

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

## THE BROMINATION OF PYRIDINE<sup>1</sup>

BY S. MARY ELIZABETH ENGLERT AND S. M. McELVAIN

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The preparation of 3-bromopyridine and 3,5-dibromopyridine by the direct bromination of pyridine has long been known as a rather difficult reaction to carry out. Nevertheless, it appears to be the simplest method available for the preparation of these particular bromopyridines in quantity. Hofmann<sup>2</sup> was able to prepare 3,5-dibromopyridine by heating pyridine dibromide,  $C_5H_5N \cdot Br_2$ , in a sealed tube for one hour at 200°. He obtained the same product by heating pyridine hydrochloride and bromine together in a sealed tube. In neither reaction did he report the formation of 3-bromopyridine. Later, Ciamician and Silber<sup>3</sup> prepared 3-bromopyridine along with 3,5-dibromopyridine by heating pyridine hydrochloride and bromine in a sealed tube as Hofmann had done. They, however, heated their mixture for a longer time (twenty-four hours) and at a higher temperature (210–230°). Their combined yield of the mono- and dibromopyridines was only 21% of the theoretical. Blau<sup>4</sup> reported an improvement over the earlier sealed-tube methods, which consisted essentially of passing a mixture of bromine and carbon dioxide through molten pyridine hydrochloride. By this procedure the combined yield of the mono- and dibromopyridines was 42% of the theoretical.

This communication reports what seems to be a distinct improvement over all of the older methods of bromination of pyridine. The procedure consists of heating a perbromide of pyridine hydrobromide at 230–250° under ordinary pressure until the evolution of hydrogen bromide ceases.

There appears to be considerable variation in the composition of the perbromides of pyridine and pyridine salts as reported in the literature. Anderson<sup>5</sup> and Hofmann<sup>2</sup> treated pyridine and pyridine hydrochloride in aqueous solution with bromine and obtained crystalline precipitates which showed fair stability and to which they assigned the formula  $C_5H_5N \cdot Br_2$ . Grimaux<sup>6</sup> treated pure pyridine with bromine and obtained a compound that crystallized in thin, red plates and melted at 126°. To this compound he assigned the formula  $(C_5H_5N \cdot Br_2)_2 \cdot HBr$ . Trowbridge and

<sup>1</sup> A portion of the thesis submitted by S. Mary Elizabeth Englert to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Master of Science.

<sup>2</sup> Hofmann, *Ber.*, **12**, 988 (1879).

<sup>3</sup> Ciamician and Silber, *Ber.*, **18**, 722 (1885).

<sup>4</sup> Blau, *Monatsh.*, **10**, 372 (1889).

<sup>5</sup> Anderson, *Ann.*, **105**, 341 (1858).

<sup>6</sup> Grimaux, *Compt. rend.*, **95**, 85 (1882).

Diehl<sup>7</sup> were unable to obtain a definite compound from bromine and pyridine in aqueous solution but in chloroform solution they obtained a compound which appeared to have the formula  $C_5H_5N \cdot Br_4$ . On standing this tetrabromide lost bromine and passed into a compound which analysis showed to have the formula  $C_5H_5N \cdot Br_2$ . Barthe<sup>8</sup> obtained from pyridine and bromine a perbromide to which he assigned the formula  $C_5H_5N \cdot Br$ . Trowbridge and Diehl also prepared perbromides of salts of pyridine. By passing bromine into an aqueous solution of pyridine hydrobromide they obtained two perbromides, one of which contained 41.95% of bromine and the other 33.66% of bromine that was present as perbromide bromine. The latter compound melted at 93° and the formula  $C_5H_5N \cdot HBr \cdot Br$  was assigned to it. The perbromide containing 41.95% of perbromide bromine was assumed to be a mixture of  $C_5H_5N \cdot HBr \cdot Br_2$  and  $C_5H_5N \cdot HBr \cdot Br$ . These investigators also prepared a perbromide in aqueous solution to which they assigned the formula  $C_5H_5N \cdot HBr \cdot Br_2 \cdot H_2O$ . It melted at 118–120° and contained 67.96% of perbromide bromine.

In the work which is reported here it was found that glacial acetic acid was a much better solvent than water for the preparation of these perbromides because both reactants (bromine and pyridine hydrobromide) were quite soluble in this medium and the perbromides which were formed, while very soluble in warm acetic acid, were quite insoluble in the cold acid. From one mole of bromine and one mole of pyridine hydrobromide in acetic acid solution there was obtained a perbromide that melted at 132–134°. The yield was 95–97% of the theoretical based on the formation of  $C_5H_5N \cdot HBr \cdot Br_2$ . While this formula requires 50% perbromide bromine content, there was found only 47% of perbromide bromine in the product that melted at 132–134°.

One mole of pyridine hydrobromide and one-half mole of bromine in glacial acetic acid solution gave a perbromide that melted at 101–103° and had 39.7% of perbromide bromine. The perbromide bromine in the compound of the formula  $C_5H_5N \cdot HBr \cdot Br$  amounts to 33.3%. The authors are not able as yet to assign satisfactory formulas to these perbromides but it is hoped that further work will throw some light on this subject.

An attempt was made to use pyridine hydrochloride instead of pyridine hydrobromide for the preparation of these perbromides but it was found that the yields from the hydrochloride were considerably lower than those from the hydrobromide and that the perbromides of pyridine hydrochloride were very deliquescent and quite difficult to handle.

When these perbromides were heated at 230–250° under a reflux condenser, there was a vigorous evolution of hydrogen bromide with the formation of 3-bromo- and 3,5-dibromopyridine. The perbromide containing 47%

<sup>7</sup> Trowbridge and Diehl, *THIS JOURNAL*, 19, 558 (1897).

<sup>8</sup> Barthe, *Compt. rend.*, 145, 75 (1907).

of perbromide bromine gave a 40% yield of 3,5-dibromopyridine but none of the 3-bromopyridine. A mixture of pyridine hydrobromide and this perbromide gave a 35% yield of 3-bromopyridine and a 10% yield of the dibromopyridine. The greatest yields of brominated pyridines were obtained when the lower perbromide was heated. In this case 36–38% yields of 3-bromopyridine and 30–36% yields of 3,5-dibromopyridine were obtained. The yield calculations were made on the basis of the bromine used in the preparation of the perbromides.

### Experimental

**Pyridine Hydrobromide Perbromide (47% Perbromide Bromine).**—To a warm (60–65°) solution of 160 g. (1 mole) of pyridine hydrobromide in 240 g. of glacial acetic acid in a large beaker, a solution of 160 g. (1 mole) of bromine in 160 g. of acetic acid was added. The resulting solution was stirred thoroughly by hand and then allowed to cool. After two to three hours there was deposited a mass of large, orange-red, needle-shaped crystals. They were filtered off and dried in a desiccator. They were quite stable and when dry melted at 132–134°. The yield was 300–310 g. (95–97% based on the formation of  $C_5H_5N \cdot HBr \cdot Br_2$ ). These crystals were analyzed for perbromide bromine by the method of Trowbridge and Diehl<sup>7</sup> and found to contain 47.0% of such bromine.

**Pyridine Hydrobromide Perbromide (39.7% Perbromide Bromine).**—This perbromide was prepared in exactly the same manner as the one described above except that 80 g. (0.5 mole) of bromine in 80 g. of acetic acid was added to the warm solution of 160 g. of pyridine hydrobromide in acetic acid. The crystals obtained melted at 101–103° and the yield averaged 205 g. Analysis showed 39.7% of perbromide bromine. There was no appreciable change in weight in either of these perbromides when they were allowed to stand in a vacuum desiccator over sulfuric acid for several days.

**3-Bromopyridine and 3,5-Dibromopyridine.**—These products were prepared in better yields from the lower perbromide. The perbromide containing 39.7% of bromine as perbromide as obtained in the preparation described above was mixed with the residue left by the evaporation of the acetic acid mother liquors. The weight of this mixture amounted to approximately the sum of the weights of pyridine hydrobromide and bromine (that is, 240 g.) used in the preparation of the perbromide. This solid mixture was heated in a round-bottomed flask under a reflux condenser in a sodium nitrate–potassium nitrate bath that was maintained at 230–250°. The solid melted at about 100° and as the liquid reached the bath temperature there was a vigorous evolution of hydrogen bromide. The evolution of hydrogen bromide gradually subsided and at the end of six to eight hours had practically ceased. During the reaction there was considerable condensation of crystals of 3,5-dibromopyridine on the cooler parts of the flask and in the reflux condenser. When the evolution of hydrogen bromide had ceased, the reaction mixture was steam distilled until no more crystals of 3,5-dibromopyridine appeared in the condenser. The distillate consisted of an acid solution and suspension of 3,5-dibromopyridine which was completely precipitated out by the addition of alkali. The precipitate was filtered off and recrystallized from alcohol. The yield was 18–22 g. of a product that melted at 110–111°. The residue left in the flask after the removal of the 3,5-dibromopyridine by steam distillation was made strongly alkaline with sodium hydroxide and again steam distilled. The distillate consisted of water, pyridine and 3-bromopyridine and as it first came over was clear, but as the proportion of water increased it became turbid and when about 250 cc. of distillate had been collected, a layer of 3-bromopyridine and some pyridine was present in the receiver. This layer was

separated, dried with solid sodium hydroxide and fractionated. The fraction that boiled at 160–175° amounted to 29–31 g. On redistillation practically all of this fraction boiled at 168–172°. The yield of the dibromopyridine was 30–36% of the theoretical and that of the 3-bromopyridine 36–38% of the theoretical based on the bromine used in the preparation of the perbromide.

The separation of 3,5-dibromopyridine from 3-bromopyridine by steam distillation of the former from acid solution was originally used by Ciamician and Silber<sup>3</sup> and is fairly satisfactory but not complete. There appears to be some of the di-substitution product left with the monobromopyridine even after prolonged steam distillation, and in the final distillation of the latter compound a small amount of the dibromopyridine usually crystallizes in the condenser.

When the perbromide of higher bromine content was heated under similar conditions, a 40% yield of the dibromopyridine was obtained but none of the 3-bromopyridine was found. It was thought that dilution of this higher perbromide with pyridine hydrobromide might increase the yield of the mono-substituted product but several runs in which 2 moles of pyridine hydrobromide was mixed with 1 mole of the higher perbromide gave an average of 10% yield of 3-bromopyridine and 30% yield of the 3,5-dibromopyridine.

### Summary

A convenient method of brominating pyridine to 3-bromopyridine and 3,5-dibromopyridine has been described. It consists of the preparation of a perbromide of pyridine hydrobromide in glacial acetic acid solution and the transformation of this perbromide by heat into the bromopyridines.

MADISON, WISCONSIN

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]  
**SYNTHETIC GLYCERIDES. I. PREPARATION AND MELTING POINTS OF GLYCERIDES OF KNOWN CONSTITUTION<sup>1</sup>**

BY H. P. AVERILL, J. N. ROCHE AND C. G. KING

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The isolation of pure triglycerides from natural fats and oils is an uncertain and laborious process because of the difficulty of complete separation. Even when pure triglycerides have apparently been obtained satisfactory evidence is not available to indicate which of the possible isomers has been found. It was thought that progress could best be made through the synthesis of glycerides of known constitution and the study of their chemical and physical properties. Data thus obtained will be valuable in the study of the components of naturally occurring fats and oils.

It seemed probable that definite relationships might be found between certain physical properties of the fats and their molecular structure if sufficient data were available to warrant conclusions. The three sets of isomers (only one having fatty acids) prepared by Fischer<sup>2</sup> indicated that

<sup>1</sup> This paper is based upon a part of the theses submitted by H. P. Averill and J. N. Roche to the Graduate School, University of Pittsburgh, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

<sup>2</sup> E. Fischer, *Ber.*, **53**, 1621 (1920).