# PARA XYLYL METHYL PARAZOLONES AND SOME DERIVATIVES

THESIS FOR THE DEGREE OF M. S.

Harold Melvin Sell

1931

Pyrazolone

Title

Chemistry

# Para Xylyl Methyl Parazolones

# and

# Some Derivatives

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**A Thesis**

Submitted to the Faculty

of

Michigan State College

In partial fulfillment of the requirements for the degree of Master of Science.

By

Harold Melvin Sell

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ACKNOWLEDGMENT

It is a pleasure that I welcome this opportunity to express my most grateful appreciation for the invaluable aid and friendly encouragement given to me by Dr. R. C. Huston under whose guidance this work was carried on.

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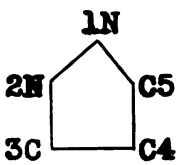
# REVIEW OF THE LITERATURE

## 1. THE CONSTITUTION OF THE PYRAZOLE GROUP

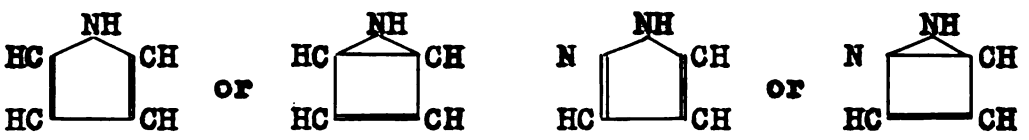
The pyrazole compounds may be classed under the name "Azoles which includes a five membered cyclic system containing nitrogen.

In the pyrazole group we have those compounds in which the molecule contains a ring composed of two nitrogens and three carbons arranged in the following manner (Ann. 279, 188; 293, 1; 328, 62).




Pyrazole may be regarded as derived from pyrrol by replacement of a methine group adjacent to an NH group by nitrogen.

The Pyrazole stands in the same relation to pyrrol as pyridine does to benzene (Ann. 238, 138).



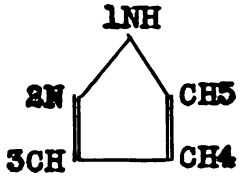

pyrrol pyrazole

The structure of the pyrazole ring has been proven by many men of whom Knorr is the most outstanding.

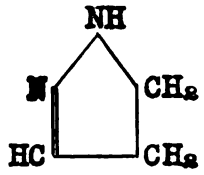
The above formulae show that pyrrol is closely related to pyrazole, and for this reason the nomenclature is that suggested by Knorr for the pyrrol derivatives.

There is a dihydro pyrazole or pyrazoline and a tetra hydropyrazole or pyrazolidine corresponding to the di and tetra

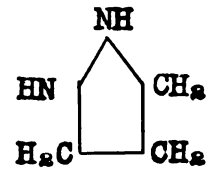
hydropyrrols.




pyrazole



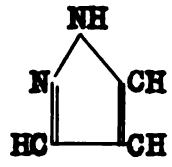

pyrazoline



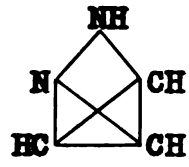

pyrazolidine

The position of a substituent group in pyrazol ring is indicated by the numbers one to five. Numbering starts with the nitrogen in the imino group and proceeds to the second nitrogen atom as illustrated in the above formula.

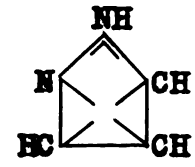
In the investigation of pyrazole compounds, Knorr came to the conclusion that the pyrazole molecule was symmetrical and that the usual pyrazole formulae were in contradiction with his results (Ann. 279, 188).




Knorr and Balbiano

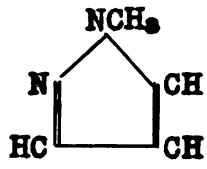



Buchner

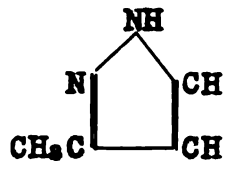



Bamberger

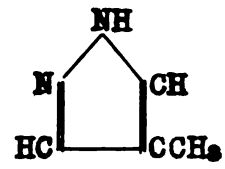
There may exist four isomers of the methyl pyrazoles.



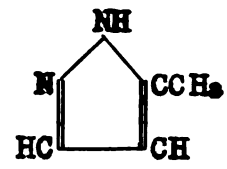

1 methyl pyrazole




3 methyl pyrazole




4 methyl pyrazole

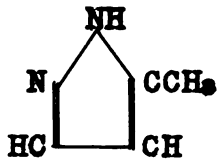



5 methyl pyrazole

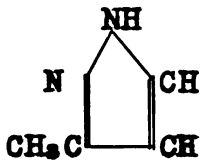
Of these four the three and five have been proved identical.

In 1893 the problem of the structure of pyrazole entered a new phase when Knorr and MacDonald discovered that 1 phenyl 3 methyl pyrazole and 1 phenyl 5 methyl pyrazole or their amino derivatives gave one and the same methyl pyrazole of boiling

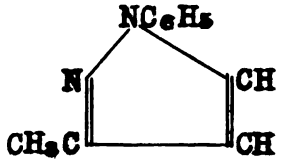
point 204°C. (Ann. 1894, 279, 188). Therefore, it is not possible to obtain the two methyl pyrazoles of the formulae.



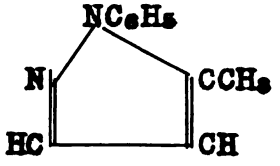

and




Claisen and Roosen obtained two isomeric phenyl methyl pyrazoles on condensing phenyl hydrazine with oxymethylene acetone. On the other hand Knorr and MacDonald failed to observe two isomeric phenyl methyl pyrazoles on condensing hydrazine hydrate with oxymethylene acetone. (Ber. 1891, 24, 1888; Ann. 1894, 278, 261, 267).

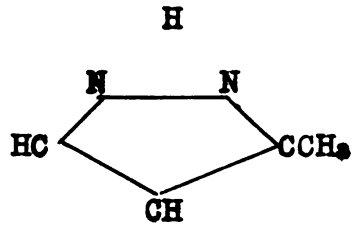



m.p. 37°C
b.p. 254-255°C
crystalline



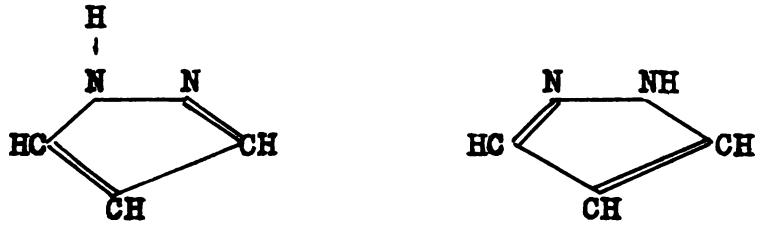

b.p. 254-255°C
sp.gr. 1.085 at 15°C
colorless liquid

From these results it appears that the positions three and five in pyrazole are equivalent to one another and that methyl pyrazole may be a mixture of two desmotropic forms of the three methyl pyrazole and five methyl pyrazole in a state of rapid and continuous interconversion. From the above results Knorr suggested the following formula for the three and five methyl pyrazole (Ann. 279, 191).



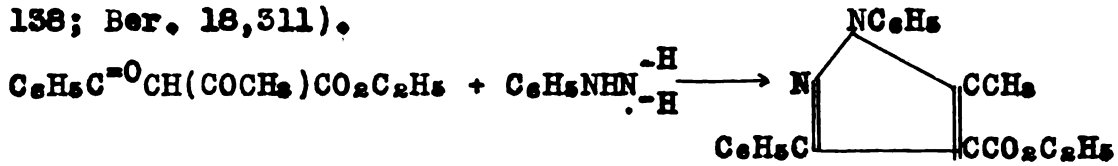
This conclusion was confirmed by the discovery that methyl pyrazole could react either as a three methyl pyrazole or a five methyl pyrazole.

Knorr assumed that one hydrogen in the pyrazole is not permanently attached to a given nitrogen but may alternate from one nitrogen to the other with a readjustment of the double bond as shown below:



I II

The first pyrazole derivative was prepared by Knorr by the reaction of benzoylacetoaceticester on phenyl hydrazine: (Ann.238, 138; Ber. 18,311).

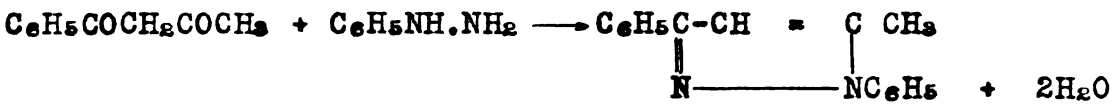


Benzoyl aceto acetic ester | Phenyl hydrazine | Ester of diphenyl methyl carboxylic acid

Later other methods were described by Knorr and other chemists for synthesis of pyrazole compounds such as the following:

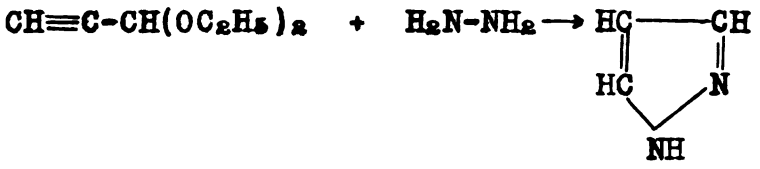
1. Diphenylmethyl pyrazole was prepared by Fischer and Bulow through the reaction of phenylhydrazine on benzoyl acetone

(Ber. 18, 2131).



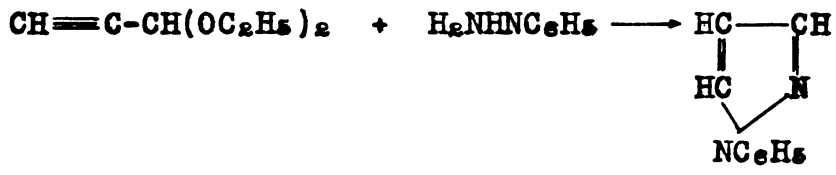
Benzoyl acetone — Phenyl hydrazine — 1,3,5 Diphenyl methyl pyrazole

2. Claisen obtained pyrazole by treating the acetal of propargyl aldehydes with hydrazine (Ber. 36, 3666).



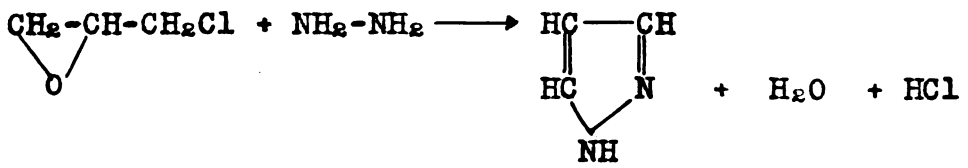
Acetal of propargyl aldehyde — Phenyl hydrazine — Phenyl pyrazole

By treatment with phenyl hydrazine a phenyl derivative was obtained:



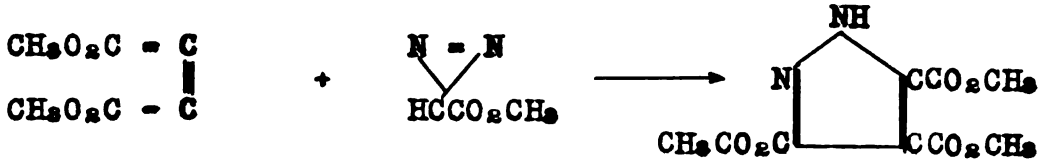
Acetal of propargyl aldehyde — Phenyl hydrazine — Phenyl pyrazole

3. Balbiano prepared pyrazole by the treatment of hydrazine hydrate upon epichlorhydrin (Ber. 23, 1103).



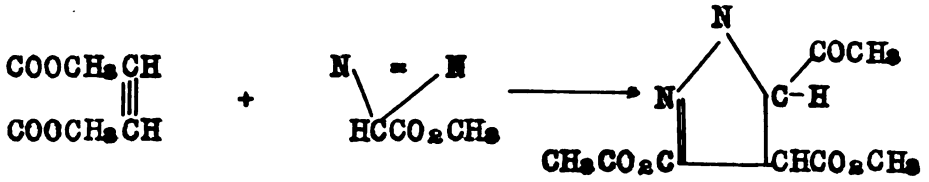
4. Buchner obtained pyrazole derivatives by the interaction of unsaturated compounds on diazo acetic ester. (Ann. 273, 222).

(a) Action of acetylene dicarboxylic acid on diazo acetic ester:



Acetylene dicarboxylic acid | Diazo acetic ester | Pyrazole tricarboxylic acid

(b) Action of diazo acetic acid on ethylene derivatives:



Fumaric ester | Diazo acetic ester | Pyrazoline tri carboxylic acid

(c) Esters of saturated and unsaturated halogen substituted acids react with diazo acetic ester to form pyrazole compounds.

$$C_2H_3Br_2(CO_2CH_3) + 3CHN_2(CO_2CH_3) \longrightarrow$$

Dibromo propionic ester | Diazo acetic ester

$$C_3H_4N_2(CO_2CH_3)_2 + 2CH_2Br(CO_2CH_3) + 2N_2$$

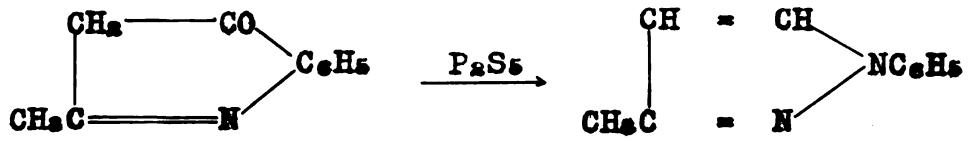
Dicarboxylic pyrazole ester | Bromo acetic ester

5. Knorr and MacDonald obtained pyrazole derivatives by the condensation of oxymethylene acetone with hydrazine hydrate (Ann. 279,190).

6. Bischler prepared derivatives of pyrazole by the action of diazonium salts on substituted aceto acetic esters. (Ber. 1892, 25, 3143; 1893, 26, 1881).

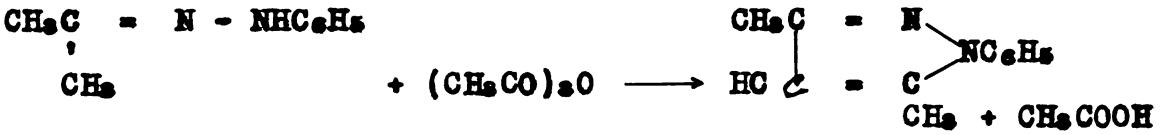
7. Stoermer and Martinsen obtained derivatives of pyrazole

by distillation of oxygen derivatives of pyrazolone with zinc dust, penta sulphide or phosphorous tetra bromide (Ann. 1907, 352, 328).



Phenyl methyl pyrazolone 1,3,5 dimethyl pyrazole

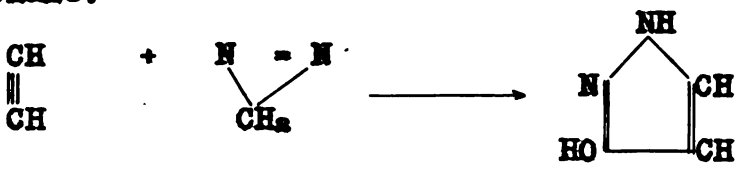
8. Certain hydrazones when heated with acid anhydrides give derivatives of pyrazole:



Aceto phenyl hydrazone Acetic anhydride 1,3,5 Phenyl dimethyl pyrazole Acetic acid

9. Claisen and Roosen prepared derivatives of pyrazole through the condensation of the aldehyde of aceto acetic ester with phenyl hydrazine and acetone oxalic acid with phenyl hydrazine (Ber. 24, 1888). They also obtained pyrazole derivatives by the action of phenyl hydrazine on oxymethylene.

10. Pechmann obtained pyrazole by the reaction of acetylene on diazo methane:



Acetylene Diazo methane Pyrazole

11. Buchner obtained pyrazole by heating 3 : 4 : 5 pyrazole tricarboxylic acid (Ann. 273, 253).

According to Knorr, the best means for the preparation of pyrazole, is the prolonged heating of 3 : 5 pyrazole dicarboxylic acid.

Knorr states that B diketones, compounds of the formula R' CO-CH R'' CO - R''' react with primary aromatic hydrazines to form pyrazole derivatives (Ann. 238, 139).

In general, compounds containing two CO groups or a CO and COOH group in the B position to one another or two double linked carbon atoms adjacent to a COOH or CO group react with hydrazine to give pyrazole derivatives (Shhmidt, Organic Chemistry, P 564).

Knorr has given a number of facts which illustrates the aromatic character of pyrazole (Ber. 1895, 28, 714-716, Schmidt, Organic Chemistry, P 567).

1. Fuming sulphuric acid converts pyrazole into a sulphonic acid (M.P. 330-335°C) which has reactions similar to aromatic sulphuric acids.

2. In halogen derivatives, the halogen is more firmly held to pyrazole nucleus than in benzene derivatives.

3. Pyrazole is nitrated with concentrated nitric acid, 4 nitro pyrazole being formed. The nitro compound may be reduced to amino compounds.

4. Amino pyrazoles resemble the aromatic bases in its behavior. It gives a color reaction with a solution of bleaching powder.

5. Diazonium salts of pyrazole can be coupled with phenols to form azo dyes. These differ from aromatic azo dyes in the

stability of their salts. On boiling these solutions there is no visible evolution of nitrogen; this occurs only on prolonged heating at higher temperatures. Diazonium salts of pyrazole, however, do not undergo the usual "diazo reaction".

6. 5-hydroxy pyrazole or pyrazolone have a phenolic character.

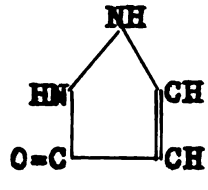
7. Towards oxidizing and reducing agents, pyrazole shows the same remarkable stability as benzene.

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

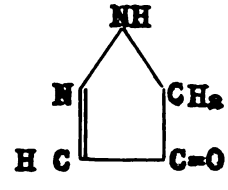
Pyrazole is a weak secondary base and it may be acetylated, benzolated and converted into derivatives of urethane and urea (Ber. 1895, 28, 716).

## II Constitution of Pyrazolone

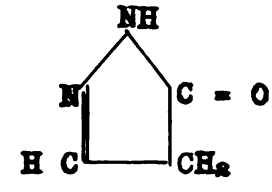
The pyrazolones or keto dehydropyrazoles are those pyrazole derivatives which have been known for the longest time. These compounds were discovered and investigated by Knorr. The pyrazolone compounds are divided into two classes; - 4 derivatives or true ketones derived from ketonic acids and 3 and 5 derivatives as derived from cyclic acid amides.




3 pyrazolone



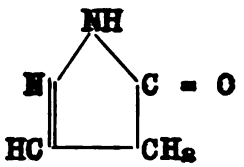

4 pyrazolone



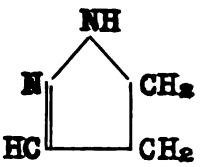

5 pyrazolone

(Ann. 238, 145).

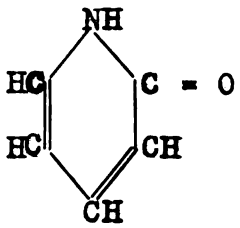
Pyrazolone bears the same relation to pyrazoline as pyridine does to pyridone:



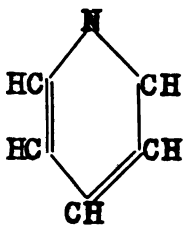
Pyrazolone



Pyrazoline



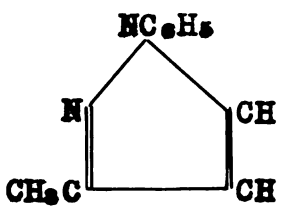
Pyridone



Pyridine

Knorr has determined the constitution of the phenyl methyl pyrazolone by the following reactions (Ann. 238, 148).

1. By distillation with zinc dust, a product is obtained which is a weak base of composition $C_{10}H_{10}N_2$ which in all its properties and reactions resembles a pyrazole base. Its salts are decomposed by water. Through the reduction with sodium and alcohol it is transformed into a base rich in hydrogen, which exhibits a reaction similar to a pyrazoline base in that it gives an intense violet color upon the addition of an oxidizable substance. These properties are identical with those of 1-phenyl-3-methyl pyrazole of the formula:-



Through its formation, the origin of 1-phenyl methyl pyrazolone from the pyrazole group is proved.

2. The methylene of aceto acetic ester is found unchanged. It undergoes a number of reactions characteristic of this group.

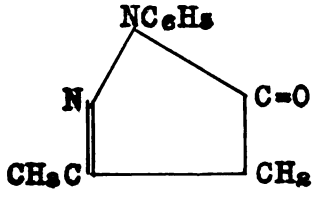
3. The oxygen in phenyl methyl pyrazolone is entirely inactive in that it cannot be combined as an hydroxyl or ketonic

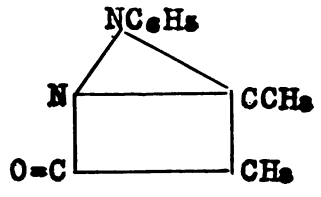
oxygen but only in the form of acid amides.

4. Phenyl methyl pyrazolone contains no more hydrogen which could combine with nitrogen. It is indeed methylated with methyl iodide attaching undoubtedly to the nitrogen atom, giving the methylated base, antipyrine, in which the molecule of phenyl methyl pyrazolone undergoes a radical change. The antipyrine no longer contains the methylene group but a methine group. This phenomena led Knorr to a false conception of the antipyrine molecule.

From the foregoing it is evident that the hydrogens in phenyl methyl pyrazolone distribute themselves as follows: five hydrogens are in the phenyl of the phenyl hydrazine, three hydrogens on the methyl group and two hydrogens on the methylene of aceto acetic ester.

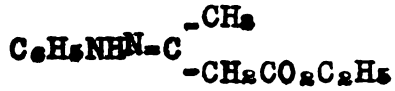
The possible formulas for phenyl methyl pyrazolone may be either of the following:



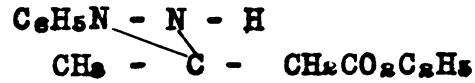




The decision of the two formula lies with the question of the constitution of the phenyl hydrazine of aceto acetic ester and the ketone and aldehyde derivatives of phenyl hydrazine for which compounds there are two formula.

I



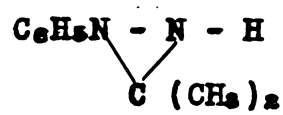
II



Phenyl hydrazine of acetoaceticester

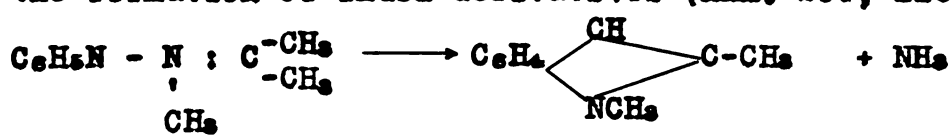
I

II



If these compounds possess formula I, then I is the formula for phenyl methyl pyrazolone, and if these compounds have a structure as in II, then II is the formula for phenyl methyl pyrazolone.

According to E. Fischer, the ketones and aldehyde derivatives of primary as well as the unsymmetrical secondary aromatic hydrazine under suitable conditions react very similar to the formation of indol derivatives (Ann. 236, 116).

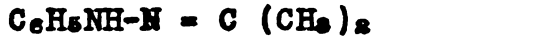


Aceto methyl phenyl hydrazine

Dimethyl indol

It is obvious that this reaction shows an analogy of atomic linkage in both classes of hydrazine derivatives.

Methyl phenyl hydrazone of acetone



Phenyl hydrazone of acetone

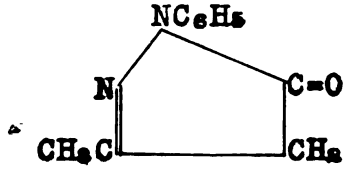
Accordingly, the primary as well as the unsymmetrical secondary hydrazine unite in the same manner with aldehydes and ketones at low temperatures while the symmetrical secondary hydrazine react with aldehydes (Ber. 19, 2239) at high temperat-

ures and with ketones the reaction, in general, is more difficult.

From this fact, it appears with great probability, that the formula for the phenyl hydrazone of aceto acetic ester is that of formula I:

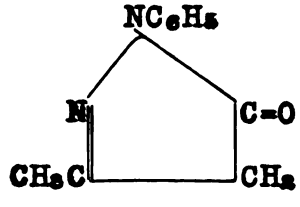
$$C_6H_5NH - N = C\begin{matrix}-CH_3\\-CH_2CO_2C_2H_5\end{matrix}$$

From the above facts, Knorr cast aside the carbizine structure for the pyrazolone and accepted the following formula for phenyl methyl pyrazolone:

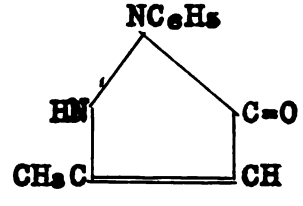



Knorr states that 1-phenyl-3-methyl-5-pyrazolone may exist in three desmotropic forms. This is described by Knorr as "double tautomerism" (Ber. 1895, 28, 706).

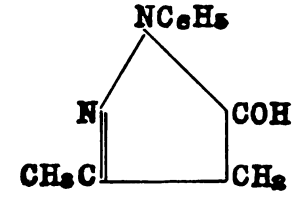
The 1-phenyl-3-methyl-5-pyrazolone itself has only been obtained in the form of one substance of melting point 127°C.




Methylene form




Imine form




Phenolic form

The imine structure is found in those compounds known as antipyrines.

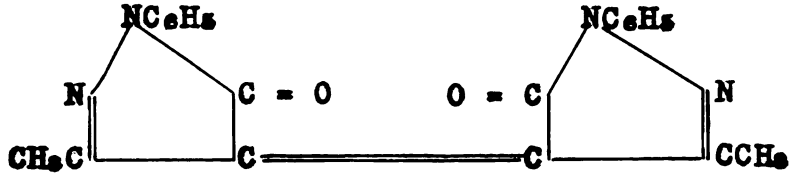
The phenolic structure is found in those compounds

such as phenyl ethers, esters, and salts of phenyl methyl pyrazolone.

The methylene structure is that type of compound which responds to pyrazole blue test.

## III The Pyrazole Blue Test

Knorr and Duden found that the oxidation of phenyl methyl pyrazolone with ferric chloride or platinum chloride resulted in the formation of pyrazole blue which represents the indigo of the pyrazole series. In a chloroform solution, a deep blue color results and in ether solution violet needles of pyrazole blue are precipitated (Meyer and Jacobson, Vol. II, 415; Ann. 238, 155; Ber. 25, 765).




Pyrazole Blue

## IV Preparation of 5-Pyrazolone

Phenyl methyl pyrazolone was prepared by Knorr in 1883 by condensing phenyl hydrazine with a Beta Ketonic ester.

To 125 gms. of phenyl hydrazine, 100 gms. of aceto acetic ester were added and warmed on a water bath. The first reaction consisted of the elimination of water with the formation of phenyl hydrazone of aceto acetic ester.

$$C_6H_5N_2H = C^{-CH_3}_{-CH_2COOC_2H_5}$$

This product was heated to a higher temperature which resulted in a ring closure with the elimination of alcohol.

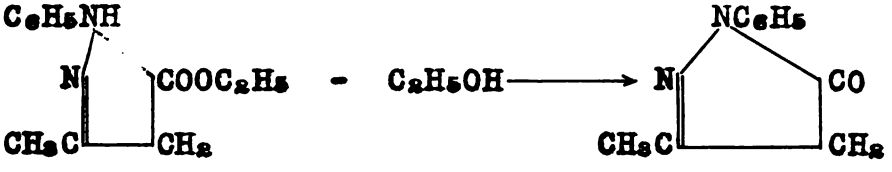
$$C_6H_5N_2H = C^{-CH_3}_{-CH_2COOC_2H_5} \longrightarrow C_{10}H_{10}N_2O + C_2H_5OH$$

The alcohol formed was distilled off, the condensation product washed with ether, and the product dried in an oven at 100°C. The product was recrystallized from water or hot alcohol. The crystals melted at 127°C (Ber. 16, 2597; Ann. 238, 147).

Equations for the reaction of aceto acetic ester in the keto form:

$$C_6H_5NHNH_2 + CH_3COCH_2C^{=O}_{-OC_2H_5} \ (-H_2O) \longrightarrow$$

Phenyl hydrazine — Aceto acetic ester

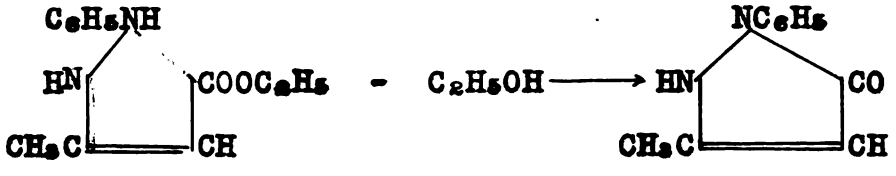



Phenyl hydrazone of aceto acetic ester — 1-Phenyl-3-methyl-5-pyrazolone

Reactions of aceto acetic ester in the enol form:

$$C_6H_5NHNH_2 + CH_3COHCHCOOC_2H_5 \ (-H_2O) \longrightarrow$$

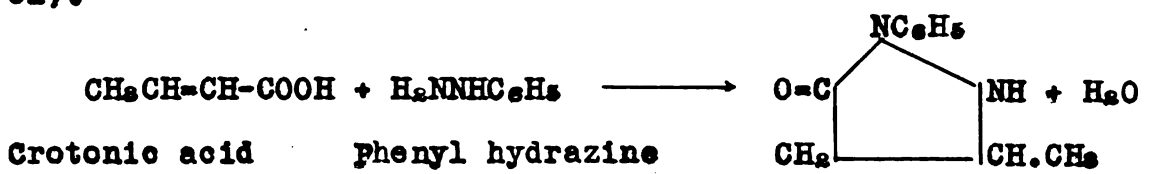
Phenyl hydrazine — Aceto acetic ester



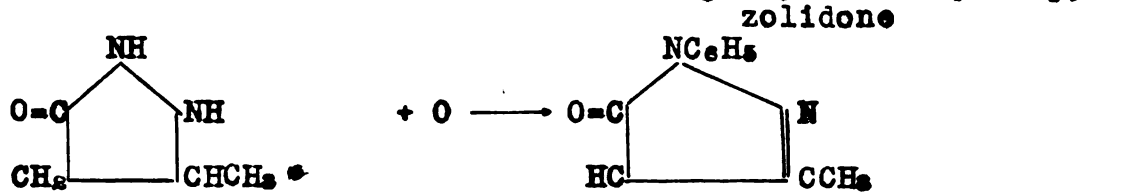

Phenyl hydrazone of aceto acetic ester — 1-phenyl-3-methyl-5-pyrazolone

Other methods for the synthesis of pyrazolones.

1. Knorr and Duden found that unsaturated acid of the acrylic acid series R.CH=CH-COOH react with hydrazines to give derivatives of pyrazolone or pyrazolidone (Ber. 1892, 25, 761).




1-phenyl-3-methyl-5-pyrazolidone




1-phenyl-3-methyl-5-pyrazolidone

1-phenyl-3-methyl-5-pyrazolone

2. Petrenk and Kretschenko have prepared dimethyl pyrazolone by the elimination of $CO_2$ from the acid formed by the condensation of phenyl hydrazine with methyl acetone dicarboxylic acid ester.

3. Knorr and Klotz prepared diphenyl pyrazolone by condensing phenyl hydrazine with ethyl benzoyl acetate (Ber. 20, 2545).

4. Knorr prepared ortho and para tolyl methyl pyrazolone through the condensation of tolyl hydrazine with aceto acetic ester. The melting point of the para compound was 137°C and that of the ortho compound 183°C. (Ber. 1884,17, 550). Huston and Brigham obtained in the preparation of O-tolyl methyl pyrazolone (m.p. 183°C) an isomeric tolyl methyl pyrazolone

having a melting point of 169°C (Brigham's Thesis 1929).

5. Klauber prepared 1, 3, 4 xylyl methyl pyrazolone by heating 1 part of the compound of the empirical formula $C_{22}H_{24}N_4O_4$ with one part of concentrated hydrochloric acid for two hours at 145°C. T he hydrochloride was decomposed with sodium acetate. The meta xylyl methyl pyrazolone was obtained as needles melting at 159°C (Monatshefte 12, 215).

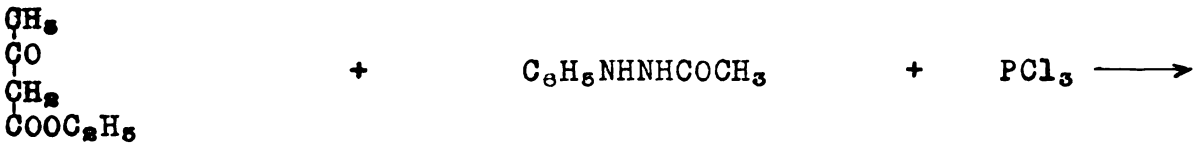
Huston and Brigham prepared P-xylyl methyl pyrazolone through the condensation of P-xylyl hydrazine with aceto acetic ester. The P-xylyl methyl pyrazolone was crystallized from alcohol and melted at 150-151°C (Brigham's Thesis).

## V Preparation of 3-Pyrazolone

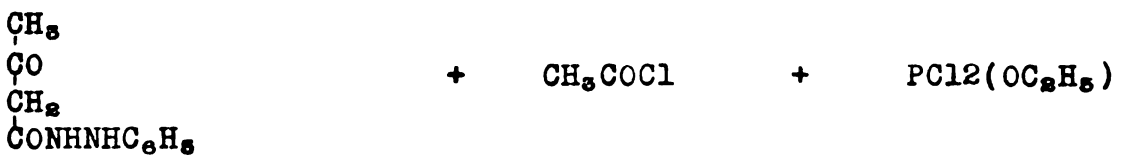
Michaelis prepared 1-phenyl-5-methyl-3-pyrazolone by the action of 15 gms of acetyl phenyl hydrazine on 13 gms. of aceto acetic ester to which 14 gms. of phosphorous trichloride have been added gradually. The mixture was refluxed until no generation of hydrogen chloride was evolved. The thick viscous solution was dissolved in a 10% solution of hydrochloric acid. The pyrazolone dissolved in the acid solution. The solution was filtered, cooled and neutralized with ammonia hydroxide.

The pyrazolone was precipitated and the product dried on a porous plate . (If the pyrazolone is dark colored it may be decolorized by boiling in an alkaline solution of animal charcoal). The yield was eight grams, due to the fact that diacetyl phenyl hydrazine was formed. The pyrazolone crystallizes from alcohol as colorless crystals. (Ann. 338, 273).

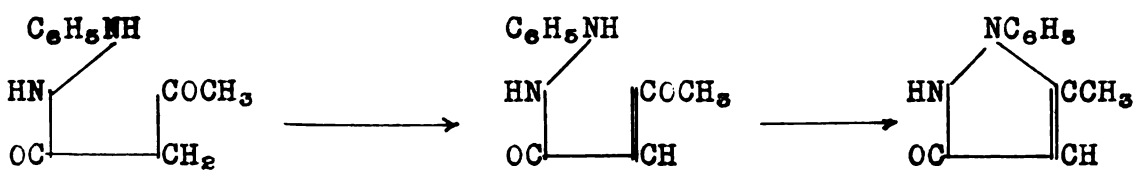
Equations showing the reactions involved:



Acetoacetic ester | Acetyl phenyl hydrazine | Phosphorous trichloride



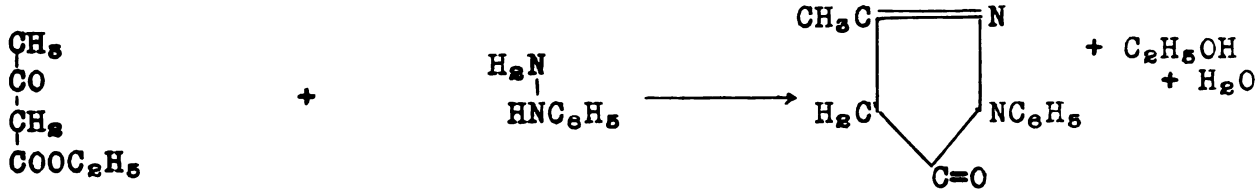
Phenyl hydrazide of acetoaceticester



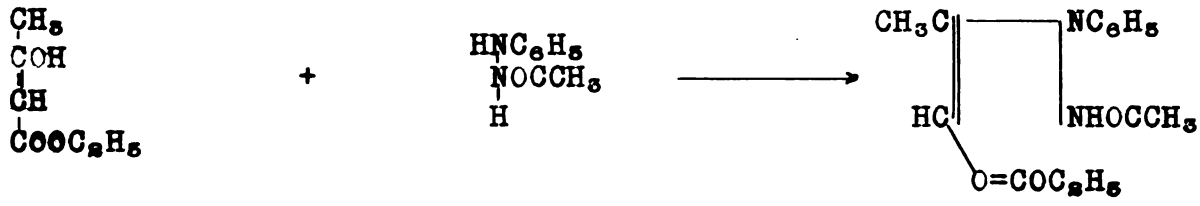
Keto form | Enol form | 1- Phenyl 5 methyl 3 pyrazolone

According to Michaelis the 3 and 5 pyrazolone may be prepared by this method but the 3 pyrazolone is more abundant than the five. In the action of free phenyl hydrazine with acetoaceticester the $NH_2$ of the phenyl hydrazine can react directly with the ketonic oxygen of the ester but in case of an acylated hydrazine the reactivity is less. Therefore the remaining group $NHC_6H_5$ rearranges with the OH of the enolized esters (Ann. 338, 273).

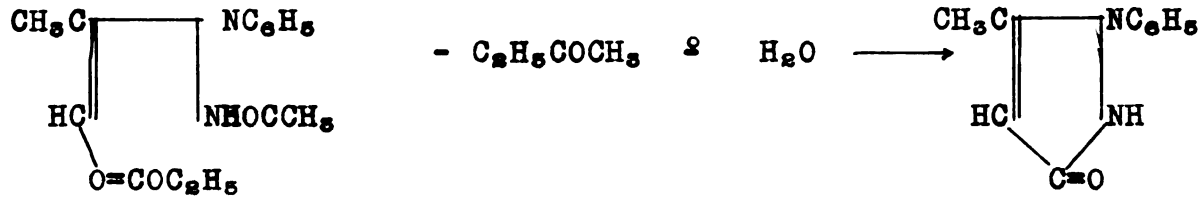
Equations showing the reactions involved:



Acetoaceticester (Keto form) | Phenyl hydrazine | 5 pyrazolone



Acetoaceticester (Enol form)



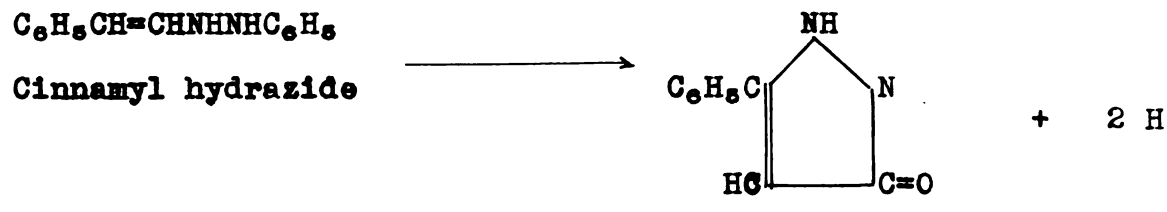
3 Pyrazolone

Other methods for the synthesis of the 3 pyrazolone.

1. Knorr and Duden prepared a 3 pyrazolone through the condensation of phenyl hydrazine with cinnamyl acid(Ber.25, 759)

Cinnamyl acid | Phenyl hydrazine

Cinnamyl hydrazide



1, 5 Diphenyl 3 pyrazolone

2. Bischler prepared pyrazolone derivatives by the action of diazonium salts on substituted acetoaceticester(Ber.25, 3143; 26, 1881). He treated diazonium chloride with phenyl acetoacetic ester.

$C_6H_5N{:}NCl$ + $C_6H_5COCH_2$ / $COCH_3$ $C\acute{O}OC_2H_5$ + $H_2O$ ⟶

Diazonium benzol chloride

Phenyl acetoacetic ester

$C_6H_5COCH_2$ / $C_6H_5NHNCOOC_2H_5$ + $HCl$ + $CH_3COOH$

The hydrazone splits off water and a pyrazolone derivative results.

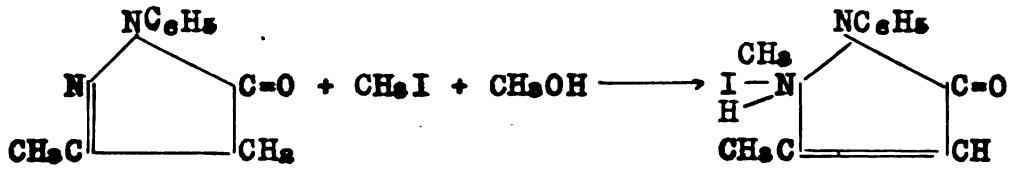
$C_6H_5CO\ CH_2$ / $C_6H_5NHNCOOC_2H_5$ − $H_2O$ ⟶ $C_6H_5C{=}CH$ / $C_6H_5N$ / $N{=}COOC_2H_5$

3. Michaelis and Behrens prepared ortho and para tolyl methyl 3 pyrazolone through the condensation of the corresponding acetyl tolyl hydrazine with acetoacetic ester and phosphorous trichloride. The pyrazolones were recrystallized from alcohol, the para compound melting at 196°C and the ortho compound at 169°C.(Ann. 338, 311).

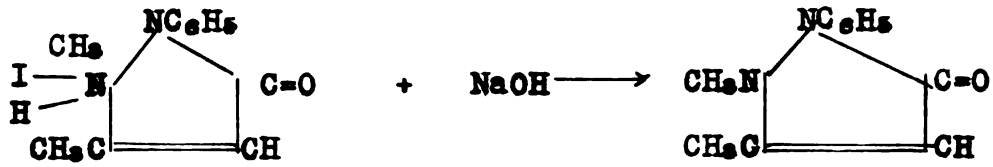
4. The para xylyl methyl 3 pyrazolone was prepared by Huston and Brigham through the condensation of para xylyl acetyl hydrazide with acetoaceticester and phosphorous trichloride. The compound was recrystallized from alcohol. m.p. 180-181°C. (Brighams Thesis)

## VI Constitution and Preparation of Antipyrine

Antipyrine is the methylated base which is obtained in the form of its hydroiodide when phenyl methyl pyrazolone is heated to 100°C together with methyl alcohol and methyl iodide. By treatment with sodium hydroxide antipyrine results. (Knorr, Ann. 238, 202; Ber. 17, 550, 2037).



Phenyl methyl pyrazolone — Hydroiodide of Pyrazolone



Antipyrine
(Knorr)
m.p. 113°C

Knorr has given the following points which he considers important for the constitution of antipyrine (Ann. 238, 205).

1. Antipyrine has without doubt a methyl group attached to the second nitrogen atom. This has been proven by the synthesis of antipyrine from symmetrical methyl phenyl hydrazine and the splitting off of this base from nitroso antipyrine by the action of alkali. The fact that aniline and methyl aniline are split off from antipyrine with zinc dust as well as the reaction of metallic sodium in a boiling alcoholic solution affords proof of the above structure.

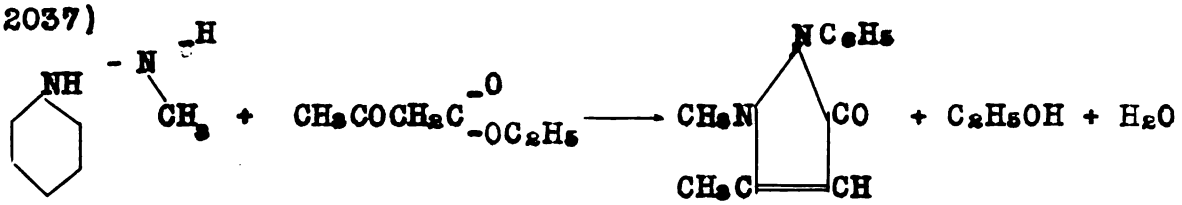
2. Antipyrine, no longer, contains the methylene group as in phenyl methyl pyrazolone, but has a methine group in place. Nitrous and nitric acid produce nitroso and nitro antipyrine of basic character. Benzaldehyde condenses with two molecules of antipyrine according to the following equation:

$$2C_{11}H_{12}N_2O + C_7H_6O \longrightarrow C_{29}H_{28}N_4O_2 + C_2H_5OH + 2H_2O$$

The reaction of bromine with antipyrine results in an addition product, $C_{11}H_{18}N_2OBr_2$ which loses hydrobromic acid when treated with cold water and forms a mono-substituted product, $C_{10}H_{11}N_2OBr$. All those derivatives of phenyl methyl pyrazolone in which one hydrogen of the methylene group has been replaced permit the preparation of antipyrine.

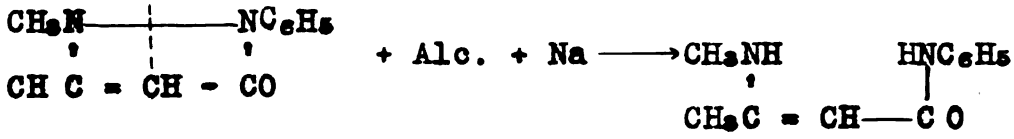
3. Antipyrine as a derivative of phenyl methyl pyrazolone must retain the pyrazole nucleus.

4. The preparation of antipyrine through the condensation of symmetrical methyl phenyl hydrazine with aceto acetic ester throws considerable light on the constitution of antipyrine in that antipyrine contains a methine group (Ann. 238, 205,206; Ber. 17, 2037)



Methyl phenyl hydrazine  Aceto acetic ester  Antipyrine

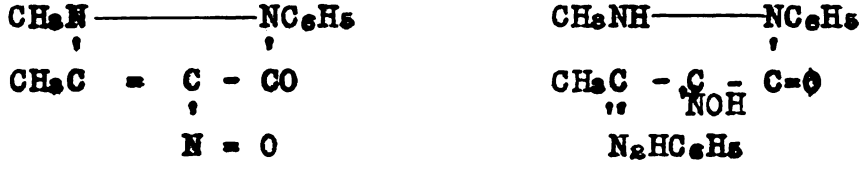
5. The action of sodium and alcohol on antipyrine ruptures the ring with the fomation of the anilide of Beta methyl crotonic acid.



Antipyrine

Anilide of Beta methyl crotonic acid

The action of heat and phenyl hydrazine on nitroso antipyrine causes the ring to be broken in the 2 and 3 position.

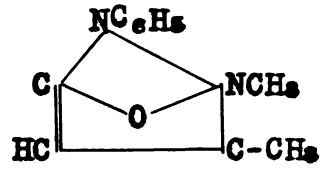


Nitroso antipyrine

Phenyl hydrazone of iso nitroso aceto acetic methyl phenyl hydrazide

The above two reactions give rise to the amide type and lend support to the above formula for antipyrine containing the group - N - CO - (Ann. 328, 78).

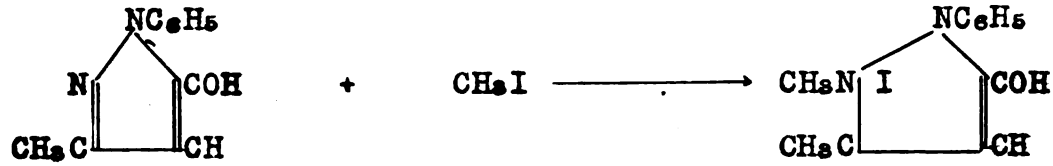
Michaelis has critized Knorr's formula and has proposed the phenol betaine formula for antipyrine (Ann. 320, 45; 331, 197)



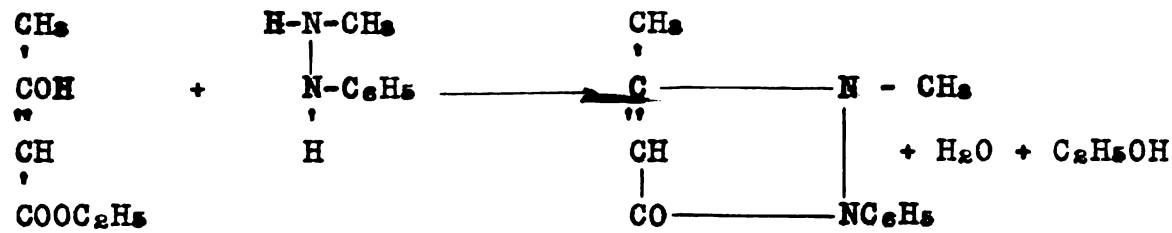
Michaelis gives the following points for the establishment of the above formula (Ann. 320, 46).

1. The formation of antipyrine through the methylation of 1-phenyl-3-methyl-5-pyrazolone is explained the simplest way by the assumption of 2 : 5 pyrazole formula, since the above

named pyrazolone reacts quite often in the hydroxyl form.

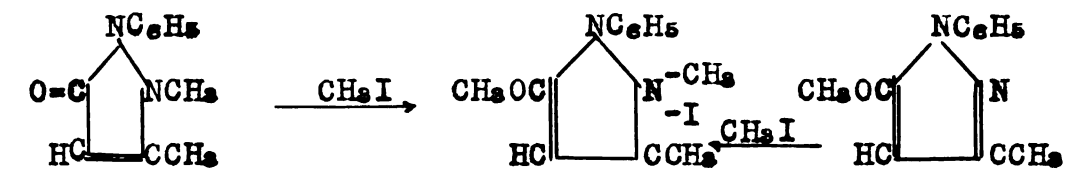


On the other hand the formation of antipyrine from symmetrical methyl phenyl hydrazine and aceto acetic ester is explained by the assumption of the isopyrazolone formula in which aceto acetic ester reacts in the enol form.



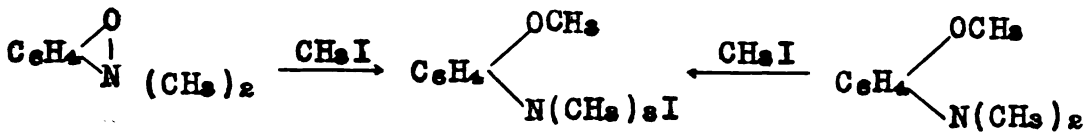
Aceto acetic ester | Phenyl hydrazine | Antipyrine

2. The behavior of antipyrine with alkyl iodides at a moderate temperature is explained on the simplest basis by the assumption of 2 : 5 pyrazole formula. The antipyrine acts in the same manner with alkyl iodides as the inner salts of phenol ammonium bases (phenol betaines) in that iodine attaches to the second nitrogen atom and the alkyl group to the carbonyl.



Antipyrine | Antipyrine pseudo methiodide | 1-phenyl-3-methyl-5-pyrazole

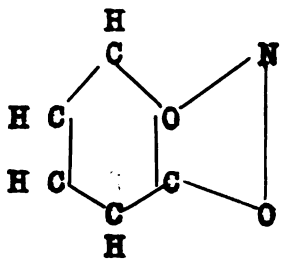
The pseudo methiodide formed is identical to the methiodide of 1-phenyl-3-methyl-5-methoxy pyrazole. Phenol betaines unite with methyl iodide in a similar manner in the presence of caustic potash. The resulting quarternary iodides are identical with those obtained from the dimethyl amino anisoles.

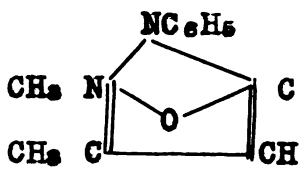



O-trimethyl ammonium phenoxide

O-dimethyl anisole

3. The proof which Knorr has advanced is that phenol betaine of Greiss reacts differently than antipyrine. This does not contradict the 2 : 5 pyrazole formula, since both compounds are constituted differently as close observations show:

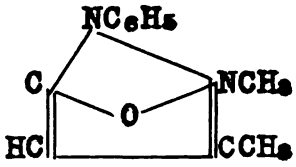


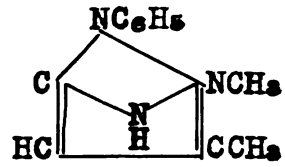

The four membered ring of the 2 : 5 pyrazole formula is only similar to phenol betaine since it contains not two carbon atoms, but only one. However, the oxygen forms a five membered ring as a result of which there must be a difference in the behavior from a single betaine ring.

4. The formation of chloro methylates from phenyl methyl pyrazolone by the interaction of phosphorous oxychloride on antipyrine gives good support for the 2 : 5 pyrazole formula. In this case,one must assume a complicated rearrangement of the isopyrazolone formula. (Ber. 32, 2400).

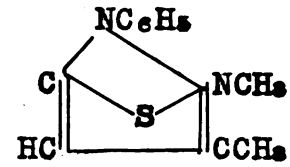
5. The 2-metho chloride of 1-phenyl-3 methyl-5-chloro pyrazole formed by the action of phosphorous oxychloride on antipyrine, yields antipyrine when treated with caustic soda. With sodium hydrosulphide, thiopyrine is formed; with ammonia and amines, imino pyrines are formed:




Antipyrine



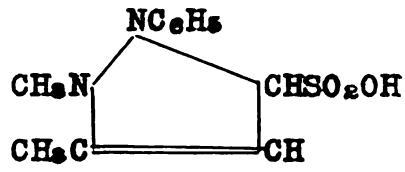

Imino pyrine




Thio pyrine

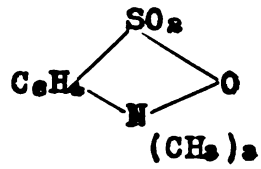
6. The constitution of thio pyrine and selanopyrin with the atomic groupings C = S and C = Se does not correpond to the properties of these compounds.

Through the oxidation of a compound with three atoms of oxygen, one can only obtain one acid of the following structure:




but the actual formula produced by experiments has the empirical

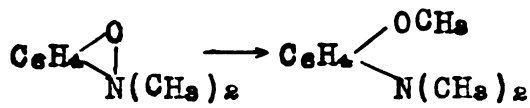
formula of $C_{11}H_{12}N_2SO_3$. Such a compound must also have acid properties since it would correspond to dimethyl sulfanilic acid which produces salts. The above oxidation is entirely different and corresponds to trimethyl sulfanilic acid.



The selenium has only a slight inclination to unite with carbon through a double bond while the selenopyrin forms quite readily and almost quantitatively. The selenium urea, $CSe(NH_2)_2$ of Verneuil, which contains a bound selenium atom, will break down through oxidation with the elimination of selenium. Seleno pyrin trioxide will change into selenopyrin dichloride quite smoothly without rupture of the molecule when treated with concentrated hydrochloric acid.

In 1896, Knorr made a detailed comparison of antipyrine with O-trimethyl ammonium phenoxide, which revealed the fact that, apart from the addition of alkyl iodide, these compounds were quite different in their behavior.

| O-Trimethyl ammonium Phenoxide | Antipyrine |
|---|---|
| O-trimethyl ammonium phenoxide rearranges through dry distillation into O-dimethyl amino anisole: | Antipyrine remains undecomposed when boiled in vacuum |



| | |
|---|---|
| O-trimethyl ammonium phenoxide is easily hydrolyzed on exposure to the air; it absorbs a molecule of water and regenerates the phenol ammonium base. | Antipyrine may not be converted into the phenol ammonium base. |
| O-trimethyl ammonium phenoxide cannot be precipitated with alkali from an aqueous solution on account of the phenolic character of the ammonium base. | Antipyrine may be precipitated with alkali in a strong aqueous solution. |

The pseudo methyl iodide of Greiss phenol betaine is stable when boiled with sodium hydroxide and when subjected to dry distillation regenerates dimethyl amino antipyrine, whereas the pseudo methyl iodide of antipyrine also regenerates antipyrine by distillation under the influence of sodium hydroxide. From the above facts Knorr rejected the phenol betaine formula for antipyrine (Ann. 328, 78).

## Properties of Antipyrine

1. Antipyrine decomposes by distillation at atmospheric pressure.

2. Antipyrine is very soluble in water, alcohol, chloroform, hot toluene and difficultly soluble in cold toluene, ether and ligroin. It crystallizes from water in large crystals

having a melting point of 113°C.

3. Antipyrine is a strong acidic base, precipitated by alkali and forms salts with acids.

Knorr also prepared antipyrine by the methylation of 1-phenyl-3-methyl-5-ethoxy pyrazolone. The methylated product was treated with sulphurous acid and supersaturated with sodium hydroxide. The antipyrine was extracted with ether and recrystallized. (Ber. 28, 712).

The ortho and para 5-tolyl antipyrine were prepared by Knorr by heating the corresponding 5-pyrazolone with methyl alcohol and methyl iodide at 100°C. The ortho compound melted at 96-97°C and the para compound at 137°C (Ber.17,550).

Klauber prepared 1, 3, 4 antipyrine by the heating of a compound having the empirical formula, $C_{33}H_{34}N_4O_4$, with methyl alcohol and methyl iodide at 130°C. The product was crystallized from ligroin. The crystals came down from ligroin in needles, melting at 113oC (Monatshefte 12, 217).

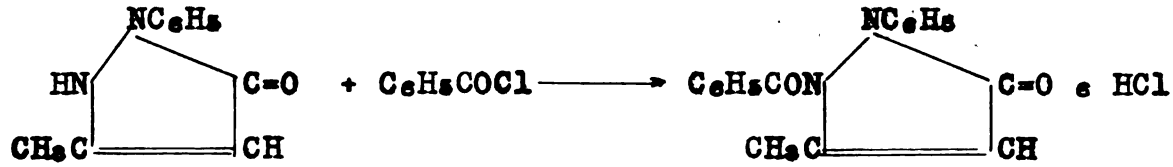
The 3 - antipyrine was prepared by Michaelis by methylation of phenyl 5-methyl-3-pyrazolone with methyl alcohol and methyl iodide. The 3-antipyrine melted at 113°C. (Ann.338,284).

The ortho and para 3-tolyl antipyrine were also prepared by Michaelis by heating the corresponding 3-pyrazolones with methyl iodide and methyl alcohol in a closed tube. The methylated product was dissolved in water and the antipyrine liberated by the treatment. with sodium hydroxide. The product was extracted with chloroform, dried with $CaCO_3$ and recry-

stallized from ligroin. The para tolyl antipyrine had a melting point of 98-100°C and the ortho tolyl antipyrine had a melting point of 97°C. (Ann. 338, 317).

VII Preparation of the Benzoyl Esters

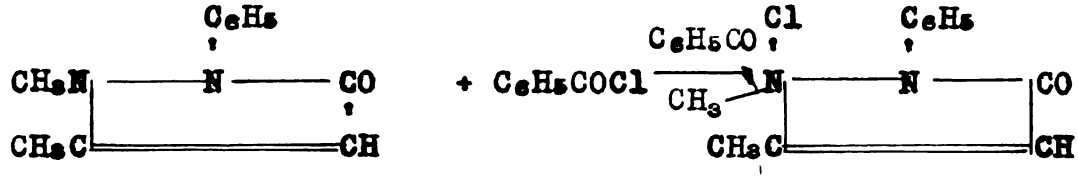
Nef prepared the benzoyl ester of phenyl methyl pyrazolone by Schotten Bauman reaction. The pyrazolone was shaken with an excess of benzoyl chloride in an alkali solution. The product was recrystallized from alcohol and melted at 75°C. (Ann. 266, 125)



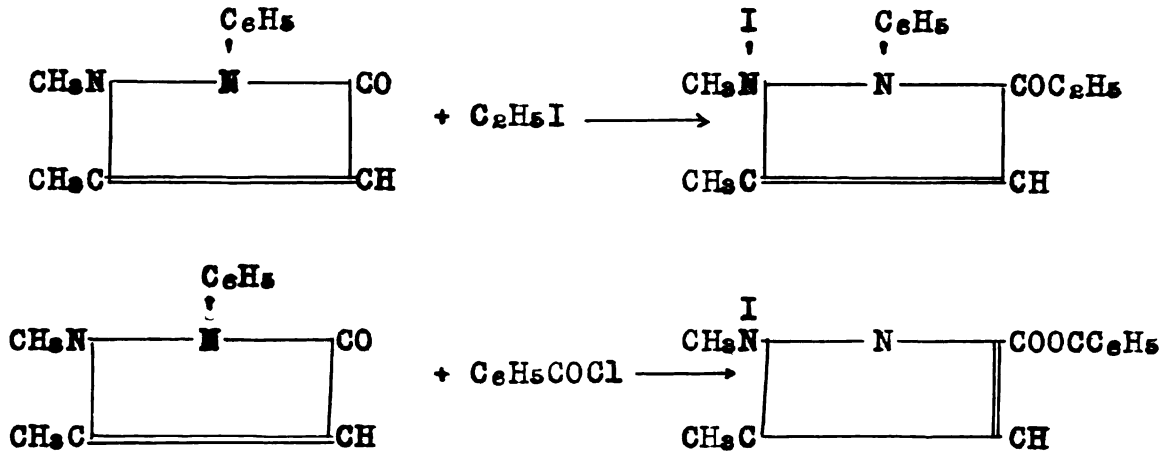
Phenyl methyl pyrazolone

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

Nef assumes that the pyrazolone reacts in the imine form and that the benzoyl residue attaches to the nitrogen atom. He assumes 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 believes that the addition of benzoyl chloride and alkyl iodides to antipyrine takes place in the same sense.




No definite decision has been made, whether the benzoyl residue is attached to the nitrogen or oxygen atom. (Ann. 293,47).

Michaelis prepared 1-phenyl-5-methyl-3-benzoyl-3-pyrazolone by shaking equal amounts of phenyl methyl 3-pyrazolone with benzoyl chloride in an alkali solution. (Schotten-Bauman reaction). (Ann. 338, 278).

The 1-phenyl-5-methyl-3-benzoyl-3-pyrazolone was recrystallized from alcohol and melted at 64-65°C.

Ortho and para tolyl 5-methyl-3-benzoyl-3-pyrazolone were prepared in the same manner. The corresponding 3-pyrazolones were shaken with benzoyl chloride in an alkaline solution and recrystallized from alcohol. The ortho compound melted at 72°C and the para compound melted at 47°C. (Ann. 338,313).

# EXPERIMENTAL PART

## I Preparation of Tolyl Hydrazine and Xylyl Hydrazine

Huston and Brigham found that the usual methods for the preparation of hydrazine could not be used with very good results in the preparation of O-tolyl and P-xylyl hydrazine, since there was much tar formed when sodium nitrite and acid were used for diazotizing.

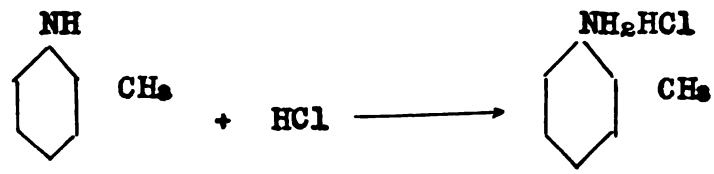
They found that by using ethyl nitrite instead as the diazotizing agent that better results could be obtained. The method was similar to that used in preparation of cyml hydrazine by Demonbreun and Kremer (Monatshefte 11, 283; 12, 211). The ethyl nitrite was prepared according to the method of Feldman (Jour. of the Am.Pharmaceutical Assn. 12, 589).

A mixture of 250 gms. of sodium nitrite and 100 gms. of alcohol were placed in a flask fitted with a dropping funnel and a condenser. The receiver was packed in ice in order to condense the ethyl nitrite which has a boiling point of 17°C. A solution of 200 gms of concentrated sulphuric acid, 1500 cc. of water and 100 gms. of ethyl alcohol was slowly dropped into the nitrite mixture. The ethyl nitrite was produced immediately and condensed in the ice cooled receiver. The yield was from 89 - 92% of the theoretical.

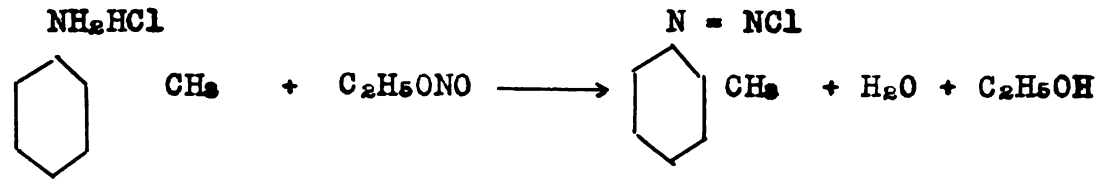
O-tolyl hydrazine was prepared by diazotizing O-toluidine with hydrochloric acid and ethyl nitrite and reduction with stannous chloride. 1228 cc. of concentrated hydrochloric acid was added to 100 gms. of O-toluidine in a large beaker in a freezing mixture. 80 gms. of ethyl nitrite in 80 cc. of alcohol were placed in a dropping funnel packed in ice.

The ethyl nitrite was added to the O-toluidine hydrochloride solution as fast as possible without the temperature of the reaction mixture rising above -10°C. The rapid addition of ethyl nitrite reduces the tendency for the formation of the amino azo compound. A mechanical stirrer was used to eliminate local over heating of the reaction mixture. A solution of 392 gms. of stannous chloride in 340 cc. of concentrated hydrochloric acid was then slowly added to the diazonium compound, keeping the reaction mixture below -5°C. The hydrazine hydrochloride was obtained as light yellow crystals, which were filtered, dried, and decomposed by caustic potash (300 gms. per 300 cc.). This liberated the free base which was extracted with ether and dried over anhydrous sodium sulfate. The ether was distilled off and hydrazine purified by fractional distillation, the greater part of the hydrazine coming over between 110-125°C at 4 mm. pressure. The yield was 64 gms. which is 56% of the theoretical. O-tolyl hydrazine has a melting point of 61-62o and a boiling point range of 95-115° under 3 mm. pressure. It is very unstable decomposing to tar on being exposed to light or air.

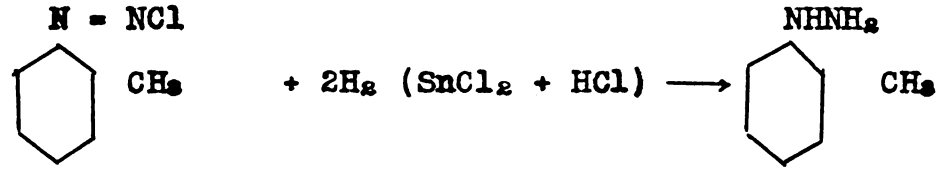
The reaction may be shown by the following equations:



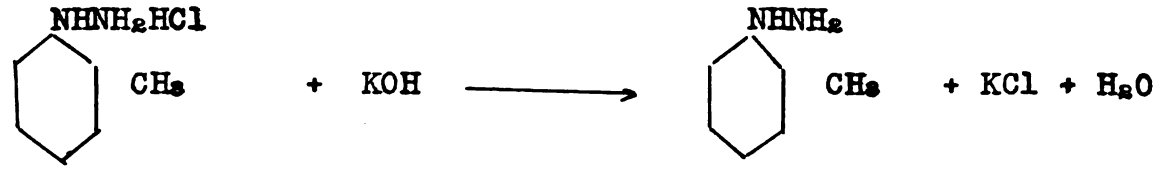

O-Toluidine O-Toluidine hydrochloride




Ethyl nitrite O-toluidine diazonium chloride



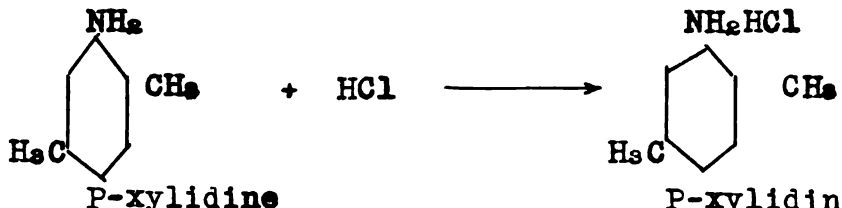

O-Tolyl hydrazine hydrochloride



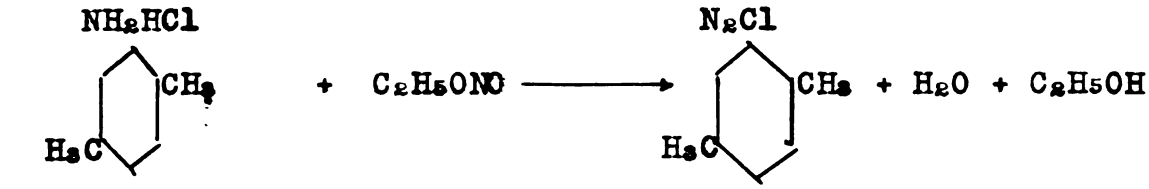

O-Tolyl hydrazine

The P-xylyl hydrazine was prepared from P-xylidine by using half quantities of the reagents in the above method. The hydrazine was purified by fractional distillation, the product coming over at 120°C at 4 mm. pressure. A yield of 38 gms. was obtained which is 68% of the theoretical. P-xylyl hydrazine has a melting point of 76-77°C and decomposes when exposed to light or air.

The reactions are shown by the following equations:

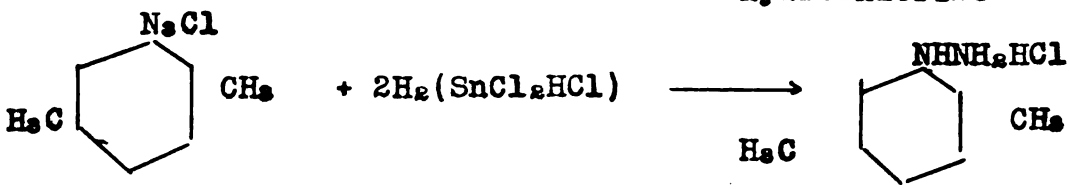



P-xylidine P-xylidine hydrochloride

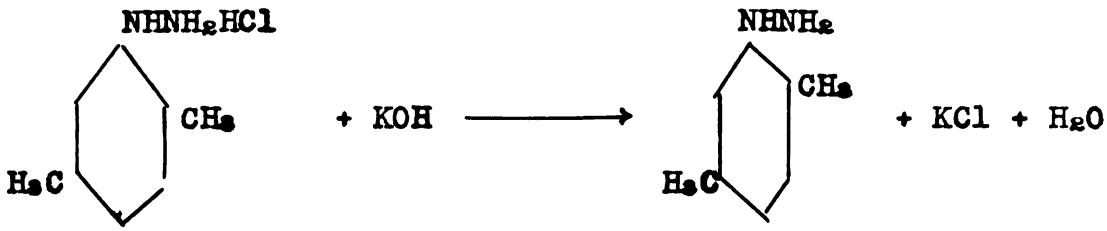



Ethyl nitrite

P-xylyl hydrazine hydrochloride




P-xylyl hydrazine hydrochloride




P-xylyl hydrazine

## II Preparation of O-Tolyl Methyl Pyrazolone

1-O-Tolyl-3-methyl-5-pyrazolone was prepared by the method used by Knorr in the preparation of 1-phenyl-3-methyl 5-pyrazolone (Ber. 16,2597; Ann. 238, 147).

To 64 gms. of O-tolyl hydrazine was added 68.6 gms. of aceto acetic ester. This was refluxed for two hours at 100°C, then for eight hours at 160-170°C. A resinous mass was obtained which solidified on cooling. This was treated with its own volume of acetone and allowed to crystallize in the ice box. A cake of yellow crystals formed which were recry-

stallized from alcohol and washed with ether. The yield was 26.5 gms. which is 30% of the theoretical based on the hydrazine used. The product melted at 183°C and was the same compound as that obtained by Knorr through the condensation of O-tolyl hydrazine with aceto acetic ester. An attempt was made to obtain the isomeric 1-O-tolyl 3-methyl-5-pyrazolone of melting point 169°C along with the 1-O-tolyl 3-methyl-5-pyrazolone of melting point 183°. The above two isomeric 5-pyrazolones were obtained by Huston and Brigham (Brigham's Thesis 1929) as a mixture through the condensation of O-tolyl hydrazine with aceto acetic ester. Nine condensations were made with the production of only one-tolyl-3-methyl-5-pyrazolone of melting point 183°C.

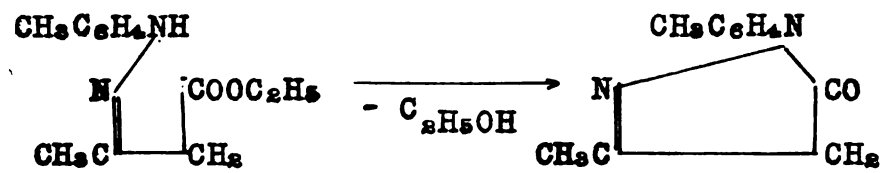
The O-tolyl methyl pyrazolone (m.p. 183°C) is soluble in hot alcohol, chloroform and benzene, slightly soluble in ether and insoluble in water and petrolic ether.

The following equations represent the reactions which take place in the preparation of the compound of melting point 183°C:

$$C_6H_4CH_3NHNH_2 + CH_3CCH_2COOC_2H_5 \xrightarrow{-(H_2O)}$$

O-tolyl hydrazine

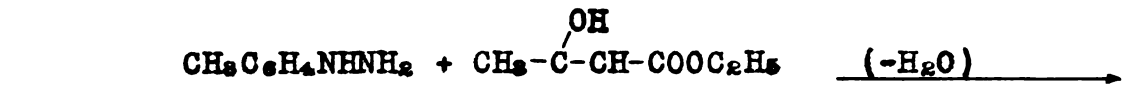
O



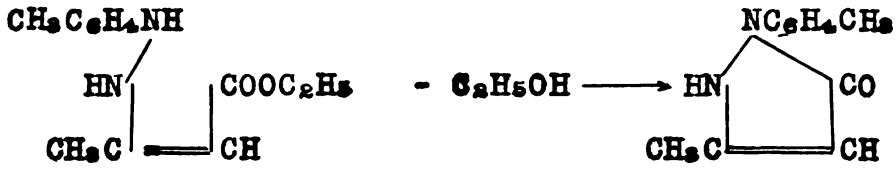

O-tolyl hydrazone of aceto acetic ester

1-O-tolyl-3-methyl-5-pyrazolone
m.p. 183
(methylene form)

The following equations represent the reactions which take place in the preparation of the compound of melting point 169°C.




O-tolyl hydrazine  aceto acetic ester




O-tolyl hydrazone of aceto acetic ester

1-O-tolyl-3-methyl-5-pyrazolone

(imine form) m.p. 169°C.

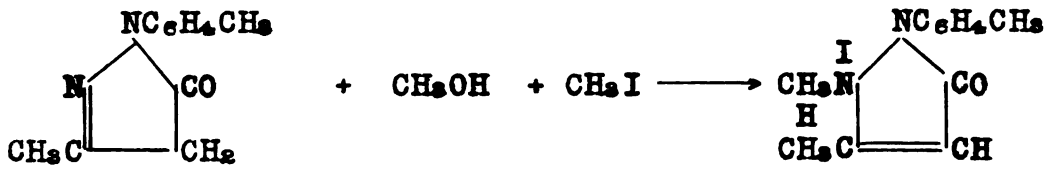
Knorr assigned the methylene form to the pyrazolones which responds to the pyrazole blue test (Ann. 238, 155; Ber. 25, 765) The 5-pyrazolone melting at 183° responded to the pyrazole blue test, while the 5-pyrazolone melting at 169°C did not respond to this test and must therefore be of the imine structure.

III Methylation of 1-O-Tolyl-3-Methyl-5-Pyrazolone

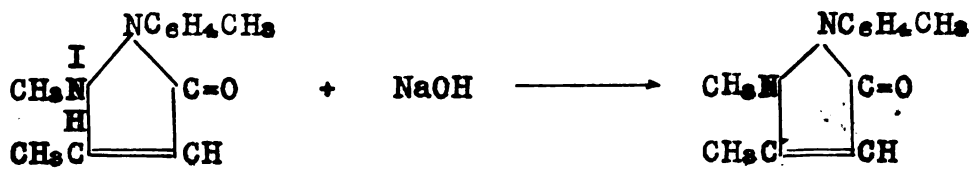
The 1-O-tolyl-3-methyl-5-pyrazolone (m.p. 183°C) was methylated by the method used by Knorr (Ber. 17, 550).

10 gms. of the pyrazolone were heated in a sealed tube (carius tube) with 10 gms. of methyl iodide and 10 gms. of methyl alcohol eight to ten hours at 120°C. The methyl alcohol was distilled off under diminished pressure. The product was dissolved in water and the tolyl antipyrine liberated by the addition of sodium hydroxide (37 gms. per 100 cc.) The crude product was crystallized from a mixture of chloroform and high test gasoline. The tolyl antipyrine was then recrystallized several times from high test gasoline. The crystals came down as long needles which melted at 90-91°C. The yield was 3.4 gms. which is 31% of the theoretical.

The reactions may be shown by the following equations:



O-tolyl-3-methyl-5-pyrazolone  Hydroiodide of 5-pyrazolone



Hydroiodide of 5-pyrazolone  Tolyl antipyrine m.p. 90-91°C

The tolyl antipyrin which was prepared by Knorr by the above method had a melting point of 96-97°C.

A nitrogen determination was run on the compound melting at 90-91°C.

The data of the determination is given below:

.1812 gms. of sample gave .0255 gms. of N

| | Calculated for $C_{12}H_{14}N_2O$ | Found |
|---|---|---|
| N | 13.86% | 14.07% |

The 1-o-tolyl-3-methyl-5-pyrazolone (m.p. 169°C) was methylated as in the above method. The tolyl antipyrine was recrystallized several times from high test gasoline. The crystals came down in long needles melting at 90-91°C.

The methylation products of the two isomeric 1-o-tolyl-3-methyl-5-pyrazolones have the same melting points (90-91°C) which indicates that 1-o-tolyl-3-methyl-5-pyrazolone (m.p. 183°C) and 1-o-tolyl-3-methyl-5-pyrazolone (m.p. 169°C) are isomers.

IV Preparation of p-xylyl-3-methyl-5-pyrazolone

1-p-xylyl-3-methyl-5-pyrazolone was prepared by the method used by Knorr in the preparation of 1-phenyl-3-methyl-5-pyrazolone (Ber. 16, 2597; Ann. 238, 147).

27 grams (1 mol.) of p-xylyl hydrazine were added to 26 gms. (1 mol.) of aceto acetic ester in a flask connected to a reflux condenser. The reaction mixture was heated on an oil bath for eight hours at 150-160oC. When the contents of the flask cooled it solidified to a dark brown resinous mass.

The resinous mass was treated with its own volume of acetone and allowed to crystallize. The crude product was crystallized from a mixture of alcohol and high test gasoline. (The product was first dissolved in the least amount of alcohol and then gasoline was added. The mixture was boiled until a homogenous solution was obtained. It was set aside and allowed to crystallize).

The xylyl methyl pyrazolone was recrystallized several times from gasoline and separated as very fine needles which melted at 164°C. The yield was 9 gms. which is 22% of the theoretical.

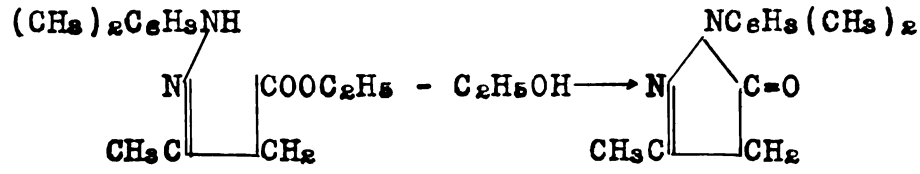
Huston and Brigham obtained a xylyl methyl pyrazolone melting at 150-151°C by the above method (Brigham's Thesis 1929).

The pyrazole blue test was applied to the xylyl methyl pyrazolone (m.p. 164°C) a positive test was obtained which indicated that the pyrazolone had a methylene structure. The test was also applied to the xylyl methyl pyrazolone (m.p. 150-151°C) and a negative test was obtained which indicated that the pyrazolone had the imine structure.

The following equations represent the reactions which take place in the preparation of the compound melting at 164°C:

$(CH_3)_2C_6H_3NHNH_2 + CH_3C^{=O}CH_2COOC_2H_5 \xrightarrow{-H_2O}$

p-xylyl hydrazine  aceto acetic ester



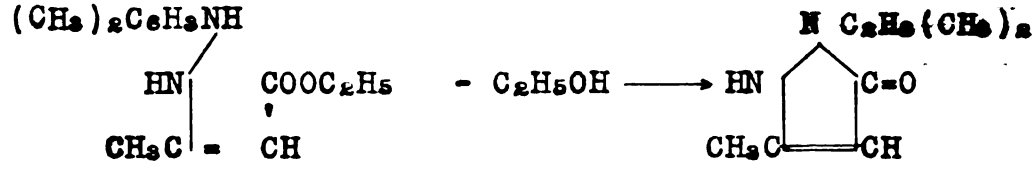
p-xylyl hydrazone of aceto acetic ester

p-xylyl-3-methyl-5-pyrazolone (methylene form) m.p. 164°C

The following equations represent the reactions which take place in the preparation of the compound melting at 150-151°C.

$(CH_3)_2C_6H_3NHNH_2$ + $CH_3C(OH)CHCOOC_2H_5$ $\xrightarrow{-H_2O}$

p-xylyl hydrazine  aceto acetic ester



p-xylyl hydrozone of aceto acetic ester

p-xylyl methyl pyrazolone (imine form) m.p. 150-151oC

A nitrogen determination was run on the compound melting at 164°C.

The data of the determination is given below:

(a) .1540 gms. of sample gave .02164 gms. of N

(b) .1398 " " " " .01947 " " "

| | Calculated for $C_{12}H_{14}N_2O$ | Found |
|---|---|---|
| (a) | | 14.05% |
| (b) | 15.86% | 13.92% |

The p-xylyl methyl pyrazolone (m.p. 164°C) is soluble in alcohol, chloroform and hot gasoline.

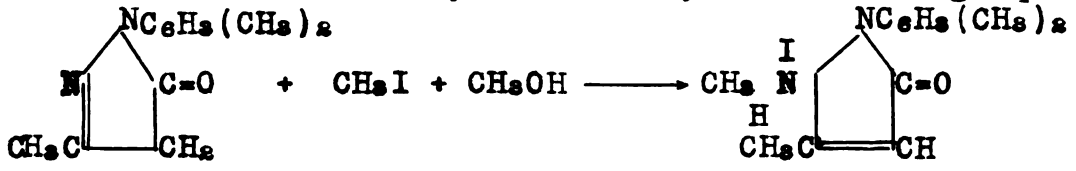
V Methylation of p-Xylyl Methyl Pyrazolone

The 1-p-xylyl-3-methyl-5-pyrazolone was methylated by the method used by Knorr in the preparation of tolyl antipyrine (Ber. 17, 550)

Seven grams of 1-p-xylyl-3-methyl-5-pyrazolone (m.p. 164°C) were heated in a sealed tube with seven grams of methyl iodide and seven grams of methyl alcohol eight hours at 130°C. The methyl alcohol was distilled off from the methylated product under diminished pressure. The product was dissolved in water and the xylyl antipyrine liberated by the addition of sodium hydroxide (37 gms. per 100 cc.). The crude product was crystallized from a mixture of alcohol and high test gasoline. The xylyl antipyrine was then recrystallized several times from high test gasoline. The crystals came down as small plates with a silver luster which melted at 97.5°C. The yield was two grams which is 27% of the theoretical.

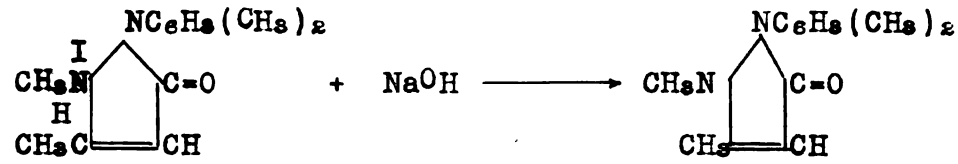
The p-xylyl antipyrine is soluble in alcohol, chloroform and soluble in hot gasoline.

The reactions may be shown by the following equations:




Xylyl methyl pyrazolone
m.p. 164°C

Hydroiodide of 5-pyrazolone




Hydroiodide of 5-pyrazolone

p-xylyl antipyrine m.p. 97.5°C

A nitrogem determination was run on this compound.

The data of the determination is given below:

(a) .1705 grams of the sample gave .02221 grams of N

(b) .1888 " " " " " .02496 " " "

| | Calculated for $C_{13}H_{16}N_2O$ | Found |
|---|---|---|
| (a) | | 13.02% |
| (b) | 12.96% | 13.22% |

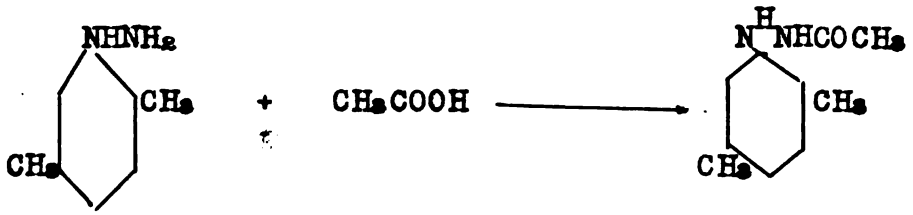
VI Preparation of 1-p-Xylyl-5-Methyl-3-Pyrazolone

The 1-p-xylyl-5-methyl-3-pyrazolone was prepared according to the method given by Michaelis (Ann. 238,310).

The acetyl xylyl hydrazide was prepared in the following way: To 35.3 grams (1 mol.) of p-xylyl hydrazine was added 17.6 grams (1 mol.) of glacial acetic acid and refluxed for six hours. The contents of the flask were then poured into water and the entire mass evaporated to dryness on a steam bath. The brown crystalline residue was dried on a porous plate, washed with a small amount of ether, and again dried on a porous plate. This was pure enough to be used in the preparation of the 3-pyrazolone. The yield was fourteen

grams which is 30% of the theoretical. Better results were obtained when the residue was recrystallized from water.

The reactions may be shown by the following equations:



p-xylyl hydrazine p-acetyl xylyl hydrazide

The 1-p-xylyl-5-methyl-3-pyrazolone was prepared by placing fourteen grams (1 mol.) of acetyl xylyl hydrazide and ten grams (1 mol.) of aceto acetic ester in a flask fitted with a reflux condenser with a delivery tube immersed in water to collect the liberated hydrogen chloride gas. To this mixture twenty-seven grams (2 1/2 mol.) phosphorous trichloride was gradually added through a reflux condenser. Then the flask was heated, gradually at first and then to a temperature which would cause the reaction mixture to reflux, until no more hydrogen chloride was evolved. The prepared pyrazolone was dissolved in a 10% solution of hydrochloric acid. The solution was cooled, filtered, and neutralized with ammonium hydroxide, which caused the pyrazolone to be precipitated.

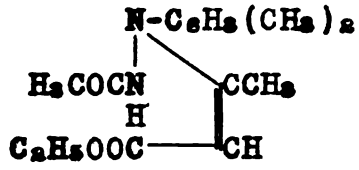
The pyrazolone was filtered off and crystallized from a mixture of alcohol and high test gasoline. The crystals came down as small cream colored crystals melting at 178-179oC. The yield was five grams which is 9.3% of the theoretical.

The 1-p-xylyl-5-methyl-3-pyrazolone is soluble in hot alcohol and chloroform, slightly soluble in cold alcohol and nearly insoluble in water and petroleum ether.

The following equations represent the reactions:

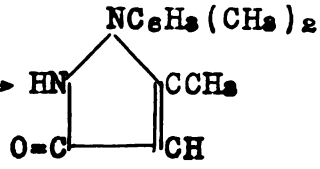
$$(CH_3)_2C_6H_3NHN{-}\overset{H}{\underset{\bullet}{C}}OCH_3 + CH_3C^{-OH}_{CHCOOC_2H_5} \quad (-H_2O) \longrightarrow$$

Acetyl p-xylyl hydrazide  Aceto acetic ester



Acetyl xylyl hydrazone of aceto acetic ester

$(-CH_3COOC_2H_5) \longrightarrow$



1-p-xylyl-5-methyl-3 pyrazolone
m.p. 178-179°C

The above 3-pyrazolone was prepared by Huston and Brigham (Brigham's Thesis 1929).

VII Benzoyl Esters of 3 and 5 Pyrazolones

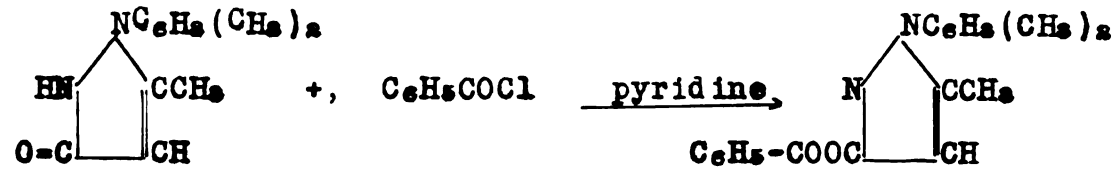
The 1-p-xylyl3-benzoyl-5-methyl-3-pyrazolone was prepared by a method similar to that used by Michaelis (Ann. 338,313).

A mixture of 4 grams 1-p-xylyl-5-methyl-3-pyrazolone, 10 grams of pyridine and 4 grams of benzoyl chloride was shaken in a stoppered 50 cc. Erlenmeyer flask and was allowed to set over night.

The contents were poured into water and washed, first with a dilute solution of sulphuric acid and then with a dilute solution of sodium carbonate. The product was crystallized several times from ligroin in an ice chest. The cry-

stals came down as small cream colored rhomboids melting at 74°C. The yield was 2.5 grams which is 41% of the theoretical.

The equation for the reaction is shown as follows:




p-xylyl-5-methyl-3 pyrazolone | benzoyl chloride | 1-p-xylyl-3-benzoyl-5-methyl-3-pyrazolone m.p. 74°C

The 1-p-xylyl-3-benzoyl-5-methyl-3-pyrazolone is soluble in alcohol, chloroform, hot ligroin and hot gasoline.

The above formula for 1-p-xylyl-3-benzoyl-5-methyl-3-pyrazolone is the one assumed by Knorr in which the benzoyl radical is attached to carbonyl group.

A nitrogen determination was run on this compound.

The data of the determination is given below:

(a) .2065 grams of the sample gave .01893 grams of N

(b) .2219 " " " " " .02068 " " "

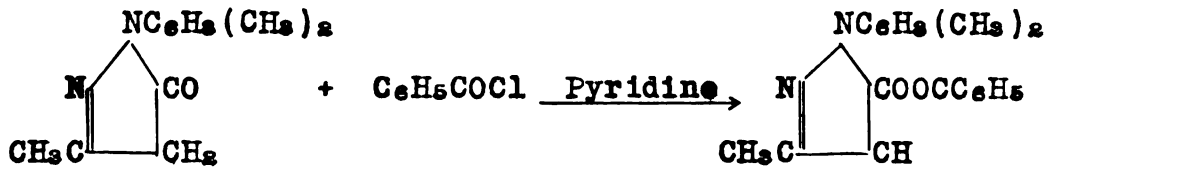
| | Calculated for $C_{19}H_{18}N_2O_2$ | Found |
|---|---|---|
| (a) | | 9.17% |
| (b) | 9.15% | 9.32% |

The p-1-xylyl-5-benzoyl-3-methyl-5-pyrazolone was prep-

ared to the method given above. A mixture of 4 grams of 1-p-xylyl-3-methyl-5-pyrazolone, 10 grams of pyridine and 4 grams of benzoyl chloride was shakened in stoppered 50 cc. Erlenmeyer flask and allowed to set over night. The contents were poured into water and washed first with a dilute solution of sulphuric acid and then with a dilute solution of sodium carbonate. The product was crystallized from high test gasoline.

The crystals came down as small white needles melting at 119°C. The yield is 4 grams which is 66% of the theoretical.

The equation for the reaction is shown as follows:




1-p-xylyl-3-methyl-5-pyrazolone

1-p-xylyl-5-benzoyl-3-methyl-5-pyrazolone
m.p. 119°

A nitrogen determination was run on this compound.

The data of the determination is given below:

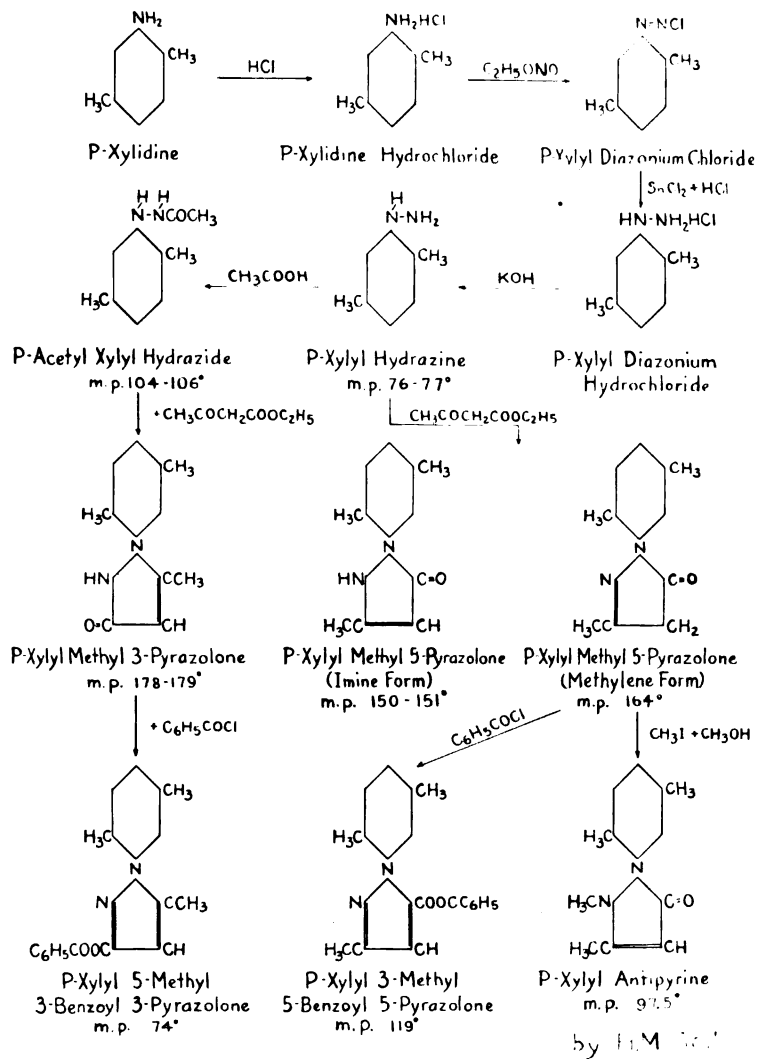
(a) .1509 grams of the sample gave .01395 grams of N

(b) .2448 " " " " " .0226 " " "

| | Calculated for $C_{19}H_{18}N_2O_2$ | Found |
|---|---|---|
| (a) | 9.15% | 9.25% |
| (b) | | 9.23% |

The 1-p-xylyl-5-benzoyl-3-methyl-5-pyrazolone is soluble in alcohol, chloroform and hot gasoline.

# P-Xylyl Methyl Pyrazolones and Some Derivatives




by H.M.