PREPARATION OF NICOTINAMIDE FROM NICOTINONITRILE

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In the preparation of nicotinic acid and its amide, one can use nicotinonitrile which is obtainable by oxidative ammonolysis of β-alkyl-substituted pyridines or quinoline. Nicotinonitrile (NN) is converted to nicotinamide (NA) by heating with solutions of acids [1] or bases [2], or by other methods.

The use of a water-insoluble basic catalyst is of considerable interest for the conversion of the nitrile group to an amide. In this connection, the ion-exchange resin AV-17 was shown to be effective. When aqueous solutions of NN were heated in the presence of AV-17 resin, NA was obtained in high yields (85-90%).

The kinetics of the hydrolysis of NN to NA was studied by means of serial scans of ultraviolet absorption spectra (Fig. 1). Samples of the reaction mixture were taken at set time intervals and their concentrations of initial and final products were determined by one of the methods described by us. The kinetics of hydrolysis was studied in 0.8-M solutions of NN at an NN-ammonia ratio of 1:1.25.

The results of the study of the effect of time and temperature on the kinetics of NN hydrolysis are shown in Table 1.

Since the hydrolysis reaction in an aqueous medium is first order with respect to NN, the rate constant can be expressed by the formula

$$K = \frac{1}{t} \ln \left(\frac{c_A^0}{c_A^0 - c_x} \right),$$

where C_A^0 is the initial concentration of NN (at $t = 0$; c_X is the concentration of NN at time t, corresponding to the linear relationship between time and $\ln = \frac{c_A^0}{c_A^0 - c_x}$ (Fig. 2).

The activation energy was determined graphically using the coordinates log K and 1/T (Fig. 3).

The optimum yield of NA (92.6%) was obtained at 60° after a reaction time of 2 h (Fig. 4). Apparently at temperatures above 60°, the anion-exchange resin undergoes significant degradation with a marked reduction in its exchange capacity. The effect of quantity of catalyst on yield and quality of recovered NA is shown in Table 2. The maximum catalyst loading corresponded to 0.4 g of NN per gram of swollen anion-exchange resin. The NA yield under these conditions was 92.7%.

Since the absorption spectra of NN and NA have absorption maxima whose position and magnitude are similar (Table 3), the determination of the individual components in the reaction mixture is difficult. By using the transmittance scale, it was possible to make use of the comparatively large differences in transmittance at λ = 237 mμ. Thus, at concentrations of each of these substances fixed at c = 0.03 mg/ml, the transmittances of their solutions differ significantly: NN-T = 57%, NA-T = 27%.

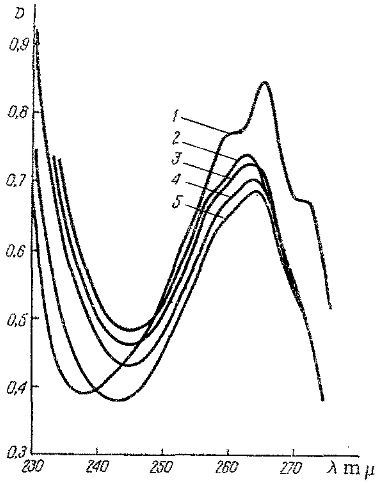

Fig. 1. Series of UV absorption spectra from reaction mixtures at 60°. 1) 0 min., start of the reaction (nicotinonitrile); 2) after 30 min; 3) after 60 min; 4) after 90 min; 5) after 120 min—nicotinamide (97%).

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TABLE 1. Effect of Time and Temperature on the Reaction Kinetics of Nicotinonitrile Hydrolysis

Temp. (°C)	Reaction duration	NA conc. (%)	NN conc. (%)	Reaction rate constant
20	30 min	10	88	$0,534 \times 10^{-4}$
	1 h 30 min	16	80	
	2 h	23	72,5	
	3 h	30	68	
	4 h	35	63,5	
	5 h	39	60	
	6 h	44	57	
40	30 min	29	66	$1,557 \times 10^{-4}$
	1 h	54	42	
	2 h	71	28	
	3 h	81,5	18	
	4 h	87	12,5	
	5 h	91	9	
	6 h	95	2	
60	30 min	61,5	35	$4,53 \times 10^{-4}$
	1 h	84	16	
	1 h 30 min	92	7	
	2 h	97	2	

Note. Activation energy (E) for all sequences was equal to 10.3 kcal/mole.

TABLE 2. Effect of Initial Concentration of NN on Yield of NA

Conc. of NN		Yield of NA	Mp (in degrees)	Quantity (g/g of NN) of catalyst AV-17 × 18 OH^-
moles/liter	%			
0,4	4,16	92,7	128—9	2,5
0,8	8,32	83,0	127—127,5	1,25
1,2	12,48	75,1	125—127,5	0,83
1,6	14,64	67,8	123—6	0,62
2,4	24,98	64,3	91—101	0,41

TABLE 3. Molar Extinction Coefficients of NA and NN

Substance	237 mμ	262 mμ
HA	$\varepsilon_2{}^1 = 0,937 \times 10^3$ $c_1 = 288 \times 10^{-4}$ g/mole	$\varepsilon_2{}^2 = 0,2343 \times 10^4$
HH	$\varepsilon_1{}^1 = 0,2439 \times 10^4$ $c = 2,46 \times 10^{-4}$ g/mole	$\varepsilon_1{}^2 = 0,2886 \times 10^{-4}$

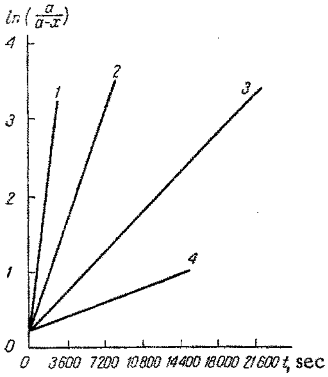

Fig. 2. Effect of temperature on the rate constant. 1) 90°; 2) 60°; 3) 40°; 4) 20°.

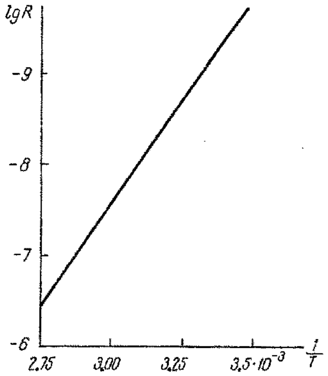

Fig. 3. Inverse effect of absolute temperature on the logarithm of the rate movement.

On this basis we worked out a rapid method for the quantitative determination of NN and NA in reaction products. In working with an SF-4A spectrophotometer the error did not exceed ±2%. This method was used for the analysis of reaction mixtures from NN hydrolysis in the course of the kinetics study.

The quantitative spectrophotometric determination of NN and NA can be accomplished by solving a system of two equations in two unknowns [3]:

$$D_1 = \varepsilon_1^1 c_1 + \varepsilon_2^1 c_2, \qquad (1)$$

$$D_2 = \varepsilon_1^2 c_1 + \varepsilon_2^2 c_2. \qquad (2)$$

From Eq. (1) we obtain c_1:

$$c_1 = \frac{D_1 - \varepsilon_2^1 c_2}{\varepsilon_1^1},$$

$$c_2 = \frac{D_2 \varepsilon_1^1 - \varepsilon_1^2 D_1}{\varepsilon_2^2 \varepsilon_1^1 - \varepsilon_1^2 \varepsilon_2^1},$$

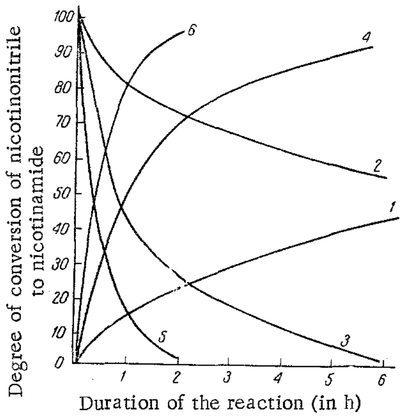

Fig. 4. The effect of reaction duration at various temperatures on the percent conversion of NN to NA. The initial concentration (0.5 g of AV-17 OH, 0.8 M NN, and 50 ml of water) taken as 100%. 1 (NA) and 2 (NN)] 20°; 3 (NN) and 4 (NA)] 40°; 5 (NN) and 6 (NA)] 60°.

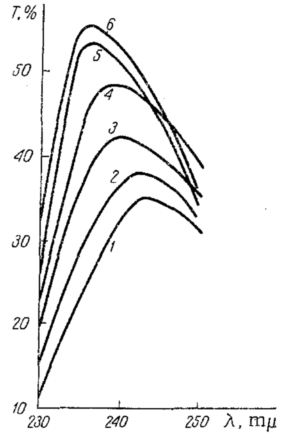

Fig. 5. Series of UV transmittance spectra for mixtures of NN and NA at different ratios: $c_{NN} + c_{NA} = 0.03$ mg/ml. 1) NA (100%) (c = 0.03 mg/ml); 2) 25% NN + 75% NA; 3) 50% NN + 50% NA; 4) 75% NN + 25% NA; 5) 95% NN + 5% NA; 6) 100% NN (c = 0.03 mg/ml).

TABLE 4. Analytical Results for Samples Having High Percentages of NA

Sample no.	Diff. spectrophotometric method		Analytical method	
	HH (in %)	HA (in %)	HH (in %)	NA (in %)
27	1.35	98.65	1.30	98.70
28	1.75	98.25	1.73	98.27
30	1.9	98.10	1.88	98.12

where D_1 is the optical density of the solution containing NN and NA, measured at λ = 237 mμ; and D_2 is the optical density of the same solution of NN and NA at λ = 262 mμ; ε_1^1 is the extinction of NN at λ = 237 mμ; ε_2^1 the extinction of NA at λ = 237 mμ; ε_1^2 the extinction of NN at λ = 262 mμ; ε_2^2 the extinction of NA at λ = 262 mμ; c_1 is the concentration of NN; c_2 the concentration of NA in the same reaction mixture. The calculated molar extinction coefficients are given in Table 3.

To increase the precision in determining NN in samples of NA, the differential spectrophotometric method [4] was used. Since the UV absorption spectrum of NN has a distinct maximum at λ = 274 mμ, while the spectrum of NA at this wavelength has the character of an absorption shoulder, one can use, in spectrophotometric estimation, a rather larger part of the optical density scale. We recommend conducting the measurement at a relative concentration of 96%.

EXPERIMENTAL

Nicotinamide. 10.4 g of nicotinonitrile (mp 48-49°) was dissolved in 250 ml of distilled water at 60°, and 25 g of ion-exchange resin AV-17 (in the OH^- form) was added with stirring. The reaction mixture was heated for 2 h at 60°. The resin was removed, washed with 100 ml of distilled water at 60°. The combined filtrates were evaporated under vacuum (20 mm). Yield: 11.04 g (90.5%), mp 128-130°.

When the nicotinonitrile hydrolysis to nicotinamide was conducted in the presence of ion-exchange resin AV-17 at 60°, samples of the reaction mixture were removed every 30 min and they were prepared for study in the same manner as the standard samples of NN and NA, i.e., at 0.03 mg/ml. A series of absorption spectra (see Fig. 1) were obtained from cuvettes one cm long on a recording EPS-3 spectrophotometer, and the optical densities at λ = 237 mμ and at λ = 262 mμ were determined for each sample. By inserting the optical density values into the equation, we determined the concentrations of both components in the sample.

Similar calculations were made for reactions at static conditions at 20, 40, 60, and 90°. The error of the method was ±0.5% when the SF-4A and Hitachi EPS-3 spectrophotometers were used.

To determine samples with high percentages of nicotinamide the differential spectroscopic method was used. Solutions were prepared at a concentration 0.3 mg/ml of pure samples of NN and NA. This concentration was taken as 100%. From this 100% solution, a solution with a 96% concentration of NA was prepared. This solution was placed in the reference cuvette in all spectroscopic measurements, instead of the usual solvent. In the same way the following synthetic mixtures were prepared (in %): NA 96 + NN 4; NA 97 + NN 3; NA 98 + NN 2; NA 99 + NN 1.

Optical density was measured at a wavelength of 274. Calculations were conducted on calibrated charts.

The results of the determination of nicotinonitrile impurities in nicotinamide samples are given in Table 4.

This method was developed on a Hitachi EPS-3 recording spectrophotometer, using the 0.3-0.7 scale, at a sensitivity of 4.

LITERATURE CITED

1. P. Finholt and T. Higuchi, J. Pharm. Sci., 51, 665 (1962).
2. B. Duesel and H. Friedman, U.S. Patent 2,471,518 (1949); Chem. Abstr., 43, 7513 (1950).
3. I. M. Kustanovich, Spectral Analysis [in Russian], Moscow (1967).
4. E. F. Kozlova and I. M. Kustanovich, Khim. Farmats. Zh., No. 5, 34 (1967).