[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

A Study of the Preparation of Alpha-Pyridyl Halides from Alpha-Aminopyridine by the Diazo Reaction

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With the exception of a few isolated compounds the alpha substituted derivatives of pyridine are all expensive and difficult to make. Because of this fact the use of these compounds in organic chemistry has been somewhat limited. This paper reports methods by which alpha-bromopyridine and alpha-cyanopyridine can be prepared cheaply and conveniently, thus providing synthetic intermediates by means of which the majority of alpha substituted pyridines can be prepared easily.

The literature contains two accounts of the synthesis of picolinic acid nitrile.[2] In both syntheses the compound is prepared by dehydration of picolinic acid amide, a compound which is rather expensive and tedious to make. Alpha-bromopyridine has been prepared from alpha-aminopyridine,[3] a compound which is easily obtained in quantity by the synthesis of Tschitschibabin and Seide.[4] However, the yield of replacement by their method is very unsatisfactory.

Tschitschibabin and Rjasanzew[3] in their studies on the diazotization of alpha-aminopyridine prepared a solid stable sodium isodiazo oxide by the action of amyl nitrite on the sodium derivative of alpha aminopyridine and reported that alpha bromopyridine and alpha iodopyridine could be prepared better by adding this solid isodiazo oxide to the respective acid than by the direct diazotization of the amine followed by substitution. They ascribed the low yield of substitution product in a side reaction in which considerable quantities of free halogen are formed. Accordingly in this Laboratory conditions were changed as much as possible to inhibit the formation of free halogen. In all cases the yield of substitution product was lower instead of higher, which suggested that free halogen in excess might increase the yield of the desired product. Such was indeed the case, the yield being doubled with an excess of one mole of halogen.

In an attempt to prepare alpha-bromopyridine by direct diazotization followed by substitution, a concentrated aqueous solution of sodium nitrite and alpha-aminopyridine was added to a saturated solution of hydrobromic acid containing excess of bromine. By this procedure a yield as high as 75% of alpha-bromopyridine was obtained. In neutral water solution alpha-aminopyridine brominates instantly in the cold with free bromine. However, bromination must not take place in concentrated hydrobromic acid at 0° since a yield as high as 87% of replacement of the amino group by bromine can be obtained by treating a solution of alpha-aminopyridine in hydrobromic acid at 0° with bromine followed by diazotization with sodium nitrite. The latter procedure gives an excellent and convenient method for the preparation of alpha-bromopyridine.

As will be shown later in the experimental part of the paper the yield falls off rapidly if less than two moles or four atoms of bromine is used in the reaction. This fact and the course of the reaction suggest that substitution takes place in the following way. Upon adding bromine to the solution of alpha-aminopyridine, a perbromide is first formed. This perbromide then diazotizes as sodium nitrite is added and the unstable diazotate adds another mole of bromine to form a diperbromide which is unstable and decomposes to form the perbromide of alpha-bromopyridine. Alpha-bromopyridine does not brominate readily in the cold with bromine.

An alternate explanation of the course of the reaction seems somewhat more probable. W. Solonina[5] some time ago discovered that nitrosyl halide was an excellent reagent for the conversion of an aliphatic amine to the halide. It is difficult to predict the effect of perbromide formation but it may render the pyridyl nucleus more aliphatic in nature. If so, substitution of the amino group in alpha-aminopyridine perbromide would take place as in any aliphatic amine. This

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(2) R. Camps, *Arch. Pharm.*, **240**, 367 (1902); H. Meyer, *Monatsh.*, **23**, 438, 900 (1902).

(3) Tschitschibabin and Rjasanzew, *J. Russ. Phys.-Chem. Soc.*, **47**, 1571 (1915); Tschitschibabin, *ibid.*, **50**, 502 (1918).

(4) Tschitschibabin and Seide, *ibid.*, **46**, 1224 (1914); Abderhalden, "Handbuch der biologischen Arbeitsmethoden," Abt. 1, Chemische Methoden, Teil 2, 2 Hälfte, Heft 7, p. 2889.

(5) W. Solonina, *J. Russ. Phys.-Chem. Soc.*, **30**, 431 (1898).

conclusion is supported by the fact that not only two moles of bromine are required for the best yield of substitution product but also two and one-half moles of sodium nitrite.

If an equivalent of alpha-bromopyridine is added to anhydrous cuprous cyanide, considerable heat is liberated and apparently an addition product is formed. Upon heating, the solid mass melts and slightly above the melting temperature a vigorous reaction takes place. If allowed to proceed of its own accord the reaction will form a tarry residue from which nothing can be isolated. However, if the reaction is controlled and the volatile material distilled off under reduced pressure a good yield of picolinic acid nitrile can be obtained.[6] Alpha-chloro- and alpha-iodopyridine also react with cuprous cyanide but the speed of reaction is somewhat different.

Experimental

Alpha-bromopyridine.—Numerous runs were made to determine the optimum conditions and amounts of reagents for the replacement of the amino group by bromine. The following procedure was found to be best.

A three-necked flask fitted with a mechanical stirrer, dropping funnel and thermometer is immersed in an ice-salt freezing mixture; 60 cc. (5 moles) of 63% hydrobromic acid is placed in the flask and 15 g. of alpha-aminopyridine cautiously added; 24 cc. (3 moles) of bromine is then added dropwise during which a solid orange perbromide separates; 27.5 g. (2.5 moles) of sodium nitrite in 40 cc. of water is then added dropwise so that the temperature does not rise above 0°. As the last of the nitrite is added vigorous evolution of gas occurs and the temperature rises to 5–10°. After the reaction is over a solution of 60 g. of sodium hydroxide in water is added slowly, keeping the temperature below 25°. The mixture is extracted with ether and the ether solution fractionated: 21.8 g. of product boiling at 91–92° (25 mm.) is obtained. The yield is 87% of the theoretical. The properties of the compound correspond to those reported by Tschitschibabin and Rjasanzew[3] for alpha-bromopyridine.

In the above reaction the concentration of the hydrobromic acid is not of great importance as the following relative yields show. The reactions were carried out as above using five moles of acid.

Concentration of acid in %	63	45	22
Yield in %	87	84	69

A large excess of sodium nitrite is desirable as is shown by the fact that 1.5 moles or 16.5 g. gave a yield of 66% of the theoretical as compared to a yield of 87% with 2.5 moles. The most important factor in giving a high yield of replacement is the presence of a large excess of free bromine as the following relative yields show.

Moles of bromine added	1	2	3
Yield in %	20	84	87

Alpha-iodopyridine.—An attempt to prepare alpha-iodopyridine by a similar procedure as was found best for the preparation of alpha-bromopyridine failed completely. The product of the reaction appeared to be chiefly a crystalline solid which was not further investigated. The following procedure was found best for the preparation of alpha-iodopyridine.

The sodium salt of the isodiazotate of alpha-aminopyridine is prepared according to the directions of Tschitschibabin and Rjasanzew.[3] A solution of 57 g. (3 moles) of hydriodic acid and 17 g. (1 mole) of iodine is cooled in an ice-bath and stirred constantly while a solution of 10 g. of the isodiazotate in 25 cc. of water is added dropwise. The temperature is then raised to 30° and sodium hydroxide solution added. The mixture is extracted with ether and the ether solution fractionated. 9.1 g. of oil boiling at 93° (13 mm.) is obtained. The yield is 65% of the theoretical. The properties correspond to those reported by Tschitschibabin and Rjasanzew for alpha iodopyridine.

Alpha-pyridyl Cyanide.—A mixture of 100 g. of alpha-bromopyridine and 50 g. of anhydrous cuprous cyanide is heated cautiously with vigorous shaking in a 200-cc. distillation flask so that the entire mass barely fuses. The flask is then set for distillation under reduced pressure and heated further until a reaction begins. It is cooled sufficiently during the reaction by occasionally immersing in water so that bromopyridine will not quite distil from the flask. As soon as the reaction appears to subside the pressure is reduced to approximately 50 mm. and as much volatile material distilled as will come over using a free smoky flame. If not quickly distilled after the reaction the entire mass goes to a tar from which only a small yield of nitrile can be isolated. The distillate is washed with dilute sodium hydroxide and the oily layer fractionated: 20 g. of unreacted bromopyridine is obtained and 40 g. of oil boiling at 118–120° (25 mm.). The yield is 74% of the theoretical.

Anal. Calcd. for $C_6H_4N_2$: C, 69.2; H, 3.85. Found: C, 69.0; H, 4.06.

The properties of the compound correspond to those reported in the literature for alpha-pyridyl cyanide with the exception of the boiling point. Meyer[2b] reported the boiling point to be 212–215°. The above compound boils at 222.5–223.5°. Sodium hydroxide in the cold slowly hydrolyzes the nitrile.

Summary

It has been found that alpha-bromopyridine can be prepared conveniently and cheaply by diazotization of alpha-aminopyridine in hydrobromic acid solution in the presence of excess bromine.

Picolinic acid nitrile can be prepared in good yield from alpha-bromopyridine by reaction with cuprous cyanide.

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(6) All attempts to prepare picolinic acid nitrile through the diazo reaction failed although Rath and Schiffmann, *Ann.*, **487**, 127 (1931), report the preparation of α-cyano-α′-methylpyridine by the same method.