# REACTIONS OF THE FORMAMIDINES WITH COMPOUNDS CONTAINING METHYLENE HYDROGEN WITH SPECIAL REFERENCE TO DI-PARADIMETHYLAMINODIPHENYLFORMAMIDINE

A THESIS SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
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BY
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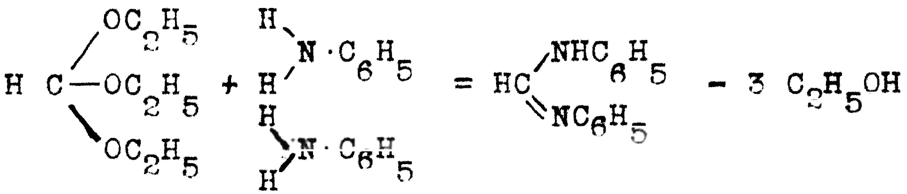
Formamidines are substituted formic acids. Thus simple formamidine $HC\begin{matrix} /\!\!/ NH \\ \diagdown NH_2 \end{matrix}$ is formic acid with the hydroxyl group replaced by an amido and the oxygen replaced by an imido group. When an H from the amido and the imido group is replaced by a radical we have a substituted formamidine. For example $HC\begin{matrix} /\!\!/ nC_6H_5 \\ \diagdown nHC_6H_5 \end{matrix}$ is diphenylformamidine.

Substituted formamidines have been synthesized in various ways, among the most common of which are; -

1. Heating formanilide.
2. Action of phosphorous trichloride on a mixture of a formanilide and amine.
3. The reaction of orthoformicester on a primary amine, orthoformic ester. And aniline giving diphenylformamidine and alcohol.



$$H\,C\begin{matrix} \diagup OC_2H_5 \\ -OC_2H_5 \\ \diagdown OC_2H_5 \end{matrix} + \begin{matrix} H\diagdown \\ H\diagup \end{matrix} N\cdot C_6H_5 \; \begin{matrix} H\diagdown \\ H\diagup \end{matrix} N\cdot C_6H_5 = HC\begin{matrix} \diagup NHC_6H_5 \\ \diagdown\!\!\diagdown NC_6H_5 \end{matrix} - 3\ C_2H_5OH$$

4. The action of amines on the isoethers of formanihde.
5. The reaction of hydrocyanicacidsesquichloride, 2HCN 3 HCl with a primary amine.

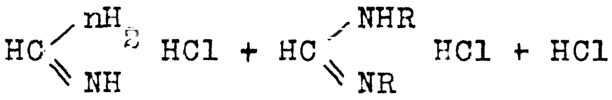
The last method is an interesting one worked out by F. B. Dains at Freiburg (Ber 35, 2496)

When dry hydrochloric acid is passed into a dry benzene solution of hydrocyanic acid, a salt, hydrocyanic acid sesquichloride is formed.

This sesquichloride will react with two molecules of an amine giving one molecule of a substituted formamidine and one molecule of formamidine itself.

I. $HN : CH \cdot NCHCl_2 \cdot HCl + RNH = HN : CH\ NH\ CH\ NR - 3\ HCl$

II. $HN : CH\ NH\ CHNR - 3\ HCl + HNHR =$



$$HC\begin{matrix} \diagup nH_2 \\ \diagdown\!\!\diagdown NH \end{matrix} HCl + HC\begin{matrix} \diagup NHR \\ \diagdown\!\!\diagdown NR \end{matrix} HCl + HCl$$

The intermediate product the result of reaction I cannot be isolated, but unites immediately with a second molecule of the amine according to reaction II.

The above reaction was carried out thus; - Suspend the hydrocyanicacidsesquichloride in dry benzol and add the amine. The insoluble hydrochloride of the salt separates out. If this is decomposed with NaOH the chief product is the substituted formamidine.

If the hydrocyanicacidsesquichloride is treated with aniline, diphnyl - formamidine results. Dains found the best method to be as follows: Dissolve a little morethan two molar weights of aniline in five times its volume of dry benzol and add one volume of the sesquichloride. The reaction goes slowly in the cold but will be completed in an hour on the water bath. The hydrochloride is insoluble in benzol but soluble in water. The addition of NaOH gives free diphenylformamidine. M. P. 143°. The hydrochloride melts at 193°.

If it is necessary to isolate the free amidine, the benzol can be distilled off and the hydrochloride broken up with NaOH; or if this is not practicable the NaOH can be added directly, the benzol may be distilled off with steam, and the amidine filtered off dried and recrystallized from benzol.

Some syntheses of formamidines by the above method (Ber 35, 2496)

Mix two molecules of mnitroanline three of pyridine and one of hydrocyamcacidsesquichloride and warm in benzol. Di - 3 - nitrophenylformamidine can be isolated which melts at 135°.

O - nitroaniline treated in a similar way gave little of the formamidine and p - nitroaniline none at all.

When two molecules of p - chloraniline and one of the sesquichloride are warmed in benzol solution, di-p-chlorphanylformidine, $ClC_6H_4NHCH:C_6H_4Cl$ is formed which crystallizes in white needles melting at 179°.

O - toluidine gives a good yield of di-o-tolylformamidine M. P. 151°.

The p-toluidine also gave a good yield of di-p-tolyformamidine.

Molecular quanities of m-xylidine and the sesquichloride react easily and smoothly in benzol solution. Fine white needles of di-m-xylformamidine result M.P. 131°
$(CH_3)_2C_6H_3$ NH CH $CH_3(CH_3)_2$ nitro-m-xylidine contains too many negative groups to react.

Pseudocumidine reacts very easily at the temperature of the water bath giving a 96 per cent yield. It is easily soluble in hot benzol from which it crystallizes in fine white needles. M.P. 160°. It is almost insoluble in hot HCl but forms a hydrochloride when dry HCl is led into it in benzol solution. M.P. 360°. Difficultly soluble in water.

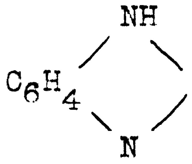
A-naphthalamine forms a hydrochloride. MP. 228°. When treated with NaOH it gives di-a-naphthylformamidine.

B-naphthalamine yields from benzol solution fine white needles of B-naphthylformamidine. M. P. 186°.

The same amidine can be made by heating one mole of orthoformicester and one mole of B-naphthylamine for two hours on a water bath. Yield good. p-aminophenol does not react, the OH group preventing the action.

P-anisidine gives di-p-anisylformamidine. This also can be readily made from p-anisidine and orthoformicester. O-anisidine and p-phenetidin act in the same way.

O-phenyldiamine gives an 80 per cent yield of benzinmidazol,



. MP. 170°

With benzidine no formanidine derivative can be isolated only benzidine hydrochloride resulting.

Thus primary amines in general react with hydrocyanic-sesquichloride or dichlormethylformamidine giving formamidine derivatives.

With chlorine derivatives, secondary and tertiary amines and bodies containing negative groups this reaction does not follow.

General reactions of substituted formamidines.

(Ber 35, 2496)

The substituted formamidines of the type $HC\begin{smallmatrix}/\!\!/\,NR\\ \diagdown\,NHR\end{smallmatrix}$ are much less stable and more reactive than the analogous amidines of the type $RC\begin{smallmatrix}/\!\!/\,NR\\ \diagdown\,NHR\end{smallmatrix}$ since the H in the CH group is already replaced in the latter there is no easy pointof attact. The first type goes very easily to an amine and a formanilide derivative.

$R\ NH\ CH : NR + H_2O = RNH\ CHO + RNH_2$

Formamidines of the type $HC\begin{smallmatrix}/\!\!/\,NR\\ \diagdown\,NHR,\end{smallmatrix}$, which are the ones under consideration in this paper, are capable of several reactions.

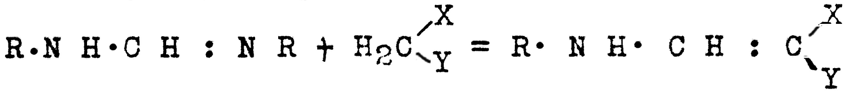
1. Form acid salts, hydrochlorides and sometimes acetates etc.

2. Form picrates.

3. Form chloroplatinates.

4. React with compounds containing methylene hydrogen.

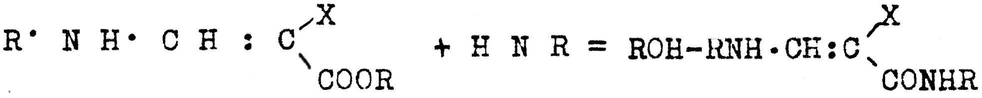
This is by far the most important reaction of the substituted formamidines. They are especially reactive toward these compounds such as acetoaceticester, malonicester, cyanaceticester, acetylacetone etc. At about 110 - 150° they react with such bodies in the following way, a primary amine being split off.



$$\mathrm{R\cdot NH\cdot CH:NR} + \mathrm{H_2C}{<}^{\mathrm{X}}_{\mathrm{Y}} = \mathrm{R\cdot NH\cdot CH:C}{<}^{\mathrm{X}}_{\mathrm{Y}}$$

The ethoxy methylene compound unites with the amine forming the aminomethylene compound $\mathrm{XY\cdot CH:NHR}$.

If the methylene compound also contains a carbethoxy group, a secondary reaction may occur. The primary amine which is first split off reacting with the carbethony group and producing alcohol.

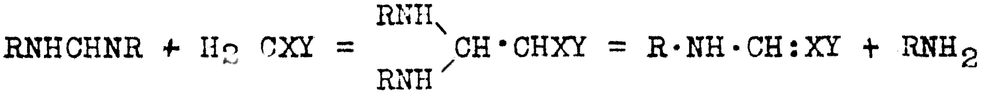


$$\mathrm{R\cdot NH\cdot CH:C}{<}^{\mathrm{X}}_{\mathrm{COOR}} + \mathrm{HNR} = \mathrm{ROH{-}RNH\cdot CH:C}{<}^{\mathrm{X}}_{\mathrm{CONHR}}$$

By this reaction one can easily make

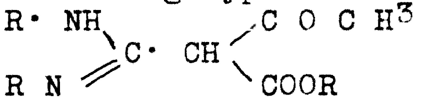
aminomethylene derivatives of acetoaceticester, acetylacetone, benzoylacetone etc.(Ber 35, 2496).

This reaction apparently occurs only when the group $H\,C\begin{matrix}\diagup N- \\ \diagdown NH-\end{matrix}$ is present. Thus the reaction with a formamidine and malonicester goes smoothly at 150° while under similar conditions the reaction occurs neither between acetdiphenylamidine and malonic ester or diphenylformamidine and ethylmolonicester. It may be that the malonic ester first adds to the double bonding and then a molecule of amine splits off.



$$RNHCHNR + H_2\,CXY = \begin{matrix} RNH \diagdown \\ \\ RNH \diagup \end{matrix} CH\cdot CHXY = R\cdot NH\cdot CH{:}XY + RNH_2$$

Troube and Eyme ( Ber 31, 3178 - 1898) observed a similar reaction. They found that under the influence of sodium ethylate on carbodiamid a body of the following type was formed.



The aminomethylene derivatives of the general form R N H· CH: CXY which can be made by this reaction have been in part described by Claissen ( Ann.d. Chem. 297, 33 - 68) and Walther and Schickler ( Jour. Für Prac. Chem. (2) 55 - 339 ). Previously they had been obtained a condensation of the compound containing methylene hydrogen with orthoformicester.

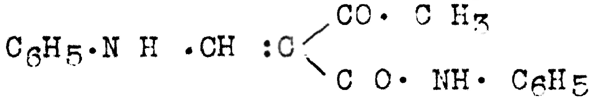
$XY\cdot CH_2 + (C_2H_5O)_2CH\cdot O\cdot C_2H_5 = XY\cdot C:CH\cdot OC_2H_5 - 2C_2H_6O$

The ethoxymethylene compound unites with the amine forming the aminomethylene compound, $XY\cdot CH:NHR$.

A history of the systhesis of compounds formed by the action of formamidines on compounds containing methylene hydrogen.

1. Reactions of acetoaceticester. ( Dains Ber. 35, 2496 ).

(a) Diphenylformamidine and acetoaceticester give the anilid of amilidomethylineacetoaceticester.

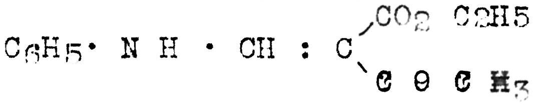


$$C_6H_5\cdot NH\cdot CH:C\begin{cases}CO\cdot CH_3\\ CO\cdot NH\cdot C_6H_5\end{cases}$$

The reaction does not go very smoothly since many terry products are formed.

1 mole of diphenylformamidine and 1 1/2 moles of acetoaceticester are heated for 1 1/2 hours at 150°. If heated too long, many terry products are formed which lower the yield. When cold it is rubbed with cold alcohol and recrystallized from alcohol or acetic acid. Yield usually 20 to 40%. M.P.156. A portion of the compound is soluble in cold alcohol and when recrystallized from ligroin melts at 45 - 46°. It is the

anilide of oxymethyleneacetoaceticester.



$$C_6H_5\cdot NH\cdot CH:C\begin{matrix}\diagup CO_2C_2H_5\\ \diagdown COCH_3\end{matrix}$$

Claissen also made this product from ethoxymethyleneacetoacetecester and aniline. ( Ann. d. Chem. 297, 77)

These results show that the reaction goes in two steps, first a free amine is formed which reacts with the ester group in the anilido group and splits off alcohol.

This same compound can be made in another way with a faily good yield. Heat molecular quantities of diphenylformamidine and acetanilide for three hours at 150 degrees. When crystallized from alcohol, the anilide melts at 156 ( Ber. 35 2496).

D - tolyl derivative .

$CH_3\cdot C_6H_4NH\cdot CH:C(CO\cdot CH_3)CO\cdot NHC_6H_4\cdot CH_3$

Heat 1 1/2 hours at 150 degrees. The portion dificultly soluble in alcohol crystallizes in needles. M.P. 172. From the alcohol mother liquor tolnidomethyleneacetoaceticester can be crystallized from ligroin M.P.71.

P- tolylderivatives.

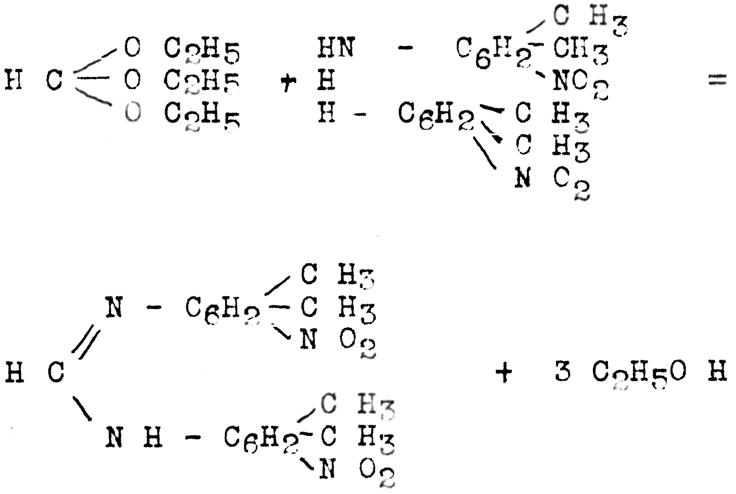
$CH_3 \cdot C_6H_4 \cdot NH \cdot CH:C(CO \cdot CH_3)CONH \cdot C_6H_4CH_3$

It is made as above. The needles from acetic acid melt at 170.

A similar xylyl derivative melts at 188°. ( Gatterman Doctors Thesis Freiburg 1903).

(b) Di-m-nitroxylylformamidine and acetoaceticester.

This formamidine was made by heating two moles of nitroxylidine and one mole of orthoformic ester.

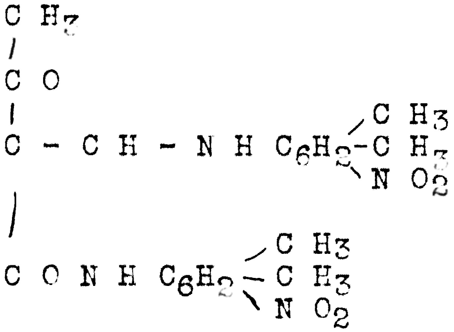


$$HC\begin{cases}OC_2H_5\\OC_2H_5\\OC_2H_5\end{cases} + \begin{array}{l}HN-C_6H_2(CH_3)(CH_3)(NO_2)\\H\\H-C_6H_2(CH_3)(CH_3)(NO_2)\end{array} =$$

$$HC\begin{cases}N-C_6H_2(CH_3)(CH_3)(NO_2)\\NH-C_6H_2(CH_3)(CH_3)(NO_2)\end{cases} + 3\,C_2H_5OH$$

It is very difficultly soluble in alcohol. Soluble in pyridine and may be thrown by alcohol. Soluble in acetone, chloroform, and benzene. MP 126.

Heat equivalent quantities of formamidine and acetoaceticester several hours at 180 degrees. Recrystallize the product several times from pyridine precipitating it with alcohol. It forms bright brown needles, soluble in benzene, difficultly soluble in acetone, chloroform and xylol, and in soluble in alcohol.M.P. 281°.



This is mono-m-nitroxylidid of m-nitro- xylidomethyleneaeitoaceticester .

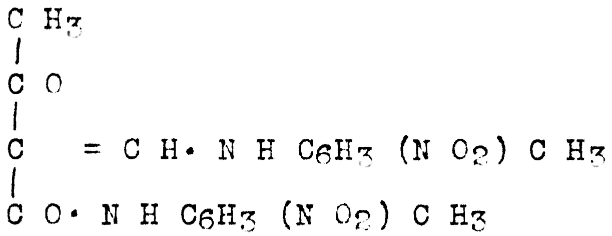
(c) Dinitrotolylformamidine and acetoacetic ester.

Dinitrotolyformamidine was made by Gaugler ( Docotrs thesis 1903) by the condensation of o-nitro-p-tolnidine and orthoformine ester.

Two moles of o-nitrotoluidine and one of orthoformicester are heated in a flask with a reflux condenser. It is recrystallized from pyridine. Forms fine yellow needles. Soluble in hot acetone and toluene, very easily soluble in hot nitrobenzene, and very difficultly soluble in ether, ligroin, and benzol.

M.P. 204. With pure materials the yield is almost quantitative. T

The nitrotoluide of o-nitro-p-toluidomethyleneacetoaceticester.



$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ C = CH\cdot NH\,C_6H_3\,(NO_2)\,CH_3 \\ | \\ CO\cdot NH\,C_6H_3\,(NO_2)\,CH_3 \end{array}$$

is made thus.

Molecular quantities of dinitrotolylformamidine and acetoaceticester are heated at 200° for a short time. The product is dissolved in pyridine and thrown down with alcohol. Small yellow srystalls. Soluble in hot pyridine and nitrobenzene, less soluble in chloroform, and difficultly soluble in alcohol, acetone, benzene, toluene, ligroin, and ether, even when hot. M.P.255°.

(d) Di-p-bromdiphenylformamidine and acetoaceticester. ( Dains and Brown J. Am. Chem. Soc. 31, 10.)

The di-p-bromdiphenylformamidine was obtained by heating p-bromaniline and orthoformic ester at 100°. The p-bromanilidomethyleneacetoaceto-p-brom anilide is made by heating the product from the above reaction with acetoaceticester at 125°. The compound contains p-bromaniline and is soluble in hot alcohol and acetic acid. It crystallizes in white needles. M. P. 190°.

5. They also made the anilidomethyleneacetoaceto-p-bromanilide by heating diphenylformainedine and acetoaceto-p-bromanilide at 125°. It forms slightly yellowish crystalls from alcohol which melt at 158°.

(e) Di-$\psi$-cumylformamidine and acetoaceticester when heated at 125° give, pseudocumidene and the $\psi$- cumidomethyleneacetoaceto-cumidide which forms white crystalls from acetic acid melting at 183°.

(f) Ethyl-$\psi$ cumidomethyleneacetoacetate is made in the same way. It forms white clumps very soluble in alcohol. M. P. 98°.

(g) Di-o-anisylformamidine and acetoaceticester.

This formamidine was made by Rüggeberg ( Thesis, Freiburg 1904) by heating the amine and orthoformic ester in a sealed tube ay 160°. It was more easily prepared by Dains and Brown who made it by heating the components in an ailbath at 140° and crystallized the product from a mixture of benzene and ligroin. It melts at 105°. ( Jour. Am. Chem. Soc. 31, 1148).

This amidine and acetoaceticester react at 150° and produce ethyl-o-methoxyanilidomethyleneacetoacetate, forming needlesshapped crystalls from alcohol melting at 112°.

(h) In a similar way methylene-di-phenetidine and acetoacetic ester yield p ethoxyanilidomethyleneacetoaceto-p-ethoxyanilide, fine yellow crystalls.

(i) Do- -naphthylformamidine and acetoaceticester.

Di-α - naphthylformamidine was made by Dains and Brown by heating molecular quantities of α-naththyl amine several hours on the water bath.

This formamidine heated with acetoacetic aster gave two products. The first consisting of fine yellow needles difficultly soluble in hot alcohol and melting at 167 - 8°, proved to be α-naphthalidomethyleneacetoaceto-α-naphthalide.

y The second was ethyl-α- napththalidomethyleneacetoacetate. Soluble in alcohol and moderately soluble in ligroin. M. P. 92°.

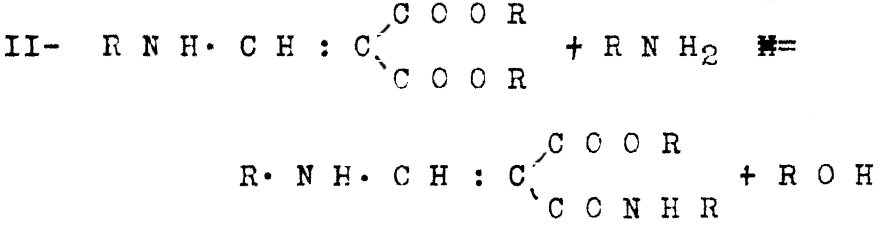
(j) From di-β-naphthylformamidine and acetoaceticester was obtained β - naphthalidomethyleneacetoaceto- β - naphthalide, forming light yellow granules from glacial acetic acid and melting at 184°.

The second product was Ethyl-$\beta$-naphthalidomethyleneacetoacetate, which formed white clumps from ligroin. Very soluble in alcohol, M. P. 95°. ( Jour. Am. Chem. Soc. 31, 1148.)

2, Reactions of formamidine with Malonic ester.

(a) Formamidines with malonic ester react in this way at 150°. ( Dains Ber. 13, 2496).

$$\text{I-}\quad RNH\cdot CHNR + H_2C(COOR)_2 = R\cdot NH\cdot CH:C(COOR)_2 + RNH_2$$

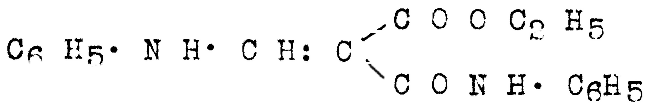


$$\text{II-}\quad RNH\cdot CH:C\begin{cases}COOR\\COOR\end{cases} + RNH_2 = R\cdot NH\cdot CH:C\begin{cases}COOR\\CONHR\end{cases} + ROH$$

The intermediate product, aminomethylenemalonicester, has not been isolated since it reacts at once with the free amine formed, according to reaction II.

(a) When diphenylformamidine and malonicester are heated three hours in a bomb tube a condensation product which can be crystallized from alcohol or acetic acid is formed. M. P. 118°.

This is the monoanilide of anilidomethylenemalonicester.



$$C_6H_5\cdot NH\cdot CH:C\begin{cases}COOC_2H_5\\ CONH\cdot C_6H_5\end{cases}$$

The same product has been made by the action of aniline and dicarboxyghitaconicester and its derivatives. ( Am. d. Chem. 123; 133, 144, and 147. Ruheman and Morrell.)

It has also been formed by the saponification of $\beta$ - anilidoethyl-$\alpha$- dicarbonic acid.

(b) o- tolylformamidine and malonic ester.

This action goes in the same way and yields, o-toluide of o-toluidomethylenemalonicethylester.

$C_6H_4(CH_3)\cdot NH\cdot CH:C(CO_2\cdot C_2H_5)\cdot CONH\cdot C_6H_4CH_3$

It crystallizes from alcohol and acetic acid. Insoluble in cold alcohol, difficultly soluble in hot alcohol, and easily soluble in hot acetic acid. Yield good. M. P. 141°. Ber. 35, 2496.

m-xylyl derivatives.

$C_6H_3CH_3NH\cdot CH:C(CO_2C_2H_5)\ CONC_6H_5(CH_3)_2$

Soluble in alcohol and glacial acetic acid. Fine white needles M. P. 140°.

Pseudocumyl derivative.

$C_6H_2(CH_3)_2NH\cdot CH:C(CO_2C_2H_5)CO\cdot NHC_6H_2(CH_3)_2$

P-chor phenyl derivative

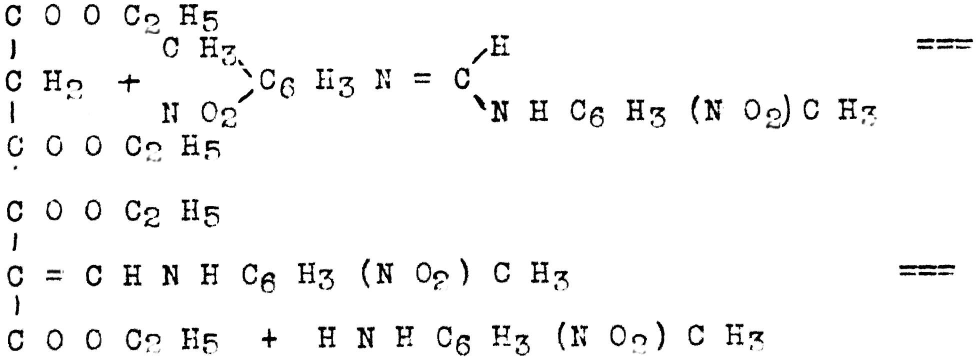
$C_6H_4CL\cdot NH\cdot CH\cdot C(CO_2H_5\overset{C_2}{\wedge})CONH\cdot C_6H_4Cl$

It requires three hours heating at 150°. Difficultly soluble in hot alcohol and cold acetic acid and more easily soluble in hot acetic acid. M. P. 176°.

(c) Dinitrotolylformamidine and malonic ester. ( Gaugler Doctors dissertation 1903 Freiburg).

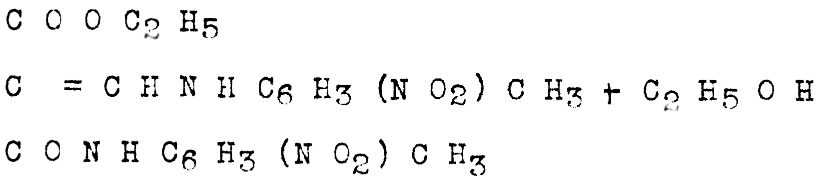
Molecular quantities of the formamidine and malonic ester were heated two to three hours on air oil bath at 180° in a flask with a reflux condenser. It was dissolved in pyridine and precipitated with a little alcohol. Yellow needles dissolved in ligroin except when hot and soluble in other common organic solvents, are produced.

This reaction goes in the customary way a molecule of primary amine being split off which reacts with the carbethoxy group giving an anilide and alcohol.



$$\begin{array}{l} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} + \begin{array}{l} CH_3 \\ NO_2 \end{array}\!\!>C_6H_3N=C\begin{array}{l} H \\ NHC_6H_3(NO_2)CH_3 \end{array} \quad ===$$

$$\begin{array}{l} COOC_2H_5 \\ | \\ C=CHNHC_6H_3(NO_2)CH_3 \\ | \\ COOC_2H_5 + HNHC_6H_3(NO_2)CH_3 \end{array} \quad ===$$



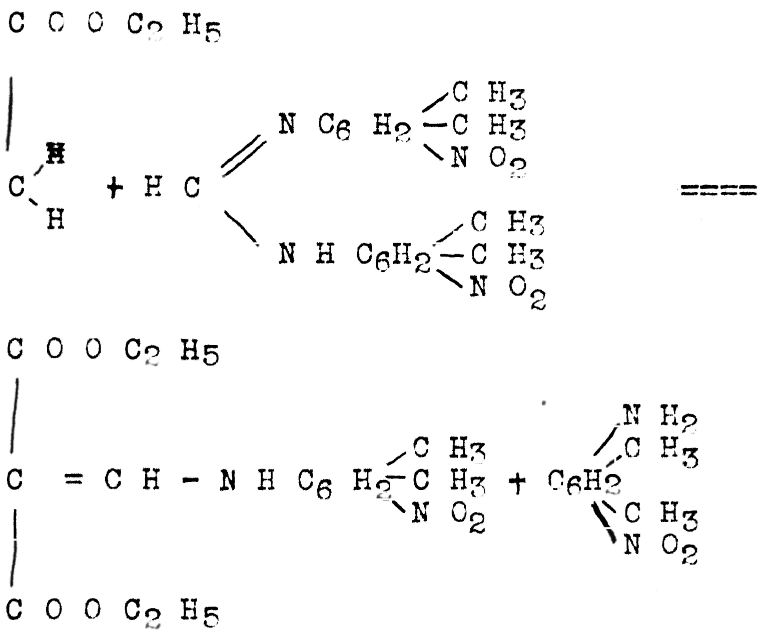
$$\begin{array}{l} COOC_2H_5 \\ C = CHNHC_6H_3(NO_2)CH_3 + C_2H_5OH \\ CONHC_6H_3(NO_2)CH_3 \end{array}$$

This mononitrotoluide of a-nitro-p-toluidomethylenemalonicester was found to give two addition products with bromine, one with three moles, M.P. 107°, and one with seven moles M. P. 120°.

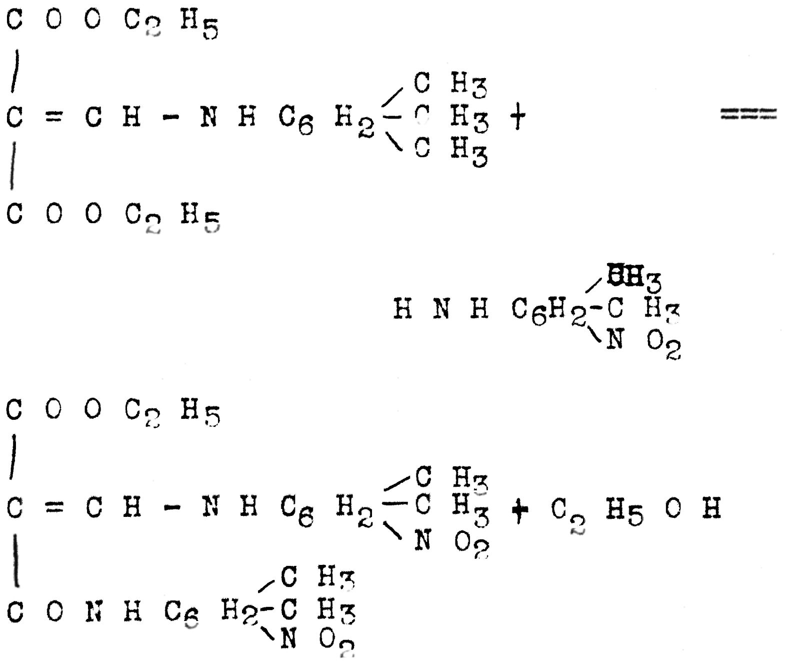
All attempts to saponify such bodies failed. Instead of getting the free acid as would be expected, both molecules of nitrotoluid/ine were split off.

(d) Do-m-nitronylformamidine and malonic ester. Gatterman ( dissertation Freiburg 1904).

Heat equivalent quantities of the formamidine and malonic ester in an oil bath at 190° for three hours. Dissolve the product in pyridine and throw down with alcohol. It forms bright yellow crystalls, soluble in chloroform, xylyl, and pyridine, quite soluble in acetone and benzene and difficultly soluble in alcohol. M. P. 225°. The reaction goes in this way:



Then the m-nitroxylidine thus formed reacts with the carbethoxy group of the substituted malonicester giving alcohol and a xylidid.



(e) Dφ- α - naphthylformamidine and malonic ester ( Dains and Brown J. Am. Chem. Soc, 31, 1149.

Heat molecular quantities on an oil bath for several hours at 150°. The α - naphhalide of ethyl- α - naphthalidmethylenemalonate wash the product with cold alcohol and recrystallize from benzol and glacial acetic acid. Yellow needles soluble in theusual solvents. M. P. 162.

The monobrom derivatives of this product was formed by dissolving it in chloroform and adding one molecule of Bromine. M. P. 227°

(f) Dφ-β-naphthylformamidine and malonic ester. ( J. Am. Chem. Soc. 31, 1148).

They react easily at 150° giving the β - naphthalide of ethyl- β - naphhalidomethylenemalonate. It is only slightly soluble in hot alcohol, but crystallizes from acetic acid in fine yellow needles whichmelt at 172°. ( J. Am. Chem. Soc. 31, 1148).

The fact that malonanilide and dφ- β -naphthylformamidine combine with the formation of β - naphthalidomethylenemalonanilide $C_{10}H_7\ NHCH: C(CONHPh)_2$ is an evidence of the reactivity of methylene hydrogen. Light yellow crystalls M. P. 289.

(g) Di-m-tolylformamidine and malonic ester. ( J. Am. Chem. Soc. 31, 1148).

This reaction produces light yellow crystalls of the m-toluide of ethyl-m-toluidomethylenemalonate.

(h) Methylene-o-phenetidine and malonic ester. ( Ibid)

This amidine is made by heating o-phenetidine and orthoformicester on an oil bath at 140° and purifying from ligroin. White needles, M. P. 81°.

This amidine reacts with malonio ester at 130° and forms o-ethoxyamlide of ethyl-o-ethoxyanilidomethylenemalonate. It separate in white needles melting at 130°.

3. Reactions of substituted formamidines with cyanacetic ester.

Inthis reaction the anilidomethylene compound of the ester is formed. There is usually no action of the amine which is formed, on the carbethoxy group. However, if highly heated this action may occur.

(a) Diphenylformamidine and cyanacetic ester ( Dains Ber 35, 2496).

Heat five grams of diphenylformamidine and three grams cyanacetic ester one and one half hours at 150°. A good yield follows without the formation of tarry products as sometimes occurs. M. P. 106-107. The product is anilidomethylenecyanaceticester.

$C_6H_5 \cdot NHCH:C(CN)CO_2C_2H_5$

Bollemont also made this compound from ethoxymethyleneaceticester and aniline ( Chem. Centr. Bl. 1901. I, 374).

If this compound is dissolved in acetic acid and treated with bromine, then poured into water and recrystallized from alcohol, a compound melting at 148° which is either the monobrom derivative or the H Br addition product, not the dibrom derivative as would be expected, is produced.

P-tolyderivative.(Ber. 35, 2496)

$CH_3 \cdot C_6H_4 \cdot NHCH:C: CCCN)CO_2C_2H_5$

Formed by heating for two hours at 150. M. P. 137. Yield quantitative. Soluble in alcohol and acetic acid.

The o-tolyl compound melts at 137-8° and the pseudocumylderivative at 195°.

4. Reactions of formamidines and benzoylacetone.

(a) O-nitrotolylformamidine and benzoylacetone.

( Gäugler Dissertation 1903 Freiburg.)

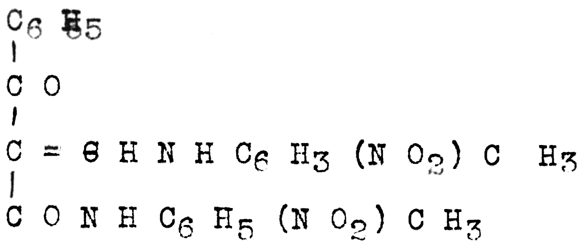
Heat molecular quantities in an oil bath at 180- 190° for three or four hours. When rubbed, and cooled in ice a solid forms. Many side reactions occur which hinder crystallization. It must be rubbed with a little alcohol filtered and recrystallized from alcohol when it melts between 112° and 125°. After several crystallizations it forms good crystalls which melt sharply at 137°. It is insoluble in ether and ligroin, and soluble in the other common organic solvents.

5. Formamidines and benzoylaceticester.

(a) P-tolylformamidine and benzoylaceticester. ( Gaügler, Dissertation 1903)

Heat molecular quantities in a flask fitted with a return condenser for five or six hours on an oil bath at 200° till melted, then at 165 - 175° for the remainder of the time. Recrystallized from benzene and a little alcohol. Forms canary yellow tables M. P. 205°.

The nitrotoluidof o-nitro-p-toluideomethylenebenzoylaceticester is the product.

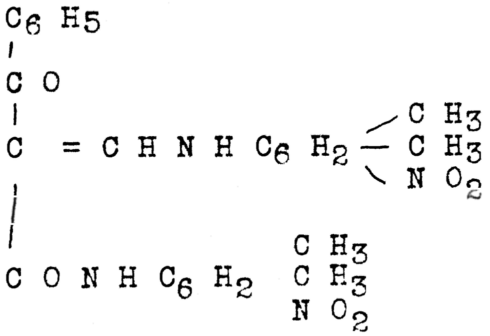


$$C_6H_5-CO-C(=CHNHC_6H_3(NO_2)CH_3)-CONHC_6H_5(NO_2)CH_3$$

(b) Di-m-nitroxylformamidine and benzoylacetic ester ( Gatterman Dissertation 1904).

Heat molecular quantities at the melting point several hours. Dissolve the product in pyridine and precipitate with alcohol. Forms yellowish white matted needles. Very soluble in pyridine and chloroform. Difficultly soluble in alcohol, acetone, benzol, and ligroin. Almost insoluble in ether.

The product is mono-m-nitroxylidide of m-nitroxylidomethylenebenzoylaceticester.

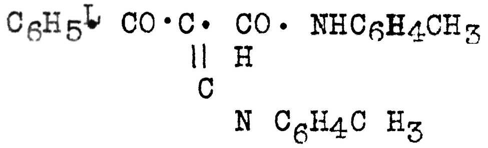


(c) Diphenylformamidine and benzoylaceticester ( Rüggeberg Dissertation, Freiburg 1904)

When heated at 150° the anilide of anilidomethylenebenzoylaceticester is formed. Gray leaflets melting at

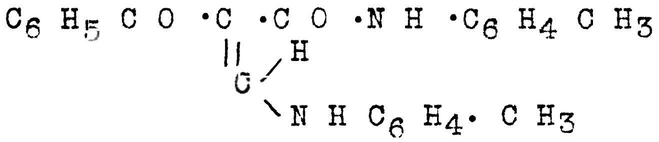
164°.

(d) O-tolytformamidine and the ester. When heated at 140° for five hours, the o-toluide of o-toluidomethyleneaceticester is formed. Silky crystalls melting at 187° are produced.



$$\begin{array}{l} C_6H_5\ CO\cdot C\cdot\ CO\cdot\ NHC_6H_4CH_3 \\ \qquad\qquad\quad \|\ \ H \\ \qquad\qquad\quad C \\ \qquad\qquad\qquad N\ C_6H_4C\ H_3 \end{array}$$

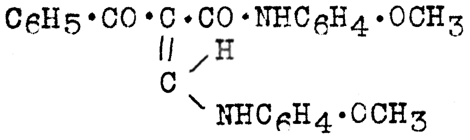
(e) P tolylformamidine and benzoylacetic ester give crystalls melting at 208°, from acetic acid.



$$\begin{array}{l} C_6\ H_5\ C\ O\ \cdot C\ \cdot C\ O\ \cdot N\ H\ \cdot C_6\ H_4\ C\ H_3 \\ \qquad\qquad\qquad \|\ \diagup H \\ \qquad\qquad\qquad C \\ \qquad\qquad\qquad\quad \diagdown N\ H\ C_6\ H_4\cdot\ C\ H_3 \end{array}$$

( Jour. Am. Chem. Soc. 31, 1146).

(f) Di-o-anisylformamidine and the ester, heated five hours at 150° give yellow needles from acetic acid melting at 199°.



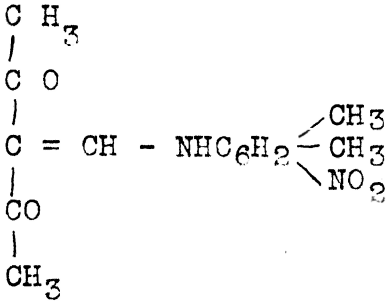
$$\begin{array}{l} C_6H_5\cdot CO\cdot C\cdot CO\cdot NHC_6H_4\cdot OCH_3 \\ \qquad\qquad\ \|\ \diagup H \\ \qquad\qquad\ C \\ \qquad\qquad\quad \diagdown NHC_6H_4\cdot OCH_3 \end{array}$$

6. Formamidines and acetylacetone.

(a) Di-m-nitroxylformamidine and acetylacetone. ( Gatterman Dissertation 1904 Freiburg).

Heat molar weights at 190°, and crystallize from alcohol. Brownish needles easily soluble in alcohol, chloroform, and benzene; difficultly soluble in ether. It melts at 140°.

Thr product is m-nitroxylidomethyleneacetylacetone.



(b) Diphenylformamidine and acetylacetone ( Dains Ber 35, 2496).

Heat molecular weights for six hours at 145° and an oily product is produced which crystallizes into a yellow mass when rubbed with HCl. Crystallizes from alcohol in yellow needles. It is p-toluidomethyleneacetone.

$CH_3\cdot C_6H_4NHCH:C(COCH_3)_2$

(c) M-xylidomethyleneacetylacetone is formed under similar conditions with xylidene. It is identified by means od its benzoyl derivative which melts at 93°. It crystallizes from alcohol in long hairlike needles. M. P. 146°. Soluble in the common organic solvents.

$(CH_3)_2.C_6H_3.NH.CH:C(CO.CH_3)_2$

(d) o-tolnidomethyleneacetylacetone formed from o-tolylformamidine and acetyl acetone. White needles melt at 124° . Crystalls from ligroin. ( Dains and Brown. J. Am. Chem. Soc. 31, 1148).

(e) m- tolnidomethyleneacetylacetone, white needles. Very soluble in alcohol. Melts at 75°.

(f) o- phenetidylmethyleneacetylacetone. Colorless needles from ligroin. Melts at 115-6°.

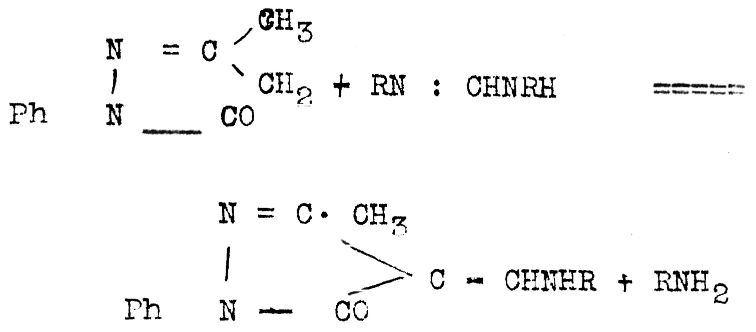
(g) α - naphthylidomethyleneacetylacetone. Bright yellow needles from alcohol, melting at 144°.

(h) β - naphthylidomethyleneacetylacetone. Brownish needles melt at 144°.

7. Formamidines and pyrazolones. ( Dains and Brown J. Am. Chem. Soc. 31, 1148).

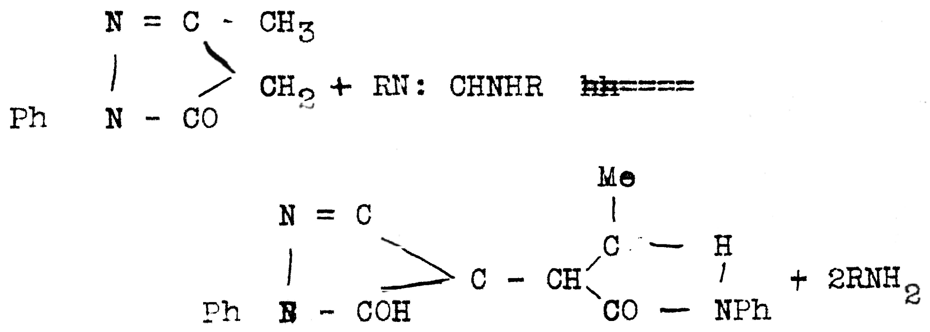
The pyrazolones are ring compounds formed by the action of phenylhydrazine on acetoacetic ester and benzoylacetic ester. They are tautameric compounds in one phase of which is a methylene hydrogen grouping.

Methylphenylpyrazolone reacts easily and smoothly in the following way:



Yielding aminomethylenepyrazolones, which contain a chromophoric group and are strongly colored red or yellow compounds.

Evidence of the above reaction being correct is furnished by the fact that a secondary product, methyl-bis-methylphenylpyrazolone, according to this reaction.



This is the first instance in which both RNH and the RN: group of the substituted formamidines have been replaced in reacting with methylene hydrogen and shows the relation between orthoformic ester and the formamidines.

(a) Methylphenylpytazolone and diphuryformamidine.

Heat at 130- 50° . Two products are formed which can be separated by fractional crystallization from alcohol and acetic acid. The more soluble compound is 1 phenyl-3-methyl-4-amlidomethylene - 5- pyrazolone. Bright yellow crystalls melting at 154°. Soluble in concentrated sulphuric acid.

The second product of orange red needles, difficultly soluble in alcohol and ether and melting at 180° is methyl-bis-methylphenylpyrazolone.

The latter may result from the direct interaction of two molecules of the pyrazolone and one of the formamidine or may be formed by a secondary reaction betwwen methylphenylpyrazolone and the aminomethylene derivative. It may be made in quantitative yield by heating methylphenylpyrazolone and - naphodomethylene-phenylpyrazolone at 150°.

(b) Methylphenylpyrazolone and di-$\beta$ -napthyl-formamidine.

Under like conditions methenyl-bis-methylphenylpyrazolone and 1-phenyl-3methyl-4- $\beta$ - naphthalidomethylene-5-pyrazolone. Yellowish brown needles melting at 151°.

The corresponding $\alpha$-naphtalidomethylenemethyphenyl-pyrazolone is deep yellow crystalls which melt at 122°.

(c) Other pyrazolones.

1- phenyl-3-methyl-4-p-toluidobrom-amlidomethylene-5-pyrazolone. Yellow needles from alcohol melting at 167°.

1-phenyl-3methyl-4-ψ-cumidomethylene-5-pyrazolone. Yellow needles from alcohol melting at 171°.

1-phenyl-3-methyl-4-p-ethoxyaniliodomethylene-5-pyrazolone.

Diphenylpyrazolone and di-o-tolylformamidine gave 1,3 diphenyl-4-0-toluidomethylene-5pyrazolone. Yellow needles from acetic acid whichmelt at 146°

Diphenylpyrazolone and di-β-naphthylformamidine give 1,3-diphebyl-4-β - naphthylidomethylene-5-pyrazolone.

8. Formamidines and acetonedicarbonicester.

( Rüggeburg Dissertation 1904 Freiburg)

Heat molecular quantities of the constituents for several hours on an oil bath at 160° until it begins to boil, and rub the cooled mixture well with alcohol. Upon long standing on ice a solid product separates out part of which is soluble in alcohol and part of which is not.

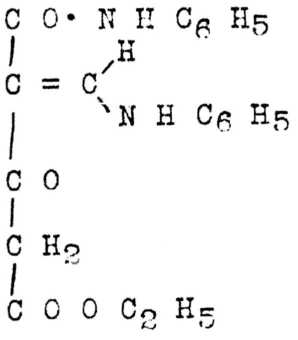
If two molecules of the amine and one of the ester were used and the heating continued for five hours the greater part of the product was the compound which was soluble in alcohol. However, when the heating was continued for five hours longer, the product insoluble in alcohol predominated.

The compound soluble in alcohol was recrystallized from acetic acid, from which it separated in rosette formed needles, which melted at 106° to112°.

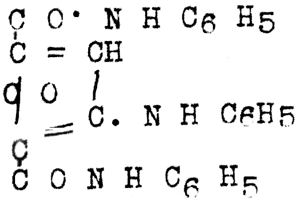
When this product was dissolved in alcohol and allowed to stand in the ice chest for a consideranle time, yellow needles melting at113° were formed.

The compound which was insoluble in alcohol was dissolved in acetic acid and brought out of solution by the addition of water. It formed rhombic crystalls melting at 249°.

The product which melted at 113° proved to be:



and the compound melting at 249° to be :



## Experimental Work

The condensation of p-aminodimethylaniline and orthoformic aster.

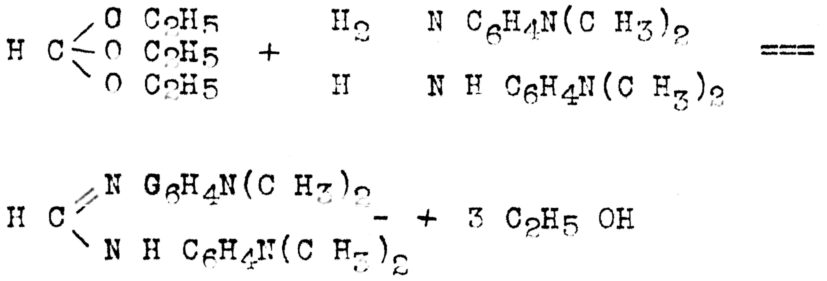
P-aminodimethylaniline when pure is clear oily liquid. It rapidly darkens upon standing due to the formation of tarry products. It was prepared by two methods. First by making nitrosodimethylaniline hydrochloride from dimethyaniline, hydrochloric acid, and sodium nitrite according to Uhlman Practical Organic Chemistry, page 181. Then reducing this with stannous chloride and hydrochloric acid. Second by reducing methylorange with Stannous chloride and hydrochloric acid.

Heat two moles of p-aminodomethylaniline and one mole of orthoformic ester in a flask fitted with a return condenser on an oil bath at 125° for about two hours. When allowed to cool and to stand several hours a product solidifies in hexagonal tablets. It was recrystallized several times from benzol. It melts at 157°.

If heated too long on the oil bath, side products are formed and it crystallizes very slowly, when allowed to stand several days, an impure solid forms which can be purified by dissolving in hot benzene, letting it partially evaporate and then causing it to precipitate by adding gasoline. It is soluble in benzene and alcohol. Insoluble in water and ether. Soluble in acids.

The product is di-p-dimethylaminodiphenylformamidine

The reaction goes in the following manner.



$$H\,C\begin{array}{l}\diagup O\,C_2H_5\\ -O\,C_2H_5\\ \diagdown O\,C_2H_5\end{array} + \begin{array}{ll}H_2 & N\,C_6H_4N(C\,H_3)_2\\ H & N\,H\,C_6H_4N(C\,H_3)_2\end{array} ===$$

$$H\,C\begin{array}{l}\diagup\!\!\diagup N\,G_6H_4N(C\,H_3)_2\\ \diagdown N\,H\,C_6H_4N(C\,H_3)_2\end{array} - + 3\,C_2H_5\,OH$$

This amino compound is especially reactive and has therefore a tendancy to go easily to tarry products making it necessary to carry on the condensation very carefully and making the products rather difficult to purify.

| | | | |
|---|---|---|---|
| Wt. | weighing bottle | 10,8651 | grams |
| " | " " and substance | 10.6264 | " |
| | Wt. Formamidine | .2390 | " |

Titration

75cc = amount of n/10 Na.OH taken

Burette readings

| HCl | NaOH |
|---|---|
| 38.4 cc. top | 22.5 |
| 38.9 cc. bottom | 24.8 |
| .5 cc Amt. used | 2.3 |

35 - 2.3 - 5 = 33.2 cc = amount of n/10 hydrochloric acid neutralized.

$\frac{33.2 \times .0014 \times 100}{2390}$ = 19.43~~1~~% nitrogen

Calculated for $C_{17}H_{22}N_4$ , 19.~~58~~ 87 % nitrogen.

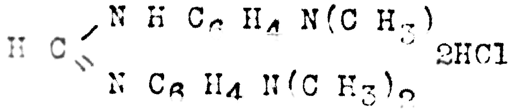
m.w. 282

## The Hydrochloride

The formamidine was dissolved in dry benzol and dry hydrochloric acid gas passed through it. Almost immediately a bright yellow precipitate was formed. Upon running the gas a short time longer the yellow precipitate changed over to a white flocculent precipitate. Each precipitate was prepared dried and titrated with n/10 NaOH using methylorange as an indicator. The hydrochloride first formed, the yellow compound, is rather difficultly soluble in water even when hot, but as alkali is slowly added the base is set free and more of the hydrochloride goes into solution so that it can all be titrated. However, the end point is rather difficult to find. It was found to contain two moles of hydrochloric acid.

The second hydrochloride the white compound was found to contain three moles of hydrochloric acid, when titrated with n/10 sodium hydroxide.

Analysis of the first compound formed.



$HC(=NC_6H_4N(CH_3)_2)NHC_6H_4N(CH_3)_2 \cdot 2HCl$

$C_{17}H_{24}N_4Cl_2$

| | | |
|---|---|---|
| Weight weighting bottle | 10.7966 | grams |
| " " " and sundtance | 10.5900 | " |
| Weight hydrochloride | .2066 | " |

### Titration

11.4 cc. of n/10 NaOH used to neutralize the acid.

$\frac{11.4 \times .00365}{.2066}$ = ~~20.14% HCl~~ 19.56 Cl.

Calculated 20.14% HCl

### Analysis of the second hydrochloride

| | | |
|---|---|---|
| Weight of weighting bottle | 8.8134 | grams |
| " " " " and substance | 8.4707 | " |
| " " hydrochloride | .3427 | " |

### Titration

~~35cc of N/10 HCl was used~~

### Burette Readings

| | H Cl | NaOH |
|---|---|---|
| Top | 37.7 | 12.2 |
| Bottom | 40.3 | 38.8 |
| Difference | 2.6 | 26.6 |

?

~~35.0 - 8.6 = 26.6 - 2.2 x .00365~~ ~~x 100~~ = ~~28.30 %~~

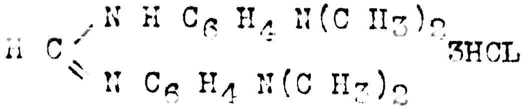
.3427

24.75

27,17% Cl

Theory for three moles ~~[illegible]~~

Formula $C_{17}H_{25}N_4Cl_3$ $C_{17}H_{22}N_4 \cdot 3HCl$



$$HC\begin{cases} NH\,C_6H_4\,N(CH_3)_2 \\ N\,C_6H_4\,N(CH_3)_2 \end{cases} 3HCL$$

The production of two such different hydrochlorides is a rather interesting reaction. In fact however, there is a chance for the formation of three hydrochlorides with this formamidine.

## The Picrate

Dissolve molecular quantities of the di-p-dimethylanilidoformamidine in hot alcohol separately. Add the hot solution. A reddish brown precipitate formed immediately. Filter it off and recrystallize from hot acetone in which it is rather difficultly soluble. It melts at 212°. It is insoluble in alcohol, benzol and gasoline.

An analysis for nitrogen by a modified kjeldahl method (Lunge Technical methods of analysis page 508)

| | | |
|---|---|---|
| Weight of weighing bottle | 12.1950 | grams. |
| " " " " and picrate | 12.0472 | " |
| " " picrate | .1 478 | " |

Titration

50 cc. of n/10 HCl was used.

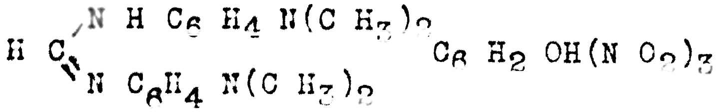
Burette Readings

| | H Cl | NaOH | |
|---|---|---|---|
| Top | 38.1 | 14.00 | cc |
| Bottom | 38.2 | 43.0 | cc |
| Acid used | .1 | 29.0 | cc |

$\frac{50. - .1 - 29.0 \times .0014 \times 100}{.1478} =$ ~~19.30~~ % 20.5 6

Calculated 19.18 %

Formula $C_{23} H_{25} O_7 N_7$



$$H\,C\begin{matrix}\diagup N\,H\,C_6\,H_4\,N(C\,H_3)_2 \\ \diagdown\!\!\diagdown N\,C_6H_4\,N(C\,H_3)_2\end{matrix}\;C_6\,H_2\,OH(N\,O_2)_3$$

All attempts to make the platinum salt failed. I tried to make it by adding platinum chloride to a water solution of the di-p-dimethylanilidoformanidine and evaporating it on a water bath and the platinum was reduced.

The same result followed when the solution was allowed to evaporate spontaneously.

Then the attempt was made to get the platinum salt by dissolving the formamidine in hot alcohol and adding platinic chloride. A yellowish precipitate formed immediately, which turned red then dark brown. It was filtered immediately and dried, but the dried mass darkened and it was found that the platinum had been reduced.

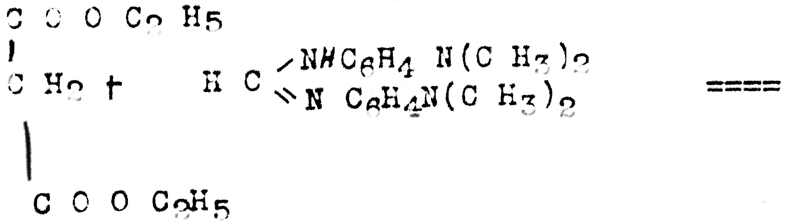
Di-p-dimethylaminodiphenylformamidine and malonic ester.

Molecular quantities of the substances were heated in a flask fitted with a return condenser, at 125° for several hours on an oil bath. After standing two days a crystalline product separated out. This was boiled up with gasoline and filtered off to remove any oily materials, and then purified by recrystallization from hot gasoline. It melts at 142°. It is soluble in benzene, gasoline, alcohol and acids. Insoluble in ether.

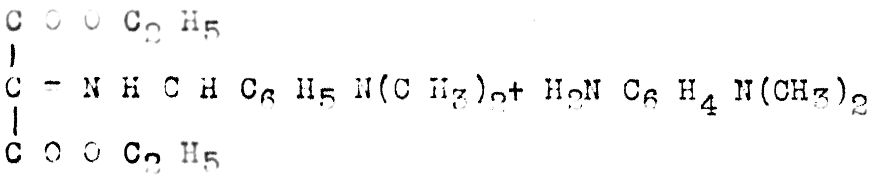
The per cent of nitrogen was determined by the Kjeldahl method.

The product formed is the anilide of ~~di~~-p-dimethyanilinoanlidomethylene,malonic ester.

The reaction goes thus.

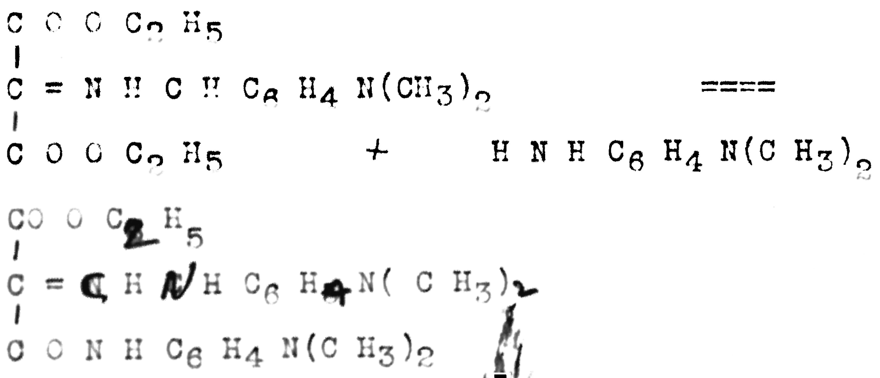


$$\begin{array}{l} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} + \quad HC\begin{array}{l} \diagup NHC_6H_4N(CH_3)_2 \\ \diagdown\!\!\diagdown N\,C_6H_4N(CH_3)_2 \end{array} \quad ====$$



$$\begin{array}{l} COOC_2H_5 \\ | \\ C = NHCHC_6H_5N(CH_3)_2 + H_2NC_6H_4N(CH_3)_2 \\ | \\ COOC_2H_5 \end{array}$$

Then the molecule of primary amine split of reacts with a carbethoxy group forming an anilide and splitting off alcohol.



$$\begin{array}{l} COOC_2H_5 \\ | \\ C = NHCHC_6H_4N(CH_3)_2 \qquad ==== \\ | \\ COOC_2H_5 \quad + \quad HNHC_6H_4N(CH_3)_2 \end{array}$$

$$\begin{array}{l} COOC_2H_5 \\ | \\ C = CHNHC_6H_4N(CH_3)_2 \\ | \\ CONHC_6H_4N(CH_3)_2 \end{array}$$

### Analysis f[illegible] nitrogen

$C_{22}H_{30}O_3N_4$ $C_{22}H_{30}O_3N_4$

| | | |
|---|---|---|
| Weight weighing bottle | 13.2445 | grams |
| " " " ahd substance | 13.2127 | " |
| " substance | .0318 | " |

### Titration

25cc of N/10 H Cl used.

Burette Readings

| H Cl | | NaOH | |
|---|---|---|---|
| 39.3 | cc | 22.2 | cc |
| 40.4 | cc | 49.7 | cc |
| 1.1 | cc | 27.5 | cc |

32.8 cc

36.5 cc

3.7 cc

~~$\frac{35.0 - 1.1 - 27.5 - 3.7 \times .0014 \times 100}{.0713}$~~ = ~~19.81%~~ nitrogen

Calculated = ~~[illegible]~~ "
14.08

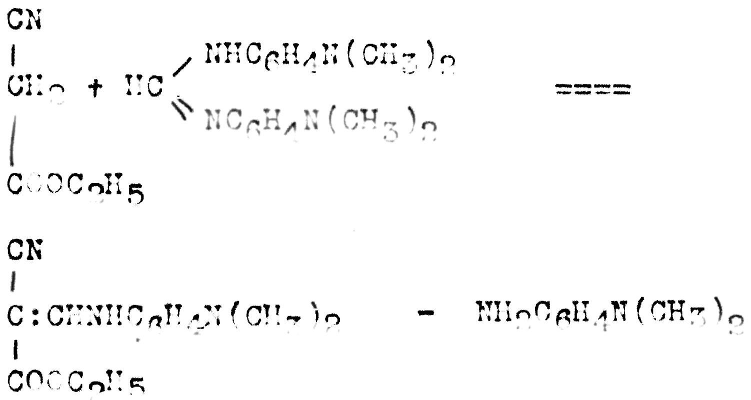
Di p- dimethylaminodiphenylformamidine and cyanacetic ester.

Heat molecular quantities of the components in a flask fitted with a reflux air condenser, in an oil bath at 125° for an hour. Upon standing a short time, a crystalline product separated out. This was purified by several recrystallizations from gasoline. It is soluble with difficulty in gasoline. Soluble in benzene and aldohol. From gasoline it forms yellowish white needle like crystal~~l~~s which melt at ~~133~~°. 134°

The product is p-dimethylamino-anilidomethylene-cyanacetic ethyl ester.

$C_{14}H_{17}O_2N_3$ > 259

The reaction goes thus:



$$\begin{array}{l} CN \\ | \\ CH_2 + HC\begin{matrix} \diagup NHC_6H_4N(CH_3)_2 \\ \diagdown\!\!\diagdown NC_6H_4N(CH_3)_2 \end{matrix} \qquad ==== \\ | \\ COOC_2H_5 \end{array}$$

$$\begin{array}{l} CN \\ | \\ C{:}CHNHC_6H_4N(CH_3)_2 \quad - \quad NH_2C_6H_4N(CH_3)_2 \\ | \\ COOC_2H_5 \end{array}$$

The free amine thus produced did not unite with the carbethoxy group to form alcohol, and this seems to be the usual reaction for a formamidine and cyanacetic ester.

A nitrogen determination gave the following results:

| | | |
|---|---|---|
| Weight of weighing bottle | 11.2701 | grams |
| " " " " and substance | 10.9931 | " |
| " " Substance | .2770 | " |

Titration

~~35 cc of N/10 HCl used.~~

~~Titrated back with N/10 NaOH~~

~~Burette Readings~~

| | H Cl | | NaOH | |
|---|---|---|---|---|
| ~~Top~~ | ~~39.3~~ | ~~cc~~ | ~~25.5~~ | ~~cc~~ |
| ~~Bottom~~ | ~~39.6~~ | ~~cc~~ | ~~33.7~~ | ~~cc~~ |
| ~~Difference~~ | ~~.3~~ | ~~cc~~ | ~~8.2~~ | ~~cc~~ |

$$\frac{35 - .3 - 8.2}{.277} \times .0014 \times 100 = 13.69\ \%\text{ nitrogen}$$

Calculated : = ~~13.88%~~ "

Di -p-dimethylaminodphenylformamidine and acetoaceticester.

Molecular quantities of the constituents were heated for an hour in a flask fitted with a return condenser on an oil bath at 125°.

The dark brown liquid was treated with acetic acid and then neutralized with dilute NaOH. Upon standing a day or two a yellowish compound separated out. This was found to consist of two compounds, one soluble in gasoline and the other very difficultly soluble in gasoline.

The soluble product was recrystallized from gasoline and a nitrogen determination made on it. It melted at [illegible].

Analysis

| | | |
|---|---|---|
| Weight of weighing bottle | 11.2732 | grams. |
| " " " " and substance | 11.1074 | " |
| " " substance | .1658 | " |

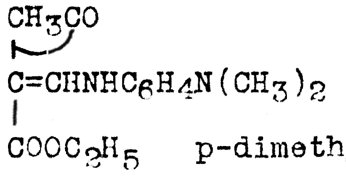
Titration

35. cc of N/10 HCl was used.

## Burette Readings

| | HCl | | NaOH | |
|---|---|---|---|---|
| Top | 40.9 | cc | 33.2 | cc |
| Bottom | 41.6 | cc | 49.7 | cc |
| Difference | .7 | c c | 16.5 | cc |
| | | | 17.0 | cc |
| | | | 25.7 | cc |
| | | | 8.7 | cc |

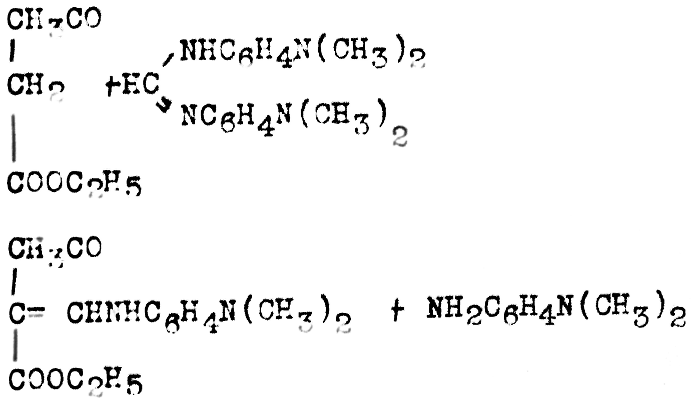
$$\frac{35.0 - .8 - \overset{25.2}{\cancel{12.7}}}{.1658} \times .0014 \times 100 = 8.86\% \text{ nitrogen}$$

Calculated for  [illegible] nitrogen.

$$\begin{array}{l} CH_3CO \\ | \\ C=CHNHC_6H_4N(CH_3)_2 \\ | \\ COOC_2H_5 \end{array}$$

p-dimethyl anino-anilidomethylene acetoacetocethyl ester.

The reaction evidently went in the following way.

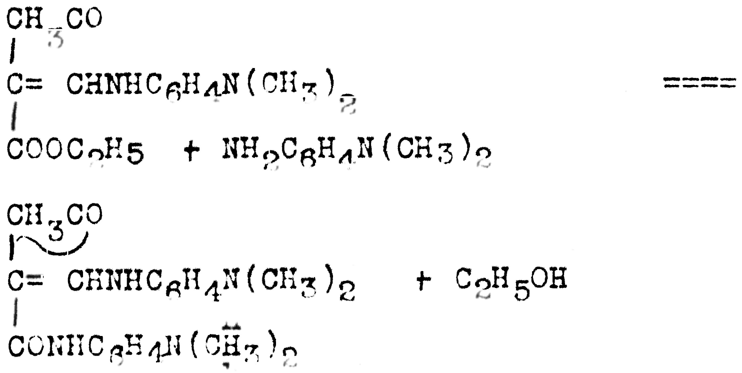


$$\begin{array}{l} CH_3CO \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} + HC\begin{array}{l} \diagup NHC_6H_4N(CH_3)_2 \\ \diagdown NC_6H_4N(CH_3)_2 \end{array}$$

$$\begin{array}{l} CH_3CO \\ | \\ C= CHNHC_6H_4N(CH_3)_2 \\ | \\ COOC_2H_5 \end{array} + NH_2C_6H_4N(CH_3)_2$$

The other product was not yet sufficiently purified for analysis . It melted ~~between 200° and 225°.~~ 178°

The free amine probably reacted with the carboxyl group thus:



$$\begin{array}{l} CH_3CO \\ | \\ C= CHNHC_6H_4N(CH_3)_2 \qquad\qquad ==== \\ | \\ COOC_2H_5 \;+\; NH_2C_6H_4N(CH_3)_2 \end{array}$$

$$\begin{array}{l} CH_3CO \\ | \\ C= CHNHC_6H_4N(CH_3)_2 \quad + \; C_2H_5OH \\ | \\ CONHC_6H_4N(CH_3)_2 \end{array}$$

This product would be p-di-methylamino-anilide of p-dimethylaminoanilidomethylene acetoaceticester.