precipitation of the amine hydrobromide was observed. The reaction mixture was filtered and the filtrate evaporated to dryness at room temperature. The residue was triturated twice in hot water to dissolve amine salts and then recrystallized from chloroform keeping heat at the minimum compatible with recrystallization requirements. The selenenamides were formed in 72, 64 and 70% yields.

1-[4(and 2)-Aminonaphthyl] 2,4-Dinitrophenyl Selenides.—The same method as described for preparation of N-aryl selenenamides was used in the reaction of 1- and 2-naphthylamines with 2,4-DNBSe bromide. These compounds were much less soluble in chloroform than the selenenamides.

Hydrogen Chloride Cleavage of N-Aryl 2,4-Dinitrobenzeneselenenamides.—Dry hydrogen chloride was bubbled through cold chloroform solutions of each selenenamide for 10 minutes. The solution changed from red to yellow and a white precipitate formed. The melting point of the precipitate was found in each case to agree with that of the corresponding amine hydrochloride.

Hydrogen Chloride Treatment of 1-[4(and 2)-Aminonaphthyl] 2,4-Dinitrophenyl Selenides.—Dry hydrogen chloride was bubbled through solutions of about 50 mg. of each selenide in 20 ml. of cold chloroform. The color changed from orange to light yellow; the original color slowly returned on standing. Attempts to isolate hydrochloride salts of the selenides by evaporation of the chloroform in air or *in vacuo* led only to recovery of the original selenide. The latter were identified by the mixed melting point technique. No evidence was observed for the presence of a naphthylamine hydrochloride based on precipitation or water extraction.

HOUGHTON, MICHIGAN RECEIVED JULY 24, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Ortho Esters, Imidic Esters and Amidines. II. Disproportionation Reactions of Nitrophenyl-, Chlorophenyl- and Tolyl-substituted Formimidates and Formamidines

BY ROYSTON M. ROBERTS, ROBERT H. DEWOLFE, AND JOSEPH H. ROSS

The study of acid-catalyzed disproportionations which may occur during syntheses involving imidic esters and amidines is continued. Reactions involving *p*-nitroaniline, *o*- and *p*-chloroaniline and *o*-toluidine derivatives are described. It is shown that the occurrence and course of the reaction are highly dependent on acid concentrationa nd are influenced more by steric and statistical factors than by the relative basicity of the amino groups involved, as has been suggested. The mechanisms of the reactions are discussed. Several new unsymmetrical N,N′-diarylformamidines are reported and some are correctly reported for the first time.

In a previous publication[1] we described an acid-catalyzed disproportionation which may occur during the preparation of N-phenyl-N′-*p*-tolylformamidine, and we mentioned that similar results were encountered in the preparation of N-phenyl-N′-*p*-nitrophenylformamidine. The purpose of this paper is to give the experimental data related to the latter compound and also to the analogous compounds derived from *o*- and *p*-chloroaniline and *o*-toluidine.

p-Nitroaniline reacts with ethyl N-phenylformimidate less readily than does *p*-toluidine and, at the higher temperatures employed, there was always some disproportionation resulting in the formation of N,N′-diphenylformamidine and N,N′-di-*p*-nitrophenylformamidine as well as the expected N-phenyl-N′-*p*-nitrophenylformamidine, even when precautions were taken against the presence of traces of acids. Because of the large differences in the solubilities of these compounds, it was feasible to separate them and identify each of them directly from reaction mixtures, which was not the case with the analogous *p*-tolyl derivatives. The ultraviolet absorption spectra of these three compounds are shown in Fig. 1.

The unsymmetrical nitro-substituted formamidine could be "disproportionated" by heating it in ethanol in the presence of an acid catalyst, producing a mixture containing the two corresponding symmetrical formamidines as well as the original substance; the more insoluble N,N′-di-*p*-nitrophenylformamidine was isolated from such a mixture. Another component of the mixture is *p*-nitroaniline. This result can be explained reasonably by reference to Fig. 1 of the preceding paper[1] of this series. The large amount of ethanol required to dissolve N-phenyl-N′-*p*-nitrophenylformamidine displaces the equilibria set up between the three formamidines and ethanol on the one hand and the two aromatic amines and two N-arylformimidates on the other in favor of a high concentration of the latter substances. When, in a second experiment, the ethanol was slowly removed from the reaction mixture by distillation, N,N′-di-*p*-nitrophenylformamidine was isolated; this is in accord with the expectation of shifting (by the removal of ethanol) the equilibria toward completeness of reaction of aromatic amines with N-arylformimidates producing the three formamidines.

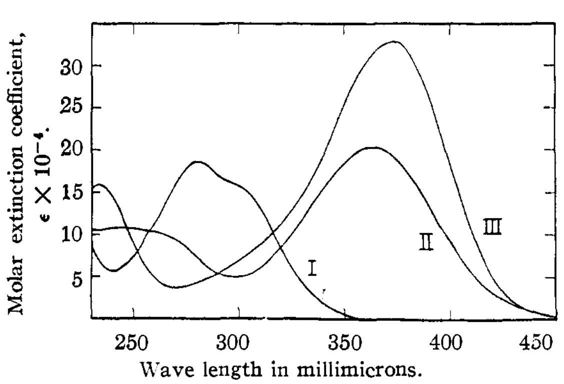

Fig. 1.—Ultraviolet absorption spectra in isopropyl alcohol: I, N,N′-diphenylformamidine; II, N-phenyl-N′-*p*-nitrophenylformamidine; III, N,N′di-*p*-nitrophenylformamidine.

The reverse of the above changes was effected by heating N,N′-diphenylformamidine and N,N′-di-*p*-nitrophenylformamidine with ethanol in nitrobenzene solution containing a trace of acid. The unsymmetrical formamidine was produced and could

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[1] R. M. Roberts, THIS JOURNAL, **72**, 3603 (1950).

be isolated from the equilibrium mixture containing all three.

Our attention was directed to the chlorine-substituted compounds by a recent publication of Knott and Jeffreys.[2] These workers observed the reaction of two molar equivalents of *p*-chloroaniline with one molar equivalent of ethyl N-phenylformimidate to produce N,N′-di-*p*-chlorophenylformamidine (equation 1) and the reaction of equimolar amounts of N-phenyl-N′-*p*-chlorophenylformamidine and *p*-chloroaniline to yield the same product (equation 2); but they reported that similar reactions with *o*-chloroaniline and its derivatives did not take place.

$$\mathrm{C_6H_5N{=\!=}CHOEt + 2ClC_6H_4NH_2 \longrightarrow}$$
$$\mathrm{ClC_6H_4N{=\!=}CH{-\!-}NHC_6H_4Cl + EtOH + C_6H_5NH_2} \quad (1)$$

$$\mathrm{C_6H_5N{=\!=}CH{-\!-}NHC_6H_4Cl + ClC_6H_4NH_2 \longrightarrow}$$
$$\mathrm{ClC_6H_4N{=\!=}CH{-\!-}NH{-\!-}C_6H_4Cl + C_6H_5NH_2} \quad (2)$$

The mechanism proposed to apply to the reactions observed involved the intermediate formation of a trianilinomethane molecule with subsequent loss of "the more electronegative group"[3] together with a proton from the other group. This interpretation appears to us unsatisfactory for the following reasons: (1) it predicts an incorrect result when applied to the reaction of Walther[4] cited as an example by Knott and Jeffreys, since *p*-toluidine is more basic than aniline (Table I); (2) it does not explain the failure of *o*-chloroaniline to react; in fact, on the basis of relative basicity alone, the *o*-chloro group should be more effective than the *p*-chloro in competing with anilino for a proton (Table I); (3) our experience with the effects of small amounts of acids on similar systems[1] would indicate acid catalysis to be a factor which could cause significant differences in these reactions and should not be overlooked.

TABLE I

COMPARATIVE BASICITY OF TOLUDINES, CHLOROANILINES AND ANILINE

	pK_a	K_b
p-Toluidine	5.17^a	1.5×10^{-9}
	5.07^b	1.2×10^{-9}
m-Toluidine	4.69^b	5.0×10^{-10}
Aniline	4.69^a	5.0×10^{-10}
	4.58^b	3.8×10^{-10}
o-Toluidine	4.39^b	2.5×10^{-10}
p-Chloroaniline	4.03^a	1.1×10^{-10}
m-Chloroaniline	3.54^a	3.5×10^{-11}
o-Chloroaniline	2.68^a	4.8×10^{-12}

[a] J. N. Brønsted, A. Delbanco and A. Tovborg-Jensen, *Z. physik. Chem.*, **A169**, 361 (1934). [b] N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

We have now examined these reactions experimentally from the viewpoints of (1) effect of the presence or absence of acid, and (2) relative basicity of the aromatic amines involved, and we have found that the first factor has a very important and the second an insignificant influence on the course of the reactions.

The reactions described above involving *p*-chloroaniline were repeated, care being taken to exclude any acid from the reaction mixtures. In the first experiment (equation 1), pure N-phenyl-N′-*p*-chlorophenylformamidine was isolated in spite of the excess *p*-chloroaniline, and in the second (equation 2), the unsymmetrical formamidine was recovered unchanged after heating it with *p*-chloroaniline. Very different results were obtained, however, in the presence of traces of acid (aniline hydrochloride); in both cases N,N′-di-*p*-chlorophenylformamidine was produced. Repetition of these experiments with *o*-chloroaniline gave similar results; *i.e.*, in the absence of acid the unsymmetrical formamidine was produced and remained unchanged; in the presence of acid N,N′-di-*o*-chlorophenylformamidine was produced in both cases. Hence, we must surmise that Knott and Jeffreys had traces of acid present in the experiments with *p*-chloroaniline but not in those with *o*-chloroaniline. Further substantiation of this idea is furnished by the melting point (122°) they report for N-phenyl-N′-*p*-chlorophenylformamidine, which is 14° below that of our analytically pure sample; traces of acid in the reaction mixture lead to products melting, after one or two recrystallizations, near this point.

Because of steric factors, one would not expect that *o*- and *p*-chloroaniline would react according to equations 1 and 2 with equal velocities or would produce the same equilibrium mixture. Likewise, one would hardly expect complete lack of reaction in the absence of acid under all other experimental conditions. We did observe an appreciable difference in the tendency of *o*- and *p*-chloroaniline to undergo reaction according to equation 1. When, with the same precautions against the presence of acid, ethyl N-phenylformimidate was treated with *six* molar equivalents of the respective chloroanilines, the crude crystalline product of the reaction involving the ortho isomer gave pure unsymmetrical formamidine upon recrystallization, whereas the product of the reaction involving the para isomer was a mixture containing a large proportion of N,N′-di-*p*-chlorophenylformamidine. Hence, disproportionation seems to occur less readily with the ortho isomer, as expected.

The same effect is shown by the corresponding toluidines; the preparation of N-phenyl-N′-*o*-tolylformamidine does not appear to be nearly so sensitive toward disproportionation as that of the para isomer.[1] Even when a 3/1 molar ratio of *o*-toluidine to ethyl N-phenylformimidate was used, the unsymmetrical formamidine was obtained in a pure state in the absence of acid. Under the same conditions, except for the presence of acid, disproportionation with the formation of N,N′-di-*o*-tolylformamidine took place. It is interesting to observe that the products reported by Zwingenberger and Walther[5] as isomers of N-phenyl-N′-*o*-tolylformamidine are, as in the case of the para isomer,[1] impure mixtures. We prepared this compound as described above and also from aniline and ethyl N-*o*-tolylformimidate and obtained the same product, which melted higher than any of those reported by Zwingenberger and Walther.

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(2) E. B. Knott and R. A. Jeffreys, *J. Org. Chem.*, **14**, 879 (1949).

(3) Presumably "more basic group" would be correct American terminology since Knott and Jeffreys refer to anilino as more electronegative than *p*-chloroanilino (see Table I).

(4) R. Walther, *J. prakt. Chem.*, **2**, 53, 472 (1896).

(5) O. Zwingenberger and R. Walther, *ibid.*, **2**, **57**, 209 (1898).

The catalytic effect of acids on the rate of reaction between formimidic esters and aromatic amines is illustrated by comparison of those experiments described above in which small amounts of aniline hydrochloride were added and those in which only the carefully purified reactants were present with trials in which small amounts of sodium *t*-butoxide were added. A mixture of ethyl N-phenylformimidate and six molar equivalents of *o*-chloroaniline heated to 100° for three hours gave no crystalline products, and an equimolar mixture of the same reactants treated similarly and then allowed to stand at room temperature deposited crystals only after more than three weeks; the product was N-phenyl-N'-*o*-chlorophenylformamidine.

Two tests of the relative basicity theory were made. N-Phenyl-N'-*p*-chlorophenylformamidine was heated with an equivalent amount of aniline and a trace of acid. If a trianilinomethane molecule, produced as an intermediate, were to lose the more basic aromatic amino group, anilino, the product would be identical with the starting material; *i.e.*, the N-phenyl-N'-*p*-chlorophenylformamidine would be recovered unchanged. It is implicit in this theory that the effect of relative basicity is more important than the statistical effect, *i.e.*, the relative number of anilino and *p*-chloroanilino groups available in the reaction mixture. Actually, a mixture of formamidines was produced, and we believe that the reverse is true. Other factors which may have an important influence on the proportion of products obtained are the melting point and the solubility of the formamidines present in the equilibrium mixture.

The mechanism of the reaction of equation 1 is probably that represented in Fig. 1 of the preceding paper,[1] and a similar mechanism for the reaction of equation 2 can be formulated by substituting RN═CH—NHR' for RN═CH—OEt and making the obvious simplifications. Equations 1 and 2 are actually incomplete, since undoubtedly N,N'-diphenylformamidine is also produced by the disproportionations. As an approximation, let us assume that the constants of all the equilibrium reactions in Fig. 1[1] are equal to one when ortho substituents are not involved. We can then calculate statistically the proportions of the three formamidines which would be present at equilibrium if we know the proportions of the two different aromatic amino groups contained in the starting materials. For example, starting with one mole of ethyl N-phenylformimidate and two moles of *p*-chloroaniline should give an equilibrium mixture containing N,N'-di-*p*-chlorophenylformamidine, N-phenyl-N'-*p*-chlorophenylformamidine and N,N'-diphenylformamidine in the molar ratio of 4/9, 4/9 and 1/9. The same equilibrium mixture should result from the reaction of one mole of N-phenyl-N'-*p*-chlorophenylformamidine with one mole of *p*-chloroaniline. Using starting materials containing two moles of anilino per mole of *p*-chloroanilino would reverse the equilibrium ratio with respect to the symmetrical compounds, whether the starting materials were imidic ester and amine or amidine and amine. Knott and Jeffreys reported a yield of N,-N'-di-*p*-chlorophenylformamidine of 62% according to equation 1 and 80% according to equation 2, both higher than predicted by simple statistics. When we carried out the reaction of N-phenyl-N'-*p*-chlorophenylformamidine with aniline, which is analogous to the reaction of equation 2, but with the ratio of anilino to *p*-chloroanilino groups reversed, the product was a mixture which was not easily separated by crystallization. These results are understandable when one considers that N,N'-di-*p*-chlorophenylformamidine is much higher-melting and less soluble than N,N'diphenylformamidine, which has a melting point and solubility similar to the unsymmetrical formamidine.

The second test involved reaction between N-*m*-chlorophenyl-N'-*p*-tolylformamidine and *p*-toluidine. The arylamino groups here differ in basicity by a factor of *ca.* 43 (Table I) and if the more basic group (*p*-toluidino) were lost from an intermediate trianilinomethane molecule, the product would be identical with the original formamidine. Again, a mixture was produced. This mixture was remarkably similar to the product melting at 86° described in the preceding paper[1]: it melted lower than any of the possible formamidines and melted sharply at the same temperature after repeated recrystallization. It was treated as in the previous case; *i.e.*, converted by picric acid to a mixture of salts which could be separated by fractional crystallization. The picrate of N,N'-di-*p*-tolylformamidine was obtained in this way, indicating that it was probably the formamidine predominating in the mixture. A Rast molecular weight determination on the constant-melting mixture substantiated this view.

Experimental[6]

N-Phenyl-N'-*p*-nitrophenylformamidine.—In a distilling flask which had been washed with ammonia and dried carefully, *p*-nitroaniline (0.1 mole) and ethyl N-phenylformamidate (0.1 mole) were heated at 180° for two hours; 4.6 ml. of alcohol was collected in an ice-cooled receiver. The reaction mixture was poured while hot into 50 ml. of dry toluene. The crystalline product was collected by filtration and washed with toluene and petroleum ether; it weighed 18.8 g. It was then boiled with 400 ml. of dry toluene which dissolved all but 1.9 g. (m.p. 235–240°). The hot filtrate from this residue when cooled deposited 12.3 g. (51%) of yellow crystals, m.p. 181–184°. This product, like those obtained in many other experiments, melted over a 2° or 3° range between 180 and 185°; it was recrystallized as many as eight times from toluene and five times from ethanol without raising the melting point above 185°. It is best purified from the less soluble N,N'-di-*p*-nitrophenylformamidine by using insufficient solvent to dissolve the whole sample and filtering the hot mixture. The sample analyzed melted at 183–185°.

Anal.[7] Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60. Found: C, 64.57; H, 4.51.

The ultraviolet absorption spectra of this compound and of the two corresponding symmetrical compounds were determined using a Beckman model DU spectrophotometer; they are shown in Fig. 1.

N,N'-Di-*p*-nitrophenylformamidine was always obtained as a by-product in the preparation of the unsymmetrical compound. It was separated as described above and purified by several recrystallizations from nitrobenzene or a mixture of toluene and nitrobenzene; it was identified by mixture melting point tests with authentic material prepared from ethyl orthoformate and *p*-nitroaniline. The pure material melts at 245–246° (considerably higher than the value reported by Walther,[4] 236–237°).

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[6] All melting points are corrected.

[7] All analyses by Clark Microanalytical Laboratory, Urbana, Ill.

N,N′-Diphenylformamidine was isolated from a reaction mixture containing originally 0.02 mole of *p*-nitroaniline and ethyl N-phenylformimidate and a small crystal of *p*-toluenesulfonic acid. This mixture was heated at 120° for two hours. The crude product (m.p. 145–155°) was extracted by dry benzene in a Soxhlet apparatus. The cooled benzene extract was filtered to remove the crystals which had separated and further crops of crystals were subsequently obtained by evaporating, cooling and diluting the benzene solution with petroleum ether. Activated charcoal was finally used to remove almost all of the yellow color from the benzene–petroleum ether solution, which then yielded white crystals, m.p. 135–138°; these did not depress the melting point of authentic N,N′-diphenylformamidine. The product which was left undissolved by the benzene in the Soxhlet thimble was recrystallized from toluene and nitrobenzene to yield N,N′-di-*p*-nitrophenylformamidine, m.p. 236–241°.

Reactions of N-Phenyl-N′-*p*-nitrophenylformamidine in Acidic Ethanolic Solution.—The unsymmetrical formamidine (0.01 mole) was boiled under reflux with 75 ml. of absolute ethanol containing 10^{-4} mole of *p*-toluenesulfonic acid for five hours. No crystals separated on cooling, so the solution was concentrated to *ca.* 15 ml. by distillation. Cooling overnight now produced 0.93 g. of crystals which melted at 105–107°. Recrystallization three times from dry benzene raised the melting point to 144.5–148.7°. A recrystallization from aqueous ethanol gave yellow crystals, m.p. 147–149°, identical by mixture melting point test with *p*-nitroaniline.

The experiment was repeated, but the ethanol was removed almost completely by distillation through a short packed column before the mixture was cooled. The crude product, after washing with dry benzene and ethanol, weighed 1.48 g. and melted at 140–207°. Extraction of this product with hot, dry benzene left an insoluble residue which was repeatedly crystallized from toluene and nitrobenzene to yield N,N′-di-*p*-nitrophenylformamidine, m.p. 241–243°, undepressed by mixture with an authentic sample.

Reaction of N,N′-Diphenylformamidine with N,N′-Di-*p*-nitrophenylformamidine in Acidic Ethanolic Solution.—The two formamidines (0.025 mole of each), N,N′-diphenylformamidine hydrochloride (5 × 10^{-4} mole), ethanol (2 ml.) and nitrobenzene (50 ml.) were heated under reflux until all the solid dissolved, and then the heating was continued 40 minutes longer. The nitrobenzene was removed by distillation at reduced pressure and the crystalline residue was washed with nitrobenzene, benzene and petroleum ether in succession; this residue weighed 7.80 g., m.p. 155–193°. It was boiled with 50 ml. of dry toluene and the hot mixture was filtered, giving an insoluble yellow residue (2.2 g., m.p. 230–236°) and a clear filtrate which on cooling deposited 4.03 g. of yellow crystals, m.p. 178–181°. Recrystallization of the latter from 100 ml. of dry toluene gave 3.76 g., m.p. 181.2–183.5°. The ultraviolet absorption spectrum of this product was identical with that (Fig. 1) of the product from the reaction of *p*-nitroaniline with ethyl N-phenylformimidate.

***p*-Chloroaniline and Ethyl N-Phenylformimidate. A. Acid-Free.**—Both reactants were distilled before use from a small amount of sodium *t*-butoxide and all glassware was rinsed with ammonium hydroxide solution and distilled water before drying. *p*-Chloraniline (0.022 mole) and ethyl N-phenylformimidate (0.011 mole) were heated at 100° for three hours in a ground glass-jointed test-tube connected through a calcium chloride-tube to a water pump. The reaction mixture was dissolved in the minimum amount of hot isopropyl alcohol and the crystals obtained by cooling slightly were collected; m.p. 128–131°. After four additional crystallizations from the same solvent, the product, N-phenyl-N′-*p*-chlorophenylformamidine, melted at 132–134.5°. The analytical sample of this compound was actually prepared from aniline and ethyl N-*p*-chlorophenylformimidate; white crystals, m.p. 133.4–135.6° (undepressed by mixture with the product from the other reactants).

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81. Found: C, 67.49; H, 4.82.

The experiment was repeated using 0.05 mole of the imidic ester and 0.30 mole of *p*-chloroaniline. The reaction mixture was dissolved in isopropyl alcohol as before, a small volume of petroleum ether was added and the solution was cooled. The small crop of crystals which separated melted at 145–158°. After three more crystallizations from the same solvent pair, a small amount of product melting at 173–177° was obtained.

B. **Acid Present.**—The same amounts of reactants as in the first experiment were used, plus 1.6 mg. (10^{-5} mole) of *p*-chloroaniline hydrochloride, and the mixture was treated in exactly the same way. The first crop of crystals from isopropyl alcohol melted at 165–173°; after four recrystallizations the m.p. was 175–180°, undepressed by mixture with pure N,N′-di-*p*-chlorophenylformamidine (m.p. 182–183°).

***p*-Chloroaniline and N-Phenyl-N′-*p*-chlorophenylformamidine. A. Acid-Free.**—Equivalent amounts (0.004 mole) of these compounds were heated at 100° for one hour; the reaction mixture was dissolved in the minimum volume of hot isopropyl alcohol and the crystals obtained by cooling were collected, m.p. 123–132°. One recrystallization raised the m.p. to 131.5–134.2°, undepressed by mixture with pure N-phenyl-N′-*p*-chlorophenylformamidine.

B. **Acid Present.**—The above experiment was repeated with 0.005-mole quantities plus 1 mg. of aniline hydrochloride. The first crop of crystals from isopropyl alcohol melted at 157–167°; five recrystallizations from the same solvent raised the melting point to 177–180°, undepressed by mixture with pure N,N′-di-*p*-chlorophenylformamidine.

***o*-Chloroaniline and Ethyl N-Phenylformimidate. A. Acid-Free.**—A 2:1 molar ratio of amine to imidic ester was treated as in the case of the para isomer. The product, crystallized once from isopropyl alcohol, melted at 106–110°; three recrystallizations raised the m.p. to 114–115.6°, undepressed by mixture with pure N-phenyl-N′-*o*-chlorophenylformamidine obtained from equimolar amounts of reactants.[8]

A reaction mixture containing 6 moles of amine per mole of imidic ester was heated similarly; the excess *o*-chloroaniline was largely removed by distillation under reduced pressure. The product which crystallized was washed with a mixture of isopropyl alcohol and petroleum ether: white crystals; m.p. 102–106.5°. Seven recrystallizations from this solvent pair gave almost pure N-phenyl-N′-*o*-chlorophenylformamidine, m.p. 112–114°.

B. **Acid Present.**—A mixture of 0.1 mole of *o*-chloroaniline, 0.05 mole of ethyl N-phenylformimidate and 0.005 mole of *o*-chloroaniline hydrochloride was heated as before. The crude reaction mixture was refluxed with a mixture of petroleum ether and dry benzene and the insoluble *o*-chloroaniline hydrochloride was removed by filtration. The filtrate was cooled, giving 4.9 g. of crystals, m.p. 111–121°. Three subsequent recrystallizations from isopropyl alcohol–petroleum ether raised the m.p. to 124–129°. Disproportionation was evident since the m.p. of pure N-phenyl-N′-*o*-chlorophenylformamidine is well below that of this product. N,N′-Di-*o*-chlorophenylformamidine was completely isolated from a reaction mixture containing originally 0.05 mole of imidic ester, 0.30 mole of amine and 0.0005 mole of amine hydrochloride. The crude product melted at 115–127°; eleven recrystallizations from isopropyl alcohol–petroleum ether gave white crystals, m.p. 139–141°, undepressed by mixture with authentic N,N′-di-*o*-chlorophenylformamidine (m.p. 142–143).

C. **In the Presence of Sodium *t*-Butoxide.**—A mixture containing 6 moles of amine per mole of imidic ester plus a few crystals of sodium *t*-butoxide was heated for three hours at 100°. The excess *o*-chloroaniline was distilled under reduced pressure; the residue did not crystallize when cooled.

A second mixture containing equimolar amounts of reactants plus a few crystals of sodium *t*-butoxide was heated similarly and allowed to stand stoppered at room temperature; after more than three weeks, crystals began to form. These were presently collected and appeared to be fairly pure N-phenyl-N-*o*-chlorophenylformamidine, m.p. 111–115°.

***o*-Chloroaniline and N-Phenyl-N′-*o*-chlorophenylformamidine. A. Acid Free.**—The experiment was carried out as with the para isomer, except that the formamidine was recovered by adding petroleum ether to the warm reaction mixture. After it was washed on the filter with petroleum

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[8] Our purest sample of N-phenyl-N′-*o*-chlorophenylformamidine melted at 116.1–116.5° which was somewhat higher than the value (113°) reported by Knott and Jeffreys.[9]

ether, the crystalline product melted at 115–116.2°, undepressed by mixture with pure starting material.

B. **Acid Present.**—The above experiment was repeated except that a small amount of aniline hydrochloride was added (10^{-3} mole per mole of reactants). The recovered formamidine was recrystallized ten times from isopropyl alcohol–petroleum ether; N,N′-di-*o*-chlorophenylformamidine, m.p. 138–140°, was obtained.

o-**Toluidine and Ethyl N-Phenylformimidate. A. Acid-Free.**—A mixture of 0.03 mole of the amine and 0.01 mole of the imidic ester was heated as before. The crude crystalline product was washed with petroleum ether; m.p. 111–112°. Four recrystallizations raised the m.p. to 113.1–113.5°. This product was also prepared from aniline and ethyl N-*o*-tolylformimidate; it was recrystallized from isopropyl alcohol–petroleum ether. The analytical sample melted at 114.4–114.9°.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71. Found: C, 80.07; H, 6.98.

B. **Acid Present.**—*o*-Toluidine (0.03 mole), ethyl N-phenylformimidate (0.1 mole) and *o*-toluidine hydrochloride (10^{-5} mole) were heated as before. The crude petroleum ether-washed product melted at 125–138°. Seven recrystallizations from isopropyl alcohol–petroleum ether raised the m.p. to 147–150°, undepressed by mixture with N,N′-di-*o*-tolylformamidine (m.p., 151–152°).

Aniline and N-Phenyl-N′-*p*-chlorophenylformamidine.—A mixture of 0.005 mole of each reactant plus a trace of sulfuric acid was heated for three hours at 100°. The crude product was recrystallized three times from petroleum ether and isopropyl alcohol–petroleum ether, giving crystals, m.p. 110–120°; after three more recrystallizations, 120–125°; after two more recrystallizations, 122–126°. Purification by recrystallization was abandoned at this point due to the small amount of material remaining; apparently extensive disproportionation took place. Previous experiments (see ref. 1, p. 3607) have shown that a symmetrical formamidine may readily be recovered unchanged after heating with ethanol and *p*-toluenesulfonic acid for two hours, so the likelihood of decomposition by means other than disproportionation under these conditions appears negligible.

p-**Toluidine and N-*m*-Chlorophenyl-N′-*p*-tolylformamidine.**—The new unsymmetrical formamidine was prepared from *m*-chloroaniline and ethyl N-*p*-tolylformimidate with the proper precautions against acid and was recrystallized from isopropyl alcohol–petroleum ether. The pure substance melted at 130–131°.

Anal. Calcd. for $C_{14}H_{13}N_2Cl$: C, 68.71; H, 5.35; mol. wt., 245. Found: C, 68.73; H, 5.20; mol. wt. (Rast), 248.

A picrate was prepared by mixing isopropyl alcohol solutions of the formamidine and picric acid and was recrystallized from the same solvent; m.p. 187–188°.

Anal. Calcd. for $C_{20}H_{16}O_7N_5Cl$: C, 50.69; H, 3.40. Found: C, 51.05; H, 3.42.

A 0.92-g. (0.0038 mole) sample of the formamidine and 0.39 g. (0.0037 mole) of *p*-toluidine were heated at 100° for three hours. No acid was added since the *p*-toluidine used had not been redistilled for several weeks. Petroleum ether was added to the warm reaction mixture, and the fine white needles which separated on cooling to room temperature were collected; m.p. 107–109°. Two recrystallizations from isopropyl alcohol–petroleum ether raised the m.p. to 109–110.5°, and four subsequent recrystallizations from the same solvent pair did not change the m.p. This product was dissolved in the minimum amount of isopropyl alcohol at room temperature and the solution was added to an equal volume of a saturated solution of picric acid in the same solvent. A yellow precipitate separated immediately; it was collected and washed with isopropyl alcohol; m.p. 170–175°. This product was recrystallized seven times from isopropyl alcohol; the m.p. was then 218–222°, undepressed by mixture with N,N′-di-*p*-tolylformamidine picrate (m.p., 220–225°), depressed to 190–205° by mixture with N,N′-di-*m*-chlorophenylformamidine picrate (m.p., 240° dec.).

The molecular weight of the product melting at 109–110.5° was determined by the Rast procedure: Calcd. for N,N′-di-*m*-chlorophenylformamidine, 265; for N-*m*-chlorophenyl-N′-*p*-tolylformamidine, 245; for N,N′-di-*p*-tolylformamidine, 224; found, 233.

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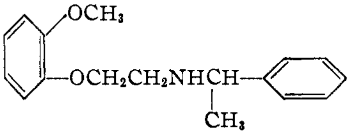
Local Anesthetics. I. Some Aryl Alkamine Ethers

By Howard B. Wright and M. B. Moore

Thirty-one alkamine aryl ethers have been synthesized and examined for local anesthetic effect. None proved more promising than β-(α-methylbenzylamino)-ethyl *o*-anisyl ether, which is approximately twice as active as procaine.

Numerous alkamine ethers of phenols[1] and arylalkanols[2] have been reported in the literature. β-(α-Methylbenzylamino)-ethyl *o*-anisyl ether (I) was prepared in this Laboratory and submitted for testing as a local anesthetic. Its interesting pharmacological properties led us to synthesize a series of alkamine aryl ethers, most of which are new. One arylalkanol ether was included in the study for comparative purposes. Preparative methods are given in the Experimental part, and all of the compounds with the exception of I were made by method B. They are listed in the tables with their physical constants and analytical data.



I

The hydrochlorides of the compounds reported have been studied pharmacologically by Dr. R. K. Richards and his staff, especially with regard to their local anesthetic value. Nearly all exhibit some degree of local anesthetic effect, exceptions being compounds 6 and 26 of Table I. However, none showed particular advantage over compound 1, which is approximately twice as effective as procaine.

Experimental[3]

Method A. **β-(α-Methylbenzylamino)-ethyl *o*-Anisyl Ether.**—β-(2-Methoxyphenoxy)-ethyl bromide, 1.15 g.

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(2) (a) W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 3795 (1949); (b) L. C. Cheney, R. R. Smith and S. B. Binkley, *ibid.*, **71**, 60 (1949); (c) W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 64 (1949).

(3) All melting points are uncorrected.