4-Hydrazino-6-ethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXVI). A 0.7-g (14 mmole) sample of hydrazine hydrate was added to 1.5 g (7 mmoles) of XVI in 30 ml of n-butyl alcohol, and the mixture was refluxed for 3 h. It was then cooled, and the precipitated substance was separated and washed on the funnel with water. Compounds XXVII and XXVIII were similarly obtained. Crystallization of XXVI from aqueous acetone gave the acetylidene derivative with mp 246-247° (dec.). Found: C 53.0; H 6.1; N 27.8%. $C_{11}H_{15}N_5O_2$. Calculated: C 53.0; H 6.1; N 28.1%.

4-Azido-6-ethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXIX). A solution of 0.35 g (5 mmole) of $NaNO_2$ in 5 ml of water was added at 5° in the course of 30 min to a solution of 1 g (4.8 mmole) of hydrazine XXVI in 15 ml of 2 N hydrochloric acid after which the mixture was stirred for 1 h without cooling. The solid material was separated, and azide XXIX was washed on the funnel with water until the wash waters were neutral.

Compounds XXX and XXXI were similarly obtained.

4-Azido-6-ethyl-8-methyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXXII). A 0.41-g (1.86 mmole) sample of XXVI and 0.8 ml of methyl iodide were added to sodium methoxide obtained from 0.04 g (1.86 mg-atom) of sodium in 10 ml of methanol, and the resulting solution was refluxed for 1 h. It was then evaporated to dryness, and the residual XXXII was washed with water.

LITERATURE CITED

1. M. P. Nemeryuk and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 2, 192 (1975).
2. R. W. Holley and A. D. Holley, J. Am. Chem. Soc., 74, 3069 (1952).
3. N. V. Sazonov and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 9, 1285 (1972).
4. N. V. Sazonov and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 2, 171 (1973).
5. C. Temple, C. L. Kussner, and J. A. Montgomery, J. Heterocyclic Chem., 5, 581 (1968).
6. F. R. Benson, L. W. Hortzel, and E. A. Otten, J. Am. Chem. Soc., 76, 1858 (1954).

PROTONATION OF PYRROLO[1,2-a]PYRIMIDINE DERIVATIVES

L. M. Alekseeva, G. G. Dvoryantseva, I. V. Persianova, Yu. N. Sheinker, M. V. Mezentseva, V. I. Shvedov, and A. N. Grinev

UDC 547.759'859:543.422.25

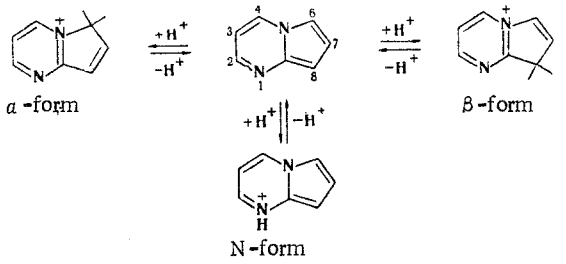
The protonation of pyrrolo[1,2-a]pyrimidine and 6,7,8,9-tetrahydropyrimido[1,2-a]indole derivatives in CF_3COOH (at −15 to +25° C) and in CF_3COOH/H_2SO_4 (at 25°) was studied by PMR spectroscopy. The investigated compounds form monocations, the structure of which corresponds to the addition of a proton to the carbon atom of th pyrrole fragment in the α position to the bridge nitrogen atom.

The high pharmacological activity of pyrazino[1,2-a]indole derivatives [1,2] and the creation of the original preparation pirazidol, which is an effective central nervous system (CNS) antidepressant [3], have stimulated research on the isosteric analogs of these systems, particularly pyrrolo[1,2-$a$pyrimidine and pyrimido[1,2-a]pyrimidine and pyrimido [1,2-a]indole derivatives. The mechanism of the biological action of a number of neurotropic agents assumes interaction of the cationoid center of the antagonist with the acid function of the corresponding receptor [4], and data on the comparative proton-acceptor capacities

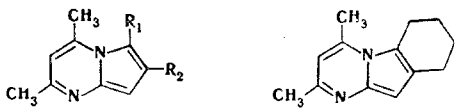
S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 686-692, May, 1976. Original article submitted May 21, 1975.

of various centers in compounds of the type under consideration are therefore of substantial interest.

A study of the protonation of azaindolizines [5] showed that in most cases addition of a proton in these systems occurs at the nitrogen atom of the "pyridine" type. Moreover, it has been observed that protonation of pyrrolo[1,2-a]pyridazine [5,6] takes place at the carbon atoms of the pyrrole fragment in the 5 and 7 positions. These results make it possible to propose three possible structures for the conjugate acid of pyrrolo[1,2-a]pyrimidine:



In order to establish the protonation center of this system we studied the spectra of the neutral molecules (in CCl_4 and $CDCl_3$) and the cations (in CF_3COOH) and measured the ionization constants in nitromethane of I-IV.



I-III IV

I $R_1=H$, $R_2=C_6H_5$; II $R_1=R_2=CH_3$, III $R_1=CH_3$, $R_2=C_2H_5$

The experimental data are presented in Tables 1-3.

Two doublets belonging to the protons of the pyrrole fragment in the 6 and 8 positions ($J_{6,8}=1.5$ Hz) are distinctly isolated in the spectrum of the neutral I molecule in CCl_4. In analogy with the spectra of indolizine derivatives and 5-, 6-, and 7-azaindolizines [7,8], the doublet located at weaker field was assigned to the C_6-H proton. The C_8-H signal in the spectra of 6-substituted pyrrolo[1,2-a]pyrimidines (II, III) is observed as a singlet at 6.23-6.28 ppm. The C_3-H signal in the spectra of I-IV is found at weaker field as compared with the signals of the protons of the pyrrole fragment and is a quartet. The splitting is

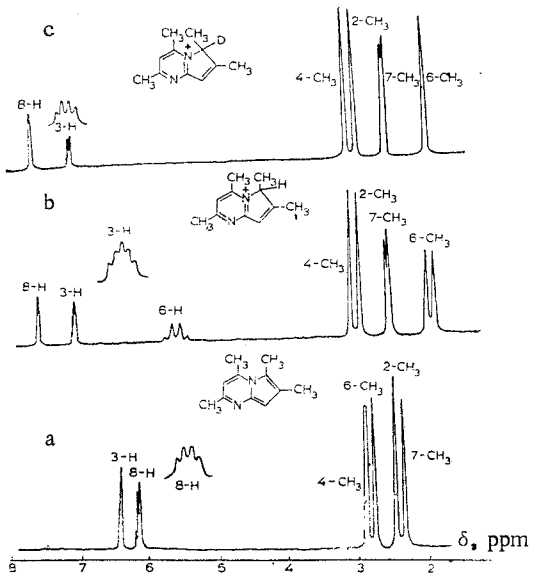


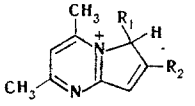
Fig. 1. PMR spectra of 2,4,6,7-tetramethylpyrrolo[1,2-a]pyrimidine (II): a) in $CDCl_3$; b) in CF_3COOH; c) in CF_3COOH/CF_3COOD (2:3).

due to spin—spin coupling (SSC) with the protons of the methyl group in the 4 position, the signal of which is observed as a doublet ($J_{3\text{-}H,4\text{-}CH_3} = 0.9$ Hz) in the spectra of I and IV (Fig. 2). The assignment of the signals of the methyl groups in the 2 and 4 positions was made on the basis of a comparison of the spectrum of I with the spectra of III and IV.

The introduction of an alkyl substituent in the pyrrole ring leads to an increase in the shielding of the methyl group attached to C_2. The shift of the C_4-CH_3 signal to the weak-field region observed in this case can be explained by the steric effect of the methyl group in the "peri" position (C_6-CH_3). The broadening of both signals, which masks splitting of the C_4-CH_3 signal due to SSC with the proton in the 3 position, is evidently associated with this effect. The assignment of the signals of the methyl groups of the pyrrole fragment follows unambiguously from a comparison of the spectra of II-IV.

An examination of the spectra of solutions of I-III in CF_3COOH (at 25°) shows that one form of the conjugate acid corresponding to the addition of a proton to the carbon atom in the 6 position (structures Iα-IIIα) is formed under these conditions.

A quartet with an intensity of one proton unit ($\delta = 5.50$-5.53 ppm), which was assigned to the proton attached to the C_6, is observed in the spectra of cations IIα-IIIα (Fig. 1).



Iα-IIIα

The signal of the methyl group in this position is observed as a doublet at 1.85 ppm ($J_{6\text{-}H,6\text{-}CH_3} = 7.5$ Hz).

The signal of the proton attached to C_8 in the spectra of both cations is shifted to the weak-field region relative to the neutral molecule ($\Delta\delta_8 = 0.73$ ppm). Close values of the weak-field shift are characteristic for the β protons of the pyrrole ring in the α forms of the conjugate acids of the indolizine derivatives ($\Delta\delta_1 = 0.7$-0.9 ppm) [9-11]. The chemical shifts of the methylene groups in the α- and β-protonated forms of the indolizines are 5.30-6.10 and 4.10-4.60 ppm, respectively. On the basis of these data, the signal with an intensity of two proton units at δ 5.76 ppm in the spectrum of I (Table 1) was assigned to the methylene group attached to C_6.

Protonation of I-III leads to a shift of the C_3-H signal and the signals of the CH_3 groups in the 2,4, and 7 positions to weak field. It should be noted that the change in the chemical shift of the proton attached to C_3 in IIα and IIIα ($\Delta\delta_3 = 1.53$ ppm) exceeds the analogous value for the proton in the 8 position ($\Delta\delta_8 = 0.73$ ppm) by a factor of approximately two. The same difference in the deshielding is observed for the methyl groups of the pyrimidine ($\Delta\delta_2 = 0.53$ ppm) and pyrrole ($\Delta\delta_7 = 0.22$ ppm) fragments. These results are in conformity with substantial "aromatization" and the associated increase in the effect of the ring currents of the six-membered ring in the cations of the investigated compounds. A change in the multiplicity of the signals of the aromatic protons is observed on passing from the neutral molecules to the cations. Thus splitting of the C_3-H signal by the protons of the C_4-CH_3 group is absent in the spectra of IIα and IIIα. The signal of the proton attached to C_8, which is a singlet in the spectrum of neutral molecule II, is a quintet in the spectrum of the corresponding cation (Fig. 1). The splitting is due to the SSC with C_6-H ($J_{6,8} = 1.2$ Hz) and the protons of the CH_3 group attached to C_7 ($J_{8\text{-}H,H\text{-}CH_3} = 1.5$ Hz). It should be noted that the C_6-H signal in the spectrum of IIα is considerably broadened because of proton exchange, and additional splitting with the proton attached to C_8 is absent. Deuterium exchange of the protons in the 6 and 8 positions is observed in the spectrum of a solution in CH_3COOH/CF_3COOD (2:3). The different rates of the process make it possible to record the C_8-H signal under conditions of complete exchange of the proton attached to C_6. This signal is in the form of a quartet; the C_6-CH_3 signal is simultaneously converted to singlet (Fig. 2). The corresponding difference in the multiplicity of the C_8-H signal due to SSC with C_6-H and C_7-CH_2 is found in the spectra of III and IIIα.

The characteristic changes in the chemical shifts and multiplicities of the signal of the protons of the two-ring system observed on protonation of pyrrolopyrimidines at C_6 can be used to establish the protonation center in related systems.

TABLE 1. PMR Spectra of the Bases and Conjugate Acids of Pyrrolo[1,2-a]pyrimidine Derivatives (I-III)

Substance	Solvent	Temp., °C	Chemical shifts*, δ, ppm						J, Hz			
			2	3	4	6	7	8	6-H, 8-H	3-H, 4-CH_3	7-CH_3, 8-H	6-H, 6-CH_3
I	CCl_4	25	2,36 s	6,14 q	2,42 d	7,13 d	7,20—7,50	6,65 d	1,5	0,9		
	$CDCl_3$	25	2,45 s	6,30 g	2,50 d			6,81 d	1,5	0,9		
	CF_3COOH	25	2,90 s	—†	2,97 s	5,76 s (2H)	7,50—8,00					
	CF_3COOH	—15	2,93 s	—†	2,98 s	5,83 s (2H)	7,50—8,00					
	CF_3COOH H_2SO_4 (4 : 1)	25	2,95 s	—†	3,00 s	5,85 s	7,50—8,00					
II	$CDCl_3$	25	2,35 s	6,00 q	2,73 br	2,65 br	2,22 br	6,23 s		0,9		
	CF_3COOH	25	2,81 s	7,53 s	3,00 s	1,85 d 5,50 q	2,48 d	7,00 quint	1,2		1,5	7,5
	CF_3COOH	—15	2,90 s	7,59 s	3,03	1,86 d 5,58 q	2,50 d	7,05 quint	1,2		1,5	7,5
	CF_3COOH H_2SO_4 (4 : 1)	25	2,92 s	7,58 s	3,05 s	1,87 d 5,59 d	2,51 d	7,07 quint	1,2		1,5	7,5
Perchlorate of II	CF_3COOH	25	2,92	7,60 s	3,05 s	1,88 d 5,58 q	2,48 d	7,05 quint	1,2		1,5	7,5
	CF_3COOH	—15	2,96 s	7,68 s	3,07	1,90 d 5,63 q	2,51 d	7,13 quint	1,2		1,5	7,5
III	$CDCl_3$	25	2,35 s	6,00 q	2,73 br	2,67 br	2,55 q	6,28 s		0,9		
	CF_3COOH	25	2,88 s	7,53 s	3,00 s	1,85 d 5,53 q	1,43 t 2,77 q	7,00 q	1,2		1,5	7,5

*Abrreviations: s is singlet, d is doublet, t is triplet, q is quartet, quint is quintet, and bs is broad signal.
†The signal is overlapped by the protons of the phenyl group.

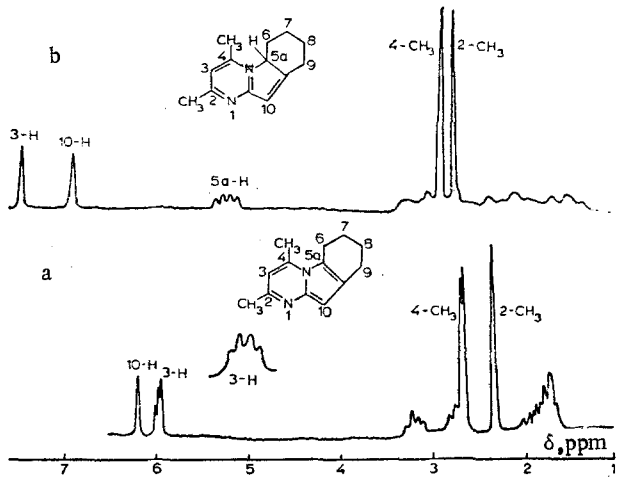
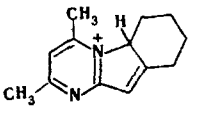


Fig. 2. PMR spectra of 2,4-dimethyl-6,7,8,9-tetrahydropyrimido[1,2-*a*]indole (IV): a) in $CDCl_3$; b) in CF_3COOH.

Thus the similar changes in the spectra of 2,4-dimethyl-6,7,8,9-tetrahydropyrimido[1-2-*a*]indole (IV) on passing from the neutral molecule to the cation (Table 2) correspond to the addition of a proton to the carbon atom of the pyrrole ring in the 5a position (structure IV).



IV a

The $C_{5a}-H$ signal ($\delta = 5.33$ ppm) is a quartet, which is due to SSC with the protons of the methylene group of the cyclohexane ring in the 6 position ($J_{\alpha,\alpha} = 9.7$ Hz, $J_{\alpha,e} = 6.0$ Hz). The chemical shifts of the protons and the methyl groups of the pyrrolopyrimide fragment in IV are extremely close to the corresponding values observed for Iα-IIIα.

The appearance of signals that could be assigned to the N_1- and C_β-protonated forms is not observed in the spectra of any of the investigated compounds with time. Consequently, of the three possible structures of the conjugate acids, the α form is thermodynamically most favorable, and this is in conformity with the higher basicity of the C_α atom as compared with N_1 and C_β.

Whereas this may be associated to a considerable degree with a decrease in the basicity due to the −I effect of the bridge nitrogen atom in the case of pyrrolo[1,2-*a*]pyridazine, in the case of pyrrolo[1,2-*a*]pyrimidine the position of the cationoid center is apparently determined by the difference in the stabilities of the N and α(β) forms of the conjugate acid, which are characterized, respectively, by o-quinoid and benzenoid structures of the six-membered fragments. In addition, it has been established for some pyrrolo[1,2-*a*]pyridazine derivatives [5] that the formation of a stable carbonium ion takes place through the N form of the conjugate acid. Signals of only the N-protonated form were present in the spectra of the perchlorates of these compounds immediately after dissolving in CF_3COOH at 25°. Complete conversion of the N form to the α form of the conjugate acid was observed with time. The spectra of CF_3COOH solutions of the perchlorate of 2,4,6,7-tetramethylpyrrolo[1,2-*a*]pyrimi-

TABLE 2. PMR Spectra of the 2,4-Dimethyl-6,7,8,9-tetrahydropyrmido[1,2-*a*]indole Base (IV) and Its Conjugate Acid

Solvent	Chemical shifts*, δ, ppm					J, Hz	
	2	3	4	5a	10	3-H, 4-CH_3	5a-H, 6-CH_2
$CDCl_3$	2,35 s	5,00 g	2,70 d	—	6,20 s	0,9	
CF_3COOH	2,88 s	7,53 s	3,00 s	5,33 q (2H)	6,98 br		9,7 (*aa*) 6,0 (*ae*)

*Abbreviations: s is singlet, d is doublet, q is quartet, and b is broad.

TABLE 3. Ionization Constants of Pyrrolo[1,2-a]pyridine and Indolizine Derivatives in Nitromethane Relative to Diphenylguanidine

Compound	Ionization constants (ΔpK_a)
2,4-Dimethyl-7-phenylpyrrolo[1,2-a]pyrimidine (I)	5.90
2,4,6,7-Tetramethylpyrrolo[1,2-a]pyrimidine (II)	3.98
2,4-Dimethyl-6,7,8,9-tetrahydropyrimido[1,2-a]indole (IV)	3.83
2-Methylindolizine (V)	3.53
2-Phenylindolizine (VI)	5.97

dine at −15 to 25° are characterized exclusively by signals of the α form of the conjugated acid (Table 1). A nitrogen-protonated form also was not observed in the protonation of pyrrolo[1,2-a]pyrimidine derivatives I and II in CF_3COOH at −15° and in CF_3COOH/H_2SO_4 (4:1) at 25°.

The ionization constants, which characterize the basicities of the same center — the carbon atom of the pyrrole fragment in the α position relative to the common nitrogen atom — of I, II, and IV, as well as 2-methyl- and 2-phenylindolizine (V and VI) in nitromethane, are presented in Table 3. A comparison of the ΔpK_a values of I, II, V, and VI shows that the basicity of this center decreases on passing from indolizine to pyrrolo[1,2-a]pyrimidine. Thus the ΔpK_a values of I and VI are 5.97 and 5.90, respectively. It is known that the overall effect of two methyl groups in the six-membered ring in the indolizine molecule [12] is 2.5 pK_a units. Consequently, the difference in the basicities of the C_α atoms in the indolizine and pyrrolo[1,2-a]pyrimidine molecules is of the same order of magnitude. It has been shown for indolizine derivatives [12] that the methyl group lowers the basicity of a carbon atom bonded to it. At the same time, the ΔpK_a value of II increases by approximately two orders of magnitude as compared with I. This is evidently associated with the different electronic effects of the substituents in the 7 position of these compounds. A considerable increase in the ionization constant is also observed on passing from 2-phenylindolizine to 2-methylindolizine (Table 3).

EXPERIMENTAL

The substituted 2,4-dimethylpyrrolo[1,2-a]pyrimidines and 2,4-dimethyl-6,7,8,9-tetrahydropyrimido[1,2-a]indole were obtained by heating the corresponding 2,4-dimethyl-8-cyanopyrrolo[1,2-a]pyrimidines and 2,4-dimethyl-10 cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole with 100% phosphoric acid, during which the cyano group was readily eliminated. A detailed description of the synthesis will be published later.

The PMR spectra of 0.15 M solutions of the compounds in CCl_4, $CDCl_3$, and CF_3COOH were recorded with an S-60 spectrometer. The chemical shifts were measured on the δ scale, and the internal standard was tetramethyl silane.

The basicity constants (ΔpK_a) of nitromethane solutions of the compounds were measured with a PHM-26 pH-meter (Radiometer, Denmark) by the method in [13].

LITERATURE CITED

1. V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, Khim.-Farmats. Zh., No. 3, 25 (1967).
2. V. I. Shvedov, L. B. Altukhova, V. V. Alekseev, and A. N. Grinev, Khim.-Farmats. Zh., No. 12, 3 (1968).
3. M. D. Mashkovskii, A. N. Grinev, N. I. Andreeva, L. B. Altukhova, V. I. Shvedov, G. Ya. Avrutskii, and V. V. Gromova, Khim.-Farmats. Zh., No. 3, 60 (1974).
4. M. Ya. Mikhel'son and N. K. Fruentov, Pharmacology of Neurotropic Agents [in Russian], Medgiz, Leningrad (1963), p. 186.
5. M. Fraser, J. Org. Chem., 36, 3087 (1971; 37, 3027 (1972).
6. W. Flitsch and U. Krämer, Ann., 35, 735 (1970).
7. W. Flitsch and U. Krämer, Tetrahedron Lett., 1479 (1968).
8. E. Kleinpeter and R. Borsdorf, J. Pharm. Chem., 314, 515 (1972).

9. W. S. F. Armarego, J. Chem. Soc., B, 191 (1966).
10. M. Fraser, A. Mellera, and B. Molly, J. Chem. Soc., B, 3288 (1962).
11. M. Fraser and S. M. Kenzie, J. Chem. Soc., B, 44 (1966).
12. W. S. F. Armarego, J. Chem. Soc., B, 4226 (1966).
13. L. M. Alekseeva, G. G. Dvoryantseva, I. V. Persianova, Yu. N. Sheinker, R. M. Palei, and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 9, 1132 (1972).

ANALOGS OF PURINE NUCLEOSIDES AND PURINE MONO- AND POLYNUCLEOTIDES. VI*. PHOSPHORYLATION OF 9-(1,5-DIHYDROXY-3-PENTYL)PURINES AND THEIR POLYCONDENSATION WITH 1',5'-DIPHOSPHATES OF 6-SUBSTITUTED 9-(1,5-DIHYDROXY-3-PENTYL)PURINES

S. A. Giller†, A. Khettskhaim, I. A. Drizina, and T. M. Krukle

UDC 547.857.07:542.953'945.32

Phosphorylation of 6-substituted 9-(1,5-dihydroxy-3-pentyl)purines with 2-cyanoethyl phosphate in the presence of dicyclohexylcarbodiimide in anhydrous pyridine gave their 1',5'-diphosphates. Oligomers containing pyrophosphate and ester bonds were obtained by polycondensation of 1',5'-diphosphates of 6-dimethylamino- and 6-oxo-9-(1,5-dihydroxy-3-pentyl)purines with the appropriate 9-(1,5-dihydroxy-3-pentyl)purines.

In the present research we studied the phosphorylation of our previously synthesized 6-amino-, 6-dimethylamino-, and 6-oxo-9-(1,5-dihydroxy-3-pentyl)purines (I-III) with 2-cyanoethyl phosphate. We obtained 9-(1,5-dihydroxy-3-pentyl)purine 1',5'-diphosphates (IV-VI) when the reaction was carried out by the method in [2] in anhydrous pyridine in the presence of dicyclohexylcarbodiimide. As in the case of phosphorylation of 1-(1,4-dihydroxy-2-butyl) thymine [3], the reagent molar ratio has a considerable effect on the yields of final products IV-VI. Thus the maximum yields of 1',5'-diphosphates IV-VI were obtained when a six-fold excess of 2-cyanoethylphosphate and, respectively, a 12-fold excess of dicyclohexylcarbodiimide were used. 1',5'-Diphosphates IV-VI were isolated by means of preparative chromatography on Dowex 50W × 4 ion-exchange resin (H^+ form). The considerable adsorption of purines on the ion-exchange resin makes it possible to efficiently separate the phosphoric acid, formed in the decomposition of 2-cyanoethyl phosphate, from the phosphorylation products and also makes it possible to separate diphosphorylated purines IV-VI from monophosphorylation products VII-IX and starting purines I-III, which are retained more strongly by the resin. However, the IV-VI isolated in this manner are not sufficiently homogeneous and require additional purification. Preparative rechromatography on A-25 QAE-Sephadex anion-exchange resin proved to be the most effective method to achieve this. In addition, we were able to purify V and VI by conversion to the corresponding barium salts, and VI was also purified by washing with ethanol. Monophosphorylation products VII and VIII were purified with columns by means of A-25 QAE-Sephadex resin. The chromatographically pure mono- and diphosphorylated

*See [1] for communication V.
†Deceased.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 693-696, May, 1976. Original article submitted March 18, 1975.