2. It has been found that for the family *Rhamnaceae* the manganese is extracted in water proportionally to its total amount in the bark.

3. A practical use of this determination is suggested leading to the establishment of a "Manganese Number" for extracts of these drugs.

OTTAWA, CANADA.

ON THE REACTIONS OF THE FORMAMIDINES. VII. THE CONSTITUTION OF SOME PYRAZOLE DERIVATIVES.

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In some previous papers it has been shown that the substituted formamidines react with compounds containing methylene hydrogen, giving rise to complexes in which the hydrogen of the methylene group has been replaced with the grouping $=\text{CHNHR}$.¹ In the case of ethyl-acetoacetate, there are formed derivatives of the two types

the latter resulting from the action of the amine set free in the first reaction with the carbethoxy group.

In a dissertation published in Freiburg in 1903, Ruggeburg investigated the action of phenylhydrazine on the anilide of anilino-methylene-benzoyl-acetic ester and obtained a pyrazole derivative to which he ascribed the formula

1,3-diphenyl-5-keto-4-anilino-methylene pyrazole. Later work² proved that phenylhydrazine reacted with the anilino-methylene derivatives of acetoacetic ester or of benzoyl-acetic ester yielding the anilide of 1-phenyl-5-methyl or phenyl-4-pyrazole carboxylic acid, a pyrazole rather than a pyrazolone ring being formed,

In the following year, a second dissertation by Jacob Gattermann formulated the reaction between hydrazine and the *p*-toluide of *p*-toluidomethylene-acetoacetic ester in the same fashion as did Ruggeburg, assuming that the product was 3-methyl-4-*p*-toluidomethylene-5-pyrazolone,

¹ *Ber.*, 35, 2497 (1902); *THIS JOURNAL*, 31, 1148 (1909); 35, 959, 970 (1913); 38, 1510 (1916).

² *Ibid.*, 31, 1156 (1909).

The following experimental work will show, however, that these derivatives should be regarded as pyrazole and not as pyrazolone compounds. It is evident that any proof of this constitution must show that the hydrazine reacts with the anilino-methylene grouping, $= \text{CHNHR}$, and not with the $-\text{COOR}$ or $-\text{CONHR}$ group.

—Molar quantities of *m*-dibromodiphenyl-formamidine and acetoacetanilide were heated in an oil bath for two hours at 140° , using a little kerosene as a solvent. From the reaction mixture was isolated *m*-bromoaniline (its benzoyl derivative melts at $135-6^\circ$ and not at 120° ,¹ and the above anilide, which crystallizes from alcohol in yellowish white needles, melting at 113° .

Calc. for $\text{C}_{17}\text{H}_{16}\text{O}_2\text{N}_2\text{Br}$: N, 7.81%; Br, 22.27%. Found: N, 7.90%; Br, 22.16%.

Synthesis of the Pyrazole Derivative.—The *m*-bromo-anilino-methylene-acetoacetanilide (4 g.) was dissolved in 100 cc. of alcohol. To this was added a concentrated solution of hydrazine sulfate together with the calculated quantity of sodium carbonate. The mixture was heated on a water bath for three hours, evaporated to dryness and extracted with methyl alcohol. The product dissolved by the methyl alcohol was purified by recrystallization from hot water, from which it separated in white rosetts of needles, melting at 179° . It contained no bromine and gave figures on analysis corresponding to the anilide of (3)5-methyl-4-pyrazole-carboxylic acid,

It is soluble in hot ethyl alcohol and in hot water, slightly soluble in benzene and readily soluble in acetone and methyl alcohol.

Calc. for $\text{C}_{11}\text{H}_{11}\text{ON}_3$: N, 20.91%. Found: 20.86%.

Had the reaction proceeded according to the Gattermann theory, there should have been obtained 4-*m*-bromo-anilino-methylene-5-pyrazolone, with only 14.3% nitrogen, which was not the case.

Acetoacet-*p*-toluide can be readily made by heating 30 g. of acetoacetic ester and 26 g. of *p*-toluidine for 3 hours at 130° . The product crystallizes from hot water in white, flat plates with a melting point of 89° .

Calc. for $\text{C}_{11}\text{H}_{13}\text{ON}$: N, 7.34%. Found: 7.53%, 7.60%.

When a mixture of 11 g. of the acetoacet-*p*-toluide, 21 g. of di-*p*-bromodiphenyl-formamidine and 10 cc. kerosene is heated for 2.5 hours at 120° , there are obtained *p*-bromoaniline and the *p*-toluide of *p*-bromoanilinomethylene-acetoacetic acid,

¹ *Ann.*, 264, 179 (1891).

which separates from hot alcohol or glacial acetic acid in white crystals with a melting point of 162° .

Calc. for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{N}_2\text{Br}$: N, 7.51%; Br, 21.43%. Found: N, 7.65%, 7.48%; Br, 21.42%, 21.57%.

The above product reacts readily with hydrazine in boiling alcohol solution, yielding a compound, which contains no bromine, crystallizes from hot water in white needles melting at 179° , and which proved to be the *p*-toluide of (3)5-methyl-4-pyrazole carboxylic acid.

Calc. for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{N}_2$: N, 19.65%. Found: 19.68%.

As a further confirmation the same pyrazole was obtained in another way. Acetoacet-*p*-toluide and diphenyl-formamidine, when heated, gave the anilino-methylene-acetoaceto-*p*-toluide,

The white crystals from alcohol melt at 162° .

Calc. for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_2$: N, 9.54%. Found: 9.50%, 9.60%.

This, treated in the usual manner with hydrazine, gave the same *p*-toluide of (3)5-methyl-4-pyrazole carboxylic acid (m. p. 179°), thus proving again that it is the $-\text{RNH}$ of the $=\text{CHNHR}$ and not of the $-\text{CONHR}$, that is removed.

***o*-Ethoxyanilide of Acetoacetic Acid**, $\text{CH}_3\text{COCH}_2\text{CONHC}_6\text{H}_4\text{OC}_2\text{H}_5$.—Molar quantities of acetoacetic ester and *o*-phenetidine were heated at 120 – 130° for 2.5 hours. The product was distilled with steam and the residue in the flask, when crystallized from gasoline, gave the above anilide, white needles which melt at 92° .

Calc. for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{N}$: N, 6.49%. Found: 6.42%.

Diphenyl-formamidine condenses readily on heating with the ethoxyanilide forming the *o*-ethoxy-anilide of anilino-methylene-acetoacetic acid,

It crystallizes from alcohol in white needles with a melting point of 135° .

Calc. for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{N}_2$: N, 8.65%. Found: 8.78%.

When this methylene derivative is treated with hydrazine sulfate and sodium carbonate or with hydrazine hydrate, pyrazole synthesis again occurs through loss of the anilino and not the ethoxyanilino group, and in better yield than in the previous cases. The *o*-ethoxy-anilide of (3)5-methyl-4-pyrazole carboxylic acid,

crystallizes from hot water in white needles and melts at 163° .

Calc. for $\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}_3$: N, 17.15%. Found: 17.03%.

That this compound still possesses basic properties is shown by the fact that it forms a hydrochloride. This was precipitated when dry hydrogen chloride was passed into a hot benzene solution of the pyrazole. It melts with decomposition at 200° .

Calc. for $\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}_3\cdot\text{HCl}$: HCl, 12.64%. Found: 12.77%.

Di-*o*-phenetidyl-formamidine and acetoacetic ester react at water bath temperature, giving the ethyl ester of *o*-ethoxy-anilino-methylene aceto acetic acid, white crystals with a melting point of 111° .

Calc. for $\text{C}_{15}\text{H}_{19}\text{O}_4\text{N}$: N, 5.06%. Found: 4.84%.

This ester on boiling in alcohol solution with hydrazine hydrate yields a low melting solid, which could be recrystallized from hot water. The colorless needles melt at 46° and on analysis give figures which correspond to the hydrate of the expected pyrazole,

Calc. for $\text{C}_7\text{H}_{10}\text{O}_2\text{N}_2\cdot\text{H}_2\text{O}$: N, 16.29%. Found: 16.50%.

The transparent crystals on standing in a desiccator over calcium chloride for several weeks changed to a white powder, due to the loss of water, and then melted at 54° .

Calc. for $\text{C}_7\text{H}_{10}\text{O}_2\text{N}_2$: N, 18.20%. Found: 18.27%.

That this is the ester of (3)5-methyl-4-pyrazol, carboxylic acid is also shown by the fact that when hydrolyzed it yields an acid melting at 228° . This acid had been previously obtained by Pechmann and Burkhard¹ from the action of diazo-methane upon citraconic acid, subsequent treatment with bromine and hydrolysis with concentrated hydrochloric acid.

This same pyrazole ester was also formed² by the action of hydrazine on 2-methyl-4-iodo-anilino-methylene-acetoacetic ester.

The 5-methyl-4-pyrazole carboxylic acid and its ester are remarkably stable towards amines, as are also its substituted amide derivatives toward hydrolysis. Thus no anilide formation was observed when the carboxylic acid or its ester was heated with aniline or *p*-toluidine at temperatures from 160 – 210° .

All efforts to hydrolyze the $\text{C}_4\text{H}_5\text{N}_2\text{-CONHR}$ derivatives in acid or alkaline solution have thus far proved fruitless.

¹ *Ber.*, 33, 3598 (1901); *THIS JOURNAL*, 38, 1516 (1916).

² *Ibid.*, 35, 975 (1913).

In the course of the experiments the two following compounds were prepared:

Acetoacet-*m*-bromo-anilide, $\text{CH}_3\text{COCH}_2\text{CONHC}_6\text{H}_4\text{Br}$, from acetoacetic ester and *m*-bromaniline, white plates from alcohol or hot gasoline, melting at 83° .

Calc. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{NBr}$: Br, 31.22%. Found: 31.16%, 31.17%.

The *m*-bromo-anilide of *m*-bromo-anilino-methylene-acetoacetic ester
 $\text{CH}_3\text{COC} = \text{CHNHC}_6\text{H}_4\text{Br}$

is the main product formed on heating a mixture of
 $\text{CONHC}_6\text{H}_4\text{Br}$
 acetoacetic ester and di-*m*-bromo-diphenyl-formamidine. It crystallized from alcohol in light yellow needles melting at 154° .

Calc. for $\text{C}_{17}\text{H}_{14}\text{O}_2\text{N}_2\text{Br}_2$: Br, 36.51%. Found: 36.50%.

Pyrazoles Obtained by the Action of Phenyl Hydrazine on Anilino-methylene-acetylacetone Derivatives and Their Constitution.—The substituted formamidines react with acetylacetone yielding methylene derivatives of the type $(\text{CH}_3\text{CO})_2\text{C} = \text{CHNHR}$,¹ which condense with phenylhydrazine forming 1-phenyl-5-methyl-4-acetylpyrazole, melting at $(104^\circ) 107-8^\circ$.²

The pyrazole had been previously synthesized by Claison³ from phenylhydrazine and ethoxy-methylene-acetylacetone.

Experiments with phenylhydrazine and anilino-methylene-acetylacetone confirmed the observations of Gattermann and Claison. When, however, pseudo-cumido-methyleneacetylacetone was used, not only was the above acetylpyrazole obtained, but it was accompanied by a compound melting at 175° , while *p*-toluido-methylene-acetylacetone under like conditions gave only the product melting at 175° , which proved to be the phenylhydrazone of the acetylpyrazole. The hydrazone can best be prepared as follows: A mixture of phenylhydrazine (an excess over two moles) and *o*-ethoxy-anilino-methylene-acetylacetone was warmed on the water bath for one-half hour. The contents of the flask became solid on cooling and when crystallized from alcohol gave a mass of golden yellow needles melting at 175° . The compound is difficultly soluble in cold gasoline, acetone, benzene and alcohol, very soluble in chloroform:

Calc. for $\text{C}_{18}\text{H}_{18}\text{N}_4$: N, 19.30%. Found: 19.25%.

The analysis and the following experiments indicate that the reaction has proceeded as follows: the formation of 1-phenyl-5-methyl-4-acetylpyrazole, which then reacts with a second mole of phenylhydrazine, yielding the corresponding phenylhydrazone,

¹ Ber., 35, 2505 (1902).

² Gaugler and Gattermann, Dissertations, Freiburg, 1903-4.

³ Ann., 295, 320 (1897).

When this hydrazone is boiled with hydrochloric acid and the acid solution diluted with water, a quantitative yield of the acetylpyrazole (104°) is obtained. In fact it is the most convenient method of preparing this compound. Conversely the acetylpyrazole warmed with phenylhydrazine gives the hydrazone (175°).

Hydrazine Derivative.—Five grams of the phenyl-methyl-acetylpyrazole were dissolved in 50 cc. of absolute alcohol, together with five cc. of a hydrazine hydrate solution. The mixture was warmed for one-half hour on the water bath and then evaporated to a small bulk (6 cc.). On standing, long, four-sided prisms separated which melted at 94.5°. The new compound is very soluble in cold alcohol and in ethyl acetate, slightly soluble in benzene and readily soluble in hot gasoline. Its analysis and reactions show it to be the hydrazine derivative of 1-phenyl-5-methyl-4-acetylpyrazole,

Calc. for $\text{C}_{12}\text{H}_{14}\text{N}_4$: N, 26.19%. Found: 25.94%, 25.94%.

Dry hydrogen chloride precipitates from a solution of the hydrazine in benzene, a hydrochloride melting at 218°. When boiled with dilute hydrochloric acid, however, it is hydrolyzed into the original pyrazole (104°) and hydrazine. The presence of a free- NH_2 grouping is shown by the fact that it reacts readily with benzaldehyde in absolute alcohol solution giving a benzal-pyrazole azine,

This forms yellow crystals from alcohol or ethyl acetate, which melt at 127°.

Calc. for $\text{C}_{19}\text{H}_{18}\text{N}_4$: N, 18.55%. Found: 18.04%.

The Azine Derivative of 1-Phenyl-5-methyl-4-Acetylpyrazole, $(\text{C}_{11}\text{H}_{12}\text{N}_2)\text{C} = \text{NN} = (\text{C}_{11}\text{H}_{12}\text{N}_2)$. — The simple pyrazole hydrazine (94.5°) can be boiled with pure ethyl acetate without change, but if a little formic or acetic acid be added and then warmed, there separates from the solvent yellow crystals melting at 174°. The same substance is slowly formed when the solution of the hydrazine in 95% alcohol is allowed to stand in the air. The acid evidently brings about a condensation of two moles of the pyrazole-hydrazine with the loss of one mole of hydrazine.

Calc. for $\text{C}_{24}\text{H}_{24}\text{N}_6$: N, 21.22%. Found: 21.41%, 21.14%.

The simple formula would be $\text{C}_{12}\text{H}_{12}\text{N}_3$, but a molar-weight determination in boiling chloroform gave 388 instead of 408, the number calculated for the formula $(\text{C}_{12}\text{H}_{12}\text{N}_3)_2$.

The azine compound (174°) on boiling with strong hydrochloric acid

yields the original pyrazole (104°), while the solution reduces Fehling's solution, which indicate the presence of free hydrazine, since neither the original azine or the pyrazole give any reduction with that reagent.

Action of Hydrazine on the Anilino-methylene-acetylacetone.—When *o*-ethoxy-anilino-methylene-acetylacetone and hydrazine hydrate are warmed in alcohol solution, there is obtained a yellow compound melting at 320°, which is soluble in hydrochloric acid, in acetic acid and in strong sodium hydroxide, slightly soluble in aniline and nitrobenzene, but insoluble in the usual organic solvents.

The same product has been isolated by Gaugler and by Gattermann,¹ who showed in addition that it formed an ethyl and an acetyl derivative indicating the presence of an =NH group. They assigned to it the formula $C_6H_7N_3$ on the basis of the analysis and a molar-weight determination of the acetyl derivative. The provisional constitution suggested was that of a triazine,

which formulation involves the loss both of ammonia and the amine.

A more probable theory would assume that it is the azine derivative of 5-methyl-4-acetylpyrazole,

In favor of this hypothesis involving the double formula are the following observations: (1) It agrees equally well with the analytical data of Gaugler and Gattermann. (2) The triazine formula is an extremely improbable one. (3) Following the analogy of the phenyl-methyl-acetylpyrazole, such as azine, would be expected. (4) The azine is also capable of yielding acetyl and ethyl derivatives.

Against the azine theory is the molar-weight determination of Gaugler, indicating the single rather than the double formula, and the stability of the compound, which was boiled for six hours with strong hydrochloric acid without any evidence of hydrolysis into the hydrazine and the methyl-acetylpyrazole.

The weight of evidence, however, is in favor of the azine formula, and it is hoped that further experimental data confirming or disproving this point can be obtained later.

Summary.

1. Derivatives of 3,5-methyl-4-pyrazole carboxylic acid can be synthesized by the action of hydrazine on the amino-methylene derivatives of acetoacetic ester.

2. Phenylhydrazine yields with the anilino-methylene-acetylacetone

¹ Dissertation, Freiburg, 1903-4.

1-phenyl-5-methyl-4-acetylpyrazole, which is capable of forming a hydrazone and azine derivatives.

3. Hydrazine and anilino-methylene-acetylacetone give an unreactive high-melting product, probably an azine.

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[CONTRIBUTION FROM CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY.]

STUDIES IN ESTERIFICATION. X. THE ESTERIFICATION OF BENZOIC AND THE TOLUIC ACIDS BY METHYL, ETHYL AND PROPYL ALCOHOLS.

BY RAYMOND FREAS¹ AND E. EMMET REID.

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Historical.

Since the work of Berthelot and Pean de St. Gilles,² in 1862, esterification has been one of the most frequently studied reactions. It has been regarded as one of the best examples of a reversible reaction and has been commonly used to illustrate the mass law. However, calculation of the results obtained by these workers shows that they do not agree closely with the mass law. Their work was done almost exclusively with the acids of the aliphatic series. They obtained 64.8 and 66.5% as the limits when methyl and ethyl alcohols were heated with benzoic acid in equivalent quantities, while with acetic acid the corresponding limits were 67.5 and 66.5%. Since ethyl alcohol gives sensibly the same limits with the two acids, their low result with methyl alcohol and benzoic acid seems doubtful. In fact, in a study of the interdependence of limits by Reid³ it was assumed that methyl and ethyl alcohols give the same limits with both acids. The first object of the present investigation was to obtain accurate values for the limits of benzoic and toluic acids with methyl, ethyl and propyl alcohols. The second object was to ascertain how closely the esterification of benzoic acid by these alcohols obeys the mass law then the proportions of acid and alcohol are varied, and the third object was to study the effect of isomerism as illustrated by the three toluic acids.

Materials.

Acids.—The benzoic, *o*- and *m*-toluic acids were the commercial C. P. products; the *p*-toluic acid was made by the Sandmeyer reaction. All were purified by boiling with animal charcoal, recrystallizing several times from boiling water (diluted alcohol for the toluic acids). They were then dried for one week in a vacuum desiccator.

Alcohols.—The alcohols used were the C. P. commercial products.

¹ From dissertation of Raymond Freas.

² *Ann. Chim. phys.*, [3] **65**, 385 (1862); **66**, 5 (1862); **68**, 225 (1863).

³ *Am. Chem. J.*, **45**, 479 (1911).