Aminonitrile (V). To a solution of 0.25 g (1 mmole) of azomethine XIX in 4 ml of acetone cyanohydrin was added three drops of piperidine and the mixture was heated for 1 h at 50-60°C. Then the reaction mixture was allowed to stand overnight. The precipitate, which had settled out, was filtered off, and 0.27 g (96%) of crystals was obtained, having mp 145-146° (from alcohol). A mixture mp test with the previously prepared aminonitrile V gave no mp depression.

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DERIVATIVES OF 1,5-NAPHTHYRIDINE-2-CARBOXYLIC ACID, THEIR N-OXIDES, AND REDOX REACTIONS OF 1,5-NAPHTHYRIDINE-2-ALDEHYDE N,N'-DIOXIDE

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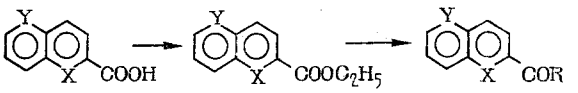
N-Oxides of amides and hydrazides of quinoxaline-2-carboxylic acids have exhibited high antibacterial activity [1]. In this connection, it was of interest to synthesize analogous derivatives of 1,5-naphthyridine-2-carboxylic acid and their N-oxides and to study the antibacterial activity of the obtained compounds. The compounds contemplated for study were obtained from the esters of the corresponding acids.

It has been shown previously that the methyl ester of 1,5-naphthyridine-2-carboxylic acid is formed via the reaction of the acid (I) with methanol in the presence of concentrated sulfuric acid [2]. Esters of the 1,5-di-N-oxides of 1,5-naphthyridine-2-carboxylic acid could not be obtained by this method; in the conditions mentioned, as well as on heating in alcohols in the presence of HCl, the main product was the starting 1,5-di-N-oxide of 1,5-naphthyridine-2-carboxylic acid (II).

The ethyl ester of 1,5-naphthyridine-2-carboxylic acid 1,5-di-N-oxide (III) was obtained in high yield on heating II with thionyl chloride in nonaqueous ethanol (see Table 1). This same method was used to obtain the ethyl ester V from 1,5-naphthyridine-2-carboxylic acid 5-N-oxide and the ethyl ester VI from I.



I, II, IV

I X=Y=N
II X=Y=N→O
III X=Y=N→O
IV X=N, Y=N→O

III, V, VI

V X=N, Y=N→O
VI X=Y=N

XIII-XVIII

XIII X=Y=N, R=NH_2
XIV X=Y=N, R=$NHNH_2$
XV X=N, Y=N→O, R=NH_2
XVI X=Y=N→O, R=NH_2
XVII X=Y=N→O, R=$NHCHCH_2C_6H_5$ (CH$_3$)
XVIII X=Y=N→O, R=$NHNH_2$

The acid IV was isolated while studying the redox reactions of 1,5-naphthyridine-2-carboxaldehyde 1,5-di-N-oxide (VII) in the presence of alkaline reagents.

It has been shown previously that pyrazine-2-carboxaldehyde 1,4-di-N-oxide (VIII), containing the aldehyde group as the hydrate, on attack by alkaline reagents behaves analogously to N-oxides of aromatic heterocycles substituted with α-hydroxyalkyl groups in positions ortho and para to the oxidized nitrogen of the ring [3, 4] and undergo oxidation of the α-dihydroxyalkyl group with simultaneous dioxidation of a heterocyclic

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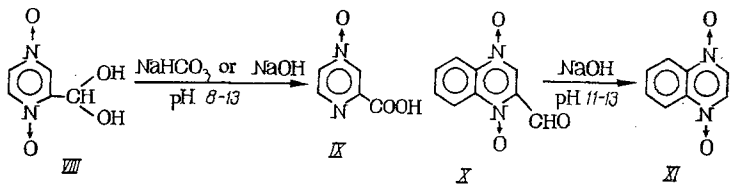
TABLE 1. Derivatives of 1,5-Naphthyridine-2-carboxylic Acid and Their N-Oxides

Compound	Yield, %	mp, °C	R_f	Found, %			Molecular formula	Calculated, %		
				C	H	N		C	H	N
III	80,0	139—140,5	0,61	57,1	4,5	11,96	$C_{11}H_{10}N_2O_4$	56,4	4,3	11,96
IV	98,7	269—270	0,06	56,79	3,18	14,6	$C_9H_6N_2O_3$	56,85	3,18	14,73
V	95,6	155—6,5	0,76	60,45	4,5	12,77	$C_{11}H_{10}N_2O_3$	60,54	4,61	12,84
VI	97	60—61,5	0,84	65,23	5,12	13,7	$C_{11}H_{10}N_2O_2$	65,34	4,98	13,85
XIII	74,8	227—8	—	62,38	4,18	24,06	$C_6H_7N_3O$	62,42	4,07	24,26
XIV	86,3	189—191	—	57,33	4,16	29,92	$C_9H_8N_4O$	57,44	4,28	29,77
XV	92	>300	0,27	57,08	3,57	22,23	$C_9H_7N_3O_2$	57,14	3,73	22,21
XVI	80,0	275—6,5	0,21	52,88	3,48	20,43	$C_9H_7N_3O_3$	52,89	3,44	20,48
XVII	47,4	178—8,5	0,76	66,42	5,08	12,84	$C_{18}H_{17}N_3O_3$	66,86	5,3	12,99
XVIII	85,2	>300	0,18	48,59	4,05	25,02	$C_9H_8N_4O_3$	49,1	3,66	25,44

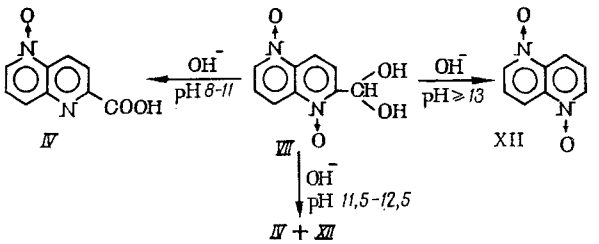
N atom, forming pyrazine-2-carboxylic acid 4-N-oxide (IX) [5] (reaction A). It has also been shown that quinoxaline-2-carboxaldehyde di-N-oxide(X), in which the aldehyde group is not hydrated, remains unchanged in aqueous sodium hydrocarbonate but in aqueous NaOH solutions, it reacts similarly as the N-oxides of certain ketones of the quinoxaline series [6], forming di-N-oxides of unsubstituted quinoxaline (XI) [5] (reaction B).



VIII IX X XI

On the basis of literature data, it would be expected that compound VII having the aldehyde group present as the hydrate [2] would undergo a reaction of type A.

The conducted study showed, however, that compound VII can undergo either type A or type B reaction, depending on the pH of the medium. Via GLC it was shown that VII in NaOH solutions at pH 8.0-11.00 was converted to IV only (reaction A), but at pH ≥13.0 the 1,5-naphthyridine di-N-oxide (XII) was formed (reaction B). At intermediate pH(11.5-12.5), a mixture of IV and XII was formed.



IV VII XII

IV + XII

These findings were confirmed preparatively: On treatment of VII with a sodium hydrocarbonate solution, the acid IV was obtained in high yield (the reaction occurred significantly slower than in the case of VIII), whereas treating VII with 2.5 N NaOH gave nearly quantitative yield of compound XII. At pH 12.25 a mixture of IV and XII was formed.

Thus, it was discovered for the first time in studies on compound VII that type B reaction is possible with heterocyclic N-oxides containing an α-dihydroxyalkyl group, and the dependence of the dual reactivity of VII (to react via type A or type B manner) on pH was demonstrated.

Amides (XIII, XV-XVII) and hydrazides (XIV, XVII) were obtained from the esters III, V, and VI.

The bacteriostatic and fungiostatic activity of the synthesized compounds was studied by in vitro testing by the method of serial dilution. The di-N-oxide derivatives of 1,5-naphthyridine-2-carboxylic acid (III, XVI, XVII, and XVIII) exhibit antibacterial activity with respect to gram-positive (Staphylococcus, Streptococcus, diphtheria bacillus, anthracoid) and gram-negative (intestinal, typhoid, dysentery, Bacillus pyocyaneus, Proteus) bacteria and tuberculosis pathogens (H_{37}, avium, and B_5).

The derivatives of 1,5-naphthyridine-2-carboxylic acid VI, XIII, XIV, and their 5-N-oxides V and XV exhibited no activity. Such a dependence between structure and antibacterial activity was observed earlier in the case of corresponding derivatives of quinoxaline and their mono- and di-N-oxides. The activity of III,

XVI, XVII, and XVIII, however, was lower than that of analogous compounds of the quinoxaline series.

It is of interest to note that the highest activity with respect to pathogens of acute bacterial infections was observed for compound III (minimal bacteriostatic concentration 15.6-31.2 μg/ml), whereas in the quinoxaline series, the highest activity was observed for amides of quinoxaline-2-carboxylic acid 1,4-di-N-oxide.

EXPERIMENTAL

The chromatography was conducted on paper using 1:1 butanol–6% acetic acid system, with UV light as the developer. PMR spectra were recorded on a JNM-4H-100 apparatus. Analytical results, yields, and melting points of the synthesized compounds are given in Table 1.

1,5-Di-N-oxide of Ethyl 1,5-Naphthyridine-2-carboxylate (III). A solution of 1.41 ml (19.9 mmole) thionyl chloride and 1.1 g (5.34 mmole) II in 27 ml nonaqueous ethanol was refluxed for 2 h, the ethanol distilled off, and the residue neutralized with a sodium hydrocarbonate solution to pH 7.0 and extracted with chloroform. Yield, 1 g (4.28 mmole) III.

Compounds V and VI were prepared analogously, with heating for 4 and 10 h, respectively. PMR spectrum for V (in deuterochloroform), δ ppm: 1.50, 4.59 (C_2H_5), 8.40 (H^3), 9.15 (H^4), 8.61 (H^6), 7.61 (H^7), 8.19 (H^8).

Reactions of Compound VII in Alkaline Media. A. A solution of 0.2 g (0.96 mmole) of compound VII in 1 ml 2.5 N NaOH was allowed to stand for 24 h at 20°C, then extracted with chloroform. The chloroform was removed and 0.15 g (0.925 mmole) of compound XII was obtained, which, according to mp (300°C) and R_f value (0.12), was identical to a sample of XII prepared by a known method [7].

B. A solution of 0.2 g (0.96 mmole) of compound VII in 15 ml freshly prepared sodium hydrocarbonate solution was allowed to stand for 6 days at 20°C, then acidified to pH 2. The precipitate was filtered off to give 0.18 g (0.946 mmole) of IV.

C. A solution of 0.2 g (0.96 mmole) of compound VII in 13 ml 0.1 N NaOH, pH 12.25, was allowed to stand for 3 days at 20°C. It was then extracted with chloroform and the chloroform removed to give 0.13 g (0.83 mmole) XII. The aqueous layer was acidified and 0.015 g (0.079 mmole) IV isolated.

1,5-Naphthyridine-2-carboxamide (XIII). Compound VI (0.45 g, 2.23 mmoles) was dissolved in 15 ml 14% alcoholic ammonium and allowed to stand in a closed flask for 12 h at 20°C. The precipitate formed was filtered off and crystallized from alcohol to give 0.29 g (1.67 mmoles) compound XIII.

Amides XI and XVI were obtained analogously to XIII.

1,5-Naphthyridine-2-carboxylic Acid Hydrazide (XIV). A solution of 0.4 g (1.97 mmoles) compound VI and 0.18 ml (4.0 mmoles) hydrazine hydrate in 2 ml nonaqueous ethanol were allowed to stand for 12 h at 20°C. The precipitate formed was filtered off and crystallized from alcohol to give 0.32 g (1.7 mmoles) compound XIV.

The hydrazide XVIII was obtained analogously to XIV.

1,5-Di-N-oxide of 1,5-Naphthyridine-2-carboxylic Acid N-β-Phenylisopropyl Amide (XVII). A solution of 0.2 g (0.85 mmole) of compound III and 0.27 g (2.0 mmole) β-phenylisopropylamine in 3 ml nonaqueous ethanol was refluxed for 12 h, then cooled to −5°C. The precipitate was filtered off and crystallized from aqueous alcohol. Yield, 0.13 g (0.4 mmole) compound XVII.

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