

THE STRUCTURE OF THE SOLID REACTION PRODUCT OF ANILINES AND ETHYL ORTHOFORMATE^{1,2}

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Lewis, Krupp, Tieckelmann, and Post (1) have presented evidence based on cryoscopic molecular-weight determination in benzene to show that the solid reaction product of aniline or isomeric chloroanilines with ethyl orthoformate is trianilinomethane, or the analogous chloro derivatives, irrespective of the reaction temperature or of the molar ratio of the reactants. According to Walther (2), aniline and ethyl orthoformate, in the molar ratio of 2:1, condense at 100° to give diphenylformamidine (I; R = C₆H₅), m.p. 139°, whilst with a molar ratio of 3:1 and at reflux temperature, Giacolone (3) claims that trianilinomethane (II; R = C₆H₅), m.p. 139°, is formed. In most chemical reactions where the formation of isomers is excluded, it is usually possible to identify, or distinguish between, two possible reaction products by recourse to elementary analysis. In the present case, as pointed out by Lewis and co-workers, such analysis cannot be decisive. The percentages of carbon, hydrogen, and nitrogen in diphenylformamidine and trianilinomethane are so similar that the small differences come within the experimental error of their determination. However, the percentage chlorine found by Giacolone for the hydrochloride of the product shows that it is accurate for trianilinomethane monohydrochloride and cannot apply to diphenylformamidine hydrochloride. He finds similar agreement with analogs. Lewis and his co-workers (1) have shown by mixed melting point determination that the products of Walther and Giacolone are identical. It is therefore clear that in both cases we are dealing with the same compound.

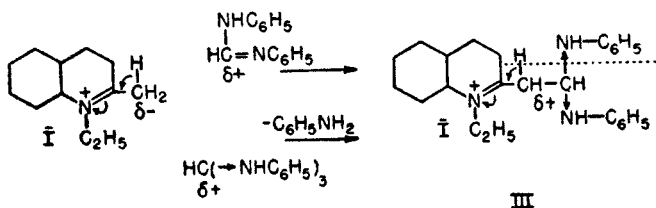
It has been generally accepted, hitherto, that the product is diphenylformamidine, and numerous patents and papers have been issued on the condensation of this substance with cyclic quaternary ammonium salts carrying a reactive methyl group (4) or with reactive keto-methylene compounds (5). Since this substance is of prime importance in the preparation of intermediates for photographic sensitizing dyes, it was thought desirable to prove, by unambiguous synthesis, its true structure.

Doubt as to the stability of a substance containing a carbon atom bonded to three secondary amino groups, as in trianilinomethane, was raised by the general instability of compounds containing a carbon bonded to two such groups. It is a general rule that the greater the number of electronegative atoms bonded to a carbon atom the more readily will the latter be attacked by nucleophilic reagents. The higher the electronegativity (−I effect) of the attached atoms,

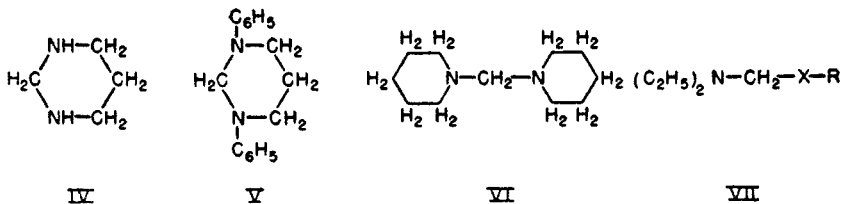
¹ From the Research Laboratories, Kodak Ltd., Harrow, England.

² Since this paper was written, Backer and Wanmaker (13) have shown by analysis of the picrate that the only solid reaction product of aniline and ethyl orthoformate is diphenylformamidine. In a later paper (14), they also showed by the same method that substituted anilines give only diarylformamidines.

the greater will be the carbon reactivity. This reactivity will, however, be tempered by any resonance stabilization present, or by any steric effects which will prevent a sufficiently close approach of the attacking nucleophilic center to the electrophilic carbon atom. Resonance stabilization is present only when the carbon atom carries a double bond. The state of electron deficiency at the carbon atom concerned may be relieved in three ways: through attack by a nucleophilic reagent, by intramolecular rearrangement, or by a spontaneous elimination reaction. The latter, however, can only occur if it results in a product of lower energy and thus higher stability. Thus, in general, it will occur most readily if, by elimination, an unsaturated resonating molecule results. Such elimination reactions are found most frequently when the molecule contains an active hydrogen atom which may be eliminated as a proton, together with one of the electronegative substituents carrying its charge to form two more stable products. Examples of such elimination reactions are manifold. An illustration of this effect in the field of the present paper is provided by the condensation of this solid reaction product with quinaldine ethiodide on fusion.



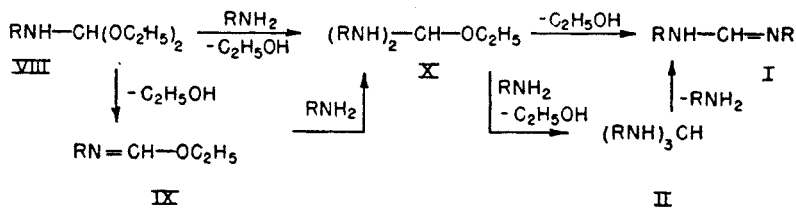
The quaternary salt carrying a nucleophilic 2-methyl carbon is attacked by the electrophilic methine carbon of diphenylformamidine or trianilinomethane. Carbon-carbon bond formation results as the proton is expelled from the reactive methyl group, the proton being taken up by the negative charge appearing on the anilino nitrogen in one case or by the simultaneously expelled negative anilino ion in the other case. The intermediate, III, results. It also possesses a highly active β -carbon atom due to the electron drain from it. This electron deficiency is, at once, relieved by expulsion of an anilino group carrying its charge, together with a second proton from the α -methylene carbon which has been activated by hyperconjugative resonance. The resultant products, 2- β -anilino vinylquinoline ethiodide and aniline, are highly stable. Intermediates of Type III have never been isolated. The last step in the above reaction is dependent upon the presence in the molecule of an active hydrogen. In the absence of such active hydrogens, a certain degree of stability is obtained. Thus, whereas tetrahydropyrimidine (IV) has only been isolated as its N,N'-di-



benzoyl derivative (6), the N,N'-diphenyl derivative (V) is stable (7). Similarly, open-chain derivatives of diaminomethane, such as VI, are relatively stable when compared with analogs derived from primary amines, but even VI is decomposed by water. Similarly, the diethylaminoethers and thioethers (VII) prepared by McLeod and Robinson (8) are stable to distillation but are attacked by water. The stability increases on replacing X = O by X = S, as would be expected from the lower electronegativity of sulfur compared with that of oxygen. Analogous compounds where R = H are extremely unstable.

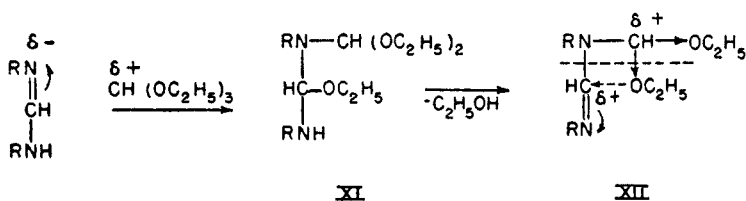
Returning to trianilinomethane containing three active N-hydrogens, we find that, by analogy, its instability would best be relieved by loss of aniline to give diphenylformamidine, the latter being stabilized somewhat by the weak resonance involving charge separation. The latter will, however, be highly stable in salt form, since proton addition will give an ion with two identical low-energy extreme resonance structures. It may, therefore, be stated that by analogy with other, related systems, one would expect the more stable end-product, diphenylformamidine, to be obtained from this reaction.

Before proceeding to the synthetic proof of the structure of the reaction product, a consideration of possible reaction mechanisms is desirable. Ethyl orthoformate contains a highly reactive electrophilic central carbon atom, owing to the strong -I effect of the three ethoxy groups. This atom is, however, protected from attack by the large effective size of the latter groups. It is considered, therefore, that for reaction with nucleophilic centers, such as amino nitrogen, the transition stage must be entered. Elimination of one molecule of alcohol will thus lead to the acetal (VIII). Goldschmidt (9) alleges that he isolated such an acetal when R = CH₃OOC·C₆H₄, although it would be expected to have a very low order of stability. He gives no analytical figures and



scanty experimental details, including a wrong formula, and repetition of the experiment gave only the amidine. The next stage in the reaction may take two courses in order to relieve the instability of the central carbon atom. Either alcohol is eliminated to give the ethylisoformanilide (IX), or condensation with a further molecule of amine and elimination of alcohol gives the intermediate (X). The same intermediate may also result by addition of amine to IX. Indeed, Comstock and Kleeberg (10) have shown that ethylisoformanilide (IX; R = C₆H₅) reacts readily with aniline to give the solid product, m.p. 138°. X may then relieve its carbon instability by loss of alcohol to give the formamidine (I), or by further reaction with the amine to give the triaminomethane (II) and hence I by loss of amine.

Claisen (11) has shown that I (or II) reacts at high temperatures with ethyl orthoformate to give IX. The hypothetical intermediate (XI) will be highly



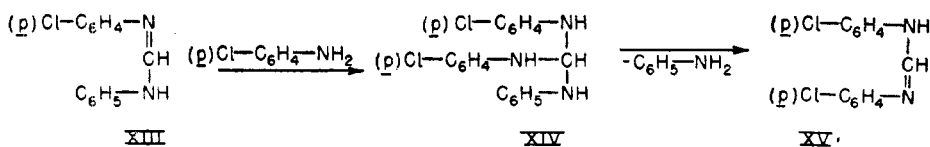
unstable and may decompose by loss of alcohol to give XII, which then relieves the electron drain from its two electrophilic carbons by migration of an ethoxy group and rupture of the C—N bond, as shown, giving two molecules of IX.

A consideration of the possible mechanism of the above reactions enables one to devise an unambiguous synthesis of diarylformamidines (I). The first step is to show that the reaction of one mole of arylamine with one mole of an ethylisoformanilide (IX; R = aryl) gives, by an addition-elimination reaction, an amidine (I) and not a triaminomethane (II). This was accomplished by condensing ethylisoformanilide (IX; R = C₆H₅) with *o*- and *p*-chloroaniline. Each resultant solid was homogeneous, and analysis showed each to contain one chlorophenyl and one phenyl residue: They must therefore be *N*-phenyl-*N'*-*o*-chlorophenylformamidine and the *p*-chloro isomer (XIII). The latter was obtained in nearly theoretical yield.

In an effort to induce a second chloroaniline molecule to add across the double bond of the amidine, ethylisoformanilide was heated with two moles of chloroaniline and the primary reaction product, the above amidine, was also heated with one mole of chloroaniline. When *o*-chloroaniline was employed, the identical unsymmetrical amidine was obtained or remained unchanged in the two cases. *p*-Chloroaniline, however, reacted with both isoanilide and amidine to give di-*p*-chlorophenylformamidine (XV), displacing the original anilino or anilino group. The identity of this compound as an amidine and not as tri-*p*-chloroanilinomethane was established by its resulting in theoretical yield from a molar mixture of ethyl-*p*-chloroisoformanilide and *p*-chloroaniline. Moreover, it was also identical (mixed m.p.) with the product obtained by Lewis and co-workers (1) from *p*-chloroaniline and ethyl orthoformate. Although the latter reports the m.p. 184° for this compound, we were not able to raise it above 181°, irrespective of the method of preparation.

These latter experiments are very pertinent to the arguments of this paper. Such a displacement of aniline was also reported by Walther (2), who obtained an unsymmetrical amidine on heating *p*-toluidine and diphenylformamidine. It implies at once that unsymmetrical trianilinomethanes are unstable since, in order to displace aniline, the *p*-chloroaniline must first add across the double bond of the unsymmetrical amidine (assumed to be the intermediate in the ethylisoformanilide reaction) to give anilinodi-*p*-chloroanilinomethane (XIV). This cannot be isolated, and the more electronegative group, anilino, is lost with a proton from a *p*-chloroanilino residue.

An unambiguous synthesis of diarylamidines having thus been established, ethylisoformanilide and aniline were reacted in molar proportions. The resultant



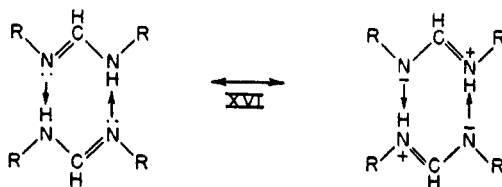
solid had m.p. 135° (crude), and the yield corresponded to a 99.5% recovery based on the loss of one mole of alcohol. One recrystallization gave a product of m.p. 139° and a recovery of 95%. The attempted addition of two moles of aniline to one of ethylisoformanilide gave the identical product, m.p. 139°, in a 94% yield based on the loss of one mole of alcohol and the utilization of only one mole of aniline. Both products gave a mixed m.p. of 139° with the products, m.p. 139°, obtained from ethyl orthoformate and aniline by the methods of Giacalone (3) and Walther (2).

Similarly, *o*-chloroaniline reacted with ethyl-*o*-chloroisoformanilide to give a solid, m.p. 140°, identical with the product obtained by Lewis and co-workers (1) from ethyl orthoformate and *o*-chloroaniline.

The foregoing affords conclusive synthetic proof that the only solid reaction product obtained from the interaction of arylamines and ethyl orthoformate is a diarylformamidine.

There remains to be explained the high molecular-weight figures obtained by Lewis and co-workers (1) and the low chlorine values obtained by Giacalone (3) for the hydrochlorides of his products.

The high molecular-weight figures may be due to intermolecular hydrogen-bonding (XVI). The resonance in the molecule will make this particularly facile. It would appear, therefore, to be fortuitous that the molecular weight



found, approximately one and one-half times that of the monomeric amidine, also corresponds to the molecular weight of the respective trianilinomethanes.

Since such bonding is likely to be weakened or lost at higher temperatures, the molecular weight of the product obtained by the method of Giacalone was determined by Rast's camphor procedure. The values found were 197 and 216, thus confirming the identity of the product with diphenylformamidine (molecular weight = 196).

Since triarylaminoethanes are not obtained by the method of Giacalone, then the analytical figures for chlorine in the hydrochlorides of his products are either incorrect or are meant to apply to the hydrochlorides of the tri-(*p*-aminophenyl)methanes which he obtained by heating his primary products with

aniline hydrochloride at elevated temperatures. To check these anomalies, diphenylformamide hydrochloride was prepared by two methods: by passing hydrogen chloride into a benzene solution of the amidine (I) prepared according to Giacalone (3), and by mixing molar quantities of ethyl orthoformate, aniline, and aniline hydrochloride, according to the method of Claisen (11). The latter method gave a 94.5% yield of solid based on the loss of three moles of alcohol and must therefore be the required product. Both products, m.p. 245°, were identical and gave the correct chlorine figures.

For the sake of completeness, ethyl-*o*-chloroisoformanilide was condensed with *p*-chloroaniline to give *N*-*o*-chlorophenyl-*N'*-*p*-chlorophenylformamide.

It is interesting to note that the same unsymmetrical amidine is obtained from ethylisoformanilide and *o*-chloroaniline as from ethyl-*o*-chloroisoformanilide and aniline. This may confirm the intermediate formation of substances of Type X which then lose the more active N-hydrogen atom, this being the same in both cases. It may not confirm this, since the N-hydrogen in these amidines is probably highly mobile, as in imidazoles and benzimidazoles, so that separation of isomers is not possible.

Since aniline hydrochloride also rearranges substituted diarylformamides to give symmetrically substituted tri-(*p*-aminophenyl)methanes (1, 3), it indicates that a chain of addition-replacement reactions must be involved.

EXPERIMENTAL³

Ethylisoformanilides. The method employed for the preparation of these reagents was essentially that of Claisen (11). The unsubstituted isoanilide was prepared by the inclusion of aniline hydrochloride, as recommended by Hamer, Rathbone, and Winton (12).

A mixture of 26.1 g. (0.2 mole) of *o*- or *p*-chloroaniline and 66 cc. (0.4 mole) of ethylorthoformate was heated in an oil-bath at 140° for two hours, when somewhat more than the calculated quantity of ethanol had distilled. This was contaminated with a little ethyl orthoformate. The product, an oil, was then distilled at atmospheric pressure. Ethyl-*o*-chloroisoformanilide was thus obtained as a colorless oil, b.p. 238–240° (769 mm.). Ethyl-*p*-chloroisoformanilide formed a colorless oil, b.p. 154° (45 mm.). In the preparation of the latter, a large quantity of di-*p*-chlorophenylformamide was also obtained.

Anal. Calc'd for C₉H₁₀ClNO: Cl, 19.35.

Found: Cl, 19.1 (*o*-isomer); Cl, 19.2 (*p*-isomer).

Diphenylformamide. (a) A mixture of 4.97 g. (0.033 mole) of ethylisoformanilide and 3.1 g. (0.033 mole) of aniline was heated for two hours on the steam-bath under slightly reduced pressure. The required amount of alcohol had then distilled. The solid product was ground under ligroin-benzene (2:1), collected, and dried. It had m.p. 135° and weighed 6.5 g. (99.5%). Recrystallized from benzene-ligroin, it formed colorless needles, m.p. 139°, in 94% yield.

(b) Proceeding as for (a) but using 6.2 g. (0.067 mole) of aniline and heating for three hours, the product obtained after washing out excess aniline with benzene-ligroin (1,2) had m.p. 139° [mixed m.p. with product from (a), 139°], yield, 94%.

N-Phenyl-*N'*-*o*-chlorophenylformamide. (a) A mixture of 24.8 g. (0.166 mole) of ethylisoformanilide and 21.7 g. (0.166 mole) of *o*-chloroaniline was heated together on the steam-bath under slightly reduced pressure for two hours. The solid obtained on cooling weighed 26 g. (73%) and had m.p. 113° after having been washed with a little methanol. From the latter solvent it formed colorless tablets, m.p. 113°.

³ Microanalyses were made by Drs. Weiler and Strauss, Oxford University, England.

(b) A mixture of 4.6 g. of ethyl-*o*-chloroisoformanilide and 2.3 g. of aniline treated as above gave the same product, m.p. 113°; the mixed melting point with the product obtained under (a) was 113°.

Anal. Calc'd for $C_{13}H_{11}ClN_2$: Cl, 15.4. Found: Cl, 15.49.

Heating ethylisoformanilide with two moles of *o*-chloroaniline on the steam-bath for three hours gave the same product, m.p. 113° [mixed m.p. with (a) and (b), 113°].

N-Phenyl-*N'*-*p*-chlorophenylformamidine. A mixture of 24.8 g. (0.166 mole) of ethylisoformanilide and 21.7 g. (0.166 mole) of *p*-chloroaniline was heated as for the *o*-isomer, giving a 100% yield of amidine. It formed colorless prisms, m.p. 122°, from methanol.

Anal. Calc'd for $C_{13}H_{11}ClN_2$: Cl, 15.4. Found: Cl, 15.1.

On employing two moles of *p*-chloroaniline for one mole of ethylisoformanilide, di-*p*-chlorophenylformamidine, m.p. 181°, was obtained in 62% yield. Mixed m.p. 181° with product obtained according to Lewis and co-workers (1) who record m.p. 184°.

N-*o*-Chlorophenyl-*N'*-*p*-chlorophenylformamidine. This amidine was readily obtained on heating molar quantities of *p*-chloroaniline and ethyl-*o*-chloroisoformanilide. It formed short, glassy needles, m.p. 155–159°, from methanol.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: Cl, 26.8. Found: Cl, 26.9.

Di-*o*-chlorophenylformamidine, m.p. 140°, was obtained in 80% yield from molar amounts of ethyl-*o*-chloroisoformanilide and *o*-chloroaniline. The melting point of 140° showed no depression on admixture with a specimen prepared according to Lewis and co-workers (1). The *p*-isomer, similarly prepared in 100% yield, had m.p. 181° and did not depress the melting point of a specimen prepared according to Lewis and co-workers (1). It was also obtained in 80% yield by fusing molar quantities of *N*-*p*-chlorophenyl-*N'*-phenylformamidine and *p*-chloroaniline on the steam-bath for one hour.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: Cl, 26.8. Found: Cl, 26.7.

Diphenylformamidine hydrochloride. (a) The base, prepared by the method of Giacolone, was treated in benzene solution with a stream of dry hydrogen chloride and the resultant precipitate recrystallized by the slow addition of ether to a warm methanol solution of the salt, giving glistening platelets, m.p. 245°, containing alcohol lost on heating for three hours at 100° and 20 mm.

Anal. Calc'd for $C_{13}H_{13}ClN_2$: Cl, 15.25. Found: Cl, 15.0.

(b) To a solution of 9.3 g. of aniline and 12.95 g. of aniline hydrochloride in 20 cc. of warm methanol was added 14.8 g. of ethyl orthoformate. A crystalline precipitate formed rapidly. After warming gently for five minutes, the reaction was complete and the required hydrochloride was completely precipitated by the addition of ether. After one recrystallization from methanol-ether, it was obtained in 94.5% yield, m.p. 245°. The mixed melting point with product obtained under (a) was 245°.

Anal. Calc'd for $C_{13}H_{13}ClN_2$: Cl, 15.25. Found: Cl, 15.1.

SUMMARY

1. Contrary to the conclusions of Giacolone (3), and of Lewis and his co-workers (1), it has been proved that the only solid reaction product of aniline and ethyl orthoformate is diphenylformamidine.

2. Analogous products were obtained when aniline was replaced by *o*- or *p*-chloroaniline.

3. Unsymmetrical chloro derivatives of diphenylformamidines were prepared.

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