Treatment of a mixture of IIIα and IIIβ and IV does not alter them.

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SYNTHESIS AND PROPERTIES OF 4-SUBSTITUTED 1,5-NAPHTHYRIDINES AND THEIR N-OXIDES

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UDC 547.834.2.07:542.943:543.422.4.25

4-Substituted 1,5-naphthyridines and their N-oxides were synthesized, and their structures and properties were studied. The IR and UV spectra of 4-hydroxy- and 4-methoxy-1,5-naphthyridines and their 1-oxides and 1-ethyl-4-oxo-1,4-dihydro-1,5-naphthyridine were examined. It is shown that 4-hydroxy-1,5-naphthyridine and its 1-oxide exist in the crystalline state in the lactam form. A quantitative estimate of the position of the tautomeric equilibrium of 4-hydroxy-1,5-naphthyridine as a function of the polarity of the solvent is given, and the tautomeric equilibrium constants and the percentages of the lactim form are calculated. The basicity constants of 4-chloro-, 4-methoxy-, 4-hydrazino-, 4-methylthio-, 4-acetamido-, and 4-amino-1,5-naphthyridines were measured. A comparison of the calculated and experimental pK_a data provides evidence in favor of the fact that the compounds are protonated at the N_1 atom. A correlation of the basicity constants with the σ substituent constants is examined.

Research on the chemistry of x,y-naphthyridines has expanded considerably in recent years in connection with the fact that biologically active compounds have been detected among derivatives of these heterocycles.

In our previously published papers we have reported the synthesis and structure of 2-substituted 1,5-naphthyridines and their N-oxides, among which substances that have antibacterial activity have been found [1]. Continuing our study of 1,5-naphthyridine derivatives we synthesized 4-substituted 1,5-naphthyridines and their N-oxides and studied their structures and properties.

Compounds II-VII were synthesized from 4-chloro-1,5-naphthyridine (I). By alkylation of III we obtained 4-alkylthio derivatives Va-c of 1,5-naphthyridine and by subsequent oxidation of them we obtained sulfones VIa, c.

Chloro derivative I is readily oxidized with hydrogen peroxide in the presence of Na_2WO_4 to give N-oxide VIII. Under more severe conditions the reaction proceeds ambiguously and is accompanied by partial replacement of chlorine by a hydroxy group. The structure of N-oxide VIII was proved by comparisons of its PMR spectrum with the spectrum of I (see Table 1): The shift of the H_8 signal in the spectrum of the N-oxide to weak field ($\Delta\delta = -0.62$ ppm), which is characteristic for the protons of aromatic heterocycles in the peri position

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 792-799, June, 1981. Original article submitted May 26, 1980.

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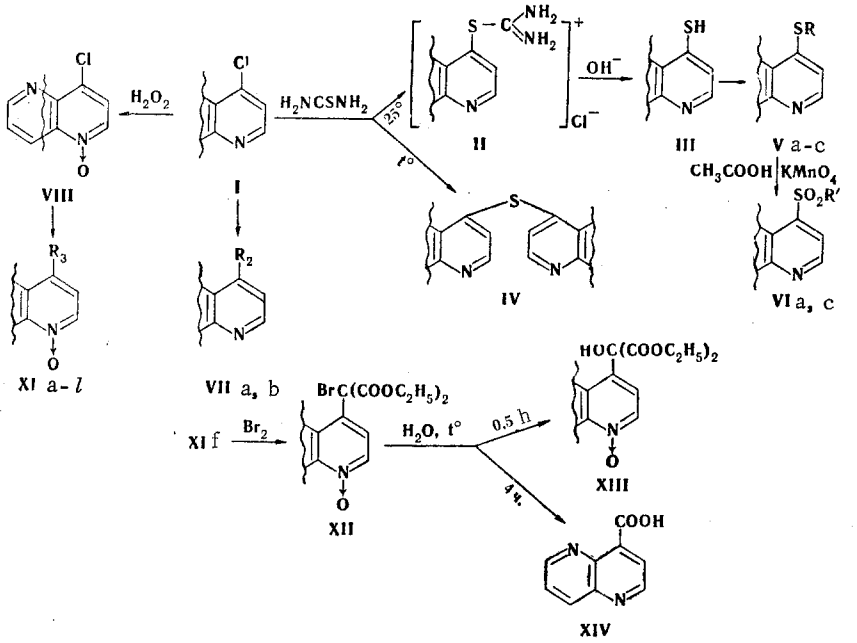


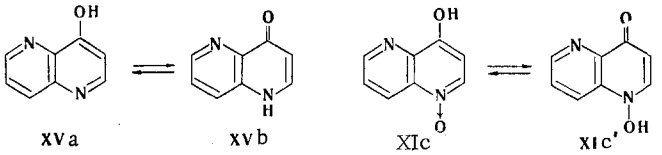
V a $R=CH_3$, b $R=CH_2CH=CH_2$, c $R=CH_2C_6H_5$; VI a $R_1=CH_3$, c $R_1=CH_2C_6H_5$; VII a $R_2=OCH_3$, b $R_2=NHNH_2$, c $R_2=HNN=CHC_6H_4NO_2$-(R); XI a $R_3=NHNH_2$, b $R_3=NHCH(CH_3)_2$, c $R_3=OH$, d $R_3=OCH_3$, e $R_3=NH_2$, f $R_3=CH(COOC_2H_5)_2$, g $R_3=CH_2COOH$, h $R_3=CH_2COOC_2H_5$, i $R_3=CH_3$, j $R_3=CHO$, k $R_3=SCH_2C_6H_5$, l $R_3=SO_2CH_2C_6H_5$

relative to the oxidized ring nitrogen [2] and the increase in $J_{2,3}$ to 6.7 Hz (instead of 4.6 Hz in the spectrum of I) constituted evidence for the presence of an $N_{(1)}\rightarrow O$ group in the molecule.

By oxidation of 4-acetamido-1,5-naphthyridine (IX) with hydrogen peroxide in the presence of Na_2WO_4 we obtained the 1,5-dioxide (X) of this compound.

We synthesized the 1-oxides (XIa-f) of 3 substituted 1,5-naphthyridines by the reaction of N-oxide VIII with the corresponding nucleophilic reagents. Depending on the hydrolysis conditions, If was converted to 1,5-naphthyridin-4-ylacetic acid 1-oxide (XIg) or 4-methyl-1,5-naphthyridine 1-oxide (XIi). The latter was oxidized with selenium dioxide to the corresponding aldehyde (XIj). Sulfone XII was obtained from XIk by oxidation with hydrogen peroxide.

By bromination of XIf with bromine in chloroform we obtained bromo derivative XII, the structure of which was proved by a comparison of its PMR spectrum with the spectrum of starting XIf (see Table 1). Pronounced resinification was observed upon attempts to hydrolyze bromo derivative XII in acidic or alkaline media; upon heating in water, the bromine was initially replaced by a hydroxy group to give XIII, whereas more prolonged heating gave 4-carboxy-1,5-naphthyridine (XIV), the structure of which was proved by the results of elementary analysis and data from the IR and PMR spectra. We have previously observed similar transformations leading to deoxidation of nitrogen and replacement of the malonic ester residue by a carboxy group when 2-quinoxalinylmalonic ester N-oxide was heated in an acidic medium [3].



In order to study the tautomerism of 4-hydroxy-1,5-naphthyridine (XV) and its 1-oxide (XIc) we examined their IR and UV spectra. The IR spectra of these compounds, like the spectrum of the synthesized model compound 1-ethyl-4-oxo-1,4-dihydro-1,5-naphthhthyridine (XVI) (all in the crystalline state) contain bands of C=O stretching vibrations at 1622-1625 cm^{-1}, which are absent in the spectra of 4-methoxy-1,5-naphthyridine (VIIa) and its 1-oxide (XId).

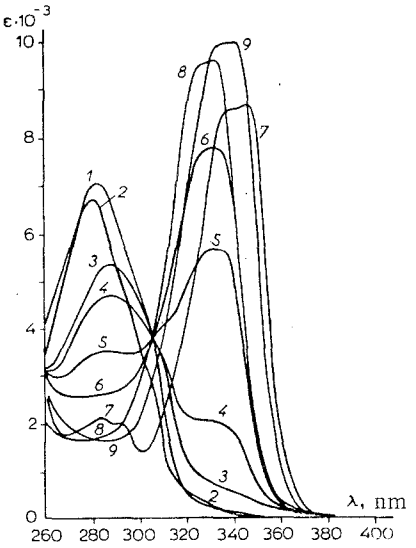


Fig. 1. UV spectra of VIIa, XV, and XVI in various solvents: 1) VIIa in alcohol; 2) VIIa in dioxane; 3) XV in dioxane; 4) XV in a mixture of dioxane with 10% alcohol; 5) XV in a mixture of dioxane with 25% alcohol; 6) XV in a mixture of dioxane with 50% alcohol; 7) XVI in dioxane; 8) XV in alcohol; 9) XVI in alcohol.

TABLE 1. PMR Spectra of 1,5-Naphthyridine Derivatives

Compound	δ, ppm							J, Hz			
	CH_3	CH_2	2-H	3-H	6-H	7-H	8-H	2,3	6,7	8'9	7,8
I	—	—	8,85 (d)	7,76 (d)	9,09 (q)	7,72 (q)	8,44 (d d)	4,6	4,1	1,6	8,6
VIII	—	—	8,47 (d)	7,64 (d)	9,15 (q)	7,77 (q)	9,06 (d d)	6,7	4,1	1,5	8,9
XIf*	1,27 (t)	4,25 (q)	8,55 (d)	7,73 (d)	9,02 (m)	7,69 (m)	9,02 (m)	6,5	—†	—†	—†
XII	1,21 (t)	4,28 (q)	8,50 (d)	8,06 (d)	8,95 (q)	7,66 (q)	9,02 (d d)	6,5	4,2	1,6	8,6

*$\delta_{(CH)}$ = 6.12 ppm (s). †Because of overlapping of the 6-H and 8-H signals we were able to determine only the sum $J_{6,7} + J_{6,8}$ = 13 Hz.

A broad absorption band at 2700 cm^{-1} (νNH) is also observed in the spectrum of XV, whereas a band at 2300-2580 cm^{-1} (νOH) is observed in the spectrum of 1-oxide XIc. Consequently, XV and XIc exist in the lactam form (XVb and XIc', respectively) in the crystalline state. The pronounced shift of the bands of the NH (XVb) and OH (XIc') groups indicates the existence of hydrogen bonds, evidently of the intermolecular type (because of the low solubilities of the compounds, we were unable to obtain the IR spectra in solutions).

Previously [4] from a comparison of the UV spectra of solutions of XV with the spectra of 4-hydroxy- and 8-hydroxyquinolines it was concluded that in polar solvents (water and acetonitrile) the hydroxy derivative exists in the lactam form (XVb), whereas in dioxane it exists primarily in the lactim form (XVa). However, the method used by these authors did not make it possible to give a quantitative estimate of the position of the tautomeric equilibrium. We made this sort of estimate in the present research by comparison of the UV spectra of tautomeric XV with the spectra of specially synthesized model compounds with fixed lactam (XVI) and lactim (VIIa) structures. The spectra of the model compounds differ appreciably from one another — in the case of XVI an absorption maximum at 340-342 nm, the intensity of which changes somewhat as the polarity of the solvent changes, is characteris-

TABLE 2. Percentage of the Lactim Form and Tautomeric Equilibrium Constants (K_T = % lactam/% lactim) for 4-Hydroxy-1,5-naphthyridine (XV)

Indexes	Alcohol: dioxane ratio, %				
	100 : 0	50 : 50	25 : 75	10 : 90	0 : 100
% lactim	4	14	36	77	92
K_T	24	6,14	1,78	0,30	0,09

tic; an absorption maximum is observed at 289-290 nm in the spectrum of VIIa, whereas absorption at 340 nm is virtually absent. The spectra of 4-hydroxy-1,5-naphthyridine (XV) in alcohol and alcohol–water mixtures are similar to the spectrum of 1-ethyl model compound XVI (maximum at 330-333 nm), whereas in alcohol–dioxane mixtures the band at 330 nm decreases in intensity as the percentage of dioxane is increased, and one observes a band at 287-290 nm, the intensity of which increases as the dioxane concentration is increased. In pure dioxane the spectrum of XV approaches the spectrum of the OCH_3 model compound VIIa (see Fig. 1).

Taking the extinction of model compound XVI at 340 nm in the solvent used as the extinction of the lactam form we calculated the percentages of the lactam and lactim forms and the tautomeric equilibrium constant, as is usually done [5, 6] (see Table 2). It is apparent from the data in Table 1 that in alcohol the percentage of the lactim form XVa is ~4%, as compared with 14% in alcohol–dioxane (1:1), and 92% in dioxane. The stabilization of the lactim form in dioxane is evidently associated with the existence in XVa of an intramolecular hydrogen bond between the OH and N_5 groups, which is cleaved in hydroxy-containing solvents.

Just as in the case of 2-substituted 1,5-naphthyridines [1], in 4-substituted 1,5-naphthyridines there are two possible protonation centers, viz., N_1 and N_5, and it may be assumed that the effect of substituents in the 4 position on the two possible protonation centers will differ. The effects of polar conjugation should play a substantial role in transmission of the effect to N_1, whereas inductive effects should play a substantial role in transmission of the effect to N_5.

We measured the pK_a values of I, Va, VIIa, VIIb, IX, and 4-amino-1,5-naphthyridine (XVII). It is apparent from the pK_a values (see Table 3) that the introduction of substituents with a predominant +C effect leads to a significant increase in the basicity as compared with unsubstituted 1,5-naphthyridine: by 4.95 pK_a units for the amino group (XVII) and by 4.3 pK_a units for the hydrazine residue (VIIb). The basicities of compounds in which the substituting groups have +C and –I effects increase to a considerably smaller extent: In the case of the 4-methoxy derivative (VIIa) the basicity undergoes an increase of only 0.96 of a unit for the 4-methylthio derivative (Va). The decrease in basicity observed when chlorine is introduced (I) is due to the small magnitude of its +C effect as compared with its –I effect.

The relative proton-acceptor capacity of the N_1 and N_5 atoms in 4-substituted 1,5-naphthyridines was estimated from the approximate calculated basicity constants corresponding to these centers, viz., pK_1 and pK_5. The higher pK value corresponds to the center at which the proton will be added. The calculations were made by the method previously used for 2-substituted 1,5-naphthyridines [7, 8]; the Hammett equation with $\rho = 6.13$, the value obtained in [1] for the 1,5-naphthyridine series, was used in the form

$$pK_a = 2.91 - 6.13\Sigma\sigma \quad (1)$$

Where possible, the σ_4 and σ_8 values were calculated from the basicity constants of the correspondingly substituted quinolines or pyridines [9]; in the remaining cases, in accordance with [8], we used $\sigma_4 = \sigma_p$ and $\sigma_8 = \sigma_m$.

A comparison of the calculated and experimental pK_a data (see Table 3) shows that the calculated pK_1 values are greater than the pK_5 values for all of the investigated compounds and that satisfactory agreement between the calculated pK_1 values and the experimental pK_a values is observed. This constituted evidence that the examined compounds are protonated at the N_1 atom.

TABLE 3. Experimental and Calculated Basicity Constants of 1,5-Naphthyridine Derivatives and σ Constants Used

Compound *	pK_a exp	pK_1 calc	pK_s calc	σ_4	σ_8
I	1,73	1,68	1,0	0,20	0,31
V*	3,87	3,83	1,44	−0,15	0,24 †
VII*	4,24	4,50	2,21	−0,26	0,115†
VII†	7,30	6,28	3,03	−0,55†	−0,02†
IX	3,81 ‡	3,58	1,62	−0,11	0,21†
XVII‡	7,86 ‡	7,20	1,88	−0,72	0,16

*The pK_a of 1,5-naphthyridine is 2.91 [11]. †According to [8], for the compounds noted it is assumed that $\sigma_4 = \sigma_p$ and $\sigma_8 = \sigma_m$; in the remaining cases the substituent constants were calculated from the pK_a values of the correspondingly substituted quinolines, whereas for IX they were calculated from those for pyridine. ‡According to [10], $pK_a = 7.7$.

The data obtained in this research made it possible to examine the correlation of the experimental basicity constants with the σ substituent constants. In selecting the σ constants we took into account the above-established mutual orientation of the substituent and the protonation center. The equation has the form

$$pK_a = 2{,}94 - 7{,}02\sigma,\ r = 0{,}99 \text{ and } S_0 = 0{,}35$$

During a study of the biological activity of the synthesized compounds it was found that thiuronium salt II and mercapto derivative III display high activity *in vitro* with respect to a number of Gram-negative and Gram-positive bacteria, tuberculosis mycobacteria, and pathogenic fungi. In the case of pathogenic fungi (dermatophytes and *Candida albicans*) the minimal fungistatic concentration of II and III ranges from 2 to 4 μg/ml. In *in vitro* tests these compounds displayed weak chemotherapeutic activity in tolerable doses.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The UV spectra of solutions of the compounds were recorded with an EPS-3 spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. The mass spectra were obtained with an MAT-112 mass spectrometer; the ionizing-electron energy was 70 eV, the temperature of the ionization chamber was 200°C, and the samples were introduced directly into the source. Chromatography was carried out on paper in a butanol–6% acetic acid system (1:1) (for III-X, XIb, e, i, k, l, and XVI) and on Silufol UV-254 plates in methanol–ethyl acetate (9:1) (for XIe, j, XIII, and XIV) and benzene–acetone (8:3) (for XIf and XII) systems. The chromatograms were developed in UV light. The basicity constants were determined by the method in [1] with an accuracy of ±0.05 pK_a units. The characteristics of the synthesized compounds are presented in Table 4.

4-Mercapto-1,5-naphthyridine (III). A solution of 0.74 g (4.5 mmole) of chloro derivative I and 0.343 g (4.5 mmole) of thiourea in 18 ml of anhydrous alcohol was stirred at 20°C for 19 h, after which 0.9 g (3.64 mmole) of thiuronium salt II was removed by filtration. A 5.5-ml sample of a 40% solution of NaOH was added to a solution of 5.1 g (22.3 mmole) of II in 30 ml of water, and the mixture was stirred at 20°C for 30 min, after which it was acidified to pH 5 to give 2.93 g of III.

Bis(1,5-naphthyridin-4-yl) Sulfide (IV). A solution of 0.83 g (5 mmole) of I and 0.38 g (5 mmole) of thiourea in 15 ml of alcohol was refluxed for 10 min, after which it was cooled, and 0.7 g of sulfide IV was removed by filtration.

4-Methylthio-1,5-naphthyridine (Va). A 0.49-ml (7.83 mmole) sample of CH_3I was added to a solution of 1.2 g (7.4 mmole) of III in 8.3 ml of 1 N NaOH, and the mixture was stirred at 20°C for 3.5 h. It was then extracted with ether to give 0.126 g of Va.

Compounds Vb, c were similarly obtained from III and allyl bromide or benzyl chloride (in the latter case the reaction was carried out at 50°C for 2 h).

TABLE 4. Characteristics of the Synthesized Compounds

Compound	mp, °C*	R_f	Found, %					Empirical formula	Calculated, %					Yield, %
			C	H	Cl	N	S		C	H	Cl	N	S	
II	154—156				14,6	23,3	13,3	$C_9H_9ClN_4S$			14,7	23,3	13,3	80,9
III	252,5—254	0,05				16,7	19,4	$C_8H_6N_2S$				17,3	19,8	81
IV	199—201	0,69	66,1	3,5		18,7	10,7	$C_{16}H_{10}N_4S$	66,2	3,5		19,2	11,0	96,7
Va	87,5—88	0,8				15,5	18,3	$C_9H_8N_2S$				15,9	18,2	96,9
Vb	40—42	0,8				14,1	15,9	$C_{11}H_{10}N_2S$				13,9	15,8	48,3
Vc	127—128	0,88				11,2	12,7	$C_{15}H_{12}N_2S$				11,1	12,7	79,8
VIa	152—153	0,7				13,5	15,6	$C_9H_8N_2O_2S$				13,5	15,4	81,6
VIc	179,5—180	0,8	63,5	4,3		9,7	11,1	$C_{15}H_{12}N_2O_2S$	63,4	4,2		9,8	11,3	87
VIIa	47—48	0,56	67,7	5,1		17,5		$C_9H_8N_2O$	67,5	5,0		17,5		75,2
VIIb	170—171	0,45	59,9	4,9		35,4		$C_8H_8N_4$	60,0	5,0		35,0		51,4
VIIc	283—284		61,5	3,8		23,9		$C_{15}H_{11}N_5O_2$	61,4	3,8		23,9		89,6
VIII	171—172	0,57			19,4	15,2		$C_8H_5ClN_2O$			19,6	15,5		79,9
IX	119—120	0,72	64,0	5,0		22,5		$C_{10}H_9N_3O$	64,2	4,8		22,5		72
X	253—253,5	0,14	55,0	4,2		18,9		$C_{10}H_9N_3O_3$	54,8	4,2		19,2		36,6
XIa	173 (dec.)					32,2		$C_8H_8N_4O$				31,8		61,8
XIb	150—150,5	0,7	54,7	6,1	14,9	17,3		$C_{11}H_{13}N_3O\times$ $\times HCl$	55,1	5,9	14,8	17,5		50,9
XIc	189—191	0,38	56,6	3,9		16,4		$C_8H_6N_2O_2\times$ $\times 1/2H_2O$	56,2	4,1		16,4		75,6
XId	92—93	0,56	53,3	5,4		13,2		$C_9H_8N_2O_2\times$ $\times 1,5H_2O$	53,3	5,4		13,8		74,2
XIe	179—180	0,22	48,4	5,3		21,0		$C_8H_7N_3O\times$ $\times 2H_2O$	48,7	5,6		21,3		75,9
XIf	119—119,5	0,4	59,2	5,2		9,2		$C_{15}H_{16}N_2O_5$	59,2	5,3		9,2		56,9
XIg	127—128	0,45	59,0	4,0		13,7		$C_{10}H_8N_2O_3$	58,8	4,0		13,7		86,6
XIh	92—93		61,5	5,1		11,8		$C_{12}H_{12}N_2O_3$	62,1	5,2		12,1		88,2
XIi	128—129	0,8	67,8	5,0		17,5		$C_9H_8N_2O$	67,5	5,0		17,5		78,9
XIj	200—201	0,59	61,7	3,7		15,8		$C_9H_6N_2O_2$	62,1	3,5		16,1		66,0
XIk	167—168	0,77	66,6	4,3		10,6	12,0	$C_{15}H_{12}N_2OS$	67,1	4,5		10,4	12,0	53,9
XIl	212—212,5	0,68				9,0	10,8	$C_{15}H_{12}N_2O_3S$				9,3	10,7	63
XII	100—101	0,18	46,9	3,8	20,4†	7,2		$C_{15}H_{15}BrN_2O_5$	47,0	3,9	20,8†	7,3		79,5
XIII	132,5—133,5	0,58	56,2	5,0		8,7		$C_{15}H_{16}N_2O_6$	56,2	5,0		8,7		36,6
XIV	168—168,5	0,47	61,7	3,8		15,9		$C_9H_6N_2O_2$	62,0	3,6		16,1		88
XVI	151—152,5	0,54	68,9	5,9		16,1		$C_{10}H_{10}N_2O$	68,9	5,8		16,1		42

*Compounds III, IV, VIII, and XIV were crystallized from alcohol, XIa, XIg, k were crystallized from aqueous alcohol, Va-c, VIIa, XIj, and XII were crystallized from heptane, XId, i and XIII were crystallized from acetone, XIb was crystallized from heptane—ethyl acetate, XIc was crystallized from ethyl acetate—petroleum ether, XIl was crystallized from 50% CH_3COOH, and XVI was crystallized from benzene. †Br.

Methyl 1,5-Naphthyridin-4-yl Sulfone (VIa). A solution of 0.88 g (6.5 mmole) of $KMnO_4$ in 20 ml of water was added gradually at 25°C to a solution of 0.36 g (2 mmole) of Va in 17 ml of CH_3COOH, after which the reaction solution was evaporated to dryness *in vacuo*, and the residue was treated repeatedly with boiling water. The aqueous solution was evaporated to dryness, and the residue was extracted with 50 ml of heptane. The extract was concentrated to 6 ml, the concentrate was cooled, and 0.34 g of sulfone VIa was removed by filtration. Sulfone VIc was similarly obtained from benzylthio derivative Vc (the reaction was carried out at 15°C, and VIc precipitated from the reaction solution).

4-Methoxy-1,5-naphthyridine (VIIa). A 0.6-g (3.65 mmole) sample of chloro derivative I was added to a solution of CH_3ONa obtained from 0.2 g (8.7 mmole) of Na and 15 ml of anhydrous methanol, and the mixture was refluxed for 4 h. It was then cooled, and the NaCl was removed by filtration. The solution was evaporated, and the residue was extracted with heptane to give 0.44 g of VIIa.

4-Hydrazino-1,5-naphthyridine (VIIb). A solution of 0.8 g (1.82 mmole) of I and 1.5 ml (0.9 mmole) of $NH_2NH_2 \cdot H_2O$ in 18 ml of alcohol was refluxed for 4.5 h, after which it was evaporated to dryness, and the residue was crystallized from ethyl acetate to give 0.15 g of VIIb.

A 2.15-mmole sample of the p-nitrobenzhydrazone (VIIc) of VIIb was obtained from 2.5 mmole of VIIb and 2.85 mmole of p-nitrobenzaldehyde.

4-Chloro-1,5-naphthyridine 1-Oxide (VIII). A solution of 0.65 g (3.94 mmole) of chloro derivative I and 0.02 g of $Na_2WO_4 \cdot 2H_2O$ in 2.5 ml of 30% H_2O_2 was stirred at 20°C for 4 days, after which it was cooled, and 0.57 g of 1-oxide VIII was removed by filtration.

4-Acetamido-1,5-naphthyridine (IX). A 1.0-g (6.8 mmole) sample of 4-amino-1,5-naphthyridine and 2 ml of acetic anhydride were refluxed in 10 ml of benzene for 4 h, after which the mixture was evaporated, and the residue was crystallized from alcohol to give 0.93 g of IX.

4-Acetamido-1,5-naphthyridine 1,5-Dioxide (X). A mixture of 0.3 g (1.6 mmole) of IX, 3 ml of 30% H_2O_2, and 0.03 g of $Na_2WO_4 \cdot 2H_2O$ was stirred at 40°C for 12 h, after which the excess H_2O_2 was decomposed with Na_2SO_3 solution, and the mixture was extracted with chloroform. The $CHCl_3$ was removed, and the residue was crystallized from alcohol to give 0.1 g of dioxide X. IR spectrum: 1685 (amide CO); 3350 and 3355 cm^{-1} (NH). PMR spectrum, δ: 13.77 (NH), 8.87 (2-H), 8.44 (3-H), 8.45 (6-H), 7.54 (7-H), and 8.7 ppm (8-H); $J_{2,3} = 7.2$, $J_{6,7} = 6.3$, $J_{6,8} = 1.1$, and $J_{7,8} = 9.1$ Hz.

4-Hydrazino-1,5-naphthyridine 1-Oxide (XIa). A 0.1-g (0.55 mmole) sample of N-oxide VIII and 0.27 ml (5.55 mmole) of hydrazine hydrate were stirred in 3 ml of alcohol at 50°C for 1.5 h, after which the mixture was cooled, and 0.06 g of XIa was removed by filtration. Mass spectrum, m/e: 176 (M^+), 160 ($M^+ - O$), 146 ($M^+ - N_2H_2$), 130 ($M^+ - O - N_2H_2$).

4-Isopropylamino-1,5-naphthyridine 1-Oxide Hydrochloride (XIb). A 0.6-g (3.32 mmole) sample of N-oxide VIII and 6 ml (70.2 mmole) of isopropylamine were heated in 30 ml of anhydrous isopropyl alcohol in an autoclave at 110°C for 7 h, after which the reaction solution was evaporated to dryness, and the residue was dissolved in 10 ml of water, and the aqueous solution was extracted with chloroform. After removal of the chloroform, 5 ml of ethyl acetate and 1 ml of a 10% alcohol solution of HCl were added to the residue, and the mixture was worked up to give 0.4 g of XIb.

4-Hydroxy-1,5-naphthyridine 1-Oxide (XIc). A solution of 0.6 g (3.32 mmole) of VIII in 11 ml of 0.1 N NaOH was refluxed for 3 h, after which it was cooled and acidified to pH 3. Workup gave 0.43 g of hydroxy derivative XIc, which gave a cherry-red coloration with $FeCl_3$ solution.

4-Methoxy-1,5-naphthyridine 1-Oxide (XId). A 0.3-g (1.66 mmole) sample of VIII was added to 7 ml of a solution of CH_3ONa [from 0.07 g (3 mmole) of Na], and the mixture was refluxed for 3.5 h. It was then evaporated, and the residue was extracted with 20 ml of methylene chloride to give 0.25 g of methoxy derivative XId.

4-Amino-1,5-naphthyridine 1-Oxide (XIe). A 0.3-g (1.66 mmole) sample of VIII was heated in 15 ml of a saturated solution of NH_3 in alcohol in an autoclave at 160°C for 17 h, after which the mixture was cooled, and the NH_4Cl was removed by filtration. The solution was evaporated to dryness, and the residue was crystallized from acetone–water (9:1) to give 0.25 g of amine XIe. IR spectrum: 1655, 3155, and 3360 cm^{-1} (NH_2). Mass spectrum, m/e: 161 (M^+) and 145 ($M^+ - O$).

4-(Dicarbethoxymethyl)-1,5-naphthyridine 1-Oxide (XIf). A 3.66-ml (24.1 mmole) sample of malonic ester was added at 35°C to a suspension of 0.39 g (16.9 mmole) of finely ground Na in 27 ml of anhydrous toluene, the mixture was heated gradually with stirring in a stream of nitrogen to 95°C, and heating was continued at the same temperature until the Na had dissolved completely. A 1.0-g (5.55 mmole) sample of VIII was then added, and the mixture was stirred at 105°C for 3 h. The liberated Na salt of XIf was removed by filtration, washed with ether, and dissolved in water. The aqueous mixture was acidified to pH 4 and worked up to give 0.96 g of XIf.

1,5-Naphthyridine-4-acetic Acid 1-Oxide (XIg). A 0.5-g (1.64 mmole) sample of XIf was refluxed for 3 min in 7.5 ml of 1 N NaOH, after which the mixture was cooled and acidified to pH 3 with 2.5 N HCl to give 0.29 g of acid XIg.

Ethyl 1,5-Naphthyridin-4-ylacetate 1-Oxide (XIh). A 0.3-g (1.47 mmole) sample of acid XIg and 0.42 ml (5.88 mmole) of $SOCl_2$ were refluxed in 8 ml of anhydrous alcohol until the solid material dissolved. The alcohol was then removed, and the residue was neutralized with a solution of $NaHCO_3$ and extracted with ether to give 0.3 g of ether XIh.

4-Methyl-1,5-naphthyridine 1-Oxide (VIi). The Na derivative of XIf, obtained as indicated above from 1 g of N-oxide VIII, was refluxed in 37 ml of 2.5 N HCl for 45 min, after which the mixture was neutralized to pH 6.5 and extracted with methylene chloride to give 0.7 g of XIi.

4-Formyl-1,5-naphthyridine 1-Oxide (XIj). A mixture of 0.48 g (3 mmole) of XIi and 1 g (9 mmole) of SeO_2 in 10 ml of anhydrous ethyl acetate was refluxed in a stream of nitrogen for 3.5 h, after which it was cooled and filtered, and the filtrate was evaporated to dryness. The residue was treated with a solution of $NaHCO_3$ to pH 7 and extracted with chloroform. The $CHCl_3$ was removed, and the residue was crystallized from ethyl acetate to give 0.35 g of XIj. PMR spectrum, δ: 11.28 (H, aldehyde), 8.85 (2-H), 8.59 (3-H), 9.17 (6-H), 7.75 (7-H), and 9.02 ppm (8-H); $J_{2,3}$ = 6.5, $J_{6,7}$ = 4.2, $J_{6,8}$ = 1.5, and $J_{7,8}$ = 8.6 Hz.

4-Benzylthio-1,5-naphthyridine 1-Oxide (XIk). A 1-ml sample of a 10% solution of NaHS was added to a mixture of 0.3 g (1.66 mmole) of VIII in 8.5 ml of $CHCl_3$, and the mixture was stirred at 20°C for 45 min, after which the chloroform layer was separated. Water (3 ml) was added to the residue to dissolve it, 0.6 ml (5.22 mmole) of benzyl chloride was added, and the mixture was heated at 50°C for 1 h. Workup gave 0.24 g of XIk.

4-Benzylsulfonyl-1,5-naphthyridine 1-Oxide (XIℓ). A 0.2 g (0.74 mmole) sample of XIk and 0.2 ml of 30% H_2O_2 were stirred in 2 ml of CH_3COOH at 20°C for 2 days, after which 0.14 g of sulfone XIℓ was removed by filtration. Mass spectrum, m e: 300 (M^+), 284 ($M^+ - O$), 236 ($M^+ - SO_2$), 220 ($M^+ - O - SO_2$), and 91 ($C_6H_5CH_2^+$).

4-(α-Bromo-α,α-dicarbethoxy)methyl-1,5-naphthyridine 1-Oxide (XII). A 0.15-ml (2.90 mmole) sample of Br_2 was added to a solution of 0.5 g (1.64 mmole) of XIf in 6 ml of $CHCl_3$, and the mixture was refluxed with stirring for 4 h. It was then cooled and neutralized with $NaHCO_3$ solution, and the organic layer was separated. The aqueous solution was extracted additionally with chloroform, the $CHCl_3$ was removed, and the residue was crystallized from heptane to give 0.5 g of bromo derivative XII.

4-(α-Hydroxy-α,α-dicarbethoxy)methyl-1,5-naphthyridine 1-Oxide (XIII). A 0.26-g (0.68 mmole) sample of bromo derivative XII was refluxed for 30 min in 30 ml of water, after which the mxiture was cooled and extracted with chloroform. The $CHCl_3$ was removed, and the residue was crystallized from ethyl acetate to give 0.08 g of XIII.

1,5-Naphthyridine-4-carboxylic Acid (XIV). A 0.2-g (0.52 mmole) sample of bromo derivative XII was refluxed in 24 ml of water for 4 h, after which the mixture was cooled and extracted with chloroform. The $CHCl_3$ was removed, and the residue was crystallized from alcohol to give 0.08 g of XIV. IR spectrum: 2600 (very broad medium band, OH) and 1720 cm^{-1} (CO). PMR spectrum, δ: 15.03 (OH), 9.27 (2-H), 8.54 (3-H), 9.02 (6-H), 7.88 (7-H), and 8.7 ppm (8-H); $J_{2,3}$ = 4.4, $J_{6,7}$ = 4.3, $J_{6,8}$ = 1.6, and $J_{7,8}$ = 8.6 Hz.

N-Ethyl-4-oxo-1,4-dihydro-1,5-naphthyridine (XVI). A mixture of 0.3 g (2.05 mmole) sample of hydroxy derivative XV, 0.1 g (4.1 mmole) of NaH, and 4 ml of DMF was stirred at 25°C for 4 h, after which 1 ml (12 mmole) of C_2H_5I was added, and the mixture was maintained at 95-100°C for 12 h. The solvent was removed, and the residue was dissolved in 3 ml of water. The aqueous solution was extracted with CH_2Cl_2, and the solvent was removed by distillation to give 0.15 g of XVI.

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