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163. **Makoto Yokoo**: Application of Azotometry. XVIII.[*1] Determination of Pyridine and its Derivatives.

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In Part XVI[1] of this series the author announced that some heterocyclic compounds such as proline and kainic acid can be determined by measuring the secondary amine in their rings by azotometry.

It was later found that piperidine can also be determined by the same method. On the other hand, as pyridine is readily reduced to piperidine by catalytic reduction over Raney nickel, the reduction method was simplified so as to allow incorporation with azotometry and it became possible to determine pyridine and some of its derivatives by a combination of the simplified reduction method with azotometry.

A few methods for the colorimetric determination of pyridine[2,3] have been reported, but as they require a control and as the pigment to be determined is unstable, establishment of a better method was desirable. Since azotometry can determine a sample directly from the volume of the nitrogen generated, it requires no control and therefore is superior to the known methods.

As mentioned above, pyridine is readily reduced to piperidine in the presence of Raney nickel, but the usual procedure used in general organic syntheses is too complicated to be incorporated in analytical method. It was found, however, that the procedure of introducing hydrogen can be omitted by using the hydrogen adsorbed on Raney nickel W-6 because 1 g. of Raney nickel W-6 adsorbs 9~13 mg. of hydrogen and the adsorbed hydrogen has reducing ability.[4] If a sample is used in an amount reducible by the adsorbed hydrogen, it can be reduced merely by shaking its solution with Raney nickel W-6 in a test tube. As the amount of the sample used in this method is 0.25~0.5 m.mole and the amount of hydrogen necessary for their reduction is 1.5~3.0 mg., 1.0~1.5 g. of Raney nickel W-6 is sufficient for one experiment.

The reduction mixture is filtered, an exact amount of the filtrate is subjected to azotometry[1] for secondary amines, and the quantity of the sample is calculated from the volume of the nitrogen generated.

Thus, pyridine, isonicotinic acid, 2-benzylaminopyridine, and N-hydroxymethyl-isonicotinamide were determined by the present method. The pyridine used in this method was made analytically pure by drying on sodium hydroxide and subsequent distillation, and other samples by recrystallization from water.

Experimental Method for Determination

1) **Reagents**—i) Raney nickel: Consisted of 50% each of Ni and Al.
ii) KNO_2 solution: About 60% solution.
iii) Sulfamic acid solution: About 20% solution.
iv) Zinc dust.
v) Devarda alloy.

[*1] This constitutes a part of a series entitled "Application of Azotometry" by Masaharu Yamagishi.

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[1] M. Yokoo: This Bulletin, **6**, 64(1958).

[2] S. Kertes, V. Kertes: Z. Anal. Chem., **156**, 68(1957).

[3] E. Asmuo, H. F. Kurandt: *Ibid.*, **149**, 3(1956).

[4] L. Kh. Friedlin, N. I. Ziminova: Doklady Akad. Nauk S. S. S. R., **74**, 955(1950).

vi) Potassium ferricyanide solution: A solution of 5 g. of $K_3Fe(CN)_6$ and 70 g. of $NaNO_3$ in 100 cc. of water.

2) Procedure—i) Preparation of Raney Nickel W-6: A solution of NaOH in 20 cc. of water was heated to 50° and 2 g. of Raney nickel was added over a period of 20 min., keeping the temperature at $50°\pm2°$. After the addition, the temperature was maintained at $50°\pm2°$ for an additional 30 min. and the resulting precipitate was washed with water by decantation to remove NaOH completely.

ii) Reduction of Pyridine: About 0.25~0.5 m.mole of pyridine was weighed exactly and washed into a test tube with a stopper, with 2 cc. of water. The Raney nickel W-6 prepared as above was also washed into the same test tube with 2~3 cc. of water and the mixture was shaken at 80~90° for 2 hr. in a water bath. When cool, the mixture was filtered, the precipitate was washed with water, and the filtrate was combined with the washing and made exactly to 20 cc.

iii) Azotometry: A 2-cc. portion of the above solution was placed in a test tube with a stopper, 0.5 cc. of AcOH and 0.5 cc. of the KNO_2 solution added, and left to stand at 30° for 30 min. Then 1~1.5 cc. of the sulfamic acid solution was added to decompose the excess HNO_2, cooling the mixture in order to prevent vigorous evolution of heat. Further, 2 g. of Zn dust was added with cooling and, after the evolution of heat subsided, 3 cc. of AcOH was added. The mixture was shaken for 30 min., allowed to stand with 0.5~1.0 g. of Devarda alloy for 30 min., and filtered. The filter was washed with water, the filtrate was combined with the washings, and diluted to exactly 25 cc. to make a test solution.

A 2-cc. portion of this test solution was subjected to ferricyanide-azotometry according to the method reported previously, and the volume of N_2 generated was converted into the value (V) in the standard state. Since $10^{-6}M$ of the $>$N-NH_2 compound produced from the sample generates 11.2 mm^3 of N_2 gas, the quantity of the sample was calculated from the following equation, in which M denotes molecular weight.

$$\text{Quantity of the sample (mg.)} = \frac{V\times M\times 25\times 20}{11.2\times 1000\times 2\times 2}=\frac{5\times M\times V}{448}$$

The result obtained by subjecting piperidine to azotometry for secondary amines is shown in Table I, that for pyridine by the present determination in Table II, and those of isonicotinic acid, N-hydroxymethyl-isonicotinamide, and 2-benzylaminopyridine by the present determination are Table III.

TABLE I.

Sample taken (mg.)	N_2 measured (mm^3)	Sample found	
		(mg.)	(%)
17.05	44.6	16.95	99.4
17.05	45.2	17.16	100.6
17.05	45.4	17.24	101.0
17.05	44.7	16.96	99.5

TABLE II.

Sample taken (mg.)	N_2 measured (mm^3)	Sample found	
		(mg.)	(%)
20.27	22.6	19.92	98.3
20.27	22.9	20.19	99.6
20.27	23.0	20.28	100.1
20.27	22.9	20.19	99.6

TABLE III.

Sample	Quantity (mg.)	N_2 measured (mm^3)				Sample found	
		1	2	3	mean	(mg.)	(%)
Isonicotinic acid	31.20	22.5	22.7	22.8	22.7	31.16	99.8
N-Hydroxymethyl-isonicotinamide	42.20	23.9	25.0	24.6	24.5	41.60	98.5
2-Benzylaminopyridine	53.50	26.5	26.0	26.4	26.3	54.00	100.9

Discussion

1. Reduction of Nitrosamines with Zinc Dust

Reduction with zinc dust of nitrosamines produced from dialkylamines and proline was conducted in conc. hydrochloric acid, but reduction by the same method of the nitrosamine produced from piperidine gave a lower value than the theoretical. In general, nitrosamines are unstable in strong acids and hydrolyzed into the corresponding secondary amines and nitrous acid. Also in the present method, the N-amino compounds produced by the reduction of nitrosamines may be decomposed in part.

Previously, Knorr[5] obtained N-aminopiperidine by the reduction of N-nitrosopiperidine with zinc dust and acetic acid. This method was also utilized and satisfactory results were obtained.

2. Kind of Raney Nickel

There are many kinds of Raney nickel having different properties, but, as Raney nickel W-6 adsorbs the largest amount of hydrogen, it was used in the present method. Usually, Raney nickel W-6, after being treated with sodium hydroxide, is washed with water in the hydrogen atmosphere, but merely washing with water by decantation was satisfactory for the present method.

3. Relationship between Temperature and Time during Catalytic Reduction

Catalytic reduction of pyridine under pressure requires a complicated apparatus, so it was conducted at atmospheric pressure in the present method. Since pyridine was reduced 60% in about 5 hours at room temperature, ca. 80~90% in 4 hours at 60°, and theoretically in 1.5~2 hours at 80~90°, as shown in Fig. 1, the reduction was carried out at 80~90° for 2 hours in the present method.

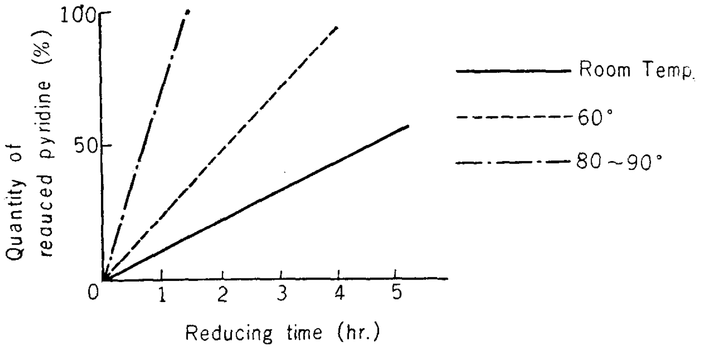

Fig. 1.

Quantity of Pyridine reduced at Room Temperature, 60°, and 80~90°

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Summary

Pyridine was determined by catalytic reduction over Raney nickel and subsequent azotometry of secondary amines. Catalytic reduction of pyridine was completed merely by shaking it with Raney nickel W-6 in a test tube, omitting the general procedure of introducing hydrogen.

Thus, pyridine, isonicotinic acid, N-hydroxymethyl-isonicotinamide, and 2-benzylaminopyridine was determined with an accuracy within 1.3%.

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[5] L. Knorr : Ann., **221**, 229(1883).