whereas, as is indicated in Formula VII, cocaine possesses a chain of 3 carbon atoms between the *N* and *O* atoms in the amino alcohol. Cocaine is considerably more toxic than procaine but for certain types of anesthesia, such as surface anesthesia, it shows stronger action than procaine because of its greater powers of penetration.

The new homologue of procaine (Formula VI) which also possesses a chain of 3 carbon atoms between the *O* and the *N* atoms of the amino-alcohol, might, therefore, be predicted to fall somewhere between procaine and cocaine in its physiological behavior, although one would expect it to be considerably more closely related to the former compound. Tests show that these predictions are entirely substantiated. The new compound is slightly more toxic than procaine; on the other hand, its effectiveness for the production of surface anesthesia is considerably greater than that possessed by its lower homolog. For certain purposes, a given result may, therefore, be obtained with a considerably smaller quantity of anesthetic, increased effectiveness more than counterbalancing the effect of slightly increased toxicity.

The writer realizes the dangers of drawing broad generalizations upon observations gathered from the testing of a small number of individual compounds, although in the present example a prediction of physiological action of a new compound predicted by analogy to structures of previously known compounds has been completely substantiated. No attempt is made, therefore, to present broader generalizations or to indulge in further speculation until a larger amount of additional experimental data is available.

URBANA, ILLINOIS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WISCONSIN AND OF VANDERBILT UNIVERSITY.]

THE PREPARATION OF *p*-PHENYLENEDIAMINE AND ANILINE FROM THEIR CORRESPONDING CHLOROBENZENES.[1]

BY ARMAND J. QUICK.

Received February 23, 1920.

The stability of the halogen atom attached to the benzene ring has been of considerable interest because it has prevented until recently, the direct synthesis of phenols and aromatic amino compounds from the halogen derivatives of the aromatic hydrocarbons. The early investigators[2] failed entirely in their efforts to replace the halogen by other groups. It was not until 1914 that Meyer and Bergious[3] reported that

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[1] This paper represents a part of a thesis presented by A. J. Quick to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the Degree of Master of Science, June, 1919.

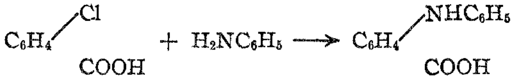
[2] *Ann.*, 104, 225 (1857); 121, 358, 362 (1862).

[3] *Ber.*, 47, 3165 (1914).

a dilute solution of sodium hydroxide converts chlorobenzene almost quantitatively into phenol at 300°, and that ammonia, under similar conditions, converts it partly into aniline.

It has long been known that certain negative groups, of which the nitro group is the best example, when in *ortho* or *para* position to the halogen atom have a marked labilizing effect on it. Engelhardt and Latchinow[1] as early as 1870 reported that they were able to convert *ortho* and *para* nitrochloro-benzene at least partially into their respective nitro-anilines by heating them with ammonia at 150°. In 1908 the *Aktien Gesselschaft fur Anilin Fabrikation*[2] took out a patent for the preparation of *p*-nitroaniline by this process. The conversion of trinitrochloro-benzene into picric acid is another illustration of the labilizing effect of the nitro group which is of commercial significance.

Ullmann[3] accidently made the discovery that metallic copper had a strong labilizing effect on nuclear halogen. While trying to condense *o*-chlorobenzoic acid with sodium phenolate in the presence of finely divided copper, Ullmann incidently used aniline as a solvent. Much to his surprise, the aniline entered into the reaction and *o*-phenyl-anthranilic acid was obtained. The reaction may be represented as follows:



$$C_6H_4\begin{matrix}\diagup Cl \\ \\ COOH\end{matrix} + H_2NC_6H_5 \longrightarrow C_6H_4\begin{matrix}\diagup NHC_6H_5 \\ \\ COOH\end{matrix}$$

This discovery opened a new field of investigation. It was soon found that *o*-chlorobenzoic acid could be condensed with phenol,[4] thiophenol,[5] and similar compounds under the influence of finely divided copper. Furthermore, it was found that *o*-chlorobenzoic acid could be condensed with glycine,[6] with methylamine,[6] and other aliphatic as well as aromatic amines and amino compounds[7] under the influence of this catalyst.

Four years after Ullmann's discovery, a series of patents appeared which deal with the conversion of chloro-substituted benzene derivatives into aromatic amino compounds by means of ammonia in the presence of copper salts. Among these patents are listed the preparation of aniline from chlorobenzene,[8] *p*-phenylenediamine from *p*-dichloro-benzene,[9] and from *p*-chloro-aniline,[10] *p*-phenylene-diamine-monosulfonic acid from *p*-dichloro-

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[1] *Z. Chem.*, 13, [N.F VI.] 232 (1870).

[2] *D. R. P.* 148,749.

[3] *Ber.*, 36, 2382 (1903).

[4] *Ibid.*, 37, 853 (1904).

[5] *Ibid.*, 37, 4526 (1904).

[6] Lassar-Cohn's "Arbeitsmethoden" (4th Ed.), 601 (1907).

[7] *D. R. P.* 145189, 146102, 146950.

[8] *D. R. P.* 204951.

[9] *D. R. P.* 202171.

[10] *D. R. P.* 204848.

benzene-sulfonic acid,[1] and from the isomeric *p*-chloro-aniline-sulfonic acids,[2] and *p*-aminophenol and some of its derivatives from *p*-chlorophenol and its corresponding derivatives.[3] There also appeared a patent for the preparation of diphenylamine from bromobenzene.[4] Cuprous iodide is used in the latter patent, whereas in the other patents copper sulfate is used, the author claiming that cuprous iodide is a much more effective catalyst.

Very recently Kitamura[5] reported that he prepared acetylaminophenol ethers by condensing acid amides with halogen substituted phenol ethers in the presence of copper as well as zinc salts.

The discovery of Ullmann has opened a wide field of investigation, but due to the fact that it had commercial possibilities, it was soon buried in patents and so found little recognition in pure synthetic organic chemistry; consequently, the information concerning the reactions already mentioned is very limited.

In this paper the action of ammonia on mono- and *p*-dichloro-benzene is studied. The objects of the work are, first, to find whether any appreciable reaction takes place; second, to study the experimental difficulties in order to ascertain whether the method is feasible for synthesis; and, third, to determine quantitatively the yields obtainable. The work was restricted to mono- and *p*-dichloro-benzene, because these were most easily prepared pure and were least liable to enter into complicated side reactions. Then, too, *p*-dichloro-benzene is a useless by-product formed in the preparation of chlorobenzene, whereas *p*-phenylenediamine, which can be obtained from it, is a valuable compound.

Experimental.

Apparatus.—The pressure bomb used for this work was made of mild steel shafting, 8.25 × 23 cm. with a boring 5 cm. in diameter and 18 cm. deep which gave it a capacity of 350 cc. and left the walls 16 mm. thick. The tube was fitted with a screw cap. Permanite, an asbestos graphite packing, was used for the gasket with very satisfactory results.

Starting Materials. *Chlorobenzene.*—This compound was prepared by the direct chlorination of benzene in the presence of anhydrous aluminum chloride which acted as a catalyzer. The compound was purified by fractional distillation and the fraction that distilled over at 131–134° was collected.

p-Dichloro-benzene was obtained from the Dow Chemical Company, Midland, Michigan. It was perfectly white and practically all distilled between 170–171° (uncorr.).

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[1] *D. R. P.* 202564.

[2] *D. R. P.* 202563, 204972.

[3] *D. R. P.* 205415.

[4] *D. R. P.* 187870.

[5] *J. Tokyo Chem. Soc.*, **39,** 1121–30 (1918); *J. Pharm. Soc.* (*Japan*), **1918,** No. 442971.

Cuprous chloride. Merck's C. P. cuprous chloride was used.

Cuprous iodide was prepared by adding potassium iodide to a saturated copper sulfate solution, filtering off the solid cuprous iodide and finally washing it with alcohol to remove the iodine. The product was almost white.

The reactions studied were primarily as represented below:

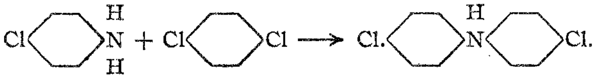
$$C_6H_5Cl + 2NH_3 \longrightarrow C_6H_5NH_2 + NH_4Cl$$

$$C_6H_4Cl + 4NH_3 \longrightarrow C_6H_4(NH_2)_2 + 2NH_4Cl$$

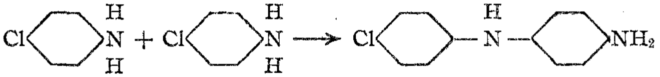
There is a possibility of other reactions taking place. Thus, the aniline formed may react with another molecule of chlorobenzene to form diphenylamine.

$$C_6H_5NH_2 + C_6H_5Cl \longrightarrow C_6H_5NH\ C_6H_5 + HCl$$

In the case of *p*-phenylenediamine, the possibilities are greater. One illustration will suffice. If one chlorine atom is replaced by an amino group, *p*-chloro-aniline is formed, which can react with a molecule of *p*-dichloro-benzene to form dichloro-diphenylamine.



Or it can react with a second molecule of *p*-chloro-aniline to form chlorophenyl-*p*-phenylenediamine, the reaction being as follows:



Although ammonia is used exclusively to remove the halogen, other reagents were suggested, such as sodamide, and zinc ammonium chloride. Then, too, the reaction of dilute solutions of sodium hydroxide, methyl alcoholate, and the like on chloro-substituted benzene could be studied with profit. The work is at present being continued on the mechanism of the catalysis. A number of metallic ammines, especially those of bivalent cobalt, are being investigated to find whether they possess the power to activate ammonia.

Study of Catalysts.—The first problem in this work was to determine whether copper salts were the only substances that had labilizing effects on nuclear halogen. Among the other substances that were tried were salts of nickel, cobalt, and zinc. These were suggested because they form complexes with ammonia that are similar to those of copper. Then too, zinc has been reported to have catalytic properties in reactions similar to those mentioned. Since negative results were obtained in all cases, it seems that the catalytic action is not dependent on the ammonium complex. Ferrous sulfate, metallic mercury, mercuric chloride, were tried next because they possess catalytic properties in other organic reactions, and finally sodium hydrogen sulfite was used because of its well-known power in aiding the conversion of β-naphthol into β-naphthylamine through ammonia. In all cases the results were negative.

Since copper salts showed decided catalytic properties, it seemed advisable to study the relative activities of a number of them. For this study a series of tubes, each containing a different copper salt, were run under identical conditions. Each tube contained 5 g. of *p*-dichloro-benzene, 18 cc. of conc. ammonia, and 0.5 g. of the catalyst. The set was heated at 200 to 210° for 12 hours, and after cooling the unaltered *p*-dichloro-benzene was filtered off, dried, and weighed, all other products of the reaction being soluble in water. The results were as follows:

	Unaltered *p*-Dichloro-benzene.	
Salt used.	G.	%
CuI	trace	....
CuCl	0.15	3.0
$CuCl_2$	0.70	14.0
$CuSO_4$	1.15	23.0

From this it can readily be seen that the cuprous salts are more active than the cupric. Indeed there is a probability that the cupric salts only become active after reduction to the cuprous condition in the reaction mixture. This assumption seems to be borne out experimentally, for on adding potassium permanganate, which insures keeping the salt in the cupric condition, no reaction took place.

Cupric acetate and nitrate seemed to have even less catalytic power than the sulfate, although these experiments were carried out under somewhat different conditions so that exact comparisons could not be made. Metallic copper, which was prepared by reducing finely divided copper oxide with hydrogen, had no catalytic effect whatsoever.

The effect of solvents on the reaction was not studied extensively. Almost all of the reactions were carried out in aqueous solutions, although in a few cases alcohol was employed as a solvent. The alcohol was saturated with dry ammonia and the *p*-dichloro-benzene and cuprous iodide added as in the other experiments. Since not a trace of *p*-phenylenediamine was produced, it seems that catalytic effect of the copper salts is limited to aqueous solutions.

Conversion of *p*-Dichloro-benzene into *p*-Phenylenediamine.—In studying the reaction of the conversion of *p*-dichloro-benzene into *p*-phenylenediamine, the first and most important problem was the identification and quantitative determination of the latter product. Direct extraction with ether or benzene yielded some *p*-phenylenediamine, but a more satisfactory method was the dry distillation of a mixture of anhydrous sodium carbonate with the hydrochloride of the base, as recommended by Ledoux,[1] which yielded a product consisting of perfectly

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[1] *Ber.*, 7, 151 (1874).

colorless plates having a m. p. of 138–139°, whereas the corrected m. p. is 140°. These crystals also gave the characteristic color test of *p*-phenylenediamine,[1] which is as follows: A drop of ferric chloride solution added to a dilute solution of the base or its hydrochloride will produce a deep green color which in a few seconds changes to a characteristic violet. With more concentrated solutions and boiling, a brown solution is obtained having the odor of quinone.

The yields obtained by either extraction or dry distillation were small; consequently these methods could not be employed for the quantitative estimation of the product. The most satisfactory method that was found for estimating the yields was based on the fact that *p*-phenylenediamine hydrochloride is insoluble in conc. hydrochloric acid, whereas the ammonium chloride, the copper salt, and almost all the impurities are soluble. The method of procedure in general was as follows:

The reddish blue reaction mixture, which was obtained by heating *p*-dichloro-benzene and ammonia together in the presence of a copper salt, was filtered to remove the undecomposed *p*-dichloro-benzene and other solid impurities. The mixture was then steam distilled until all the ammonia was driven off. The solution remaining in the flask was allowed to cool, then was filtered, and finally saturated with hydrogen chloride. As the solution approached saturation, crystals separated out and soon filled the container. These were filtered off, dried and weighed. As a general rule the crystals were colored reddish, and it was difficult to decolorize them. The most effective decolorizing agent found was activated charcoal, and by means of it a light gray product was obtained.

Although the product could not readily be prepared colorless, it was nevertheless fairly pure even without recrystallization as the following analysis shows:

Subs., 0.3000: AgCl, 0.4675.
Calc. for $C_6H_4(NH_2)_2.2HCl$: Cl, 39.19. Found: 38.43.
The sample was taken from the product obtained from Expt. 5. See Table II.

The method of analysis was as follows: The crude product was first dried in warm air, then in a desiccator over solid sodium hydroxide for 24 hours. A weighed sample of this was mixed with pure anhydrous sodium carbonate and then gently heated. After no more fumes were given off, indicating that the free base had been removed, the mass was extracted with boiling water, filtered, the filtrate acidified with nitric acid, and the silver chloride precipitated in the usual way. Besides the analysis given, others were made of the various products and the results were in almost all cases similar to the one recorded.

In the series of experiments on the preparation of *p*-phenylenediamine which will be taken up now, 3 factors were studied in particular: tem-

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[1] Mulliken, "Identification of Pure Organic Compounds," **2,** 112 (1916).

perature, concentration of ammonia, and the presence of mild reducing agents in conjunction with the copper salt.

TABLE I.

Expt.	Concentration of ammonia, %.	Temp. ° C.	Undecomposed $C_6H_4Cl_2$. G.	Yield of $C_6H_4(NH_2)_2$. G.	2HCl. %.
1	10	180–190	20	7	14
2	14	210	0	29	60
3	27	205	0	39	80

The reaction mixture in all cases consisted of 40 g. of *p*-dichloro-benzene, 240 cc. of ammonium hydroxide (of the strength indicated in the table) and 5 g. of the catalyst which was cuprous iodide in No. 2 and cuprous chloride in Nos. 1 and 3. The time of heating was 18 hours.

The yields recorded are the yields obtained by saturating the solution with hydrogen chloride. It does not include the product which remained in solution, and which by experiment was found to vary from 5–8 g. in 200 cc. of solution.

Before discussing the results as set down in the table, the individual experiments will be discussed in order to bring out the details which could not be incorporated in the table.

Expt. 1 was carried out according to the procedure already given. On concentrating the solution a brick red precipitate separated which was filtered off before the solution was neutralized. This precipitate will be discussed later. The product was colored red.

Expt. 2 again yielded a little of the red precipitate, and the product was also reddish.

Expt. 3 again yielded a colored product, but no amorphous red precipitate was obtained.

Although it is difficult to draw many definite conclusions from the results given, it appears that the optimum temperature is above 200°, for below this temperature the reaction is incomplete, especially with dilute solutions of ammonia.

The yield is dependent to a certain extent on the concentration of ammonia. Thus it was found that with 5 to 6% solutions of ammonia the reaction was very incomplete even at elevated temperatures. Dilute solutions, furthermore, cause the formation of a red amorphous precipitate previously mentioned. The nature of this precipitate has not yet been intensively investigated, but from its general behavior it appears to be a condensation product. It melts with decomposition above 200°, yielding some *p*-phenylenediamine, some basic gases, and a charred mass. On exposure to air it undergoes slight oxidation and turns bluish black. It dissolves in water, producing a green solution which turns pink when acidified. It is insoluble in ether, but soluble in alcohol, and in conc. hydrochloric acid. It still contains chlorine.

It was observed that when metallic iron was added in the form of iron filings in conjunction with the copper salt, the solution obtained was yellow instead of red, and the product grayish white. This yellow solution when allowed to stand exposed to the air slowly turned red. Although the product was improved in appearance, the reaction was markedly retarded. With powdered aluminum the reaction was completely stopped. The results of a few typical experiments are as follows:

TABLE II.

Expt.	Reducing agent.	Conc. of ammonia. %.	Temp. ° C.	Undecomp. $C_6H_4Cl_2$. G.	Yield of C_6H_5 $(NH_2)_2$. G.	2HCl. %.
1	Iron filings	10	220	7	32	65
2	Iron filings	27	190	10	13	26
3	Activated charcoal	27	200	0	30	61
4	Activated charcoal	14	200	trace	24	48
5	None	14	210	0	26	53

The reaction mixture consisted of 40 g. of *p*-dichloro-benzene, 240 cc. of ammonium hydroxide, and 5 g. of cuprous chloride. Time: 18 hrs.

Expt. 1 was run in the regular way. A reddish solution was obtained which was filtered to remove the iron and undecomposed *p*-dichlorobenzene. The latter was separated from the iron by extraction with ether. The red solution was neutralized, concentrated to 200 cc. and finally saturated with hydrogen chloride. There is a possibility that the product was slightly contaminated with ammonium chloride which also crystallized out because of the high concentration of that compound due to the fact that the large excess of ammonia was not driven off but neutralized directly.

Expt. 2 yielded a yellow solution out of which a light gray product was obtained.

Expt. 3. In this experiment activated charcoal was employed. On opening the bomb, the walls were found covered with tiny leaves of metallic copper. The solution was pale yellow and gave a grayish product.

Expt. 4. This experiment was run under the same conditions as Expt. 3 except that a more dilute solution of ammonia was employed. The solution was reddish, and gave a red precipitate when it was concentrated. The product was red.

Expt. 5. This experiment was very much like Expt. 4 with the exception that no charcoal was added. The solution was red and yielded a colored product.

Again a few general conclusions can be drawn. In concentrated solutions of ammonia certain reducing agents such as iron filings and activated charcoal have a marked favorable effect on the appearance of the final product. The former, however, tends to hinder the reaction, while activated charcoal is free from this objection. These effects are not noticed in dil. ammonia solutions.

The Conversion of Chlorobenzene into Aniline.—The preparation of aniline from chlorobenzene is of greater scientific interest than it is of practical importance. Outside of the patent already mentioned in the introduction no mention of this reaction can be found in the literature.

The object of this work is to find, first, whether aniline is actually produced; second, what conditions are necessary and what yields are obtainable; and third, whether condensation such as the formation of diphenylamine takes place.

The experiments on chlorobenzene like those of dichloro-benzene, were carried out in the steel bomb at a temperature around 200°. The procedure was simple. The contents of the bomb were acidified and steam distilled, whereupon the undecomposed chlorobenzene distilled off. As soon as the distillate was clear, the distillation was stopped, and residue remaining in the flask was made alkaline with sodium hydroxide and again steam distilled. The aniline came over as a light brown oil. It was extracted with ether and dried over solid sodium hydroxide. The product was fairly pure aniline, for almost all distilled at 183°. The liquid remaining in the flask after the aniline had been steam distilled off was extracted with ether, but the extract yielded nothing, thus showing the absence of diphenylamine, for this compound is non-volatile in steam and soluble in ether. In the experiments as listed in Table III one can see that an appreciable amount of chlorobenzene is unaccounted for. Part of the loss may have been due to failure in not removing all the aniline and chlorobenzene, but other compounds may have been forming which were not isolated.

TABLE III.

50 g. of chlorobenzene was employed in every experiment.
Time of heating: 18 hours.

Expt.	Ammonia used. Cc.	Ammonia used. %.	Temp. ° C.	Undecomp. C_6H_5Cl. G.	Yield of aniline. G.	Yield of aniline. %.	Catalyst used.
1........	150	25	195	9	16	39	$CuSO_4$
2........	150	27	230	0	16	39	CuCl
3........	150	27	200	[a]	13	32	CuCl
4........	150	14	200	[a]	14	34	CuCl
5........	125	27	210	12	13	32	CuCl
6........	150	27	210	40	0	0	CuI
7........	150	14	210	30	0	0	CuI

[a] The chlorobenzene was not determined.

From the results as tabulated in the above table one can see that the yield is low. Expt. 1 followed the directions as given in the patent in all details except that the time of heating was 18 hours instead of 20. The patent, however, claims an 80% yield, whereas in this experiment it was found that not even half that yield was obtainable.

The concentration of ammonia between 14 and 27% seems to have no marked effect. The effect of temperature is greater. In order to bring about a complete decomposition of chlorobenzene a temperature higher than 200° must be employed, but even then the yield is not increased.

One striking fact brought out in Expts. 6 and 7 is that cuprous iodide does not seem to possess catalytic properties in either conc. or dil. ammonia.

As has already been mentioned, no diphenylamine could be isolated in these experiments. Since a certain patent previously discussed claims that bromobenzene and aniline react in the presence of cuprous iodide to form diphenylamine, it was considered advisable to try it out. The directions were followed exactly. A mixture of 30 parts of aniline, an excess of bromobenzene, and one part of cuprous iodide were heated for 15 hours with a reflux condenser. Little reaction took place, although the reaction mixture turned blue in color. Practically all the aniline and bromobenzene were recovered. No diphenylamine could be detected.

A similar mixture was heated under pressure in the steel bomb. Chlorobenzene, however, was used instead of bromobenzene. A temperature of 220° was maintained for 18 hours. Again no diphenylamine could be isolated.

Summary.

A number of inorganic salts, including various salts of copper have been investigated to determine their labilizing effect on the chlorine in *p*-dichloro-benzene.

p-Phenylenediamine has been prepared by the action of ammonia on *p*-dichlorobenzene in the presence of cuprous salts. The methods used for isolating the free base as well as the hydrochloride have been described.

Aniline has been obtained by the action of ammonia on chlorobenzene in the presence of a copper salt.

An attempt to condense chlorobenzene and aniline in the presence of cuprous iodide has failed.

The author takes this opportunity to express his thanks to Professors R. Fischer, L. Kahlenberg and G. L. Clark for helpful suggestions.

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