SYNTHESIS OF DERIVATIVES OF α-PHENYLDINICOTINIC ACID AND 2-PHENYL-3,5-BIS(5-PHENYL-2-OXAZOLYL)-PYRIDINE

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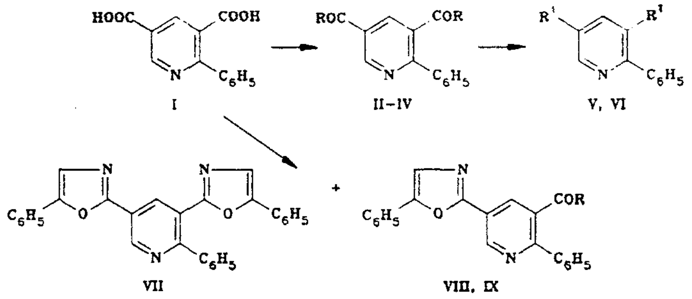
The dichloride, diethylamide, and amide were obtained from α-phenyldinicotinic acid. 2-Phenyl-3,5-diamino- and 3,5-dicyanopyridine were synthesized from the amide. 2-Phenyl-3,5-bis(5-phenyl-2-oxazolyl)pyridine and 2-phenyl-3-carboxy-5-(5-phenyl-2-oxazolyl)pyridine were obtained. The luminescence properties of the synthesized compounds were studied.

Derivatives of pyridinecarboxylic acids, particularly N-substituted amides, have found wide application in the treatment of tuberculosis and heart diseases. Nicotinamide is a fragment of the coenzymes NAD and NADP, which enter into the composition of dehydrogenases.

In this connection many derivatives of picolinic, nicotinic, and isonicotinic acids have been synthesized and studied. However, the information regarding pyridinecarboxylic acids is limited. In our laboratory we obtained the previously unknown α-phenyldinicotinic acid (I) by oxidation of 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-3',4'-dehydro-6'-piperidyl)pyridine, formed in the reaction of β-picoline with phenyllithium [1]. The syntheses of some derivatives of this acid, as well as diamino-, dicyano-, and dioxazolylphenylpyridines, are described in the present communication.



II R=Cl; III $R=N(C_2H_5)$; IV, IX $R=NH_2$; V $R^1=NH_2$; VI $R^1=CN$; VIII R=OH

2-Phenyl-3,5-bis(chloroformyl)pyridine (II) in the form of a stable crystalline substance is formed when acid I is treated with thionyl chloride. 2-Phenyl-3,5-bis(N,N-diethylcarbamoyl)- and 3,5-di(carbamoyl)pyridine (III, IV), respectively, were obtained in quantitative yields from dichloride II and diethylamine and ammonia.

2-Phenyl-3,5-diaminopyridine (V) — a stable crystalline substance — was synthesized from amide IV by the Hofmann method, while 2-phenyl-3,5-dicyanopyridine (VI) was isolated in quantitative yield in the dehydration of amide IV by means of phosphorus oxychloride [2]. Compounds V and VI are of interest as synthones in the syntheses of new heterocyclic compounds.

In research involving the study of luminescing substances considerable attention is directed to compounds that contain an aryloxazole fragment [3, 4]. In this connection we undertook the synthesis of 2-phenyl-3,5-bis(5-phenyl-2-oxazolyl)pyridine (VII). Compound VII was isolated in 31% yield in the condensation of acid I with ω-aminoacetophenone in the pres-

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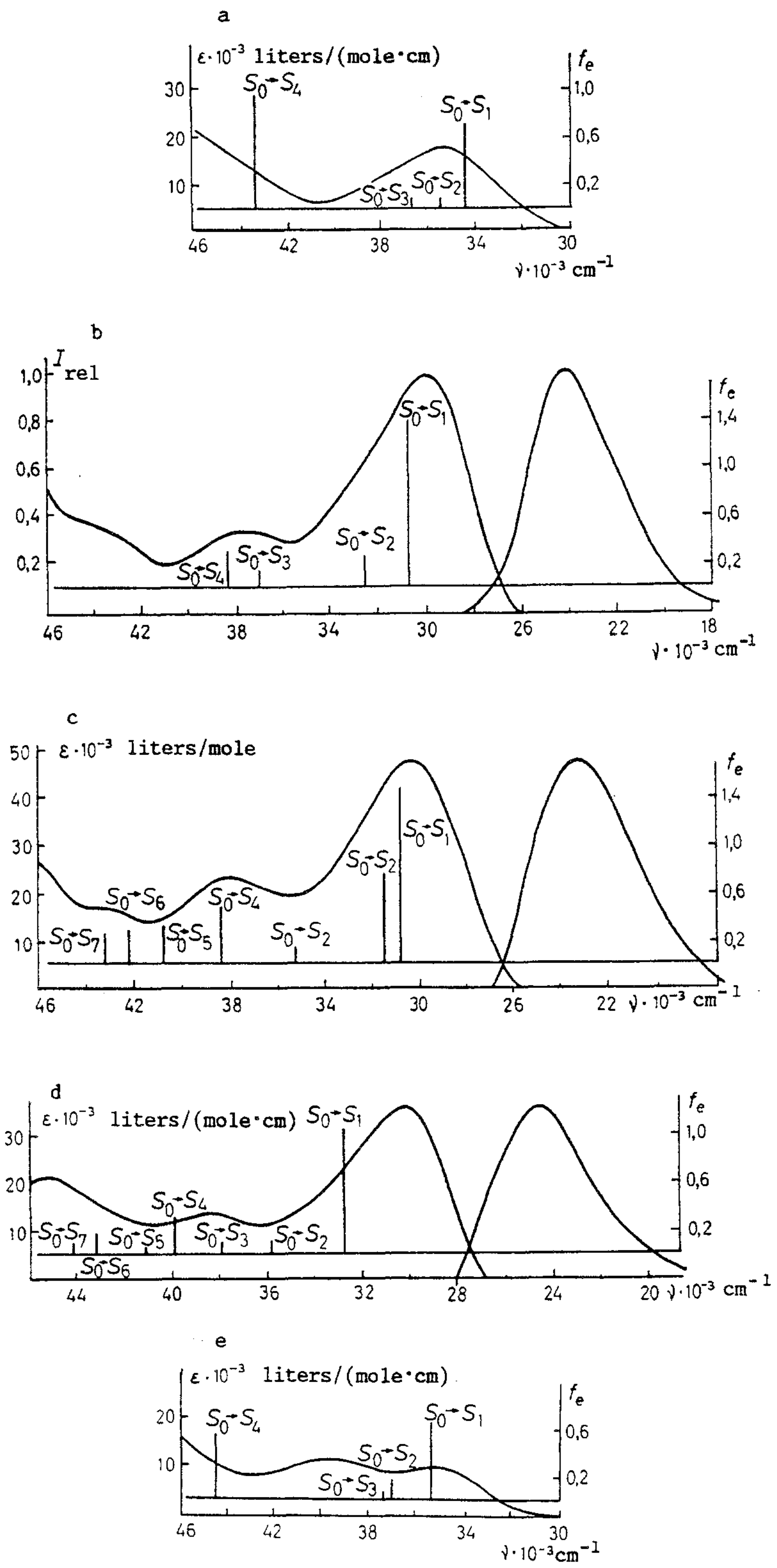

Fig. 1. Experimental UV absorption and fluorescence spectra in ethanol and calculated frequencies and oscillator forces of the electron transitions of pyridines: a) VI; b) IX; c) VII; d) VIII; e) I. The I_{rel} value is presented for IX because of its low solubility.

ence of phosphorus oxychloride [4]. 2-Phenyl-3-carboxy-5(5-phenyl-2-oxazolyl)-pyridine (VIII) was isolated from the reaction mixture in approximately the same yield. The yields of these products depend on the ratio of the starting reagents. Thus at an acid I:amino ketone ratio of 1:1.5 the yields of VII and VIII are, respectively, 14.5% and 36.5%, as compared with 30.6% and 21.3% at a ratio of 1:2.

It has been previously proposed [1] that monoderivatives of dibasic I are formed when there is a sterically unhindered group in the 5 position. In this connection it was necessary to establish the structure of VIII. In its ^{13}C NMR spectrum the carbon atom of the carboxy group (δ 165.57 ppm) is observed in the form of a doublet with spin-spin coupling constant $^3J_{C_3,H_4}$ = 4.5 Hz. The absence of a similar constant of spin-spin coupling of the carboxy carbon atom with the α-proton of the pyridine ring excludes the alternative 2-phenyl-5-carboxy-3-(5-phenyl-2-oxazolyl)pyridine structure.

Data from the mass spectra of VII and VIII, as well as 2-phenyl-3-carbamoyl-5-(5-phenyl-2-oxazolyl)pyridine (IX), obtained by treatment of acid VIII with thionyl chloride and then with ammonia, confirm the structure of acid VIII. The intense peak of an $[M - H]^+$ ion that is observed in the fragmentation of VII as a result of cyclization of the phenyl radical in the $C_{(2)}$ position at the heteroatom of the oxazole ring is not formed in the fragmentation of acid VIII under the influence of electron impact; this confirms the presence of an oxazole substituent in the 5 position in VIII.

The characteristics necessary for analysis of the absorption spectra, viz., the probabilities and polarizations of the electron transitions, the π-bond orders, the π-electron charges, the π-dipole moments, and the numbers of localization of the electron excitation [5], were calculated for I, VIII, VII, and IX by the Pariser–Parr–Pople (PPP) method.

The experimental UV absorption spectrum of acid I consists of three bands (Fig. 1e) The long-wave absorption band has a maximum with a rather high intensity (ε 1.07·10^4, λ_{max} 286 nm) and lies at 31,000-37,000 cm^{-1}; the band does not have a pronouced vibrational structure and, according to the calculations, is formed by the $S_0 \to S^1_{\pi\pi^*}$ electron transition.

TABLE 1. Spectra-Luminescence Characteristics of the Synthesized Compounds

Compound	Transition	Calc.		Exptl.					
		ν, cm^{-1}	f_e	ν_{abs}·10^3 cm^{-1}	λ_{abs}, nm	ε·10^4, liters/(mole·cm)	ν_{fl}, cm^{-1}	λ_{fl}, nm	η_{fl}
I	$S_0 \to S_1$	35332	0,725	34,9	286	1,07			
	$S_0 \to S_2$	36892	0,111						
	$S_0 \to S_3$	37188	0,071	39,1	256	1,12			$\leqslant$0,01
	$S_0 \to S_4$	44596	0,670						
VIII	$S_0 \to S_1$	32800	1,203	30,4	329	3,71	24 875	402	
	$S_0 \to S_2$	35800	0,090						
	$S_0 \to S_3$	37900	0,120	38,2	262	2,20			0,12
	$S_0 \to S_4$	39800	0,450						
VIIIa	$S_0 \to S_1$	29475	0,299						
	$S_0 \to S_2$	34081	0,751						
	$S_0 \to S_3$	38295	0,402						
	$S_0 \to S_4$	38610	0,951						
VII	$S_0 \to S_1$	30900	1,512	30,3	330	4,74	23 584	424	
	$S_0 \to S_2$	31600	0,850						
	$S_0 \to S_3$	35400	0,150	38,0	263	2,52			0,03
	$S_0 \to S_4$	38450	0,503						
IX	$S_0 \to S_1$	30919	1,405	30,2	331	1,0*			
	$S_0 \to S_2$	32776	0,151						
	$S_0 \to S_3$	37370	0,151	38,0	263	0,37*	24 038	416	0,05
	$S_0 \to S_4$	38454	0,299						
IXa	$S_0 \to S_1$	29907	0,302						
	$S_0 \to S_2$	34457	0,819						
	$S_0 \to S_3$	38124	0,533						
	$S_0 \to S_4$	38924	0,400						
VI	$S_0 \to S_1$	34405	0,839	35,3					
	$S_0 \to S_2$	35575	0,067						
	$S_0 \to S_3$	36661	0,029		283	1,83	24 154	414	<0,01
	$S_0 \to S_4$	43444	0,969						

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*The relative absorption intensity I_{rel} is presented, since the substance is only slightly soluble.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp,* °C	Mass spectrum: molecular and characteristic ions, m/z (I_{rel}, % relative to the maximum peak)	IR spectrum, ν, cm^{-1}	Yield, %
II	$C_{13}H_7Cl_2NO_2$	65...67	M^+, 279 (13); $[M-Cl]^+$, 244 (75); $[M-COCl]^+$, 216 (14), $[M-Cl-HCl]^+$, 208 (87); $[M-2COCl]^+$, 153 (37)**	1755, 1769 split (C=O)	41
III	$C_{21}H_{27}N_3O_2$	125...126	M^+, 353 (65); $[M-C_2H_5]^+$, 324 (41); $[M-N(C_2H_5)_2]^+$, 281 (100), $[M-CON-(C_2H_5)_2]^+$, 253 (22); $[M-2CO(C_2H_5)_2]^+$, 153 (15)	1634, 1624 (C=O)	69
IV	$C_{13}H_{11}N_3O_2$	325...327	M^+, 241 (100); $[M-H]^+$, 240 (56); $[M-NH_2]^+$, 225 (33); $[M-NH_3]^+$, 224 (17); $[M-CONH_2]^+$, 212 (16); $[M-2CONH_2]^+$ 168 (18)	3391, 3340 sh 3216, 3166 (NH_2); 1704, 1664 vs (C=O); 1630 (δ_{N-H})	76
V	$C_{11}H_{11}N_3$	173...175	M^+, 185 (100); $[M-H]^+$, 184 (85); $[M-NH_3]^+$, 168 (10), $[M-H-NH_3]^+$, 167 (16); $[M-H-HCN]^+$, 157 (11)	3450, 3430, 3370, 3360 (NH_2); 3234, 1655 vs (δ_{N-H})	40
VI	$C_{13}H_7N_3$	125...126	M^+, 205 (100); $[M-CN]^+$, 179 (28); $[M-HCN]^+$, 178 (60); $[M-CN-HCN]^+$, 152 (14); $[M-2HCN]^+$, 151 (35)	2242...2233 (C≡N)	90
VII	$C_{29}H_{19}N_3O_2$	165,5...166,5	M^+, 441 (50); $[M-H]^+$, 440 (100), $[M-C_6H_5CO]^+$, 336 (11), $[M-C_6H_5CO-HCN]^+$, 309 (11); $[M-C_6H_5CO-C_6H_4]^+$, 250 (22)		31
VIII	$C_{21}H_{14}N_2O_3$	261...262	M^+, 342 (100); $[M-H]^+$, 341 (10); $[M-CO_2]^+$, 298 (18)	~3450 (OH); 1716 (C=O), 1685	36
IX	$C_{21}H_{15}N_3O_2$	292...294	M^+, 341 (100); $[M-H]^+$, 340 (35); $[M-NH_2]^+$, 325 (15)	3358, 3198 (NH_2); 1673 (C=O); 1630 (δ_{N-H})	81

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*The compounds were crystallized: II and IV from n-heptane, III, VII, VIII, and IX from ethanol, V from benzene, and VI from isopropyl alcohol.

**The chlorine-containing ions are presented for the ^{35}Cl isotope.

Three bands are observed in the absorption spectra of VII-IX. The long-wave band of high intensity [$\varepsilon = (3.71\text{-}4.74)\cdot 10^4$] for VIII and IX is formed by the $S_0 \rightarrow S_1$ transition (Table 1, Fig. 1). In the case of VII the long-wave absorption band is formed by two transitions, viz., $S_0 \rightarrow S_1$ and $S_0 \rightarrow S_2$, which are accompanied by transfer of electron density in two directions: from the phenyloxazole fragments in the 3 and 5 positions to the pyridine ring. The short-wave and middle bands lie at 41,000-50,000 cm^{-1} and 35,000-41,000 cm^{-1}, respectively. The positions and structures of these bands depend only slightly on the introduction of various substituents (—CONH$_2$, —COOH, phenyloxazolyl) into the β position of the pyridine ring. According to the calculations, they are formed by electron transitions of medium intensity: short-wave $S_0 \rightarrow S^6$—$S_0 \rightarrow S^{10}$ electron transitions and middle $S_0 \rightarrow S^3$—$S_0 \rightarrow S^5$ electron transitions (Fig. 1). The position and structure of the long-wave absorption band undergo little change on passing from acid VIII to amide IX (ν 30,200-31,000 cm^{-1}); the long-wave absorption band in the spectra of VIII and IX becomes more intense than in the case of starting acid I and is expressed more distinctly. The half width of this band is 2600 cm^{-1} for VIII, as compared with 3000 cm^{-1} for VII, 2700 cm^{-1} for amide IX, and 2500 cm^{-1} for starting acid I. A bathochromic shift (on the order of 4000 cm^{-1}) of the long-wave absorption band occurs on passing from I to VIII, VII, and IX (Table 1, Figs. 1b-1d).

The absorption spectrum of dinitrile VI (Fig. 1a) consists of two bands; the long-wave band is shifted to a shorter-wave region (ν 35,300 cm^{-1}) than the same band for acid I, while its intensity is considerably lower.

It follows from a comparison of the experimental data from the electronic absorption spectra with the theoretical calculation for VIII and IX and with their alternative isomers, respectively, 2-phenyl-5-carboxy-3-(5-phenyl-2-oxazolyl)pyridine (VIIIa) and 2-phenyl-5-carbamoyl-3-(5-phenyl-2-oxazolyl)pyridine (IXa) (Table 2), that the carboxy group in VIII and IX is in the 3 position. This conclusion is in agreement with the PMR spectral data presented above.

Compounds VIII, VII, IX, and VI have fluorescence. The diffuse character of the fluorescence bands in this series is the same as for the long-wave absorption band of these substances. The longest-wave band is the fluorescence band of VII. The $S^1_{\pi\pi^*}$—T^* value of the energy interval ($\Delta E(S_1$—$T_n) < 1000$ cm^{-1}) was evaluated on the basis of the energy diagrams of the relative position of the S and T levels (Fig. 2). It follows from this that for VIII, VII, and IX the nonemissive transitions predominate over the radiation transitions. The maximum quantum yield was obtained for acid VIII ($\eta = 0.12$), as compared with 0.03 and 0.05 for VII and IX, respectively, and it is less than 0.01 in ethanol for nitrile VI.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord UR-75 spectrometer. The PMR spectra of VIII were measured with a Bruker WM-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded with a Bruker WM-400 spectrometer (100.6 MHz). The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 eV.

The experimental UV absorption spectra and fluorescence spectra were investigated in benzene, DMF, and ethanol at a concentration of the dissolved substance of $1\cdot 10^{-5}$ mole/liter. The UV absorption spectra were measured with a Specord M-40 spectrophotometer in quartz cuvettes with a thickness of 10 mm. The fluorescence spectra and quantum yields were measured

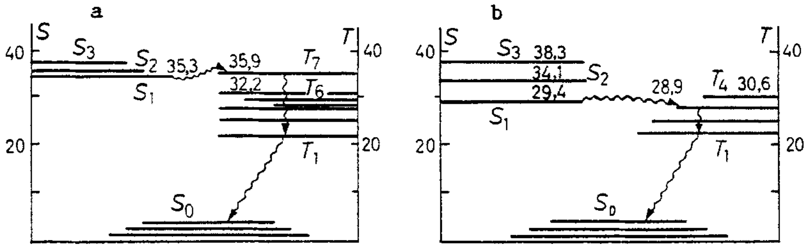

Fig. 2. Diagrams of the relative positions of the S^* and T^* levels: a) base molecule I; $\Delta E(T_7\text{-}S_1) = 635$ cm^{-1}; b) VIII molecule; $\Delta E(S_1$—$T_3) = 504$ cm^{-1}.

in ethanol with an SLM-4800S spectrofluorimeter. Anthracene ($\eta = 0.22$) was used as the standard.

The quantum-chemical calculations were made by means of the program developed by A. A. Ustenko. The program realizes the semiempirical Pariser—Parr—Pople (PPP) method within the π-electron approximation with self-consistence of the bond lengths and the bond orders and with allowance for the configuration interaction for the excited states. The standard parametrization for the atoms and bonds was used in the calculations, and 25 singly excited configurations were taken into account. The calculations were made with an EC-1055M computer.

The characteristics of the synthesized compounds are presented in Table 2. The results of elementary analysis for C, H, and N for IV-IX, for N and Cl for II, and for N for III were in agreement with the calculated values.

2-Phenyl-3,5-bis(chloroformyl)pyridine (II). A 2.2-g (8.9 mmole) sample of acid I was refluxed with 25 ml (350 mmole) of freshly distilled thionyl chloride until the acid had dissolved completely. The excess thionyl chloride was removed by distillation, 20 ml of dry benzene was added, and the mixture was again distilled to dryness. Heptane was added to the residue. After a few hours, the crystals were removed by filtration to give 1.03 g of dichloride II in the form of yellow crystals.*

2-Phenyl-3,5-bis(N,N-diethylcarbamoyl)pyridine (III). A 20-ml sample of freshly distilled diethylamine was added gradually with stirring and cooling to dichloride II obtained from 2 g (8 mmole) of acid I and 25 ml (350 ml) of thionyl chloride, after which the precipitate was removed by filtration, washed with water, and dried to give 2 g of diamide III.

2-Phenyl-3,5-di(carbamoyl)pyridine (IV). A 50-ml sample of a 25% solution of ammonia was added with vigorous stirring to dichloride II obtained from 2 g (8 mmole) of acid I and 25 ml (350 mmole) of thionyl chloride dissolved in 20 ml of dry dioxane. After 30 min, the precipitated crystals were removed by filtration and washed with water to give 1.5 g of diamide IV in the form of white crystals.

2-Phenyl-3,5-diaminopyridine (V). A 0.5-ml (10 mmole) sample of bromine was added with vigorous stirring and cooling to —10°C to a solution of 1.27 g of NaOH in 14 ml of water, after which 1 g (4.5 mmole) of diamide IV was added to the reaction mixture at 0°C. After 15 min, the reaction mixture became colorless and clear; it was then allowed to stand for 45 min. Sodium chloride (2 g) was added, and the mixture was extracted with ether (three 75-ml portions). The ether extract was dried with sodium hydroxide, the ether was removed by distillation and the dark-red residue (0.72 g) was refluxed in 100 ml of benzene with activated charcoal and 1.5-2 g of crystalline sodium bisulfite. The precipitate that formed when the benzene solution was cooled was removed by filtration to give 0.26 g of diamine V in the form of colorless acicular crystals.

2-Phenyl-3,5-dicyanopyridine (VI). A 0.56-ml (6 mmole) sample of phosphorus oxychloride was added to a solution of 0.48 g (2 mmole) of diamide IV in 20 ml of DMF, and the mixture was stirred for 2 h at 20°C and then allowed to stand overnight. It was then decomposed with 100 ml of water, and the aqueous mixture was extracted with methylene chloride (three 50-ml portions). Workup of the residue after removal of the solvent by distillation gave 0.36 g of nitrile VI in the form of pale-cream-colored crystals.

2-Phenyl-3,5-bis(5-phenyl-2-oxazolyl)pyridine (VII) and 2-Phenyl-3-carboxy-5-(5-phenyl-2-oxazolyl)pyridine (VIII). A 2.23-g (16.5 mmole) sample of ω-aminoacetophenone and 25 g [160 mmole (15 ml)] of phosphorus oxychloride were added to 2 g (8 mmole) of acid I, after which the temperature of the reaction mixture was brought up to 110°C in the course of 50 min with stirring in a stream of nitrogen. The mixture was then cooled and poured into 200 ml of ice water, and the aqueous mixture was neutralized with a 25% solution of ammonia. The resulting resinous mass was triturated to a powdery state, washed with water, and dried (mass 3.7 g). Chloroform (75 ml) was added, and the undissolved crystals were removed by filtration and washed with alcohol (~20 ml) to give 0.38 g of colorless crystals of acid VIIId. ^{1}H NMR spectrum (in d_6-DMSO), δ: 9.36 (1H, d, J = 2 Hz, H_6), 8.64 (1H, d, J = 2 Hz, H_4), 7.89 (1H, s, $H_{5'}$), 7.4-7.9 ppm (10H, m. C_6H_5). ^{13}C NMR spectrum (in d_6-DMSO), δ: 165.57

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*In all of the subsequent experiments dichloride II was not isolated, and the corresponding reagent was added to the residue after removal of the benzene by distillation.

(CO), 157.65 [$C_{(2)}$], 128.66 [$C_{(3)}$], 133.98 [$C_{(4)}$], 121.05 [$C_{(5)}$], 147.37 [$C_{(6)}$], 124.40, 157.42 (C atoms of the oxazole ring), 127.06, 128.0-128.76, 124.23 (C atoms of the phenyl ring), 139.06, 128.98, 128.0-128.76 ppm (C atoms of the 2-phenyl ring).

The chloroform was removed from the chloroform mother liquor by distillation. The residue (1.68 g) was chromatographed with a column (h = 23 cm, d = 3.4 cm) packed with Al_2O_3. Elution with n-heptane—ethyl acetate (1:3) gave 0.72 g of colorless crystals of dioxazolylpyridine VII.

2-Phenyl-3-carbamoyl-5-(5-phenyl-2-oxazolyl)pyridine (IX). The chloride obtained from 1 g (3 mmole) of acid VIII and 15 ml (220 mmole) of thionyl chloride was dissolved in 100 ml of dioxane, 20 ml of a 25% solution of ammonia was added to the solution, and the mixture was shaken. After 20 min, the white crystals were removed by filtration, washed with water, and dried to give 0.81 g of amide IX.

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