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REACTION OF PYRIDINE-3,4-DICARBOXYLIC ACIDS WITH HYDRAZINE AND ANILINE

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In studying the reaction of dienes with maleic anhydride (1), we obtained several new pyridine-3,4-dicarboxylic acids. The present paper describes their condensation with hydrazine and aniline.

The presence of two adjacent carboxyl groups in the molecule of these acids suggests the possibility of obtaining several types of derivatives; in such cases the main direction of the process is determined by the individual features of the starting compounds. Thus, esters of the simplest *o*-dicarboxylic acids of the benzene series and of five-membered heterocycles (with the exception of thiophene) give dihydrazides with hydrazine; esters of thiophene dicarboxylic acids form cyclic hydrazides (2), while the anhydride of 3,6-diphenylphthalic acid gives only the N-aminoimide (3). From esters of the two previously known pyridine-3,4-dicarboxylic acids (unsubstituted (4) and 2,6-dimethyl-substituted (2)), as well as from quinolinic acid anhydride (5), cyclic hydrazides were obtained from hydrazine, although it was noted that the free quinolinic acid does not form a cyclic compound. As our investigation has shown, 5,6-dimethyl-, 2,6-dimethyl-, and 5-hydroxy-2-methylpyridine-3,4-dicarboxylic acids, even upon brief heating with hydrazine, are converted into cyclic hydrazides (pyrido-(3,4)-pyridazinediones) I in 60–80% yields, but in the case of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid this same reaction leads to formation of the N-aminoimide of the acid II.

I – II ,

a) $R = H,\ R' = R'' = CH_3;$

b) $R' = H,\ R = R'' = CH_3;$

c) $R' = OH,\ R = CH_3,\ R'' = H;$

d) $R'' = H,\ R = R' = CH_3;$

e) $R = R' = R'' = CH_3.$

Fig. 1

Figure 1: Fig. 1

Fig. 2

Figure 2: Fig. 2

2,5-Dimethylpyridine-3,4-dicarboxylic acid, in which the COOH groups are likewise blocked by CH_3 groups, as in the 2,5,6-trimethyl analog, gives on treatment with hydrazine the N-aminoimide II with a small admixture of hydrazide I . Prolonged heating of the reaction mixture leads to a change in its composition, the content of aminoimide gradually decreasing, while the yield of hydrazide increases to 60%. The isomerization of the aminoimide is accelerated by the presence of hydrazine that has not entered into the reaction, since pure II in a neutral medium is isomerized under the same conditions by only 10%.

In contrast to the 2,5-dialkyl-substituted acids, 5-hydroxy-2-methylpyridine-3,4-dicarboxylic acid gives exclusively hydrazide II with hydrazine.

In this case the formation of a new six-membered ring is apparently facilitated by the possibility of such a position of the OH group, in which it is turned away from the carboxyl, whereas in 5-methyl derivatives such a configuration is excluded.

The most stable derivatives of pyridine-3,4-dicarboxylic acids are the cyclic hydrazides I. As shown by the example of hydrazide

Fig. 1

Fig. 2

Id, it is formed as the final reaction product upon the action of hydrazine on the acid (after rearrangement of the aminoimide), its amide and N-phenylimide. Hydrazide Ia was obtained in high yields by treatment with hydrazine of the free acid, its dianilide, dimethyl ester, and also the monomethyl ester. An attempt to obtain from the monoester a monohydrazide of noncyclic structure led only to the formation of Ia. Cyclic hydrazides of pyridine-3,4-dicarboxylic acids are slightly colored, high-melting compounds, very stable, insoluble in organic solvents; they dissolve in aqueous ammonia, mineral acids, and hot acetic acid, and are titrated with aqueous alkali solutions as monobasic phenols (hydrazide of 5-hydroxy-2-methylpyridine-3,4-dicarboxylic acid as a dibasic phenol).

Upon oxidation of alkaline solutions of hydrazides of alkylpyridinedicarboxylic acids with hydrogen peroxide, weak luminescence is observed, but solution Ib luminesces intensely. Similarly to analogous compounds of the phthalazine series, pyridopyridazinediones give monochlorides upon treatment with $POCl_3$ and are alkylated by esters of toluenesulfonic acid.

Fig. 3

Fig. 3

Figure 3: Fig. 3

Figure 1 shows the absorption spectra of hydrazides Ia (λ_max 312 mμ, lg ϵ_max 3.72), Ib (λ_max 270 and 310 mμ, lg ϵ_max 3.78; 3.79), Iv (λ_max 306 and 375 mμ, lg ϵ_max 3.79; 3.93), and Id (λ_max 288 and 328 mμ, lg ϵ_max 3.73; 3.79).

Substituted N-aminoimides are insoluble in aqueous alkalis, but dissolve in alcohols; upon heating in the presence of basic catalysts they are converted into isomeric hydrazides, and with aldehydes give condensation products. The absorption spectra of N-aminoimides in the UV region differ from the spectra of hydrazides and are similar to the spectra of the corresponding imides unsubstituted at nitrogen and N-phenylimides. The absorption curves of the imide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid (**III**) and its N-phenylimide (**IV**) (Fig. 2), with practically coincident maximu-

maxima (308 and 310 mμ) and values of the absorption coefficient differing only slightly ($\lg\varepsilon_{\text{max}}$ 3.83 and 3.88), are very close to the curve of the N-aminoimide of this acid. A change in the degree of substitution of the pyridine portion of the molecule (Fig. 3, spectra of aminoimide IIg (λ_{max} 272 mμ, $\lg\varepsilon_{\text{max}}$ 3.69) and the N-phenylimide of 2,5-dimethylpyridine-3,4-dicarboxylic acid (V) (λ_{max} 300 mμ, $\lg\varepsilon_{\text{max}}$ 3.78)) likewise causes only a small shift of the maximum of the curve, but does not change its character.

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Experimental Part

N-Aminoimide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid (IId). A mixture of 6 g of 2,5,6-pyridine-3,4-dicarboxylic acid and 1.5 g of hydrazine hydrate was heated in 10 ml of ethylene glycol for 15 min. Yield of IId 60%, m.p. 211-212° (from methanol).

Found, %:	C 58.74; 58.88; H 5.48; 5.51; N 20.70; 20.20
$C_{10}H_{11}N_3O_2$. Calculated, %:	C 58.52; H 5.41; N 20.46.

N-*o*-Oxybenzylideneaminoimide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid. 1.6 g of N-aminoimide was boiled with 1.6 g of salicylaldehyde in alcoholic solution for 2 h. Yield of condensation product 89-92%, m.p. 191-191.5° (from methanol).

Found, %: C 66.17; 66.12; H 4.85; 4.90
$C_{17}H_{15}N_3O_2$. Calculated, %: C 66.01; H 4.89.

N-*p*-Oxybenzylideneaminoimide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid was obtained in 80% yield, m.p. 233–234.5°.

Found, %: C 66.36; H 4.79
$C_{17}H_{15}N_3O_2$. Calculated, %: C 66.01; H 4.89.

N-Aminoimide of 2,5-dimethylpyridine-3,4-dicarboxylic acid (IIg). The precipitate obtained after heating 2,5-dimethylpyridine-3,4-dicarboxylic acid with hydrazine was extracted with boiling alcohol. The substance insoluble in alcohol was pyridazinedione Ig (0.07 g, yield 5%), m.p. 328–331°. From the alcoholic extract, 1.35 g (67.5%) of IIg was isolated, m.p. 175–178°.

Found, %: C 56.19; 56.01; H 4.69; 4.58
$C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.76.

2,5-Dimethylpyrido-(3,4-*d*)-pyridazinedione (Ig). 4 g of 2,5-dimethylpyridine-3,4-dicarboxylic acid and 1 g of hydrazine hydrate were boiled in 3 ml of glycol for 1 h; the mixture was acidified with dilute acetic acid, and Ig was washed with boiling alcohol. Yield 2.4 g (60%); after sublimation in vacuum, m.p. 333° (with decomposition).

Found, %: N 22.30
$C_9H_9N_3O_2$. Calculated, %: N 21.97.

2,6-Dimethylpyrido-(3,4-*d*)-pyridazinedione (Ib) was obtained in 70% yield after 15 min boiling of a mixture of the acid with hydrazine in glycol, m.p. 290–293° (with decomposition).

Found, %: C 55.84; H 4.57
$C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.76.

Literature data: m.p. 302° (with decomposition) (2).

5,6-Dimethylpyrido-(3,4-d)-pyridazinedione (Ia), yield 62.5% (15 min heating), m.p. 333° (with decomp.).

Found, %: C 55.85; 56.03; H 4.78; 4.91
$C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.76.

The yield of Ia from the dimethyl ester of the acid and hydrazine was 89%, and from the dianilide and hydrazine 70.2%.

5-Oxy-2-methylpyrido-(3,4-d)-pyridazinedione (Ib). Yield 78% (10 min boiling), m.p. 308° (with decomp.).

Found, %: C 49.47; 49.60; H 3.89; 3.88
$C_8H_7N_3O_3$. Calculated, %: C 49.74; H 3.66.

2,5,6-Trimethylpyrido-(3,4-d)-pyridazinedione (Id). 5 g of the N-phenylimide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid was boiled with 14 g of hydrazine hydrate in 20 ml of glycol for 6 h; yield of Id 73%, m.p. 316° (with decomp.).

Found, %: C 58.38; H 5.52; N 20.95
$C_{10}H_{11}N_3O_2$. Calculated, %: C 58.52; H 5.41; N 20.46.

The yield of Id from the acid and hydrazine (2 h boiling) was 20%, and from the acid imide (m.p. 218–220°) and hydrazine 65%.

Reaction of pyridine-3,4-dicarboxylic acids with aniline. A mixture of the acid and aniline (1 : 4) was heated at 160–180° for 2–4 h, and the precipitate obtained was recrystallized from methanol (see Table 1).

Table 1

Substance	M.p., °C	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
N-Phenylimide of 2,5-dimethylpyridine-3,4-dicarboxylic acid	133.5–134	51	71.2171.34	4.724.74	71.41	4.79
N-Phenylimide of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid	152–154	62	72.0072.16	5.345.39	72.17	5.30
N-Phenylimide of 2,6-dimethylpyridine-3,4-dicarboxylic acid	145–146	52.8	71.12	4.91	71.41	4.79

Substance	M.p., °C	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Dianilide of 5,6-dimethylpyridine-3,4-dicarboxylic acid	190–192	40	72.8872.67	5.495.40	73.02	5.54

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Note: Figure translations are in progress. See original paper for figures.