles show the same remarkable stability to oxidizing and reducing agents as does benzene.

7. Pyrazolone, or 5-hydroxy pyrazole, has a pronounced phenolic character.

8. Homologues of pyrazole resemble those of benzene in being readily oxidized to the corresponding carboxylic acids.

Pyrazole can also be acylated, benzolated, or converted into derivatives of urethane and urea.

II. Synthesis of Pyrazole and Derivatives

Pyrazole itself was first prepared by E. Buchner in 1899 by heating 3:4:5-pyrazole tricarboxylic acid (8). It was later prepared by Balbiano by heating epichlorhydrin with hydrazine hydrate (9). Von Pechmann obtained pyrazole by reacting acetylene with diazo methane. Claisen accomplished the synthesis by treating the acetal of propargyl aldehyde with hydrazine (10). According to Knorr the best method for the preparation of pyrazole is the decarboxylation by prolonged heating of 3:5-pyrazole dicarboxylic acid.

Knorr in 1883 prepared the first pyrazole derivative, preparing 1-phenyl-3-methyl-5-pyrazolone by the action of phenyl hydrazine on acetoacetic ester (11,12,13). He later prepared the ethyl ester of 1,3-diphenyl-5-methyl pyrazole-4-carboxylic acid by the reaction of benzoylacetoacetic ester on phenyl hydrazine (1,14).

Knorr described a number of syntheses for pyrazolone derivatives, such as: (a) the condensation of β-keto acids with hydrazine, (b) the reaction of β-diketo compounds of the general formula R'-CO-CHR"-COR"' with hydrazines, (c) the condensation of hydrazines with unsaturated aldehydes and ketones of the type R'-CO-CR"-CHR"' and HCO-CR'-CHR", and (d) by boiling the phenyl hydrazones of unsaturated aldehydes and ketones having a double bond in the α-position with glacial acetic acid (1).

Many other methods have been described for the preparation of pyrazole derivatives, such as:

1. Buchner prepared derivatives of pyrazole by the reaction of diazoacetic ester with various unsaturated compounds (15).

a. By the reaction of diazoacetic ester with acetylene dicarboxylic acid to give the methyl ester of pyrazole tricarboxylic acid.

b. By the action of diazoacetic ester on ethylene derivatives, such as the ester of fumaric acid to form pyrazoline tricarboxylic ester.

c. Combination of diazoacetic ester with the ester of saturated and unsaturated halogen-substituted esters, such as dibromo propionic ester to give pyrazole dicarboxylic ester.

2. Bischler prepared pyrazole derivatives by the action of diazonium salts on substituted acetoacetic esters (16,17).

3. Claisen prepared phenyl pyrazole by the treatment of the acetal of propargyl aldehyde with phenyl hydrazine (10).

4. Fischer and Bulow prepared diphenyl methyl pyrazole by the reaction of phenyl hydrazine with benzoyl acetone (18).

5. Claisen and Roosen obtained the phenyl methyl pyrazoles by condensing oxymethylene acetone with phenyl hydrazine. They prepared derivatives through the condensation of acetone oxalic acid with phenyl hydrazine, and also by the condensation of the aldehyde of acetoacetic ester with phenyl hydrazine (6,7).

6. Knorr and MacDonald prepared phenyl methyl pyrazole by the condensation of hydrazine hydrate with oxymethylene acetone (2).

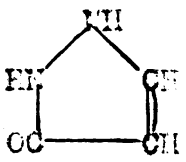
7. Certain hydrazones heated with acid anhydrides yield pyrazole derivatives, aceto phenyl hydrazone with acetic anhydride giving 1-phenyl-3,5-dimethyl pyrazole.

8. Stoermer and Martinsen prepared pyrazole derivatives by distilling the oxygen derivatives, such as the pyrazolones, with zinc dust, phosphorus pentasulfide, or phosphorus tetrabromide (19).

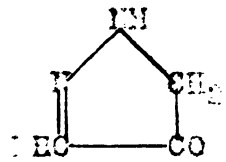
In general, compounds containining two CO groups or a Co and COOH group in β-position to one another or two doubly-linked carbon atoms adjacent to a COOH or CO group react with hydrazines to give pyrazole derivatives (20).

III. Constitution of the Pyrazolones

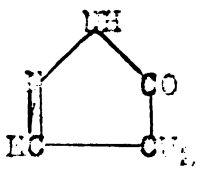
There are three ketonic derivatives of pyrazoline which can be divided into two classes: the 4-derivatives or true ketones as derived from keto-acids, and the 3- and 5-derivatives or pyrazolones which are the cyclic acid amides (1).



3-pyrazolone

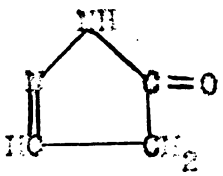


4-ketopyrazoline

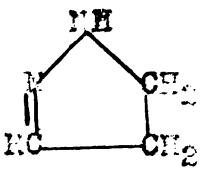


5-pyrazolone

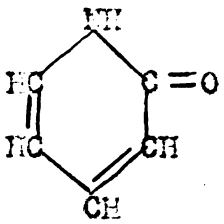
Pyrazolone bears the same relation to pyrazoline as pyridone does to pyridine.



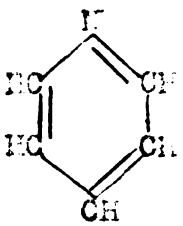
Pyrazolone



Pyrazoline

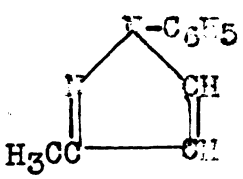


Pyridone



Pyridine

Knorr established the constitution of pyrazolone by distilling phenyl methyl-5-pyrazolone with zinc dust to obtain a weak base with a composition $C_{10}H_{10}N_2$. The base so obtained resembled the pyrazole bases. Its salts are decomposed by water. The weak base on reduction with sodium and alcohol was changed into a base rich in hydrogen which resembled the pyrazoline bases, giving a violet color with oxidizing agents (1). Knorr showed then that the base obtained by the reduction of the pyrazolone to be 1-phenyl-3-methyl-pyrazole with the formula:



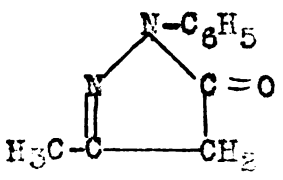
By the method of its formation, the origin of the pyrazolone from the pyrazole group was shown.

The methylene group of acetoacetic ester is found still unchanged in the phenyl methyl pyrazolone. The oxygen in the pyrazolone cannot be combined as a hydroxyl or ketonic oxygen as it is inactive and must occur in a form similar to the acid amides.

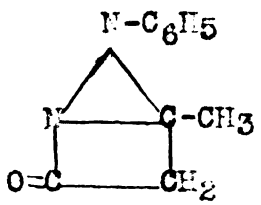
The phenyl methyl pyrazolone contains, then, no more hydrogen which could combine with nitrogen. The pyrazolone can be methylated by treatment with methyl iodide giving, undoubtedly through the nitrogen atom, the methylated base, antipyrine. In the formation of the antipyrine, though, the molecule undergoes a radical change, the antipyrine no longer containing a methylene group but rather a methine group. This change in the molecular structure lead Knorr to a false conception of the antipyrine molecule.

From the above considerations it was evident that the ten hydrogens of the phenyl methyl pyrazolone were distributed as follows: five on the phenyl group, three on the methyl, and two on the methylene group from the aceto acetic ester.

There were, then, only two possible formulas for the phenyl methyl pyrazolone:

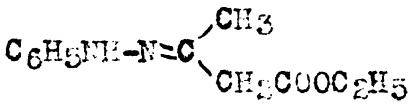


I.



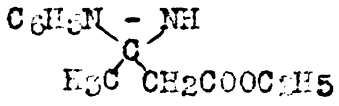
II.

The choice between these two formulas depends upon deciding which is the more probable formula for the phenyl-hydrazone of aceto acetic ester:



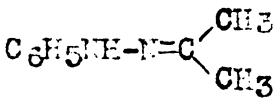
1.

or



2.

The situation here is the same as presented by the phenylhydrazones of the aldehydes and ketones for which there are the same types of possible formulas:



1.

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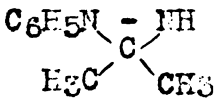
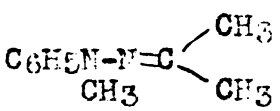


2.

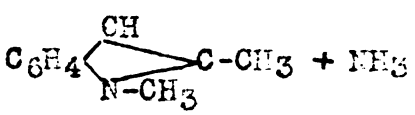
Acetone phenylhydrazone

If the phenylhydrazones have the formula represented as 1, then I would be the formula for the phenyl methyl pyrazolone; if their structure is shown by 2, then II is the formula for the pyrazolone.

According to E. Fischer, the ketone and aldehyde derivatives of primary as well as the unsymmetrical secondary hydrazines react under the proper conditions in a manner similar to the formation of indol derivatives (22).

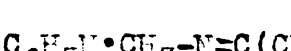


Acetone methyl phenylhydrazone



Dimethyl indol

It is obvious then that in both classes we have the same types of linkages in the hydrazine derivatives.



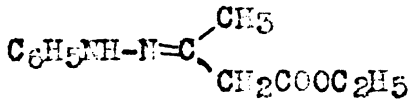
Methyl phenyl hydrazone of acetone

Phenylhydrazone of acetone

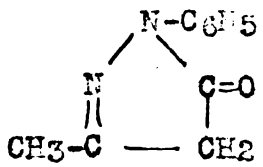
The primary hydrazines and the unsymmetrical secondary hydrazines, then, react in the same way with aldehydes and ketones

at low temperatures. The symmetrical secondary hydrazines react with aldehydes at high temperatures and with ketones with difficulty (23).

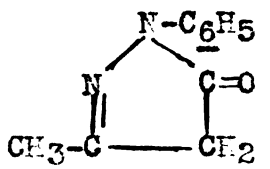
From the above considerations, it seems most probable that the formula for the phenylhydrazone of aceto acetic ester is formula 1. :



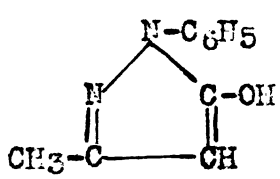
Knorr on the basis of these facts rejected the carbazine structure for the pyrazolone and accepted formula I. for phenyl methyl pyrazolone:



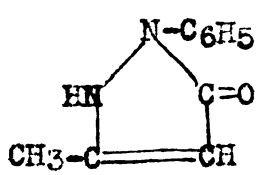
Knorr stated that 1-phenyl-3-methyl-5-pyrazolone may exist in three desmotropic forms, and called the phenomena "double tautomerism" (5).



Methylene form



Phenolic form

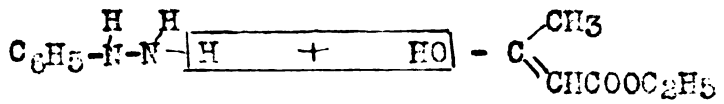


Imine form

Numerous attempts have been made to obtain the various desmotropes from reaction mixtures. It would be expected that the methylene and phenolic forms would exist in a regular enol-ketp equilibrium. It was thought possible, though, to isolate the imine form as a distinct compound, but only one form of each pyrazolone has been obtained. Only one 1-phenyl-3-methyl-5-pyrazolone has been obtained which has a melting point of 127°C. The preparation of two isomeric 1-o-tolyl-3-methyl-5-pyrazolone was reported, but further investigation has shown that the com-

pound believed to possess the imine structure is actually the condensation product of the pyrazolone with a second molecule of aceto acetic ester which Knorr had reported in his work on the phenyl methyl pyrazolone (1,24).

A mechanism was proposed to account for the formation of the imine form by assuming the reaction of the enol of aceto acetic ester with phenylhydrazine to form the phenylhydrazone by a simple splitting out of water. Here, of course, the formula for the phenylhydrazone would be different than that given by the reaction of the keto-form of the ester. The explanation would account, however, for the difference in the position of the double bond in the imine form (24,25).

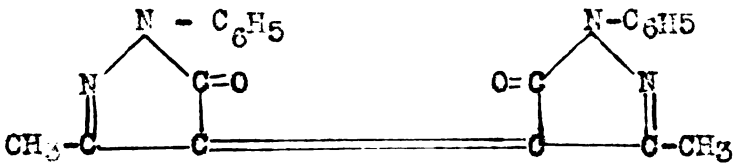


Phenylhydrazine. Aceto-acetic ester.

It seems improbable that the reaction can be explained by this simple mechanism. The reaction probably goes by way of the usual carbonyl addition mechanism.

The imine structure of the pyrazolones is found only in those compounds known as the antipyrines. The phenolic form is found in such compounds as the phenyl ethers, esters, and salts of the alkali metals.

The methylene form is that structure which gives the pyrazole blue test. The oxidation of phenyl methyl pyrazolone with ferric chloride or platinum chloride results in the formation of pyrazole blue which represents the indigo of the pyrazole series. In chloroform solution, a deep blue color results, and from ether solution, violet needles of pyrazole blue are precipitated (1,26).



Pyrazole Blue

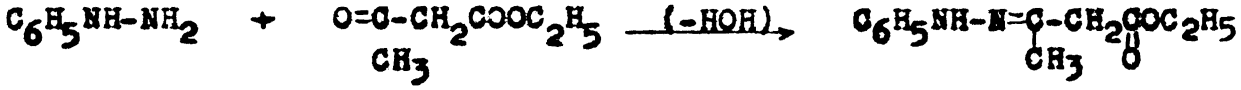
It is apparent that substitution of one of the hydrogens of the methylene group by certain groups will make the formation of pyrazole blue impossible.

IV. Synthesis of the Pyrazolones

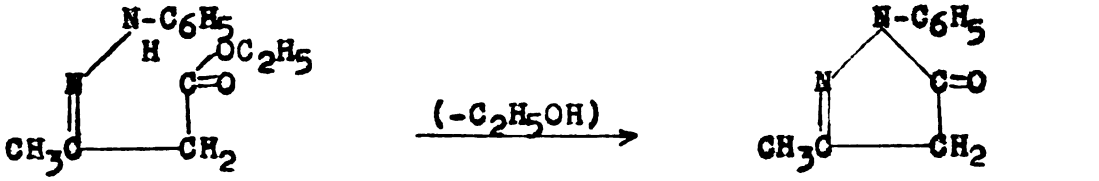
A. Preparation of the 5-Pyrazolones

The 5-pyrazolones can be prepared by the condensation of aryl hydrazines with beta-keto esters. In 1883 Knorr prepared the first pyrazolone, preparing 1-phenyl-3-methyl-5-pyrazolone by condensing phenyl hydrazine with acetoacetic ester (1,11).

To 125 gms. of phenyl hydrazine, 100 gms. of acetoacetic ester was added and the mixture then warmed on a steam bath. The first reaction was the formation of the phenyl hydrazone of acetoacetic ester with the elimination of water. Ring closure was effected by heating at a higher temperature with the elimination of alcohol.



Phenyl hydrazine Acetoacetic ester Phenyl hydrazone of acetoacetic ester



1-Phenyl-3-methyl-5-pyrazolones

The alcohol formed was distilled off, the mixture cooled, and the product washed with ether. The pyrazolone was dried in an oven at 100° C. and was purified by recrystallization from hot water or hot alcohol. The phenyl methyl pyrazolone melted at 127° C.

Knorr and Duden prepared pyrazolone derivatives by the condensation of unsaturated acids of the acrylic acid series (i.e. crotonic acid) with hydrazines (26).

Petrenk and Kretschenko prepared a dimethyl pyrazolone by the elimination of CO_2 from the acid formed by the condensation of phenyl hydrazine with methyl acetone dicarbonylic acid ester.

Knorr and Klotz prepared diphenyl pyrazolone by condensing phenyl hydrazine with ethyl benzoyl acetate (27).

Stolz obtained 1-phenyl-5-pyrazolone by the oxidation of 1-phenyl pyrazolidine with ferric chloride (28).

Knorr prepared the ortho and para tolyl methyl pyrazolones by the condensation of the tolyl hydrazines with acetoacetic ester. (29)

Klauber prepared the meta-xylyl methyl pyrazolone (30).

Huston and Brigham prepared p-xylyl methyl pyrazolone by the condensation of p-xylyl hydrazine with acetoacetic ester (24).

Blaise obtained 1-phenyl-3-ethyl-5-pyrazolone by the reaction of ethyl propionyl acetate with phenyl hydrazine (31).

Knorr and Blank prepared 1-phenyl-3-methyl-4-ethyl-5-pyrazolone by the condensation of α-ethyl acetoacetic ester with phenyl hydrazine (32). They also prepared 1-phenyl-3,4-dimethyl-5-pyrazolone by heating methyl acetoacetic ester with phenyl hydrazine (33).

Knorr heated dimethyl acetoacetic ester with phenyl hydrazine to prepare 1-phenyl-3,4,4-trimethyl-5-pyrazolone.

Emmerling and Kristeller prepared 1-phenyl-3-ethyl-4-methyl-5-pyrazolone by condensing ethyl α-propionyl propionate with phenyl hydrazine (35).

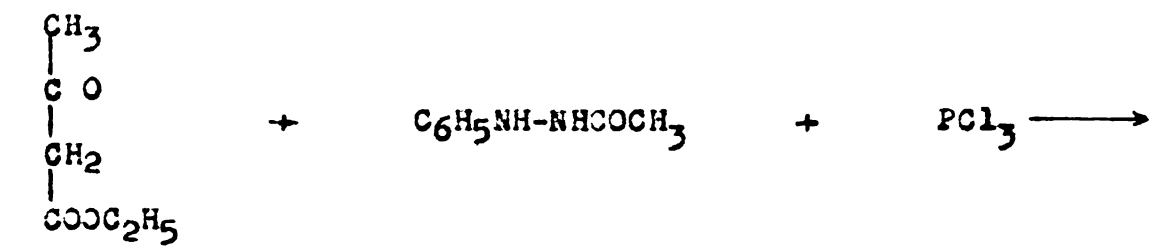
Schroeter prepared 1-phenyl-3-ethyl-4-methyl-5-pyrazolone by condensing methyl propionyl propionate with phenyl hyrazine (36).

IV. B. Preparation of the 3-Pyrazolones

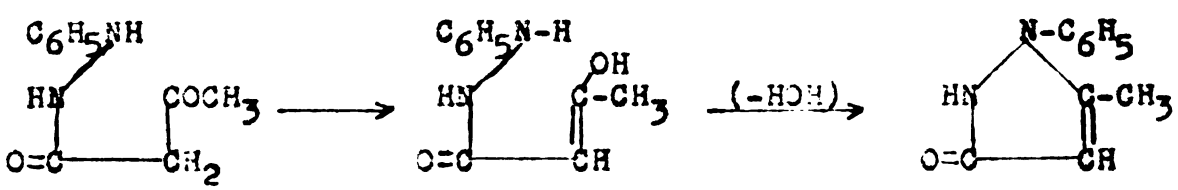
Michaelis prepared 1-phenyl-5-methyl-3-pyrazolone by condensing acetoacetic ester with acetyl phenyl hydrazine in the presence of phosphorus trichloride. To 15 gms. of acetyl phenyl hydrazine and 13 gms. of acetoacetic ester, 14 gms. of phosphorus trichloride were gradually added, and the mixture was refluxed until no more hydrogen chloride was evolved. The viscous solution was dissolved in 10% hydrochloric acid, cooled, and filtered. The acid was neutralized with ammonium hydroxide, precipitating the pyrazolone.

The crude product was dried on a porous plate. If the pyrazolone was dark-colored it was boiled with animal charcoal in alkaline solution. The 3-pyrazolone was purified by recrystallization from alcohol (37).

Equations showing the reactions involved:



Acetoacetic ester — Acetyl phenyl hydrazide — Phosphorus trichloride



Phenyl hydrazide of acetoacetic ester — Enol form — 1-Phenyl-5-methyl-pyrazolone-3

According to Michaelis, the 5- as well as the 3- pyrazolone is produced by this method, but the latter is much more abundant. In the reaction with acylated hydrazines, the reactivity is much less than in the reaction of the hydrazines with ketonic oxygen.

Knorr and Duden prepared 1,5-diphenyl-3-pyrazolone by the condensation of phenylhydrazine with cinnamyl acid (26).

Bischler obtained a derivative of 1,5-diphenyl-3-pyrazolone by the action of diazonium chloride on phenyl acetoacetic ester. Other substituted acetoacetic esters can be employed (18).

Michaelis and Behrens prepared the ortho and para tolyl methyl-3-pyrazolone by condensing the corresponding acetyl tolyl hydrazine with acetoacetic ester and phosphorus trichloride (23)

Huston and Brigham obtained p-xylyl-5-methyl-3-pyrazolone by the condensation of para-xylyl acetyl hydrazide with acetoacetic ester and phosphorus trichloride (24).

Stolz obtained 1-phenyl-pyrazolone-3 by heating the ethyl ester of β-chlorolactic acid with phenyl hydrazine (39)

Fichter, Enzensuer, and Uellenberg prepared 1-phenyl-r-methyl-3-pyrazolone by heating the ethyl ester of β-bromomethacrylic acid with phenyl hydrazine (40).

Michaelis and Drews condensed α-methyl acetoacetic ester with β-acetyl phenyl hydrazine and phosphorus trichloride to obtain 1-phenyl-4,5-dimethyl-3-pyrazolone. They also prepared 1-phenyl-5-methyl-4-ethyl-3-pyrazolone by using α-ethyl acetoacetic ester (41).

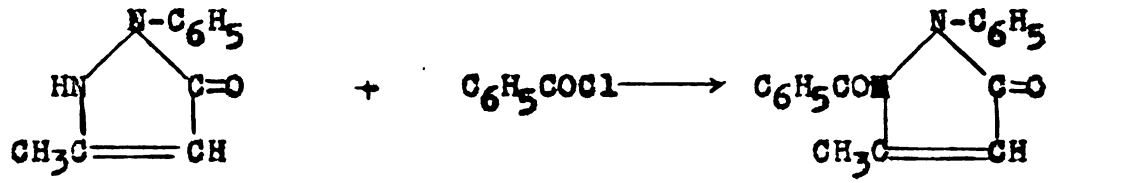
A la mode

a spaniel.

parasol

V. Benzoyl Esters of the Pyrazolones

Nef prepared the benzoyl ester of 1-phenyl-3-methyl-5-pyrazolone by the Schotten-Bauman reaction, shaking the pyrazolone in alkali solution with an excess of benzoyl chloride. The ester was purified by recrystallization from alcohol (42).

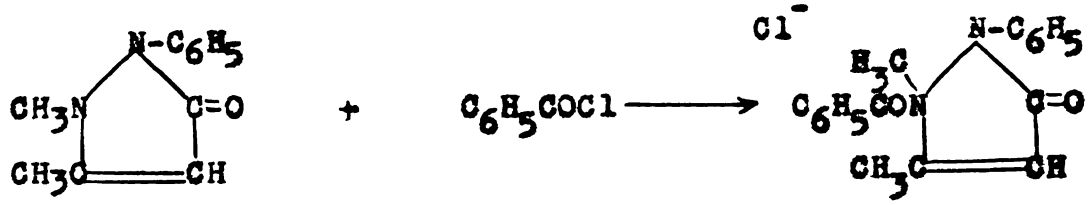


1-Phenyl-3-methyl-5-pyrazolone

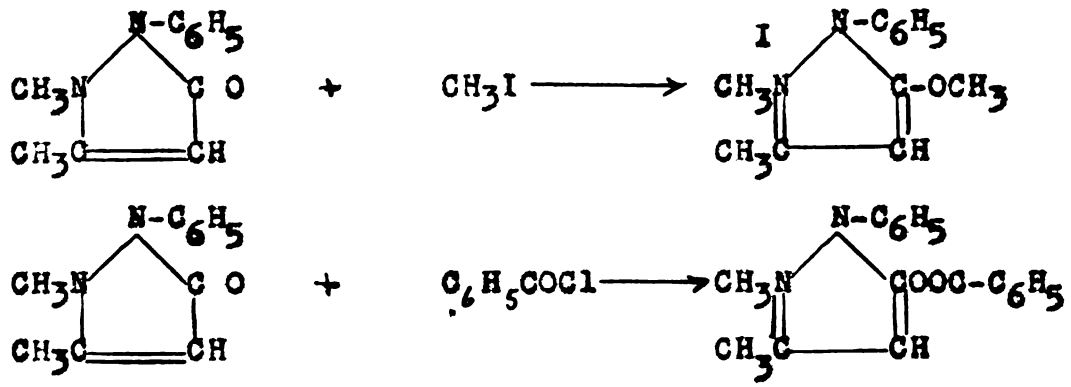
1-Phenyl-2-benzoyl-3-methyl-5-pyrazolone

Nef assumed that the pyrazolone reacts in the imine form and that the benzoyl residue attaches to the nitrogen to give a benzamide derivative.

Nef assumed that the addition of benzoyl chloride to antipyrine takes place in a different sense than the addition of alkyl iodides to antipyrine.



On the other hand, Knorr believed that the addition of benzoyl chloride and alkyl iodides takes place in the same sense (21).



No conclusion has been reached as to whether the benzoyl residue is attached to the nitrogen or the oxygen atom, but Knorr's explanation is generally accepted.

Michaelis prepared the 1-phenyl-5-methyl-3-benzoyl-3-pyrazolone by the Schotten-Bauman reaction (37).

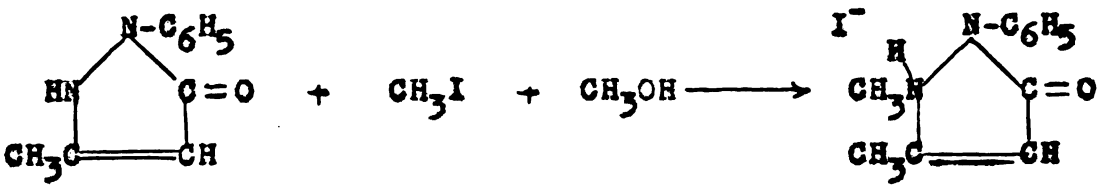
Michaelis also prepared the benzoyl esters of ortho and para 1-tolyl-3-methyl-5-pyrazolone by the same method (38).

Huston and Sell prepared the benzoyl esters of p-xylyl-5-methyl-3-pyrazolone and p-xylyl-3-methyl-5-pyrazolone by shaking the pyrazolones with benzoyl chloride in pyridine solution (25).

VI. Methylation of the Pyrazolones - Antipyrine

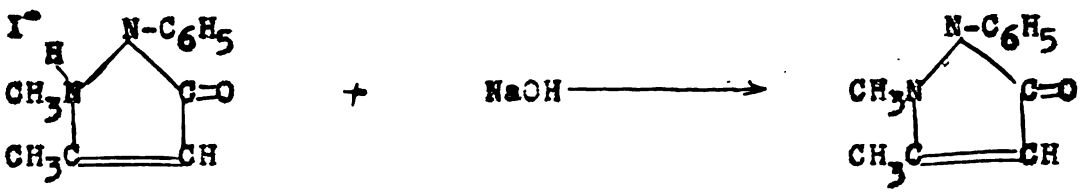
Antipyrine is the methylated base which is obtained in the form of its hydroiodide when 1-phenyl-3-methyl-5-pyrazolone is heated to 100° C. in a closed tube with methyl iodide and methyl alcohol. The antipyrine is liberated by treating the hydroiodide with sodium hydroxide.

Knorr prepared antipyrine by this method as crystals which after recrystallization melted at 113° C. (29,43).



Phenyl methyl pyrazolone

Hydoriodide of of the pyrazolone



Antipyrine (Knorr)

Knorr established the structure for antipyrine to be that shown by the formula above (1,32).

Antipyrine is a strong acidic base which is precipitated by alkali and forms salts with acids. It has a stable molecular structure and can be boiled in vacuum without rearrangement. It decomposes, however, when distilled at atmospheric pressure. Antipyrine is very soluble in water, alcohol, chloroform, and hot toluene and is difficultly soluble in ether and ligroin.

Knorr also prepared antipyrine by the methylation of 1-phenyl-3-methyl-5-ethoxy-pyrazolone. The methylated product

was treated with sulfurous acid, and thenthe solution was supersaturated with sodium hydroxide. The antipyrine was extracted with ether and recrystallized (5).

Knorr obtained the ortho and para tolyl antipyrines by heating the corresponding pyrazolone with methyl iodide and methyl alcohol at 100° C. (29).

Klauber prepared the meta-xylyl antipyrine (30).

Michaelis prepared the 3-antipyrine by methylating the 1-phenyl-5-methyl-3-pyrazolone with methyl iodide and methyl alcohol. He also prepared the ortho and para 3-tolyl antipyrines by methylating the corresponding 3-pyrazolones with methyl iodide and methyl alcohol. The hydroiodides were dissolved in water and the antipyrines liberated by treatment with sodium hydroxide. The product was extracted with chloroform, dried over $CaCO_3$, and purified by recrystallization from ligroin (38).

Stolz methylated 1-phenyl-4-methyl-5-pyrazolone by prolonged heating with methyl iodide and methyl alcohol (28).

Michaelis and Drews prepared 1-phenyl-2,5-dimethyl-4-ethyl-3-pyrazolone by heating the 3-pyrazolone with methyl iodide (42).

Knorr methylated 1-phenyl-3,4-dimethyl-5-pyrazolone to obtain 2,3,4-trimethyl-1-phenyl-5-pyrazolone (4-methyl antipyrine) (33,34). He also prepared 4-ethyl antipyrine by methylation of the corresponding pyrazolone (32).

Emmerling and Kristeller prepared 1-phenyl-2,4-dimethyl-3-ethyl-5-pyrazolone by heating the pyrazolone in a closed tube with methyl iodide and methyl alcohol at 110° C. The methylated product was obtained as crystals with a melting point of 37-38° C. and having a boiling point at 18 mm. of 208-210°C. The product was soluble in alcohol, ether, chloroform, and benzene

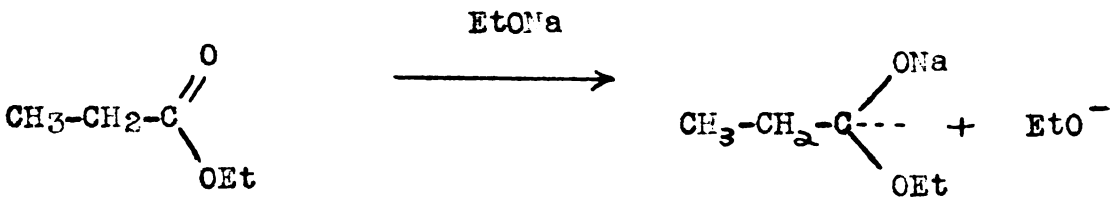
and was difficultly soluble in water (35).

EXPERIMENTAL PART

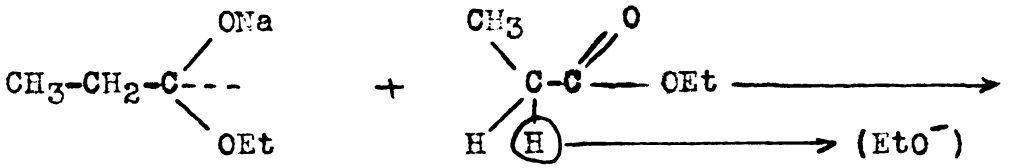
I. Preparation of Ethyl-α-Propionyl Propionate

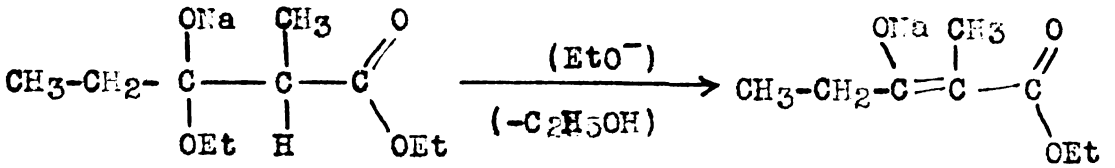
The ethyl propionyl propionate was prepared by boiling ethyl propionate with strong sodium ethoxide using the procedure of McElvain (44).

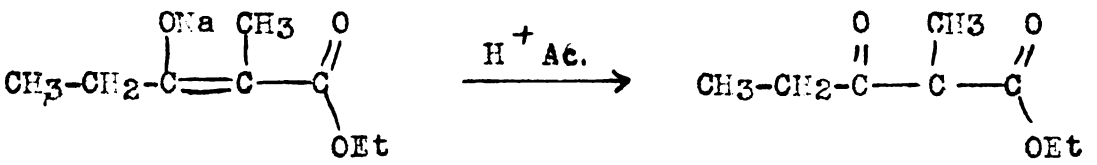
The reaction can be shown by the following equations:



Ethyl Propionate







Ethyl α-propionyl propionate

The ethyl propionate used was first distilled taking only the fraction coming over at 96.5-98,5°C. at 735 mm. To remove any alcohol remaining, the ester was treated with 2% by weight of P_2O_5 and allowed to stand for twenty-four hours. It was again fractionated, distilling from over P_2O_5. B.P.= 97.5-98.5 @ 735 mm. n_D^{20}=1.3811.

The sodium ethoxide was prepared alcohol free and as free as possible of sodium hydroxide. The ethoxide was prepared in the reaction flask, a three-neck two-liter flask equipped with a dropping funnel with $CaCl_2$ tube and a mercury-seal stirrer.

In the flask was placed 500 ml. of xylene which had been dried several days over sodium. To this was added 47 gms. (2 moles) of rough-cut clean sodium. The flask was then heated until the sodium had melted, and allowed to cool. The suspension was stirred vigorously until the sodium had solidified in particles the size of fine 'buck-shot'. The xylene was decanted off, and the sodium washed several times with absolute ether to remove the xylene. The sodium was then covered with 500 gms. of anhydrous ether.

In the dropping funnel was placed 96 ml. (2 moles) of absolute alcohol diluted with 200ml. of dry ethyl ether. The flask was equipped with a packed column with distilling head. The contents of the dropping funnel was added dropwise to the contents of the flask with vigorous stirring and the mixture refluxed until all the sodium had disappeared. The heat of the reaction was sufficient to distill off most of the ether. The remaining solvent was distilled off.

To the sodium ethoxide in the flask was added 612 gms. (6 moles of ethyl propionate. When the reaction had subsided, the flask was heated, and the mixture was refluxed with stirring for one hour. The alcohol formed was then distilled off continuously through the column. When 200 ml. had been collected, an additional 408 gms. (4 moles) of pure ester was added, and another 200 ml. of alcohol (with some ester) was distilled off. A final 202 gms. of ester was then added, and the distillation continued until the mixture in the flask became quite viscous.

The temperature of the reaction mixture was allowed to reach about 150°C. It was found that the last portions of ethyl propionate distilled off were free of alcohol as indicated by the refractive index.

To the residue in the flask, 150 gms. of glacial acetic acid in 300 ml. of water was added with cooling and stirring. The ester was separated and the aqueous layed extracted with three 100 ml. portions of ether. The ester was fractionated by vacuum distillation using a vigreaux column. B.P. 88-90°C. at 12 mm. $n_D^{20} = 1.4228$. Yield: 250 gms. (80%)

The modification of McElvain's technique by using a packed column to continuously remove the alcohol as eliminated permitted the condensation to be carried out using half of the quantity of ethyl propionate prescribed by McElvain. The time required is about half that otherwise needed. These advantages were gained without any decrease in the yield.

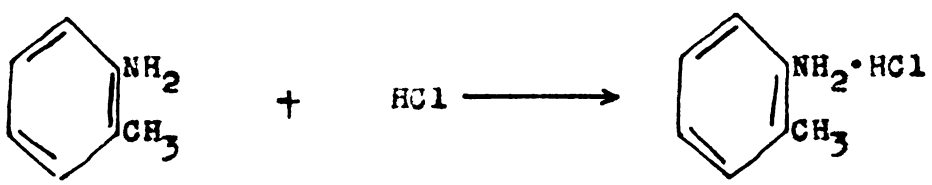
II. Preparation of O-Tolyl Hydrazine

Huston and Brigham found that there was less decomposition and formation of tar when ethyl nitrite was used for diazotization instead of sodium nitrite. The method used was similar to that used for the preparation of cymyl hydrazine by Demonbreun and Kremer (45).

Ethyl nitrite was prepared using Feldhaus' method (46).

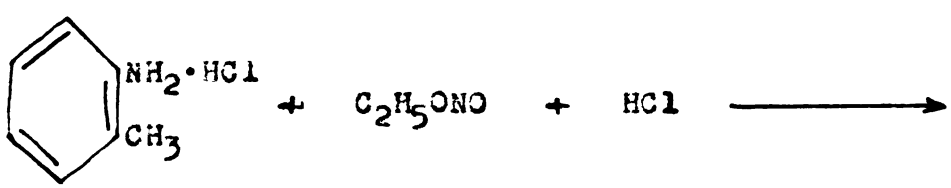
500 gms. of sodium nitrite and 200 gms. of alcohol were placed in a 5-l flask equipped with a dropping funnel and a condenser for downward distillation. A solution of 400 gms. of concentrated sulfuric acid, 3000 ml. of water, and 200 gms. of alcohol was dropped slowly into the nitrite mixture. The ethyl nitrite produced was collected in an ice-cooled receiving flask. B.P. = 17°C. Yield: 85-90%.

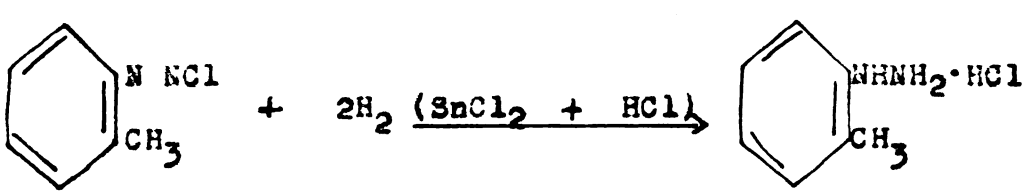
The orthotolyl hydrazine was prepared by diazotizing o-toluidine with hydrochloric acid and ethyl nitrite with subsequent reduction using stannous chloride.



o-Toluidine

o-Toluidine hydrochloride





o-Toluidine diazonium chloride

o-Tolyl hydrazine hydrochloride

To 107 gms. (1 mole) of O-toluidine was added 1300 ml. of concentrated hydrochloric acid, and the mixture was placed in an alcohol bath and cooled to -40° C. Ninety grams of ethyl nitrite in 100 ml. of alcohol was cooled with dry ice and then added to the solution of o-toluidine hydrochloride as rapidly as possible without the temperature rising above -10° C. The rapid addition of ethyl nitrite reduces the tendency for the formation of the amino-azo compound. A mechanical stirrer eliminated local overheating.

A solution of 450 gms. of stannous chloride in 500 ml. of concentrated hydrochloric acid was cooled and added slowly to the diazonium chloride so as to keep the temperature below -5° C. The hydrazine hydrochloride was obtained as light yellow crystals. These were filtered off, dried, and decomposed with caustic potash (300 gms. per 300 ml.). The liberated free base was extracted with ether and dried over anhydrous sodium sulfate. The ether was distilled off, and the hydrazine purified by fractional distillation collecting the fraction 110-125° C. at 5 mm. The yield was 84 gms. (69%).

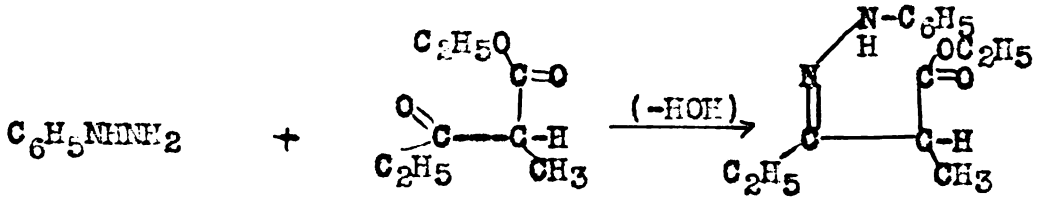
O-tolyl hydrazine has a melting point of 61-62° C. and a boiling point range of 95-115° C. at 3 mm. pressure. It crystallizes on condensing as white needles in rosettes which turn yellow rapidly. The hydrazine is unstable and slowly decomposes on exposure to light and air. It can be stored for some time as the hydrochloride.

By carrying out the diazotization with sodium nitrite in aqueous alcohol and adding it to the reaction mixture to keep the temperature down to -20° C., it was possible to obtain the o-tolyl hydrazine in good yield (55-60%).

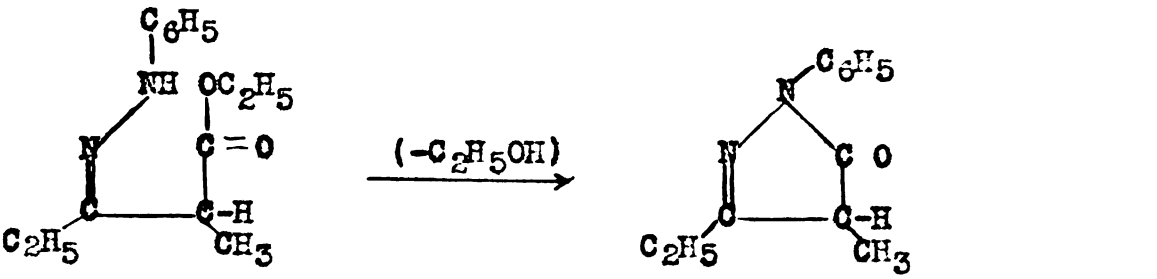
III. Preparation of 1-Phenyl-3-Ethyl-4-Methyl-5-Pyrazolone

The pyrazolone was prepared in the manner described by Emmerling and Kristeller, condensing phenyl hydrazine with ethyl-α-propionyl propionate.

The reaction is shown by the following equations:



Phenyl hydrazine Ethyl -propionyl propionate Ester Phenylhydrazone



1-Phenyl-3-ethyl-4-methyl-5-pyrazolone

To 22 gms. of phenyl hydrazine was added 32 gms. of ethyl propionyl propionate. The reaction is exothermic, the temperature rising to 87°C. The reaction mixture was heated on the steam bath in an open flask for fifteen minutes. Water splits off readily, and it is advisable to allow it to escape. The mixture was then heated gradually to 140°C. with the elimination of alcohol. It was found advisable to use an air condenser to let the alcohol out of the reaction flask and yet return the reactants. Removal of the alcohol seems to increase the yield considerably and allows the temperature of the reaction mixture to rise more rapidly. Heating was continued until a sample of the oily mixture became solid on cooling. This required only about fifteen minutes or twenty minutes. The viscous mass was ground

with ether whereby it solidified to a white crystalline mass. There first crystals obtaines from the reaction mixture were small rhomboids with a melting point of 110-112°C. These were washed with a small amount of ether and allowed to dry. Yield: 37.4 gms. (91.7%)

A number of condensations were carried out to determine the effect of temperature on yield, and the optimum temperature was found to lie between 100°C and 140°C.

Condensations were made varying the proportions of the reactants. With a ratio of ester to hydrazine of 2:1, the yield is decreased to about 80%. Moreover, with an excess of hydrazine there is a great increase in dark-colored oily decomposition products which make the purification of the pyrazolone much more difficult.

The pyrazolone was purified by recrystallization from dilute alcohol, and an interesting phenomenon was observed. The entire yield on first crystallizing out of the reaction mixture was rhomboid crystals, which on repeated recrystallizations changed to the monoclinic form. The proportion of monoclinic crystals constantly increased until finally the entire product had that crystal form. The melting point of these white needles was 112-113°C.

Taking a mixed melting point with the two crystalline forms, the melting point was depressed to 100-104°C. The possibility that the two were isomeric forms of the pyrazolone was considered, also the possibility of adsorbed impurities. It was also a possibility that the monoclinic crystals were a hydrated crystal. It was found however, that the change in form occured even with recrystallization from absolute alcohol. The same phenomenon was observed using acetone as the solvent.

Both crystal forms of the pyrazolone were analyzed for the elements with the following results:

$C_{12}H_{14}N_2O$ - rhomboid

	carbon	hydrogen	nitrogen
Theoretical	71.28	6.93	13.86
Found	71.41	7.08	14.03

$C_{12}H_{14}N_2O$ - monoclinic

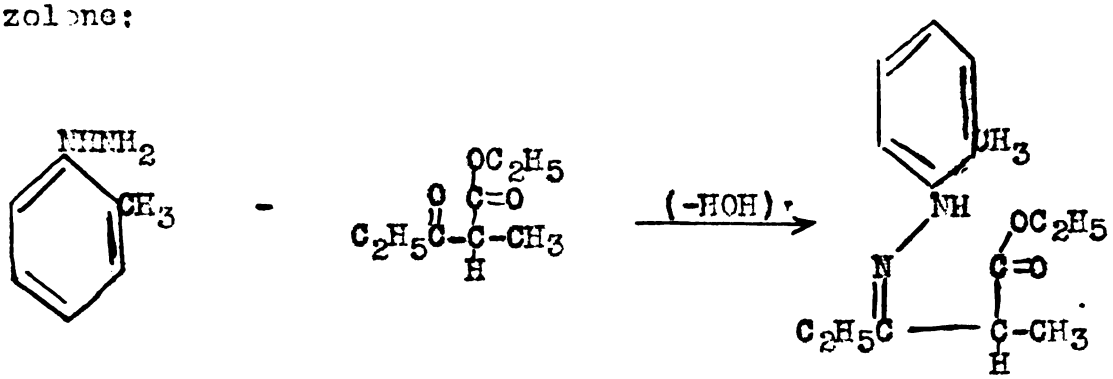
	carbon	hydrogen	nitrogen
Theoretical	71.28	6.93	13.86
Found	71.05	6.95	13.97

Benzoyl esters were prepared from the two crystalline forms, and both were found to give one benzoyl derivative melting at 70-71°C. A mixed melting point using the benzoates prepared from the two forms showed no depression. It appears possible that the forms may be isomers, or it may be they are simply polymorphic forms of the same compound. Neither possibility has been confirmed or discredited.

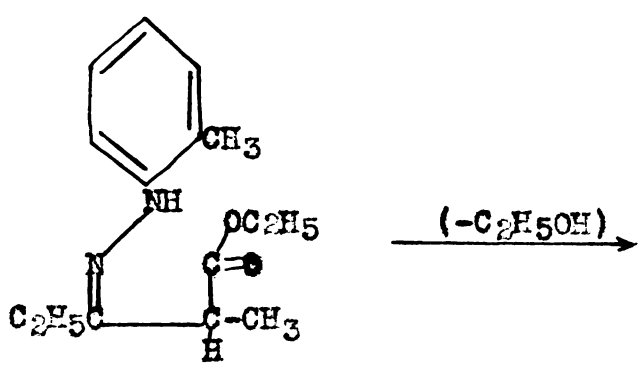
The pyrazolone was found to be solutle in both alkali and mineral acids. It is soluble in alcohol, acetone, and chloroform, and is difficultly soluble in ether and water.

IV. Preparation of 1-O-Tolyl-3-Ethyl-4-Methyl-5-Pyrazolone

The o-tolyl-3-ethyl-4-methyl-5-pyrazolone was prepared by the same method used by Emmerling and Kristeller, condensing o-tolyl hydrazine with ethyl-α-propionyl propionate. The equations below show the reactions in the formation of the pyrazolone:



o-Tolyl hydrazine — Ethyl α-propionyl propionate — o-Tolyl hydrazone of the ester



1-o-Tolyl-3-ethyl-4-methyl-5-pyrazolone

Twenty-four grams (0.2 mole) of O-tolyl hydrazine was added to 32 gms. (0.2 mole) of the ester. The reaction mixture splitting off water is exothermic, the temperature of the reaction mixture going to 94°C. where the mixture starts to boil. The reaction was carried out on a steam bath for thirty minutes and then heated to 150°C. over a thirty minute period. The mixture was cooled somewhat, and the viscous mass was ground with ether and pyrazolone solidified to a white crystalline mass.

Here, as with the phenyl-3-ethyl-4-methyl-5-pyrazolone, the first crystals were rhomboids. Their melting point was 148-149°C. The yield was 35.9 gms. (83.1%)

On recrystallizing from dilute alcohol a number of times, the pyrazolone was gradually converted to monoclinic crystals, melting point at 155-156°C. The mixed melting point of the two forms was 130-134°C.

Grinding the resinous mass of the reaction mixture with acetone and letting it stand also gave rise to rhomboids which after repeated recrystallizations were changed into white needles melting at 155-156°C.

The pyrazolone was analyzed for the elements with the following results:

$C_{13}H_{16}N_2O$

	Carbon	hydrogen	nitrogen
Theoretical	72.3	7.41	12.96
Found	73.1	7.25	13.11

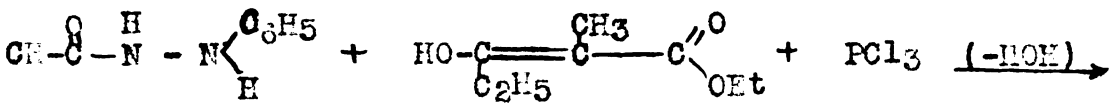
Many attempts were made to prepare the benzoyl ester of the pyrazolone with both of the two crystal forms, but without success. Both the regular Schotten-Baumann and the modification using pyridine were used without being able to isolate the benzoyl derivative.

The pyrazolone is soluble in alcohol, chloroform, and toluere. It is difficultly soluble in ether, ligroin, and petroleum ether.

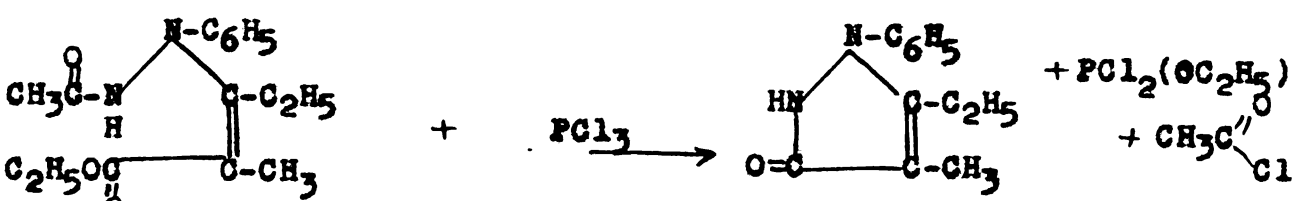
V. Preparation of 1-Phenyl-4-Methyl-5-Ethyl-3-Pyrazolone

The 1-phenyl4-methyl-5-ethyl-3-pyrazolone was prepared according to the method given by Michaelis (37). Acetyl phenylhydrazide was condensed with ethyl-α-propionyl propionate.

The reactions involved in the condensation are shown in the equations:



Acetyl Phenylhydrazine Enol of Ethyl α-Propionyl Propionate



Acetyl phenyl hydrazone of ethyl propionyl propionate

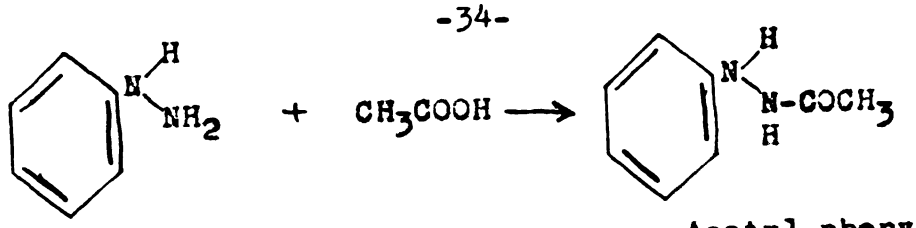
1-Phenyl-4-methyl-5-ethyl-3-pyrazolone

The acetyl phenylhydrazide was prepared in the following way:

To 44 gms. (0.4 mole) of phenylhydrazine 30 gms. (0.5 mole) of glacial acetic acid were added, and the mixture was refluxed for six hours. The reaction mixture was poured into water, and the entire mass was evaporated to dryness on the steam bath. The brown crystalline mass was dried on a porous plate, washed with ether and again dried on a porous plate. The product was recrystallized from hot water, and when pure, had a melting point of 129-130°C. The yield was 29.4 gms. or 49% of the theoretical.

The acetyl phenylhydrazide crystallizes in large colorless leaves. It is insoluble in alcohol, ether, and petroleum ether, and is soluble in hot water.

The reaction is shown by the following equation:



Acetyl phenyl hydrazide
(Hydracetin)

The 3-pyrazolone was prepared by placing 30 gms. (0.2 mole) of ethyl-α-propionyl propionate in a flask with a reflux condenser. Through the reflux condenser 34 gms. (0.25 mole) of phosphorus trichloride were added slowly. The flask was heated, and the mixture refluxed until no more HCl was evolved. The reaction mixture was poured with stirring into a 10% solution of hydrochloric acid. The solution was filtered and then neutralized with ammonium hydroxide precipitating the 3-pyrazolone. The pyrazolone was filtered off and was purified by recrystallization from dilute alcohol. The product came down as small cream colored crystals melting at 97-98°C. The yield was 15 gms. (35%) The 3-pyrazolone is soluble in ether and nearly insoluble in water and petroleum ether.

A nitrogen determination was run on the 3-pyrazolone. The results obtained were:

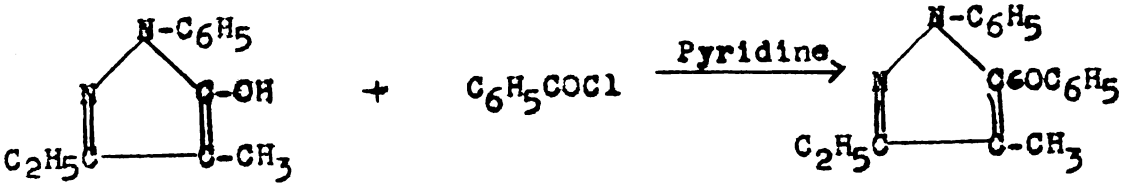
$C_{11}H_{14}N_2O$	nitrogen
Theoretical	16.9%
Found	14.1

VI. Preparation of the Benzoyl Ester of 1-Phenyl-3-Ethyl-4-Methyl-5-Pyrazolone.

The benzoyl ester of the pyrazolone was prepared by a method similar to that used by Michaelis (38).

A mixture of 5 grams of pyrazolone, 10 gms. of pyridine, and 5 gms. of benzoyl chloride was shaken together in a stoppered 50 ml. erlenmyer flask and allowed to stand for twenty-four hours.

The contents were poured into water and washed well with water, then with dilute sulfuric acid, (5%) then with a dilute solution of sodium carbonate (5%), and finally washed again with water. The product was purified by recrystallization from dilute alcohol and came down as fine white needles melting at 70-71°C. Yield: 4 gms. (53%)



The formula shown is in accord with Knorr's formula for the benzoyl esters in which the benzoyl residue is attached to the carbonyl group.

The 1-phenyl-3-ethyl-4-methyl-5-benzoyl-5-pyrazolone is soluble in alcohol, chloroform, and in hot gasoline and hot lingroin; slightly soluble in carbon tetrachloride and insoluble in water and petroleum ether.

A nitrogen eleterminetion was run on the benzoyl ester:

$C_{19}H_{18}N_2O_2$	nitrogen
Theoretical	[illegible]
Found	8.98

The 3,5-dinitro benzoyl ester of the pyrazolone was prepared by condensing 3,5-dinitro benzoyl chloride with 1-phenyl 3-ethyl-4-methyl-5-pyrazolone in pyridine solution. The product was handled as described above and was purified by recrystallization from dilute alcohol. The 3,5-dinitro-benzoate came down as cream-colored needles melting at 91-92°C.

VIII. Methylation of 1-o-Tolyl-3-ethyl-4-methyl-5-pyrazonone

The pyrazolone was methylated using the method employed by Knorr in the preparation of tolyl antipyrine. (29).

Ten grams of the pyrazolone were heated in a sealed Carius tube with 10 gms. of methyl iodide and 10 gms. of methyl alcohol for six hours at 110° C. The methyl alcohol was distilled off under reduced pressure and the hydroiodide dissolved in water. The methylated product was liberated by the addition of sodium hydroxide (37 gms. per 100 ml. of aqueous solution).

The product was extracted either with chloroform or with ether and dried over anhydrous calcium oxide. The product was purified by dissolving in hot gasoline and letting stand in the ice chest. The product came down as a viscous oil which can be crystallized in the ice chest but which liquifies at room temperature. The same oily product was obtained from three methylations which were run.

Attempts to obtain a crystalline product using a number of different solvents (water, ligroin, gasoline and chloroform, and gasoline and alcohol) were unsuccessful. The product is evidently an oil.

VIII. Summary

A study was made of the condensation of the phenyl and o-tolyl hydrazines with ethyl-α-propionyl propionate to give the 1-aryl-3-ethyl-4-methyl-5-pyrazolones.

The 1-phenyl-3-ethyl-4-methyl-pyrazolone was prepared and was found to come down as rhomboid crystals melting at 110-112° C. The rhomboids on repeated recrystallizations were changed to monoclinic crystals with a melting point of 112-113° C. (Yield 92%).

The 1-o-tolyl-3-ethyl-4-methyl-5-pyrazolone was prepared and it too came down at first as rhomboid crystals. M.P. 148-149° C. After recrystallization these were changed into monoclinic crystals melting at 155-156° C. (Yield 83%).

In both of the above cases a mixed melting point of the two crystal forms was found to show a depression of about 10°C.

Acetyl phenyl hydrazide (hydracetin) was condensed with ethyl-α-propionyl propionate to give 1-phenyl-4-methyl-5-ethyl-3-pyrazolone which came down as fine cream-colored crystals with a melting point 97-98° C. (Yield 35%).

The benzoyl ester of 1-phenyl-3-ethyl-4-methyl-5-pyrazolone was prepared as was obtained as fine white needles melting at 70-71° C. (Yield 53%). The dinitro- (3,5-) benzoate was also prepared. The crystals came down as cream-colored needles with a melting point of 91-92° C.

Attempts to prepare the benzoyl ester of 1-o-tolyl-3-ethyl-4-methyl-5-pyrazolone were unsuccessful.

The o-tolyl-3-ethyl-4-methyl-5-pyrazolone was methylated and the product came down as a viscous oil. Attempts to obtain

the methylated product in a crystalline form at room temperature were unsuccessful. The 1-o-tolyl-2,4-dimethyl-3-ethyl-5-pyrazolone is apparently an oil at ordinary temperatures.

BIBLIOGRAPHY

1. Knorr, Ann. 238, 137 (1887).
2. Knorr, Ann. 279, 188 (1895).
3. Knorr, Ann. 293, 1 (1896).
4. Knorr, Ann. 328, 62 (1903).
5. Knorr, Ber. 28, 715 (1895).
6. Claisen and Roosen, Ber. 23, 1338 (1890).
7. Claisen, Ann. 278, 261, 267 (1893).
8. Buchner and Fritsch, Ann. 273, 253 (1893).
9. Balbiano, Ber. 23, 1103 (1890).
10. Claisen, Ber. 36, 3666 (1903).
11. Knorr, Ber. 16, 2597 (1883).
12. Knorr, Ber. 17, 149 (1883).
13. Knorr, Ann. 238, 147 (1887).
14. Knorr, Ber. 18, 311 (1884).
15. Buchner, Ann. 273, 214 (1893).
16. Bischler, Ber. 25, 3143 (1892).
17. Bischler, Ber. 26, 1881 (1893).
18. Fischer and Bulow, Ber. 18, 2131 (1884).
19. Stoermer and Martinsen, Ann. 352, 322 (1907).
20. Schmidt, Organic Chemistry, 564-567.
21. Knorr, Ann. 293, 58 (1896).
22. Fischer, 236, 116 (1886).
23. Cornelius and Homolka, Ber. 19, 2239 (1886).
24. Brigham, Tolyl and Xylyl Derivatives of Pyrazolone (1929).
25. Sell, Para Xylyl Methyl Pyrazolones (1931).
26. Knorr and Klotz, Ber. 20, 2545 (1887).
27. Knorr and Duden, Ber. 25, 761 (1892).

28. Stolz, Ber. 38, 3275 (1905).

29. Knorr, Ber. 17, 550 (1884).

30. Klauber, Monatsh. 11, 283; 12, 215 (1890, 1891).

31. Blaise, Compt. rend. 132, 979 (1901).

32. Knorr and Blank, Ber. 17, 2050 (1884).

33. Knorr, Ann. 238, 162 (1887).

35. Emmerling and Kristeller, Ber. 39, 2452 (1906).

36. Schroeter, Ber. 49, 2719 (1916).

37. Michaelis, Ann. 338, 273 (1905).

38. Michaelis and Behrens, Ann. 338, 310 (1905).

39. Stolz, Ber. 27, 407 (1894).

40. Fichter, Enzenauer, and Uellenberrg, Ber. 33, 498 (1900).

41. Michaelis and Drews, Ann. 350, 321 (1906).

42. Nef, Ann. 266, 125 (1892).

43. Knorr, Ann. 328, 202 (1887).

44. McElvain, J. Am. Chem. Soc. 51, 3129 (1929).

45. Demonbreun and Kremers, J. Am. Pharm. Assoc. 12, 589 (19230.

46. Feldhaus, Ann. 126, 73 (1863).