Summary of Results.

1. Phenylisoxazolone reacts with the formamidines, yielding substituted aminomethylene derivatives of the phenylisoxazolone.

2. Benzal and anisalmethylisoxazolone give with the formamidines substituted aminomethylenemethylisoxazolones and the benzal or anisal derivatives of the amines.

3. In some cases the substituted isoxazolones form bromine compounds, which, under the influence of solvents, rearrange to *p*-bromophenyl compounds.

4. When hydroxylamine acts on the amides of aminoethyleneaceto or benzoylacetic acids, there are formed derivatives of 5-methyl or phenylisoxazole-4-carboxylic acids.

5. These isoxazoles, under the influence of alkalies, rearrange to substituted amides of acetyl or benzoylcyanacetic acid.

6. A number of compounds have been made to illustrate the reactions involved.

ON THE REACTIONS OF THE FORMAMIDINES. IV.

BY F. B. DAINS, O. O. MALLEIS AND J. T. MEYERS.

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The following paper[1] constitutes a further study of the reactivity of the substituted formamidines with compounds containing methylene hydrogen,[2] the general purpose being to ascertain whether there is any special relation between the nature of the substituting group and the reactions of the formamidines.

The previous papers have shown that the general reaction between the formamidines and a compound containing methylene hydrogen can be formulated as follows:

$$XYCH_2 + RN : CHNHR = XYC : CHNHR + RNH_2.$$

If Y, for instance, is a carbethoxy group, $—COOC_2H_5$, the freed amine may react with it to give an amide CONHR and alcohol. Whether this secondary reaction occurs or not is largely a question of temperature, the lower the temperature, the less the amide formation, although in the case of malonic ester, this secondary reaction seems always to occur.

Derivatives of p-Benzyloxyaniline. — The free amine was readily prepared by the reduction of the nitro compound with iron and acetic acid, according to the method of Spiegel and Sabbath.[3] The free amine was dissolved in benzene and dry hydrochloric acid gas passed into the

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[1] The work though incomplete is published at this time owing to the departure of one of the authors from the university.

[2] See previous paper. Also *Ber.*, **35**, 2496; THIS JOURNAL, **31**, 1148.

[3] *Ber.*, **34**, 1944.

solution. This precipitated the hydrochloride which melts at 222–223°, a melting point 10° higher than the one given in literature.

The benzoyl derivative, $PhCONHC_6H_4OCH_2Ph$, crystallizes from alcohol in white leaflets, which melt at 226–7°. Analysis:

Calculated for $C_{20}H_{17}O_2N$: N, 4.84; found: N, 4.72.

The *p*-aminophenylbenzyl ether shows the usual action of amines toward aldehydes. When it is warmed gently with benzaldehyde, it combines, with loss of water, to form *benzal-p-benzyloxyaniline*, $PhCH_2OC_6H_4N = CHPh$ melting at 118°. It is difficultly soluble in hot alcohol and crystallizes from gasoline in white flakes. Analysis:

Calculated for $C_{20}H_{17}ON$: N, 4.88; found: N, 4.82.

The corresponding *anisal-p-benzyloxyaniline* from the amine and anisic aldehyde is fairly soluble in hot alcohol and gasoline and very soluble in chloroform. It has a melting point of 150°. Analysis:

Calculated for $C_{21}H_{19}O_2N$: N, 4.41; found: N, 4.49.

Di-p-benzyloxydiphenylformamidine, $C_7H_7OC_6H_4N : CHNHC_6H_4OC_7H_7$.—The free amine reacts readily at water bath temperature with orthoformic ester, giving a 77% yield of the formamidine, which separated from benzene in white crystals with a melting point of 153°. It is soluble also in chloroform, acetone and alcohol. Analysis:

Calculated for $C_{27}H_{24}O_2N_2$: N, 6.86; found: N, 6.89.

The *amidine* dissolved in benzene gives with hydrochloric acid gas, a white hydrochloride which melts at 261° and slowly decomposes on standing. Analysis:

Calculated for $C_{27}H_{25}O_2N_2Cl$: HCl, 8.20; found: HCl, 8.08.

The yellow picrate from molar quantities of the formamidine and picric acid in alcohol solution, after crystallization from acetone, melted at 209°. Analysis:

Calculated for $C_{34}H_{27}O_9N_5$: N, 10.99; found: N, 11.36.

When the formamidine and cyanoacetic ester are heated at 120–30°, they combine and from the reaction mixture can be isolated aminophenylbenzyl ether and ethyl *p-benzyloxyanilidomethylenecyanoacetate*, $PhCH_2OC_6H_4NHCH : C(CN)COOC_2H_5$. This latter forms brownish crystals from benzene, with a melting point of 120°. Analysis:

Calculated for $C_{19}H_{18}O_3N_2$: N, 8.70; found: N, 8.79.

Malonic ester reacts in the usual manner with the formamidine and gives the *p-benzyloxyanilide of p-benzyloxyanilidomethylenemalonic ethyl ester*, white crystals which melt at 131°. Analysis:

Calculated for $C_{32}H_{30}O_5N_2$: N, 5.37; found: N, 5.37.

From acetoacetic ester and the amidine, when heated at 120–25°, both the possible products can be obtained. Thus there was isolated a light yellow compound melting at 95°, which proved to be *ethyl p-benzyloxy-*

anilidomethyleneacetoacetate, $PhCH_2OC_6H_4NHCH : C(COCH_3)COOC_2H_5$. Analysis:

Calculated for $C_{20}H_{21}O_4N$: N, 4.13; found: N, 4.42.

Part of the benzyloxyaniline had reacted, however, with the carbethoxy group of the above compound (m. p. 95°) giving the *p-benzyloxyphenylamide of p-benzyloxyanilidomethyleneacetoacetic acid,* fine yellow needles, which melt at 164°. It is nearly insoluble in hot gasoline and alcohol, but dissolves in boiling acetone and benzene. Analysis:

Calculated for $C_{31}H_{28}O_4N_2$: N, 5.69; found: N, 5.61.

Previous experiments have shown[1] that the methylene hydrogen in methylphenylpyrazolone reacts with great ease with the formamidines. This was found to be also the case here, and there was obtained *1-phenyl-3-methyl-4-p-benzyloxyanilidomethylene-5-pyrazolone,* red needles from alcohol melting at 181°. Analysis:

Calculated for $C_{24}H_{21}O_2N_3$: N, 10.97; found: N, 11.13.

Derivatives of p-Aminodimethylaniline.—Orthoformic ester (1 mol) and *p*-aminodimethylaniline (2 mols) were heated at 125° for two hours. On standing the di-*p*-dimethylaminodiphenylformamidine gradually separates out in hexagonal tablets. It is best purified by crystallization from benzene and then melts at 157°. Overheating must be avoided both in the preparation of and the reactions with this compound, as it tends to form tarry products difficult to purify. Analysis:

Calculated for $C_{17}H_{22}N_4$: N, 19.87; found: N, 19.44.

Hydrochlorides of the Di-p-dimethylaminodiphenylformamidine.—Since the compound is an amidine and contains in addition two dimethylamino groups, three hydrochloric acid salts are possible and in fact all three were obtained. When dry hydrochloric acid gas is passed into a benzene solution of the formamidine, a bright yellow precipitate is formed, which as the stream of gas is continued changes to a white flocculent precipitate. The yellow salt, which melts at 233° was found to be the mono-hydrochloride, while the white compound formed by longer passage of the gas melts at 193° and contains three molecules of hydrogen chloride. Analysis of the yellow salt:

Calculated for $C_{17}H_{22}N_4HCl$: Cl, 11.13; found: Cl, 11.67.

Analysis of the white salt:

Calculated for $C_{17}H_{22}N_4.3HCl$: Cl, 27.17; found: Cl, 26.69.

In one case figures were obtained which indicated the formation of the dihydrochloride.

The picrate which is insoluble in alcohol, benzene and gasoline forms reddish brown crystals from acetone and melts at 172°. With malonic ester, the amidine yields, on heating at 125°, the *dimethylaminophenylamide of p-dimethylaminoanilidomethylenemalonic ethyl ester,*

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[1] THIS JOURNAL, 31, 1153.

$$(CH_3)_2NC_6H_4NHCH : \underline{CCONHC_6H_4N(CH_3)_2COOC_2H_5}$$

which melts at 142° after recrystallization from hot gasoline. It is also soluble in benzene, alcohol and acids. Analysis:

Calculated for $C_{22}H_{28}O_3N_4$: N, 14.14; found: N, 13.60.

Cyanoacetic ethyl ester reacts in the usual way with the formation of *p*-dimethylaminoanilidomethylenecyanoacetic ethyl ester,

$$(CH_3)_2NC_6H_4NHCH : C(CN)COOC_2H_5,$$

white needles which melt at 134°. Analysis:

Calculated for $C_{14}H_{17}O_2N_3$: N, 16.23: found: N, 15.86.

When the amidine was heated with acetoacetic ester, there was obtained, beside some free aminodimethylaniline, a product melting at 178°, which proved to be the *p-dimethylaminophenylamide of p-dimethylaminoanilidomethyleneacetoacetic acid,*

$$(CH_3)_2NC_6H_4NHCH : C(COCH_3)CONHC_6H_4N(CH_3)_2,$$

Analysis:

Calculated for $C_{21}H_{26}O_2N_4$: N, 15.31; found: N, 15.13.

A small amount of a compound melting at 88° and easily soluble in gasoline was also isolated. This was doubtless the dimethylaminoanilidomethyleneacetoacetic ethyl ester, but the amount was too small for a good analysis.

Derivatives of p-Iodoaniline.—This is easily obtained by following the method used by Wheeler and Liddle in the preparation of the iodine derivatives of the toluidines.[1] Orthoformic ester and *p*-iodoaniline combine readily at water bath temperature giving a good yield of di-*p*-iododiphenylformamidine,[2] $IC_6H_4N : CHNHC_6H_4I$, which is almost insoluble in hot gasoline and acetone, difficultly soluble in chloroform and acetic acid and moderately soluble in boiling benzene and alcohol. It crystallizes in white needles melting at 175°. A product pure enough for use can be obtained, however, by simply grinding the original material in a mortar and washing with gasoline. Analysis:

Calculated for $C_{13}H_{10}N_2I_2$: N, 6.26; found: N, 6.28.

Hydrochloric acid gas precipitates from a benzene solution of the amidine the white HCl salt, which melts at 249°. Analysis:

Calculated for $C_{13}H_{10}N_2I_2.HCl$: HCl, 7.53; found: HCl, 7.38.

The picrate, which forms dark yellow crystals from acetone, has a melting point of 226°.

With cyanoacetic ester, the iodoformamidine reacts at 125° yielding *ethyl p-iodoanilidomethylenecyanoacetate,* $IC_6H_4NHCH : C(CN)COOC_2H_5$, brownish needles from alcohol melting at 154°. Analysis:

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[1] *Am. Chem. J.*, **42**, 445.

[2] This compound, as well as the malonic ester derivative was first obtained in this laboratory by Mr. E. F. Kohman, now Fellow at Yale.

Calculated for $C_{12}H_{11}O_2N_2I$: N, 8.19; found: N, 8.27.

Under like conditions malonic ethyl ester gives the *p-iodophenylamide of p-iodoanilidomethylenemalonic ethyl ester,*

$IC_6H_4NHCH : C(COOC_2H_5)CONHC_6H_4I$,

white crystals difficultly soluble in alcohol and very soluble in chloroform. It melts at 176°. Analysis:

Calculated for $C_{18}H_{16}O_3N_2I_2$: N, 4.99; found: N, 5.18.

Acetoacetic ester unites with the formamidine at temperatures from 100–125° to give iodoaniline and two other products, one easily soluble in gasoline and the other insoluble. The first consists of white crystals which melt at 96° and is *ethyl p-iodoanilidomethyleneacetoacetate,* $IC_6H_4NHCH : C(COCH_3)COOC_2H_5$. Analysis:

Calculated for $C_{13}H_{14}O_3NI$: N, 3.90; found: N, 4.15.

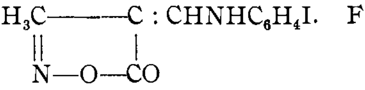
The second product, the *p*-iodophenylamide of *p*-iodoanilidomethyleneacetoacetic acid, is soluble in hot alcohol, benzene and glacial acetic acid and its presence is due to the action of the *p*-iodoaniline upon the $COOC_2H_5$ group. It has a melting point of 184°. Analysis:

Calculated for $C_{17}H_{14}O_2N_2I_2$: N, 5.27; found: N, 5.21.

p-Iodoanilidomethyleneacetylacetone, $(CH_3CO)_2C : CHNHC_6H_4I$, from the amidine and acetylacetone, crystallizes from alcohol in slightly yellow needles melting at 180°. Analysis:

Calculated for $C_{12}H_{12}O_2NI$: N, 4.26; found: N, 4.12.

An isoxazolone derivative can be obtained by heating, at a temperature of not over 140°, a mixture of benzalmethylisoxazolone and the iodoformamidine. Benzene separates the easily soluble impurities and benzal-*p*-iodoaniline from the less soluble *3-methyl-4-p-iodoanilido-5-isoxazolone,* CH_3C———$C : CHNHC_6H_4I$. From acetone this forms yellow crystals melting at 208°. Analysis:



$$\begin{array}{l} CH_3C\text{———}C : CHNHC_6H_4I \\ \;\;\|\qquad\quad\;| \\ \;\;N\text{—}O\text{—}CO \end{array}$$

Calculated for $C_{11}H_9O_2N_2I$: N, 8.54; found: N, 8.34.

For purposes of comparison and further identification of the *p*-iodoaniline, the benzaldehyde and anisic aldehyde derivatives were prepared. *Benzal-p-iodoaniline* from a molar mixture of the two components melts at 85° and is easily soluble in alcohol, acetone and benzene, difficultly soluble in gasoline and chloroform. Analysis:

Calculated for $C_{13}H_{10}NI$: N, 4.56; found: N, 4.48.

Anisal-p-iodoaniline crystallizes from alcohol in white needles melting at 151°. Analysis:

Calculated for $C_{14}H_{12}ONI$· N, 4.16; found: N, 4.45.

Derivatives of 5-Iodo-2-aminotoluene.—The method of Wheeler and Liddle[1] gave good results in the preparation of this compound.

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[1] *Am. Chem. J.*, **42**, 501.

The iodoacettoluide (m. p. 176°) was treated in chloroform solution with bromine (one mol) in order to see whether a bromiodoacettoluide would be formed. The result showed, however, that the bromine replaced quantitatively, not the hydrogen of the ring, but the iodine, since the product obtained was 5-bromo-2-acettoluide (m. p. 158–9°). The same substitution was noted in the case of *p*-iodoacetanilide, which was changed by the action of bromine into *p*-bromoacetanilide.

Benzaldehyde and the iodotoluidine combine easily giving *benzal-5-iodo-2-aminotoluene*, PhCH : $NC_6H_3ICH_3$, white needles with a melting point of 55°. Analysis:

Calculated for $C_{14}H_{12}NI$: N, 4.45; found: N, 4.37.

The iodotoluidine reacts in the usual manner with orthoformic ester at water-bath temperature yielding *di-5-iodo-di-o-tolylformamidine*, $ICH_3C_6H_3N$: $CHNHC_6H_3CH_3I$, which separates from benzene or 75% alcohol in white needles that melt at 169°. Analysis:

Calculated for $C_{15}H_{14}N_2I_2$: N, 5.88; found: N, 5.60.

A benzene solution of the amidine with hydrochloric acid gas gave a white *hydrochloride*, which melted at 254°. Analysis:

Calculated for $C_{15}H_{14}N_2I_2.HCl$: N, 5.47; found: N, 5.42.

From this salt the free base is best obtained by solution in pyridine and precipitation with water. The same hydrochloride is obtained by heating the amidine with concentrated hydrochloric acid, though boiling the salt in alcohol saponified it completely, giving the iodotoluidine.

The diiododitolylformamidine shows the same reactivity toward compounds containing methylene hydrogen, as do the other formamidines. With acetoacetic ester, it yields ethyl *5-iodo-o-toluidomethyleneacetoacetate*, which after crystallization from alcohol melts at 137–8°. Analysis:

Calculated for $C_{14}H_{16}O_3NI$: N, 3.76; found: N, 3.85.

A second product difficultly soluble in alcohol and acetic acid crystallized from a mixture of benzene and gasoline in silky needles and melted at 238°. This proved to be the *5-iodo-o-tolylamide of 5-iodo-o-toluidomethyleneacetoacetic acid*. Analysis:

Calculated for $C_{19}H_{18}O_2N_2I_2$: N, 5.00; found: N, 4.89.

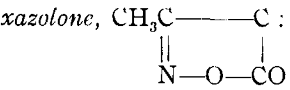
The *5-iodo-o-toluidomethylenecyanoacetic ethyl ester*, $ICH_3C_6H_3NHCH$:- $C(CN)COOC_2H_5$, melts at 207°. Analysis:

Calculated for $C_{13}H_{13}O_2N_2I$: N, 7.87; found: N, 7.84.

Malonic ester and the iodotoluidine yield the *5-iodo-o-tolylamide of 5-iodo-o-toluidomethylenemalonic ethyl ester*, which has a melting point of 201°. Analysis:

Calculated for $C_{20}H_{20}O_3N_2I_2$: N, 4.76; found: N, 4.84.

When the formamidine and benzalmethylisoxazolone are heated at 120°, there is formed benzal-5-iodotoluidine and *4-iodotoluidomethylene-5-*

isoxazolone, 

$$\begin{array}{l} CH_3C\text{———}C:CHNHC_6H_3CH_3I \\ \;\| \qquad\quad\;\; | \\ N\text{—}O\text{—}CO \end{array}$$

which separates from glacial acetic acid in needles melting at 209°.

Calculated for $C_{12}H_{11}O_2N_2I$; N, 8.19; found: N, 8.19.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA.]

THE CONDENSATION OF VANILLIN AND PIPERONAL WITH CERTAIN AROMATIC AMINES.

BY ALVIN S. WHEELER.

Received June 6, 1913.

In extension of the work done in this laboratory upon the condensation of chloral with aromatic amines,[1] we have carried out the condensation of the aldehydes, vanillin and piperonal, with *p*-aminobenzoic acid, its ethyl ester, and also with *p*-anisidine. Pawlewski[2] has described the product obtained by the condensation of anthranilic acid with vanillin, stating it to be an amorphous substance. We find that the para acid yields with vanillin a crystallin product with a melting point 40° higher. The condensation of anthranilic acid with piperonal was carried out by H. Wolf.[3] Our product with the para acid melts 44° higher. The products with the ethyl ester have very much lower melting points. The work with the ester was undertaken with the hope of discovering more cases of isomerism, a few cases having already been observed in similar reactions. No indications of isomerism, however, were noted in handling the two ester derivatives.

The condensations take place readily in a boiling solvent with the loss of one molecule of water, one molecule of each constituent taking part in the reaction. By working at low temperatures it is sometimes possible to bring two molecules of the amine into combination with one of the aldehyde. In the reaction between the free para acid and piperonal a small quantity of a low melting substance, m. 171–3°, was isolated and the amount was greatly increased by using two molecules of the acid. Notwithstanding many analyses, no satisfactory figures could be obtained for a dibenzylidene derivative.

The condensation product of *p*-aminobenzoic acid with vanillin is unique among the benzylidene derivatives in that it is the only one that takes up a molecule of water of crystallization. Exposed to a moist atmosphere it gradually assumes a reddish color. If it is recrystallized

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[1] Wheeler and Weller, THIS JOURNAL, **24**, 1063 (1902). Wheeler, *Ibid.*, **30**, 136 (1908). Wheeler and Jordan, *Ibid.*, **31**, 937 (1909).

[2] *Ber.*, **37**, 596 (1904).

[3] *Monatsh.*, **31**, 903.