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A PREPARATION OF 2-CHLOROPYRIDINE

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A PREPARATION OF 2-CHLOROPYRIDINE

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DISSERTATION COMMITTEE

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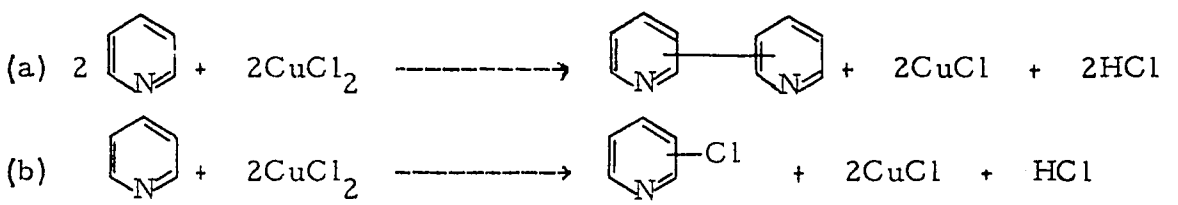
INTRODUCTION

The purpose of this investigation was to study the liquid phase reaction of cupric chloride and pyridine or pyridine salts, as a method of introducing halogen into the pyridine ring.

The usual methods for introducing halogen into homocyclic aromatic ring compounds, such as benzene, are not practical for pyridine. Benzene can be chlorinated or brominated with the free halogen in good yields at moderate temperatures, whereas pyridine can be directly chlorinated and brominated only in the vapor phase at temperatures from 250°C to 450°C. The replacement of the primary amino group with halogen through a diazonium salt intermediate is generally applicable to homocyclic aromatic ring compounds. The requisite primary amines are easily prepared by reduction of the nitro-aromatic compounds, which are in turn, easily prepared by direct nitration of the hydrocarbon. By contrast, direct nitration of the pyridine ring requires extremely drastic conditions; amino groups on the 2- and 4- positions of the pyridine ring do not give the normal diazonium reaction. These circumstances have necessitated the use of special methods, which are described below for the introduction of halogen into the pyridine ring.

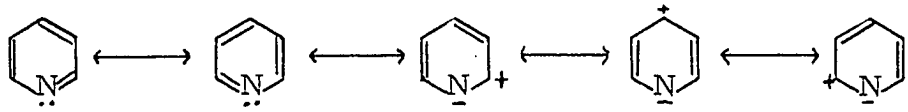
The idea of the use of cupric chloride as a chlorinating agent grew out of the observation that in the Ladenburg rearrangement (1) of alkylpyridinium halides to 2- and 4- alkyl pyridines, cupric chloride could be substituted for the presumed catalyst, cupric chloride. If it is assumed that in this reaction the cupric chloride is reduced to cuprous chloride, it must follow that the cupric chloride is oxidizing something. The two most likely suppositions are (a) the formation of bipyridyls and (b) the halogenation of the pyridine ring. These two possibilities can be represented in equation form as follows:



As is described in detail in the experimental section, it has been found that substantial yields of 2-chloropyridine can be obtained by heating a mixture of pyridine hydrochloride and cupric chloride. No bipyridyls have been detected in the product of the reaction. Still better yields of 2-chloropyridine were obtained by introducing a slow stream of gaseous chlorine into the liquid-phase mixture of pyridine hydrochloride and copper halide salts.

The unusual properties of pyridine are explained as being the result of the influence of the nitrogen atom on the distribution and availability of electrons. Pyridine is extremely stable and aromatic in character. The resonance energy (from heat of combustion) of 43 Kcal per

mole in pyridine reflects the contributions to the resonance hybrid of both nonpolar and polar structures (2).



As expected from the above resonance contributions, pyridine is a weaker base than ordinary tertiary amines. The unshared electrons associated with the nitrogen atom are relegated to orbitals that have more s character than do singly bonded nitrogen atoms in like structures. Therefore, the electrons are less available for forming bonds with protons.

The resonance theory also helps explain the following unique properties of the pyridine molecule: (a) the great inertness towards nitration, sulfonation, and halogenation, (b) the susceptibility to attack by such reagents as sodium amide, (c) 3-substitution when attacked by nitric acid, sulfuric, or halogens and 2-substitution when attacked by sodium amide, (d) the reactivity of the 2- and 4- halogen derivatives as contrasted with inert 3-halogen derivatives, (e) the normal aromatic diazotization reaction of the 3-aminopyridines, but the abnormal reaction of the 2- and 4- isomers, and (f) the presence of active hydrogens in the methyl groups of the 2- and 4- picolines, but not in 3-picoline. These properties depict the typical "aromatic" nature of the 3-position and the "anomalous" nature of the 2- and 4- positions (3). Since the 2- and 4- positions are shown in resonance forms to be electron deficient

centers, it is resonable to assume that chlorination in these positions must be by some mechanism other than an electrophilic attack. The electron deficient 2- and 4- positions would tend to repell the positive entering groups (chloronium ions) that are involved in chlorination by an electrophilic attack.

Barnes (4) groups the chemical properties of the pyridine system into three broad categories: (a) Properties roughly parallel to the benzene system, modified in some degree by the presence of the ring nitrogen. These include the typical electrophilic substitution reactions as sulfonation and halogenation which are more difficult than with benzene, and the radical reactions which are rather similar. (b) Properties unusual for the benzene system. These include the various reactions in which the key step involves interaction of the pyridine ring system with a base or nucleophilic reagent, as in the amination by sodamide or the addition of organometallic compounds. (c) Properties associated with the unshared electron pair on the ring nitrogen. The formation of salts, quaternary compounds, and N-oxides is of major interest, especially in the recent literature. The formation and subsequent transformations of salts, quaternary compounds, and N-oxides have, of course, no analogies among benzene derivatives.

Numerous methods of preparing chlorinated pyridines from pyridine derivatives have been reported. Cupric chloride has been used in several instances for the chlorination of hydrocarbons; the use of

cupric chloride for the chlorination of pyridine is new.

In 1922, Tizard and colleagues (5) reported that the halogenation of methane and of other hydrocarbons is effected by the action of cupric chloride or other metallic halides having a dissociation pressure of at least 0.01 atmosphere at temperatures of about 500°C. or lower. They produced a mixture of carbon tetrachloride, chloroform, methylene chloride, and methyl chloride, by passing methane through a heated tube containing cupric chloride upon a carrier of pumice. The preparation of 1,1-dichloroethylene with ehtylene and cupric chloride was carried out in 1942 by Kotaro Shimo (6). A British patent (7) was issued to Socony-Vacuum Oil Company in 1947 for the chlorination of saturated hydrocarbons with cupric chloride. The hydrocarbons are chlorinated in a 3-stage process comprising: (a) suspending an inert, finely divided porous solid, impregnated with cupric chloride in a stream of the hydrocarbon at a temperature above 400°C; (b) separating the impregnated powder containing reduced cupric chloride from the gaseous stream; and (c) fractionating the gaseous product to recover chlorinated hydrocarbon. In 1948, the Canadian government issued a patent (8) to the Shell Development Company for a similar process. A hydrocarbon containing an unsaturated linkage between two non-tertiary C atoms of aliphatic character is brought into contact with a carrier material and an effective amount of a metal chloride from the group of cupric chloride and ferric chloride, at sufficient velocity to maintain the particles in

suspension and at an elevated temperature, for sufficient time to effect chlorination of the unsaturated hydrocarbons and the reduction of the metal chloride to the lower state of valence. The solid phase contained about 14 percent by weight of cupric chloride and 4 percent by weight of sodium chloride impregnated in activated alumina. Erich Adler (9) produced trans-1, 2-dichloroethylene by passing ethylene gas through a solution of cupric chloride and mercuric chloride in hydrochloric acid. A continuous process of chlorinating gaseous paraffinic hydrocarbons with cupric chloride was developed by Fontana and Everett (10). Reduced cupric chloride, supported on a finely divided solid, is suspended in an oxygen-containing, hydrogen chloride gas stream, where the cuprous ion is oxidized continuously at 325°C. to 400°C. The resulting carrier supported cupric compounds are transferred as a suspension to a separate reaction zone where it is kept at 400°C. in a stream of the gaseous hydrocarbon to be chlorinated. After the chlorinated products are separated the cuprous chloride and hydrogen chloride are recirculated as indicated by the equations:

$$2CuCl + 1/2\ O_2 \longrightarrow CuO \cdot CuCl_2$$

$$CuO \cdot CuCl_2 + HCl \longrightarrow 2CuCl_2 + H_2O$$

$$2CuCl_2 + RH \longrightarrow 2CuCl + RCl + HCl$$

More recently, Ware and Borchert (11) reported the chlorination of aromatic hydrocarbons by cupric chloride. A study was made of the

reaction of cupric chloride with anthracene to yield 9-chloro- and 9, 10-dichloroanthracenes, cuprous chloride and hydrogen chloride. The reaction with cupric chloride was also carried out successfully with other polynuclear compounds that include benzene, naphthalene, phenanthrene, tetracene, and pyrene. Although the analogy between the above study and our work on the chlorination of pyridine with cupric chloride is obvious, we had worked with our reaction at least a year before the study of Ware and Borchert was published.

Pyridines containing halogen in the nucleus are obtained with difficulty by the direct action of halogens on pyridines. In contrast to the facility with which aromatic compounds undergo substitution by halogen, pyridine at room temperature forms only perhalides. Chlorination and bromination have been reported as occurring at high temperatures in the gaseous phase, in the presence of charcoal or pumice. At temperatures of 300°C. to 400°C. without a catalyst, substitution by chlorine occurs in the 3- and 5- positions, but at 500°C. bromination gives a good yield (46%) of products substituted in the 2- and 6- positions. At lower temperatures, a catalyst has a decisive influence, ferrous bromide directing to the 2- and 4- positions, whereas cuprous bromide gives 2-bromo- and 2, 6- dibromo-pyridines. At 500°C., catalysts have no influence. The reason for the change of reactive positions with the change of temperature and catalyst is not fully understood but it is interesting to note the similar temperature effect observed in the bromination

of bromobenzene with ferric bromide as the catalyst (12). It may be that at the lower temperature substitution occurs by ionic attack and at higher temperatures by free radical attack.

Chlorination of N-alkylpyridones by means of phosphorus pentachloride or oxychloride gives halogenopyridines. O. Fischer (13) applied the method to the N-alkyl 2-pyridones. Phosgene has been used (14) to accomplish the same results. The method sometimes affords both mono- and di-chloropyridines. N-Methyl 2-pyridone and phosphorus pentachloride gives both 2-chloro and 2, 5-dichloro-pyridines. The 2- and 4- bromo- or chloro-pyridines are obtained by the action of phosphorus oxychloride on the corresponding hydroxy pyridines (15).

3-Aminopyridine can be diazotized and converted into 3-chloropyridine by the Sandmeyer method, but 2- and 4- aminopyridine require special treatment. 2-Bromopyridine, for instance, is obtained when bromine, followed by sodium nitrite, is added to 2-aminopyridine in hydrobromic acid (16), and 4-aminopyridine similarly gives 4-bromopyridine (17). Many unsuccessful attempts have been made to apply the Sandmeyer and Gattermann methods to 2- and 4- aminopyridines; however, 4-chloro-2-aminopyridine is converted by the Sandmeyer method into 2, 4-dichloropyridine (18).

Other methods for preparing the halogenopyridines include decarboxylation of the appropriate halogenopyridine carboxylic acids (19); mercuration of pyridine followed by treatment with bromine when 3-bromo-

and 3, 5-dibromopyridine are formed (20); and chlorination with thionyl chloride (15).

The preparation of 2-chloropyridine by the method described in this Thesis has certain inherent advantages over methods heretofore reported. As compared to Wibaut's (21) direct chlorination in the gaseous phase, the requisite apparatus is much simpler and the laboratory operations are less complex. By using pyridine hydrochloride, rather than pyridine, and with enough cupric chloride to raise the boiling point of the pyridine hydrochloride to 260°C. - 270°C., it is easily possible to get the equivalent of Wibaut's conditions without resorting to a gas phase reaction or to the use of above-atmospheric pressure.

As compared to the preparation of 2-chloropyridine starting with derivatives of pyridine, this method has the advantage of using pyridine itself as starting material, thus avoiding lower over-all yields resulting from less-than-quantitative yield in each step of a multi-step process.

Preliminary experiments indicated that 2-bromopyridine could be prepared by substituting cupric bromide and pyridine hydrobromide for the corresponding chlorides, although with lower yields. It was also found that antimony pentachloride could be substituted for cupric chloride but with a lower yield of 2-chloropyridine. Stannic chloride, phosphorus pentachloride and ferric chloride were tried as substitutes for cupric chloride, but without success. There seems little to gain in trying to substitute chlorides of multivalent metals other than copper for cupric

chloride unless a substantial increase in yield resulted.

As mentioned on page 2, the formation of some of the bipyridyls were expected. None was isolated or detected. Hein and Retter (22) have reported the preparation of bipyridyls from pyridine and cupric or ferric chloride at 500°C. and 50 atmospheres pressure. The conditions used in this work are, of course, much different from those of Hein and Retter.

EXPERIMENTAL

MATERIALS - The pyridine used was the Fischer certified grade obtained from the Fisher Scientific Company. The cupric chloride dihydrate and the other metallic chlorides used in the investigation were analyzed grade reagents manufactured by the J. T. Baker Company. The chlorine gas which was used in the continuous process was delivered from a cylinder of this gas obtained from the Matheson Company.

This experimental work was begun with no clear idea as to how to start because similar reactions from which procedures could be imitated or modified, were not found in the literature. Lacking such precedents, a series of procedures were tried in the hope that some combination of conditions would be found which would give some yield of a recognizable product. After finding such favorable conditions, if they could be found, it was hoped and assumed that further experimentation could be carried out in a more logical sequence.

The first phase of this work turned out to be long, discouraging, and unproductive. Little, if any, information was obtained from which inferences could be made and upon which the next experiments could be

planned. From hindsight there was a two-fold problem (a) to find conditions under which a reasonable yield of a recognizable product was produced and (b) to find a method of isolating a product when it was produced. Both had to be resolved simultaneously.

A detailed description of each of these preliminary experiments would be long and of doubtful value. Instead, a generalized description of the trend of these experiments is given, along with detailed descriptions of representative experiments.

The first experiments were essentially heating a mixture of pyridine hydrochloride and anhydrous cupric chloride under a reflux condenser for various lengths of time and attempting to recover some product from the flask contents at the conclusion of the heating period. At reflux temperature the cupric chloride dissolved in the melted pyridine hydrochloride forming a brown to black liquid with the simultaneous evolution of a large volume of hydrogen chloride gas from the top of the reflux condenser.

The flask contents, when cooled, solidified to a black, intractable mass. Every possibility that could be thought of was tried, unsuccessfully, to recover a product from this solid. These included:

(a) adding dilute sodium hydroxide, filtering off the precipitated copper compounds, and extracting the filtrate with an immiscible solvent. Filtering proved to be difficult since the precipitated material resisted the passage of fluid through it. No appreciable amount of a product remained

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(a) adding dilute sodium hydroxide, filtering off the precipitated copper compounds, and extracting the filtrate with an immiscible solvent. Filtering proved to be difficult since the precipitated material resisted the passage of fluid through it. No appreciable amount of a product remained

after evaporating the solvent.

(b) adding dilute ammonium hydroxide in the hope that the copper compounds could be converted to water soluble copper-ammonia-complex ionic compounds, extracting with an immisible organic solvent such as benzene or ether, and then distilling off the solvent. The ammonium hydroxide seemed only partly effective in decomposing whatever copper compounds were present. Only unreacted pyridine remained when the solvent was evaporated.

(c) adding enough sodium hydroxide to make the suspension basic followed by steam distillation. No organic product other than pyridine was recovered from the steam distillate.

The evolution of substantial amounts of hydrogen chloride was both interesting and encouraging. Pyridine hydrochloride (b.p. 222°C) boils without decomposition, that is, without the evolution of hydrogen chloride. Cupric chloride is stable up to a temperature of above 900°C; it could not of itself give hydrogen chloride. The only reasonable conclusion seemed to be that a reaction was occurring and that the failure to obtain a product probably lay in failure to get it out of the reaction mixture. The quantity of hydrogen chloride evolved from a mixture of one mole of pyridine hydrochloride and one mole of cupric chloride was estimated by dissolving the evolved gas in water and titrating aliquots with a standard solution of a base. About 0.4 mole of hydrogen chloride was produced.

Having failed to obtain more than a trace of product of doubtful purity and uncertain identity by any of the methods of recovery enumerated above, the possibility of distilling a product out of the reaction flask was considered. Since 2-chloropyridine boils approximately sixty degrees higher than does pyridine, it was assumed that the hydrochloride of chloropyridines would boil at a higher temperature than does pyridine hydrochloride. If so, the best that could be expected would be a distillate of pyridine hydrochloride containing a small amount of the chloropyridine salts. Fortunately, this expectation was wrong. It was found that by carefully controlling the flask temperature so that only very slow distillation resulted, the distillate contained substantial amounts of 2-chloropyridine with only small amounts of pyridine hydrochloride. After some practice yields of approximately 20 percent of 2-chloropyridine were obtained. Following is a typical experiment:

PREPARATION OF 2-CHLOROPYRIDINE WITH CUPRIC CHLORIDE - A mixture of 80 ml (1.0 mole) of pyridine, 105 ml (excess) of concentrated hydrochloric acid and 170.5 g. (1.0 mole) of cupric chloride dihydrate in a one liter, three neck, round bottom flask equipped with a thermometer in a thermometer well extending into the flask contents, a dropping funnel, and a condenser arranged for distillation, was heated to boiling. The

fraction boiling from 100°C. to 140°C. (mainly water and hydrogen chloride) was discarded. The temperature of the reaction mixture then rose rapidly to approximately 260°C., accompanied by the rapid evolution of hydrogen chloride gas which was absorbed in water in a gas trap. The rate of heating was adjusted so as to give very slow distillation; the temperature of the exit vapors rose gradually from 140°C. to 220°C. while the temperature of the flask contents remained in the range of 260°C. to 270°C. Heating was discontinued when the vapor temperature reached 220°C., at which time the distillate was mostly pyridine hydrochloride. Total time for the distillation was approximately 4 hours.

The 140°C. - 220°C. fraction was made alkaline with ammonium hydroxide and extracted with three 50 ml portions of benzene. Without drying, the benzene solution was fractionally distilled through an eighteen inch Vigreux column giving, after a forerun of some pyridine, 10 grams to 11.5 grams (18% - 20% yield) of 2-chloropyridine, boiling point 170°C. - 172°C.

The 170°C. - 172°C. fraction was identified as 2-chloropyridine by converting it into 2-methoxy pyridine and comparing the melting point of the picrate of the latter compound with the melting point reported in the literature and with the melting point of the picrate of 2-methoxypyridine made from an authentic sample of 2-chloropyridine. Attempts to make the picrate of 2-chloropyridine were not successful.

PREPARATION OF THE PICRATE OF 2-METHOXYPYRIDINE FROM THE 170°C. - 172°C. FRACTION - Five grams of the product boiling at 170°C. - 172°C. (0.044 moles) were added to a solution of 4 grams of sodium (0.17 mole) in 35 ml of anhydrous methanol. The solution was refluxed for six hours, then cooled; the sodium chloride which had formed was filtered off and washed with anhydrous methanol, the washing being added to the filtrate. Dry hydrogen chloride was then bubbled into the methanol solution to convert 2-methoxypyridine to its hydrochloride. After distilling off and discarding the methanol, the residue was made alkaline with dilute sodium hydroxide and steam distilled. The distillate containing 2-methoxypyridine was extracted with ether, the ether evaporated off, and to the residue was added a warm solution of 2 grams of picric acid in 20 ml of ethanol. The resulting picrate was recrystallized to constant melting point of 158°C. - 159°C. from ethanol. Grave (23) reported a melting point of 158°C. - 159°C. for the picrate of 2-methoxypyridine.

Five grams of 2-chloropyridine obtained from Distillation Products Industries (Eastman Kodak Company) were converted into the picrate of 2-methoxypyridine in exactly the same manner, giving crystals which also melted at 158°C. - 159°C. A mixture of equal amounts of 2-methoxypyridine picrate from these two sources also melted at 158°C. - 159°C.

Attention was now turned to modification of the procedure described on page 14, and to other procedures in an effort to increase yields of product. These consisted of experiments at above-atmospheric pressure, the use of a complex crystalline salt, $CuCl_2 \cdot 2Py \cdot 2HCl$ (Py = pyridine) as starting material, and modifications of procedure for recovery of product from the reaction mixture. Typical experiments are described below.

Experience to this point had indicated that little or no reaction occurred between pyridine hydrochloride and cupric chloride below approximately 240°C. To attain this temperature it was necessary to use substantial quantities of cupric chloride dissolved in the pyridine hydrochloride in order to raise the boiling point of the latter compound to 240°C. Preliminary experiments were run using pyridine (rather than pyridine hydrochloride) and cupric chloride in sealed glass tubes so as to attain higher temperatures than were possible in an open container. It was found that pyridine and cupric chloride did react to give 2-chloropyridine in a sealed container if heated for a long period of time at 170°C. The quantity of product obtained was not large enough to counterbalance the inconvenience of working in sealed containers. A description of a typical experiment follows:

REACTION OF PYRIDINE AND CUPRIC CHLORIDE IN A SEALED TUBE - Thirteen grams (0.1 mole) of anhydrous cupric chloride and eight grams (0.1 mole) of pyridine were sealed in a thick wall glass tube. The tube was heated in a Carius furnace at 170°C. for 4 days. After cooling the tube, it was opened and its contents were washed into a beaker, made alkaline with ammonium hydroxide and extracted with three 15 ml portions of benzene. The benzene extract was fractionated through an eighteen inch Vigreux column. Two grams (18.1% yield) of 2-chloropyridine, boiling at 170°C. - 172°C., were obtained.

During the mixing of pyridine, hydrochloric acid and cupric chloride for experiments such as those described on page 14, it was noticed that large yellow crystals would separate from such mixtures when they were cooled. Presumably these crystals have the composition $CuCl_2 \cdot 2Py \cdot 2HCl$ as reported by Lang (24). Presumably this complex compound was formed at some time during the mixing and heating of pyridine, hydrochloric acid and cupric chloride. It seemed barely possible that there could be an advantage in using pyridine, hydrochloric acid and cupric chloride in this 2:2:1 ratio by using the crystalline complex compound of this composition as starting material. Accordingly, some reaction runs were made which resulted in an improvement of the yield of 2-chloropyridine from about 20% to about 26%. Following is a description of a typical experiment.

PREPARATION OF $CuCl_2 \cdot 2Py \cdot 2HCl$ - Into a paste made by mixing equal molar quantities of cupric chloride and pyridine was slowly added enough hydrochloric acid to barely effect solution of all solids. Crystals began forming as the solution cooled. After standing overnight, the mixture was filtered and the long yellow needles of $CuCl_2 \cdot 2Py \cdot 2HCl$ were washed with anhydrous ether and dried in the atmosphere. The water soluble crystals melt with decomposition at 140°C. to 160°C. A yield of 85% of the theoretical was obtained.

PREPARATION OF 2-CHLOROPYRIDINE BY HEATING CRYSTALLINE $CuCl_2 \cdot 2Py \cdot 2HCl$ - One hundred and ten grams (0.5 mole) of crystalline $CuCl_2 \cdot 2Py \cdot 2HCl$ were placed in a two-neck 500 ml round bottom flask equipped with a thermometer in a thermometer well which extended into the flask contents, and connected to a condenser set for distillation. On heating, the crystals melted to a dark yellow liquid at 160°C. A substantial quantity of hydrogen chloride gas was evolved. When the liquid temperature reached approximately 240°C., distillation began. The flask temperature was held at the 260°C. - 270°C. temperature range until distillation ceased. The distillate came over within the previously observed 140°C. - 220°C. range. This distillate was made alkaline with ammonium hydroxide, then extracted with benzene. Fifteen grams (26.5%) of 2-chloropyridine (b.p. 170°C. - 172°C.) were obtained by fractionally

distilling the benzene extract through an eighteen inch Vigreux column.

Attention was then turned to the possibility of increasing the overall yields by modifying procedures for recovery of crude 2-chloropyridine from the reaction procedures. In all experiments so far described, crude 2-chloropyridine was removed from the reaction mixture by slow distillation beginning with the temperature of the liquid mixture at about 240°C. As distillation proceeded, the temperature of the reaction mixture rose gradually, reaching approximately 270°C. when the distillate temperature reached about 220°C. At this stage the distillate was largely pyridine hydrochloride. Continuing distillation past this stage did not increase the yield of 2-chloropyridine; the reaction mixture appeared to be decomposing and the flask was likely to break.

Wibaut (15) has reported that 2-chloropyridine will distill, along with water, from an aqueous solution of hydrochloric acid. Little or no pyridine will distill from such a solution. It seemed possible that further amounts of 2-chloropyridine could be recovered by allowing the reaction mixture to cool after the distillate temperature had reached 220°C., adding hydrochloric acid and repeating the distillation until the distillate temperature again reached 220°C. It was found that this did indeed happen and that by using several portions of hydrochloric acid, recovery could be improved so as to increase the yield of 2-chloropyridine to approximately 40%. A description of a typical experiment follows:

PREPARATION OF 2-CHLOROPYRIDINE - Into a one liter, three-neck flask attached to a condenser arranged for distillation and equipped with a thermometer in a thermometer well extending down into the flask contents and with a dropping funnel were placed 80 ml (1.0 mole) of pyridine, 105 ml (excess) of 37% hydrochloric acid and 170.5 grams (1.0 mole) of cupric chloride dihydrate. The reaction mixture was heated and the distillate boiling below 140°C. was discarded. The temperature of the reaction mixture then rose rapidly to approximately 260°C. with the evolution of hydrogen chloride. The rate of heating of the mixture was adjusted so as to cause very slow distillation. As distillation proceeded the temperature of the distilling vapor rose gradually from 140°C. to 220°C., at which point the distillate became largely pyridine hydrochloride. Total time for distillation of the 140°C. - 220°C. fraction was approximately four hours. The reaction mixture was allowed to cool to about 100°C. and 100 ml of 1:1 concentrated hydrochloric acid-water solution were added to the reaction mixture and distillation was resumed. Again the fraction boiling up to 140°C. was discarded and heating was adjusted so as to cause slow distillation while the vapor temperature rose slowly to 220°C. Distillation was again interrupted, the flask contents cooled and successive additional 100 ml portions of 1:1 concentrated hydrochloric acid-water were added, repeating the distillation as described following each addition of a 1:1 hydrochloric

acid-water portion.

All material distilling at 140°C. - 220°C. was combined, made alkaline with ammonium hydroxide and extracted with three 50 ml-portions of benzene. On distilling the benzene solution through an 18 inch Vigreux column, a forerun of pyridine was followed by a 40% - 41% yield of 2-chloropyridine, boiling point 170°C. - 172°C.

TABLE 1 summarizes the amounts of the 140°C - 220°C. fraction (crude 2-chloropyridine) obtained in each step of the recovery process for three different experiments using this procedure.

Attention was then turned to the effect of varying the ratio of cupric chloride and pyridine hydrochloride as this might affect the yield of 2-chloropyridine. A series of runs were made using the procedure described on page 20, with the ratio of cupric chloride to pyridine varying from 0.18:1 to 2:1. It was found that yields of 2-chloropyridine did vary appreciably if the ratio of cupric chloride to pyridine was decreased below 1:1. These results are summarized in TABLE 2.

It now seemed of interest to determine if the residue of copper compounds remaining in the reaction flask, after carrying out the procedure described on page 20, could be regenerated and used for the preparation of more 2-chloropyridine. Accordingly, a run was made by the procedure described on page 20 which gave the expected yield

TABLE 1

DATA FROM THREE CUPRIC CHLORIDE-PYRIDINE HYDROCHLORIDE EXPERIMENTS

	Experiment 1	Experiment 2	Experiment 3
	Ml 140°C. - 220°C. Distillate		
Initial	30	32	31
From 1st 100 ml 1:1 HCl	14	11	12
2nd 100 ml 1:1 HCl	8	5	6
3rd 100 ml 1:1 HCl	5	6	5
4th 100 ml 1:1 HCl	6	5	4
5th 100 ml 1:1 HCl	1	2	5
6th 100 ml 1:1 HCl	0	0	0
Total	64	61	63

Total Yield of 2-Chloropyridine (b.p. 170-172°C)

29g (40.8% yield) 27.2g (40.5% yield) 26g (40.6% yield)

TABLE 2

EFFECT OF VARYING MOLAR RATIOS OF CUPRIC CHLORIDE AND PYRIDINE

Moles of $CuCl_2$ Used	Moles of Pyridine Used	Moles of Unreacted Pyridine Recovered	Moles of 2-Chloropyridine Obtained	*% Yield of 2-Chloropyridine
.09	0.5	.48	0	0
.18	0.5	.42	.009	10.9
.36	0.5	.22	.061	22.0
.45	0.5	.20	.118	39.8
.54	0.5	.18	.13	41.0
1.00	0.5	.18	.133	41.6

*The percentage yield of 2-chloropyridine was calculated from the amount of pyridine consumed.

of approximately 40% of 2-chloropyridine. To the residue of copper salts (and possibly organic material) in the flask was added one mole of pyridine and somewhat more than one mole of 37% hydrochloric acid. After distilling off water and excess hydrogen chloride, a slow stream of chlorine gas was introduced into the flask contents while distillation was continued at a slow rate. The 140°C. - 220°C. fraction gave, on purification, an approximately 60% yield of purified 2-chloropyridine without the use of additional distillations with portions of 1:1 hydrochloric acid which was necessary to obtain a 40% yield in the absence of chlorine. Five consecutive repetitions of this procedure, in each case adding pyridine and hydrochloric acid to the residue in the reaction flask, gave 63.4% to 69% yields of 2-chloropyridine (based on pyridine consumed) and with no indication of any diminution in yield with successive runs. A detailed description follows:

PREPARATION OF 2-CHLOROPYRIDINE USING CHLORINE AND CUPRIC CHLORIDE - A run exactly as described on page 20 was carried out, giving 30 grams of 2-chloropyridine (42.6% yield based on amount of pyridine consumed). To the cooled residue in the flask was added 80 ml (1.0 mole) of pyridine and 105 ml of 37 per cent hydrochloric acid. Heating was begun and the distillate coming over up to 140°C. was discarded. At this point chlorine gas was introduced below the surface of the liquid in the reaction flask at such a rate that only a small amount of chlorine

escaped from the surface of the liquid. Introduction of chlorine gas was continued while the rate of external heating was such that distillation proceeded slowly. Distillation was continued until the temperature of the distilling vapor reached 220°C. After cooling, another 80 ml (1.0 mole) of pyridine and 105 ml of 37 per cent hydrochloric acid were added to the residue in the reaction flask and the procedure just described, including the use of chlorine gas was repeated. Pertinent data for each such repetition is given in TABLE 3.

In each case the 140°C. - 220°C. fraction was made alkaline with ammonium hydroxide, extracted with three 50 ml portions of benzene and the resulting benzene extract distilled through an 18 inch Vigreux column.

When it was established that 2-chloropyridine was produced by the reaction of cupric chloride and pyridine or pyridine hydrochloride, it was thought that either or both 4-chloropyridine and bipyridyls would also be formed. No positive evidence of the formation of either could be found. The sensitive test of Hein and Retter (22) for 2, 2' -bipyridyl (an intense red color with aqueous ferrous sulfate) was consistently negative. The only indication that some 4-chloropyridine might be produced was a small amount of black, resin like material which remained in the flask after distillation of the crude 2-chloropyridine (the 140°C. - 220°C. fraction). 4-Chloropyridine is known to polymerize readily.

TABLE 3

REACTION OF CHLORINE-CUPRIC CHLORIDE WITH

PYRIDINE HYDROCHLORIDE

	Moles $CuCl_2$	Moles Pyridine Added	Moles Pyridine Recovered	Moles 2-Chloro-Pyridine Produced	% Yield 2-Chloro-Pyridine
Initial run	1	1	.38	.26	42.6
1st run with Cl_2	-	1	.13	.55	64.5
2nd run with Cl_2	-	1	.11	.60	69
3rd run with Cl_2	-	1	.14	.54	63.4
4th run with Cl_2	-	1	.11	.56	64
5th run with Cl_2	-	1	.11	.57	65
6th run with Cl_2	-	1	.13	.55	64.5

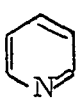
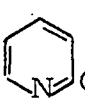
A few experiments were done on the use of the chlorides of polyvalent elements other than copper. Using the procedure described on page 20, it was found that a 28% yield of 2-chloropyridine could be obtained using antimony pentachloride rather than cupric chloride. Stannic chloride and ferric chloride gave no appreciable yield of 2-chloropyridine.

The possibility of preparing 2-bromopyridine from pyridine hydrobromide and cupric bromide was investigated in preliminary fashion. In an open container and using the procedure described on page 20, seven grams of product boiling at 193°C. - 195°C. were obtained. The reported boiling point of 2-bromopyridine is 193.5°C - 194°C. A noticeable evolution of bromine occurred when the pyridine hydrobromide-cupric bromide mixture was heated. Using the procedure described on page 17, 2.8 grams of product were obtained by heating 22 grams of cupric bromide (0.1 mole) and 8 grams (0.1 mole) of pyridine in a sealed tube.

SUMMARY AND CONCLUSIONS

A convenient laboratory method, using simple equipment and inexpensive starting materials, has been developed for the preparation of 2-chloropyridine in a liquid-phase reaction at atmospheric pressure. Consistent yields of approximately 65% of 2-chloropyridine, based on the amount of pyridine consumed, can be obtained. Approximately one mole of cupric chloride must be used for each mole of pyridine initially; the residue of copper salts can be used without replenishment or purification to convert additional molar portions of pyridine to 2-chloropyridine indefinitely and without perceptible decrease in yields. This procedure could be readily adapted to continuous, rather than batch, operation if that were desired.

Experimental work reported in this thesis is only partly consistent with what would seem to be the most reasonable over-all equation for the reaction, as follows:

(1)  + $2CuCl_2$ ⟶  + HCl + Cu_2Cl_2

(2) $Cu_2Cl_2 + Cl_2 \longrightarrow 2CuCl_2$

(in procedures where chlorine is used)

There is, as yet, not enough data to justify speculation as to the mechanism of this reaction. Such data will be difficult to obtain.

The 2:1 ratio of cupric chloride to pyridine is reasonably consistent with the 40% yield of 2-chloropyridine (based on pyridine unaccounted for) using the procedure described on pages 20-21 if it were assumed that there was a 10% loss in purification and recovery. It is also possible that a part of this 10% discrepancy could be accounted for by the formation of some 4-chloropyridine, none of which was recovered. The amount of evolved hydrogen chloride (see page 13) is also consistent with the stoichiometric relationships of equation (1) with the same assumptions as to loss in purification and recovery. It should be noted that this reasoning would lead to a conclusion that the use of a 2:1 ratio of cupric chloride to pyridine should give substantially higher yields of 2-chloropyridine than the 40% yield obtained from a 1:1 ratio. As shown in TABLE 2, page 24, this conclusion is not borne out by experiment. A 2:1 ratio of cupric chloride to pyridine gave essentially the same yield as did the 1:1 ratio. Furthermore, the lessened yields of 2-chloropyridine shown in TABLE 2 as the ratio of cupric chloride to pyridine was made smaller could be interpreted as either being due to insufficient cupric chloride as oxidizing agent or as being due to a lower temperature and thus a slower or less complete reaction.

The increase in yield of 2-chloropyridine from 40% to about 65% with the use of chlorine gas is difficult to explain. It might be considered

that the use of chlorine in effect increased the ratio of cupric chloride to pyridine by oxidizing cuprous chloride back to cupric chloride. Again if this is the explanation, the use of a 2:1 ratio of cupric chloride to pyridine should have resulted in an increased yield. It should also be noted that in the absence of chlorine, approximately a 20% yield of 2-chloropyridine was produced unless portions of 1:1 hydrochloric acid were added with additional distillation steps, in which case another 20% yield of 2-chloropyridine was obtained. (procedures on pages 14 - 16 and pages 21, 22). Using chlorine, approximately 65% yields of 2-chloropyridine resulted without the addition of portions of 1:1 hydrochloric acid and the additional distillations (procedure on page 25). It is not apparent how the very small amount of gaseous chlorine which passed over with the distillate could have substituted for distillation with several portions of 1:1 hydrochloric acid in improving recovery (as contrasted with improving conversion).

Both cupric and cuprous salts readily form complex compounds with ammonia and with amines in general. In the reaction flask there were present at least two amines, pyridine and 2-chloropyridine and, at least in the absence of chlorine, copper ions in both states of oxidation. Presumably at least some understanding of the substances present in this system would be required before an over-all equation could be written with assurance and certainly before seriously proposing a mechanism for the reaction or reactions. Such an investigation would

be long and involved and seems beyond the reasonable scope of this Thesis.

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