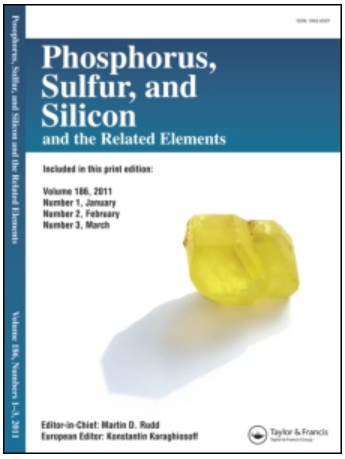

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THE SYNTHESIS AND STRUCTURE OF P(III)-PHOSPHORYLATED 2-AMINOPYRIDINES AND THEIR DERIVATIVES

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THE SYNTHESIS AND STRUCTURE OF P(III)-PHOSPHORYLATED 2-AMINOPYRIDINES AND THEIR DERIVATIVES

E. E. NIFANTYEV,† V. V. NEGREBETSKY, M. K. GRATCHEV, G. I. KUROCHKINA, A. R. BEKKER, L. K. VASYANINA and S. G. SAKHAROV

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A number of the derivatives of 2-aminopyridine and diisopropyl-phosphinous, neopentylene- and pyrocatecholphosphorus acids 1–3 and also the diphosphorylated derivative 4 have been obtained. Phosphinite 1 was alkylated by triethyloxoniumtetrafluoroborate with the formation of quasi-phosphonium salt 5 and was protonated by hydrogen chloride at the endocyclic nitrogen atom to form pyridinium salt 6. The structure of all obtained compounds was studied by ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR spectroscopy and it was shown that they exist predominantly in the phosphoaminopyridine form A.

Key words: 2-Aminopyridine; phosphorylating agent; prototropic equilibrium; amino-imino tautomerism; exocyclic; endocyclic.

INTRODUCTION

Diaza compounds, imidazolides and pyrazolides, in the molecules of which nitrogen atoms are included into a conjugated system, rank high among amide acids of trivalent phosphorus (AATP). In contrast to the simplest dialkylamides these derivatives show high phosphorylating activity already at lowered temperatures (−50°C) in relation to proton donor nucleophiles. In connection with this they became widely used in the synthesis of complex natural compounds, for example, phosphorylated sugars,[1] oligonucleotides.[2] At present time the reasons of such high activity of diaza phosphamides are unclear; to this effect there are only preliminary suppositions of no general character.[3]

In the previous studies, connected with the search for new phosphorylating reagents, we revealed that the activity of some acyclic diaza AATP, for instance, P(III)-amidines and -hydrazines, can be increased due to protonation or by increasing of their N—H acidity.[4] Taking into consideration this fact we aimed at searching effective phosphorylating reagents among new P(III)-amides of prototropic type. The P(III)-derivatives of α-aminoazaheterocycles were first referred to such compounds.

A priori it can be assumed that the phosphorylation of the selected systems may lead to obtaining products, containing phosphorus both at exocyclic nitrogen atom,

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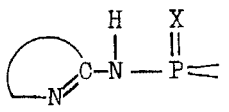
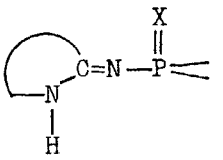
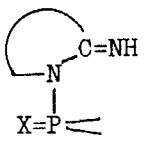
which can exist in two tautomeric forms A and B, and at endocyclic nitrogen atom, form C:



A



B



C

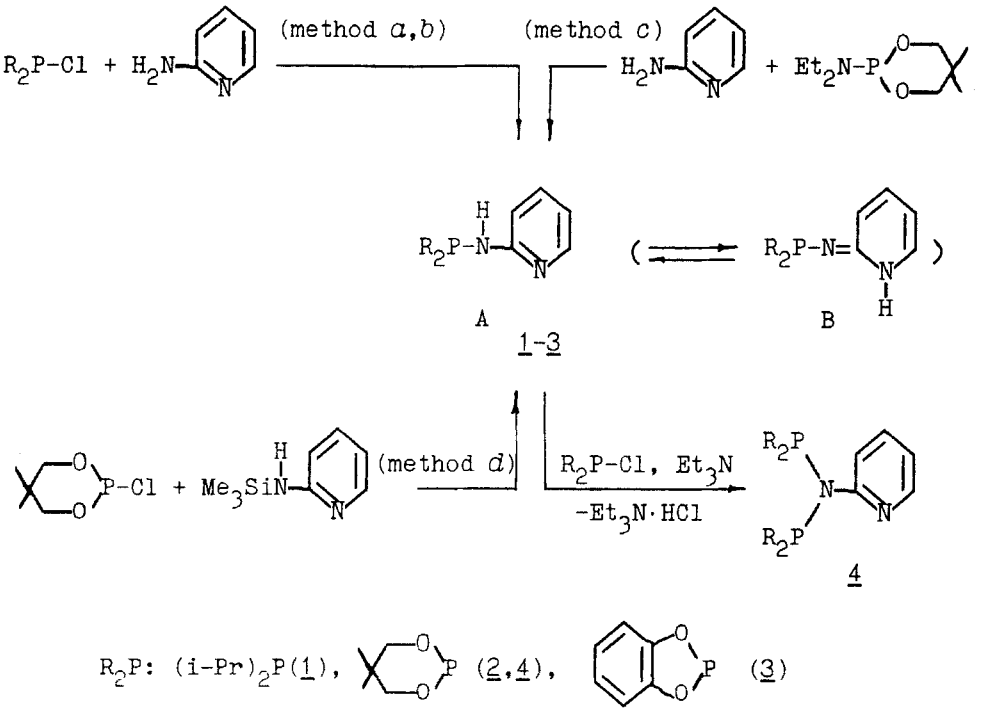
As to the derivatives of pentavalent phosphorus (X = O, S), the problem of the identification of these forms, especially A and B, have been discussed comparatively for a long time, however reliable conclusions have been made only recently with the help of NMR spectroscopy in relation to some structures.[5] In the series of the respective derivatives of trivalent phosphorus the problem of identification of these forms has not been solved yet. In the literature there is a limited number of papers devoted to the synthesis of such compounds but their structures have not been strictly proved (see, for example[6]); the basic problems of synthetic and structural chemistry of these systems have not all been solved yet.

The present work is devoted to the study of the synthesis and to the determination of the structure of P(III)-phosphorylated 2-aminopyridines. Systems of various chemical nature were chosen: the derivatives of diisopropyl phosphinous acid 1, neopentylene- 2 and pyrocatechol- 3 phosphorus acids. It was originally supposed that in the given series the increase of electronegativity of the phosphorus-containing substituent (1 < 2 < 3) would lead to a certain shift of a possible prototropic equilibrium towards form B (in case of phosphorylating at exocyclic nitrogen atom). The anticipated shift must be stimulated also by the appearance of a positive charge at the phosphorus or nitrogen atoms as a result of, for example, alkylation and protonation. The research of the possibility of such tautomerism is the second purpose of the presented work.

RESULTS AND DISCUSSION

Amides 1–3 were obtained with 60–85% yield from 2-aminopyridine and chloroanhydride of the respective acid in benzene in the presence of triethylamine as an acceptor of hydrogen chloride (amides 1–3, method *a*) or a second equivalent of 2-aminopyridine (amide 2, method *b*). Amide 2 was synthesized by transamination with 75% yield from 2-aminopyridine and diethylamide of neopentylenephosphorous acid on heating up to 115°C simultaneously distilling off diethylamine (method *c*) and also with 70% yield from 2-(trimethylsilylamino) pyridine and chloranhydride of neopentylenephosphorous acid (method *d*). Reaction of amide 2 with the equivalents of chloroanhydride of neopentylenephosphorous acid and triethylamine yields the diphosphorylated product 4 in 67% yield (Scheme I).

Phosphinite 1 is easily alkylated by triethyloxoniumtetrafluoroborate to form salt 5 and is protonated by hydrogen chloride under the conditions of carrying out the

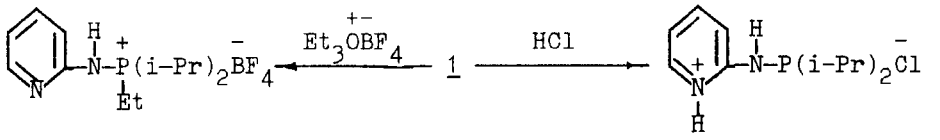


SCHEME I

synthesis of phosphinite 1 from equimolecular quantities of chlorophosphinite and 2-aminopyridine without triethylamine in homogenizing solvent ($CHCl_3$, CH_3CN) to form salt 6 (Scheme II).

It is interesting to note that analogous protonation by hydrogen chloride on synthesizing amide 2 in homogenizing solvent does not lead to the formation of the salt of type 6, but results in the formation of the expected mixture: unreacted chlorophosphite, product 2 and hydrochloride of 2-aminopyridine in approximate mole ratio: 1:1:1. This fact is indicative of the essential electron donating influence of the phosphorus residue in amide 1 in comparison with amide 2. As a result of this the basicity of the pyridine nitrogen atom in amide 1 becomes higher than that in the initial 2-aminopyridine.

We investigated compounds 1–3, 5, 6 by NMR ^1H, ^{13}C, ^{15}N, ^{31}P spectroscopy to determine the position of phosphorylation and in connection with possible amino-



5 6

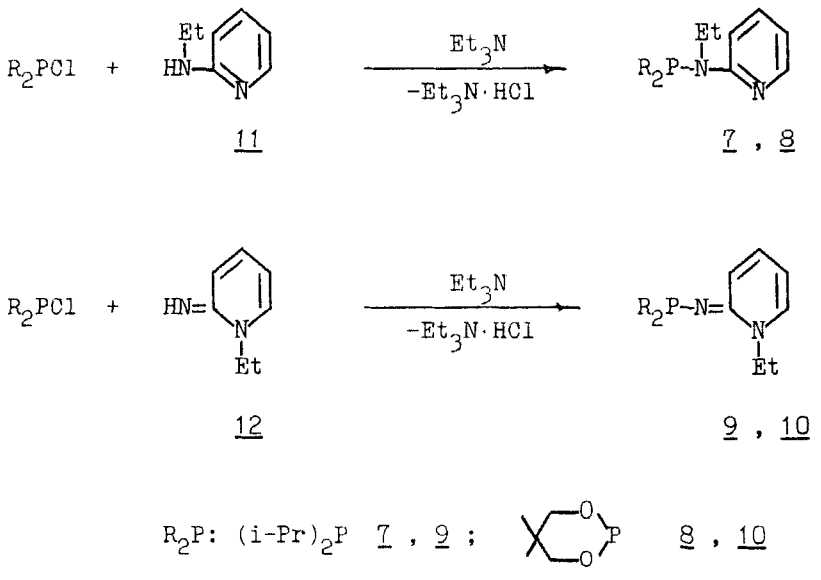
SCHEME II

imino tautomerism A ⇌ B. To obtain more complete information we additionally synthesized compounds with "fixed" structural forms A - 7, 8 and B - 9, 10. Amides 7–10 were obtained from 40–79% yield, similar to compounds 1, 2 (method *a*), from chloroanhydrides of phosphinous, or phosphorous acids and 2-(ethylamino)-pyridine 11, or 1-ethyl-2-imino-1,2-dihydropyridine 12, respectively (Scheme III).

It should be noted that unlike imine 12 amino-imini transitions are possible for pyridine derivative 11 and phosphorylation can occur both at exo- and endocyclic nitrogen atom. We showed that compounds 7, 8 are the structures which are phosphorylated only at the exocyclic nitrogen atom. It follows from the presence of the coupling constants of the methylene protons of N-ethyl group with phosphorus (Table I).

To make correct signal reference in ^1H and ^{13}C NMR spectra the synthesized compounds were studied by the methods of correlation 2D-spectroscopy COSY and HETCOR. The C^6 carbon signal in the ^{13}C NMR spectra is only identified according to downfield shift and to the greater value of the constant $^1J_{CH}$. In the ^{13}C NMR spectrum of compound 10 without decoupling from protons C^2 and C^2 the carbon signals show an additional triplet due to the interaction with methylene protons of the N-ethyl group ($^3J_{C^2H_2}$ 5.3, $^3J_{C^6H_2}$ 4.7 Hz), which disappears at selective irradiation of methylene protons. Further, we managed to assign the signals of all pyridine protons and carbons by inspecting the H,H-COSY and H,C-HETCOR spectra. It turned out that the downfield signal in the ^1H NMR spectra did not always belong to H^6 proton. For instance, in the ^1H NMR spectrum of compound 10 on substituting the solvent $CDCl_3$ for C_6D_6 the H^6 signal moves to lower field due to the ASIS effect[7] and in C_6D_6 the downfield signal already belongs to the H^3 proton.

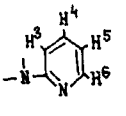
The analysis of the ^1H and ^{13}C NMR spectra (Tables I and II) of compounds



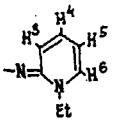
SCHEME III

TABLE I

The parameters of ^1H NMR spectra of compounds 1–12 (c 0.5 mol·l^{-1}) (δ)



1-8,11



9,10,12

Compound	Solvent	H^3 ($^3J_{H^3H^4}$, Hz)	H^4 ($^4J_{H^4H^6}$, Hz)	H^5 ($^3J_{H^4H^5}$, Hz)	H^6 ($^3J_{H^5H^6}$, Hz)	Other signals
1	C_6D_6	7.31 (8.5)	7.14 (2.0)	6.41 (7.1)	8.21 (4.2) (a)	0.92-0.97(m,12H,CH_3),1.48(m,2H,C<u>H</u>CH_3), 5.03(d,1H,NH,$^2J_{HNP}$9.2Hz)
	$CDCl_3$	6.97 (8.5)	7.27 (b)	6.46 (8.5)	7.88 (4.2)	0.89-0.93(m,12H,CH_3),1.63(m,2H,$CHCH_3$), 5.1(d,1H,NH,$^2J_{HNP}$8.8Hz)
2	C_6D_6	6.82 (8.4)	7.05 (1.9)	6.43 (7.2)	8.25 (5.1) (c)	0.16,1.09(2s,6H,CH_3),3.09,3.70(2m,4H, CH_2),5.99(br.s.,1H,NH)
	$CDCl_3$	6.76 (8.4)	7.48 (2.1)	6.76 (8.4)	8.16 (5.1)	0.77,1.27(2s,6H,CH_3),3.46,4.10(2m,4H, CH_2),5.59(br.s.,1H,NH)
	DMSO-d^6	6.73 (8.8)	7.49 (b)	6.71 (8.8)	8.08 (4.9)	0.71,1.15(2s,6H,CH_3),3.35,4.10(2m,4H,CH_2), 7.88(d,1H,NH,$^2J_{HNP}$3.0Hz)
3	C_6D_6	6.26 (8.12)	6.91 (b)	6.34 (8.1)	7.78 (5.4)	6.71,6.92(2m,4H,CHarom.),7.49(br.s.,1H,NH)
	$CDCl_3$	6.59 (7.8)	7.33 (b)	6.66 (7.8)	7.87 (4.6)	6.83,6.99(2m,4H,CHarom.),7.40(br.s.,1H,NH)
4	C_6D_6	7.09 (7.8)	7.16 (2.0)	6.51 (7.8)	8.32 (3.9)	0.37.0.99(2s,12H,CH_3),3.30,4.03(2m,8H,CH_2)
5	$CDCl_3$	7.07 (8.2)	7.52 (b)	6.87 (8.2)	8.03 (4.06)	1.17(t,3H,$CH_2C\underline{H}_3$),1.24-1.33(m,12H,$CHC\underline{H}_3$), 2.43(m,2H,CH_2P,$^2J_{HCP}$9.2Hz),2.96(m,2H,CH), 7.12(br.s.,1H,NH)
6	$CDCl_3$	7.5 (8.8)	7.87 (b)	6.89 (8.8)	7.96 (5.54)	0.99-1.11(m,12H,CH_3),1.95(m,2H,C<u>H</u>CH_3), 8.25(br.s.,2H,NH)
7	C_6D_6	7.16 (7.14)	7.16 (b)	6.42 (7.4)	8.3 (5.2)	1.03-1.06(m,12H,$CHC\underline{H}_3$),1.28(t,3H,$CH_2C\underline{H}_3$), 2.25(m,2H,$C\underline{H}CH_3$),3.70(m,2H,NCH_2,$^3J_{HCNP}$5.6Hz)
8	C_6D_6	7.17 (6.6)	7.07 (b)	6.44 (6.6)	8.3 (5.2)	0.53,0.92(2s,6H,CCH_3),1.43(t,3H,$CH_2C\underline{H}_3$), 3.57-3.61(m,4H,OCH_2),4.11(m,2H,NCH_2, $^3J_{HCNP}$3.7Hz)
9	C_6D_6	7.51 (9.2)	6.50 (b)	5.32 (9.2)	6.30 (6.6)(d)	1.03(t,3H,$CH_2C\underline{H}_3$),1.28-1.31(m,12H,$CHC\underline{H}_3$), 1.95(m,2H,C<u>H</u>CH_3),3.60(m,2H,NCH_2)

TABLE I (*continued*)

Compound	Solvent	H^3 ($^3J_{H^3H^4}$, Hz)	H^4 ($^4J_{H^4H^6}$, Hz)	H^5 ($^3J_{H^4H^5}$ Hz)	H^6 ($^3J_{H^5H^6}$, Hz)	Other signals
10	C_6D_6	7.10 (9.2)	6.47 (b)	5.39 (9.2)	6.25 (6.4)	0.5, 1.46(2s, 6H, CCH_3), 0.98(t, 3H, $CH_2\underline{CH_3}$), 3.37, 4.51(2m, 4H, OCH_2), 3.51(m, 2H, NCH_2)
	$CDCl_3$	6.92 (9.6)	7.07 (b)	6.04 (6.4)	7.22 (6.6)	0,20, 1.00(2s, 6H, CCH_3), 1.05(t, 3H, $CH_2\underline{CH_3}$), 2.91, 3.99(2m, 4H, OCH_2), 3.75(m, 2H, NCH_2)
11	C_6D_6	6.01 (8.1)	7.12 (2.1)	6.38 (8.1)	8.28 (5.2)	0.91(t, 3H, CH_3), 3.09(q, 2H, CH_2), 4.24(br.s., 1H, NH)
	CD_3CN	6.40 (8.4)	7.37 (2.0)	6.49 (8.4)	7.98 (5.9)	1.16(t, 3H, CH_3), 3.26(q, 2H, CH_2), 5.14(br.s., 1H, NH)
12	C_6D_6	5.88 (9.4)	6.29 (2.4)	5.23 (9.4)	6.25 (7.2)	1.09(t, 3H, CH_3), 3.63(q, 2H, CH_2), 5.50(br.s., 1H, NH)
	CD_3CN	6.21 (9.2)	6.70 (1.7)	5.69 (9.2)	6.99 (6.6)	1.20(t, 3H, CH_3), 3.81(q, 2H, CH_2), 4.9(br.s., 1H, NH)

a) $^5J_{H^3H^6}$ 0.9, $^4J_{H^3H^5}$ 0.9, $^4J_{H^3P}$ 2.8, $^5J_{H^6P}$ 0.4 Hz;

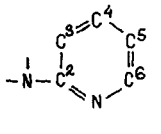
b) $\leqslant$0.5 Hz;

c) $^5J_{H^3H^6}$ 0.9, $^4J_{H^3H^5}$ 0.9 Hz;

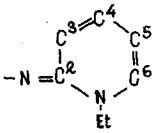
d) $^5J_{H^6P}$ 4.2 Hz.

TABLE II

The parameters of ^{13}C NMR spectra of compounds 1–6, 8–10 (c 1.0 mol·l^{-1}) (δ)



1-6, 8



9, 10

Compound	Solvent	C^2 ($^2J_{CP}$, Hz)	C^3 ($^3J_{CP}$, Hz)	C^4	C^5	C^6	Other signals
1	C_6D_6	162.3 (18.0)	109.9 (10.8)	137.9	114.9	148.8	17.7(CH_3, $^2J_{CP}$7.2Hz), 19.3(CH_3, $^2J_{CP}$21.7Hz), 27.0(CH, $^1J_{CP}$10.8Hz)
2	C_6D_6	158.0 (15.3)	109.7 (11.5)	138.3	115.9	149.1	22.7(CH_3), 23.0(CH_3), 33.2($\underline{C}CH_3$, $^3J_{CP}$4.5Hz), 70.0(CH_2, $^2J_{CP}$2.4Hz)
3	C_6D_6	155.8 (13.4)	111.4 (6.1)	138.6	117.6	148.4	113.5(OC$\underline{C}$arom.), 123.2(O$\underline{C}$arom., $^3J_{CP} \leqslant$ 1Hz), 146.5(Oarom., $^2J_{CP}$7.3Hz)

Compound	Solvent	C^2 ($^2J_{CP}$, Hz)	C^3 ($^3J_{CP}$, Hz)	C^4	C^5	C^6	Other signals
4	C_6D_6	157.7 (≤1.0)	120.0 (≤1.0)	137.8	122.0	149.5	22.9(CH_3),23.0(CH_3),32.8($\underline{C}CH_3$,$^3J_{CP}$2.0Hz), 72.1(CH_2, $^2J_{CP}$3.1Hz)
5	$CDCl_3$	153.2 (2.5)	112.2 (3.3)	139.2	118.2	147.0	6.1($CH_2\underline{C}H_3$,$^2J_{CP}$6.3Hz),12.7(CH_2,$^1J_{CP}$56.3Hz), 16.0(CH_3,$^2J_{CP}$6.9),16.3(CH_3,$^2J_{CP}$7.1Hz), 23.5(CH,$^1J_{CP}$53.5Hz).
6	$CDCl_3$	157.5 (12.4)	111.6 (≤1.0)	133.8	113.5	143.7	17.3(CH_3,$^2J_{CP}$7.0Hz),18.0(CH_3,$^2J_{CP}$8.4Hz), 25.6(CH,$^1J_{CP}$9.9Hz)
8	C_6D_6	157.9 (24.1)	111.5 (19.7)	137.2	116.2	148.3	15.6($CH_2\underline{C}H_3$),21.8($C\underline{C}H_3$),23.1($C\underline{C}H_3$),32.8 ($\underline{C}CH_3$,$^3J_{CP}$7.9Hz),37.2($\underline{C}H_2CH_3$),73.6(OCH_2, $^2J_{CP}$4.6Hz)
9	C_6D_6	158.6 (25.5)	118.6 (30.7)	134.4	102.7	137.7	14.1($CH_2\underline{C}H_3$),17.8($C\underline{C}H_3$,$^2J_{CP}$8.3Hz),19.4 ($C\underline{C}H_3$,$^2J_{CP}$20.0Hz),27.7(CH,$^1J_{CP}$12.0Hz), 45.5($\underline{C}H_2CH_3$)
10	C_6D_6	154.4 (23.3)	117.6 (22.9)	136.5	105.8	138.2	14.0($CH_2\underline{C}H_3$),22.9($C\underline{C}H_3$),23.0($C\underline{C}H_3$), 33.0($\underline{C}CH_3$,$^3J_{CP}$3.5Hz),46.2($\underline{C}H_2CH_3$),67.7 (OCH_2,$^2J_{CP}$≤1Hz)

with the known structure in the aminoform A (4, 7, 8, 11) and iminoform B (9, 10, 12) and the comparison of these with the spectra of the present compounds 1–3, 5, 6, measured in various solvents, permitted us to offer some critera for the identication of forms A and B. Thus in the ^{1}H NMR spectra of compounds with fixed iminoform B - 9, 10, 12 a more upfield shift of the ^{3}H and ^{4}H proton signals is observed compared to that of compounds with fixed aminoform A - 7, 8, 11. Besides this, amino-form A is characterized by lower values of the coupling constants of ^{3}H, ^{4}H protons (6.6–8.4 Hz) and ^{5}H, ^{6}H protons (5.1–5.9 Hz) of the pyridine ring compared to compounds with fixed iminoform B - 9, 10, 12: 9.2–9.6 Hz and 6.6–7.2 Hz, respectively.

As it was shown earlier[8] on the simplest derivatives of 2-aminopyridine, the indicated differences can be connected with the disturbance of aromaticity and the increase of the double bonding in the position 3, 4 and 5, 6 of the pyridine ring in the iminoform B. Furthermore, the presence of $^2J_{HNP}$ constant in phosphinite 1 distinctly indicates the existence of this compound predominantly in the aminoform A. Unfortunately, in ^{1}H NMR spectra of the most other compounds the NH proton signal appears as a widened line as a result of rapid intermolecular exchange (Table I). The presence of the large coupling constant of the H^6 proton with the phosphorus atom through five bonds (4.2 Hz), which is absent in amide 10, has become an interesting peculiarity of compound 9 in iminoform B. Such high value of $^5J_{H^6P}$ was earlier observed in phosphoryliminothiazolines containing an analogous bond chain H—C—N—C=N—P in a planar zig-zag configuration.[9] Long range constants $^4J_{H^3P}$ (2.8 Hz) and $^5J_{H^6P}$ (0.4 Hz) were also observed for compound 1.

In ^{13}C NMR spectra the iminoform B is characterized by a larger upfield shift of the C^5 and C^6 carbon signal in comparison with the aminoform A ($\Delta\delta > 10$ ppm) (Table II). But $^2J_{CNP}$ constant in compounds in aminoform A turned out to be changed within high limits. Probably, it is connected with the possible existence of various rotameric forms around the C—N bond, while such possibilities for compounds in iminoform B are more limited.

The alkylation of the phosphorous atom of the salt 5 was confirmed by the presence in ^1H NMR spectrum coupling constant of the methylene protons of ethyl group with phosphorus and in ^{13}C NMR spectrum, by the observation of the direct coupling constant of carbon with phosphorus. We encountered some difficulties on determining the structure of salt 6. The absence of the direct coupling constant of phosphorus with proton in ^{31}P NMR spectrum and the presence of the coupling constant of phosphorus with amide proton permitted to assume the structure of aminoform A with protonation of more basic and "hard" endocyclic nitrogen atom. It is also confirmed by the larger upfield shift of C^2 and C^6 carbon signals in compound 6 in comparison with amide 1 as a result of the appearance of positive charge, mainly localized at the endocyclic nitrogen atom.

The absence of the couplings of protons and carbons of position six of the pyridine ring with phosphorus permits also to exclude the consideration of the structure with phosphorylated endocyclic nitrogen atom (form C). In addition, the second phosphorylation (the synthesis of compound 4) also occurs not at endocyclic but at exocyclic nitrogen atom which is confirmed by the complete equivalence of the two phosphorus residues in ^1H, ^{13}C and ^{31}P NMR spectra.

Taking into account the complexity of the problem we additionally used ^{15}N NMR data to prove the structures of amides 1–3, 5–6. Such approach was successfully used earlier on studying amino-imino transitions in 2-aminopyridine and its alkylated derivatives of various prototropic forms.[10] On comparing the data of the chemical shifts of ^{15}N signals in compounds 1–3, 5, 6 with those in compounds of fixed structure 4, 8, 10 (Table III) and with known data[10] it is seen that ^{15}N signals of endocyclic nitrogen of aminopyridine fragment in form A are in the interval of δ = 256–300, while ^{15}N signals of the same nitrogen in form B are in the interval of δ = 133–170; ^{15}N signals of exocyclic nitrogen in form A are in the interval of δ = 53–115 and ^{15}N signal of the same nitrogen in form B are in the interval of δ = 135–196. The analysis of the ^{15}N chemical shifts in the studied compounds with regard to known data[10] and the ^{15}N chemical shifts in compounds with fixed structure 4, 8, 10 shows that amides 1–3, 5 exist mainly in the aminoform A. The large upfield shift of ^{15}N signal is indicative of the protonation of endocyclic nitrogen atom of amide 6 and the localization of positive charge at it.[11] It was additionally shown with ^{15}N NMR in DEPT mode at −30°C (under conditions of slow exchange of amide protons) that the exocyclic nitrogen atom of amide is the secondary one. Besides this, in ^{15}N NMR spectrum of compound 1 without decoupling from protons in accordance with aminoform A the exocyclic nitrogen atom also shows the direct coupling with proton (Table III).

Thus, by using NMR spectroscopy on various nuclei we showed that the studied compounds 1–3, 5, 6 exist in predominant tautomeric aminopyridine form A. It was also established that alkylation occurs at the phosphorus atom and protonation at the endocyclic nitrogen atom of the pyridine fragment. Such modification does not lead to a noticeable transition into iminopyridine form B and it is indicative

TABLE III

The parameters of ^{15}N NMR spectra of compounds 1–6, 8, 10 ($CDCl_3$, c 1.0 mol·l^{-1}) (δ)

Compound	1	2	3	4	5	6	8	10
$^{15}N_{exo}$	66	98	116	b	b	83	112	196
($^1J_{NP}$, Hz)	(56)[a]	(67)	(83)			(58)	(73)	(65)
$^{15}N_{endo}$	263	268	268	300	256	173	280	170
($^3J_{NP}$, Hz)	(11)	(c)	(12)	(c)	(c)	(c)	(9)	(c)

a) $^1J_{NH}$ 81 Hz;

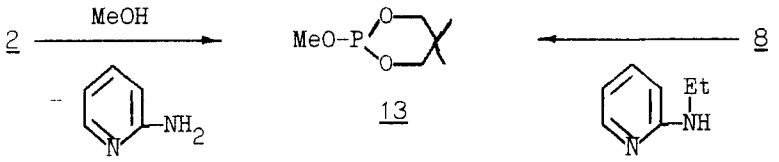
b) not determined;

c) $\leqslant$0.5 Hz.

of the stability of the aminopyridine fragment in relation to the disturbance of its aromaticity.

In the present work we compared the relative rates of methanolysis of amide 2 and its analogue 8 in fixed form A (Scheme IV).

It turned out that in the first case alcoholysis occurred noticeably faster: $\tau_{1/2}$ 15 and 65 min respectively (37°C, $CHCl_3$, reagent concentration—1 mol·l^{-1}). The reaction was carried out directly in the probe of the NMR spectrometer, the reaction control was performed by the integration of the ^{31}P signals of initial amides 2, 8 and reaction product—2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 13. Thus in the series of P(III)-phosphorylated 2-aminopyridines the presence of prototropic hydrogen in phosphamide fragment leads to an increasing phosphorylating activity.



SCHEME IV

EXPERIMENTAL

All the experiments are performed in an atmosphere of dry nitrogen and in dried solvent.[12] 2-(Trimethylsilylamino)pyridine was obtained from 2-aminopyridine and hexamethyldisilazan as described.[13] The preparation of the derivatives of aminopyridine 11 and iminopyridine 12 was described[14,15] previously. To make kinetic measurements of the methanolysis of amides 2 and 8 they were purified from traces of hydrochlorides of amines by treating them with butyllithium according to the recommendations.[16]

^1H and ^{13}C NMR spectra were obtained on a Bruker AM-400 spectrometer and ^{15}N, ^{31}P spectra—on Bruker MSL-300 and Bruker WP-80 spectrometers on frequencies 400.0, 100.5, 30.4 and 32.4 MHz respectively. The spectra of 2D-spectroscopy H,H-COSY and H,C-HETCOR were registered on a Varian XL-400 spectrometer according to the standard programs. Internal TMS standard for ^1H and ^{13}C NMR spectra and external NH_3 and 85% H_3PO_4 standards for ^{15}N and ^{31}P NMR spectra were used, respectively.

The kinetic studies of methanolysis of amides 2 *and* 8. The composition of reaction mixtures was controlled by ^{31}P NMR on a Bruker WP-80. The conditions of the spectrum registration: spectral width—12 kHz, pulse width—3 ms, number of scans—64, relaxation delay—1s. The accuracy of thermostabilizing— ± 0.5°C.

2-Pyridineaminodiisopropylphosphine 1. Diisopropylchlorophosphine (7.63 g, 50.0 mmol) was added dropwise with stirring to the solution of 2-aminopyridine (4.71 g, 50.0 ml) and triethylamine (5.36 g, 53.0 mmol) in benzene (20 mmol) at 20°C. The suspension was stirred at 20°C for 4 hrs. The precipitate was filtered off and the solvent was evaporated under reduced pressure. The residue was distilled in vacuum to give 2-pyridineaminodiisopropylphosphine (8.94 g, 85.0% yield), b.p. 99–100°C at 1 mm Hg, m.p. 43–45°C. Found, %: C 62.75, H 9.02, P 14.90. Calcd. for $C_{11}H_{19}N_2P$, %: C 62.82, H 9.13, P 14.73. ^{31}P NMR (C_6H_6): δ = 48.

2-(2-Pyridineamino)-5,5-dimethyl-1,3,2-dioxaphosphorinane 2.
(*a*) By analogy with aminophosphine 1, from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (7.13 g, 42.0 mmol), 2-aminopyridine (4.00 g, 42.0 mmol) and triethylamine (5.06 g, 50.0 mmol) in benzene (30 ml) 2-(2-pyridineamino-5,5-dimethyl-1,3,2-dioxaphosphorinane (7.13 g, 75.0% yield) was obtained, b.p. 111–112°C at 1 mm Hg, m.p. 84–85°C. Found, %: C 53.52, H 6.90, P 13.25. Calcd. for $C_{10}H_{15}N_2O_2P$, %: C 53.08, H 6.70, P 13.69. ^{31}P NMR (C_6H_6): δ = 114.
(*b*) By analogy with aminophosphine 1, from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (7.13 g, 42.0 mmol) and 2-aminopyridine (8.0 g, 84.0 mmol) in benzene (30 ml) and amide 2 (6.65 g, 70.0% yield) was obtained, b.p. 110–111°C at 1 mm Hg, m.p. 84–85°C. ^{31}P NMR (C_6H_6): δ = 114.
(*c*) The mixture of 2-diethylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane (2.06 g, 10.0 mmol) and 2-aminopyridine (0.94 g, 10.0 mmol) was heated and stirred for 6 hrs at 110–115°C under distilling off diethylamine. The residue was distilled in vacuum to obtain amide 2 (1.70 g, 75.0% yield), b.p. 112–113°C at 1 mm Hg, m.p. 84–85°C. ^{31}P NMR (C_6H_6): δ = 114.
(*d*) The solution of 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (4.16 g, 24.5 mmol) and 2-(trimethylsilylamino) pyridine (4.08 g, 24.5 mmol) in benzene (20 ml) was kept for 4 hrs at 20°C. Trimethylchlorosilane was distilled off under reduced pressure, the residue was distilled in vacuum to obtain amide 2 (3.88 g, 70.0% yield), b.p. 111–112°C at 1 mm Hg, m.p. 84–85°C. ^{31}P NMR (C_6H_6): δ = 114.

2-(2-Pyridineamino)-3,4-benzo-1,3,2-dioxaphospholane 3. 2-Chloro-4,5-benzo-1,3,2-dioxaphospholane (8.71 g, 50.0 mmol) was added dropwise to the solution of 2-aminopyridine (4.70 g, 50.0 mmol) and triethylamine (5.36 g, 50.0 mmol) with stirring in benzene (20 ml) at 20°C. The suspension was stirred at 20°C for 2 hrs. The residue was distilled off and the solvent was removed under reduced pressure. The residue was recrystallized from benzene-light petroleum mixture (1:2) to obtain 2-(2-pyridineamino)-3,4-benzo-1,3,2-dioxaphospholane (6.97 g, 60.0% yield), m.p. 70–71°C. Found, %: C 57.15, H 3.67, P 13.46. Calcd. for $C_{11}H_9N_2O_2P$, %: C 56.89, H 3.91, P 13.34. ^{31}P NMR (C_6H_6): δ = 137.

2-Bis-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)aminopyridine 4. 2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (1.12 g, 6.6 mmol) was added dropwise to the solution of 2-(2-pyridineamino)-5,5-dimethyl-1,3,2-dioxaphosphorinane 2 (1.50 g, 6.6 mmol) and triethylamine (0.73 g, 7.2 mmol) with stirring in benzene (7 ml) at 20°C. The suspension was stirred at 20°C for 6 hrs. The residue was filtered off and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane to obtain 2-[bis-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)] aminopyridine (1.58 g, 67.0% yield): m.p. 102–103°C. Found, %: C 60.05, H 6.92, P 17.08. Calcd. for $C_{15}H_{24}N_2O_4P_2$, %: C 50.27, H 6.77, P 17.29. ^{31}P NMR (C_6H_6): δ = 126.

2-Pyridineaminodiisopropylethylquasiphosphonium tetrafluoroborate 5. Triethyloxonium tetrafluoroborate (0.76 g, 4.8 mmol) was added to the solution of 2-pyridineaminodiisopropylphosphine 1 (1.0 g, 4.8 mmol) with stirring in benzene (6 ml) at 20°C. The suspension was stirred at 20°C for 2 hrs. The low layer was separated and washed with diethyl ether (3 times in 1 ml). The residue was dried in vacuum (1 mm Hg) at 50°C for 2 hrs to obtain 2-pyridineaminodiisopropylethylquasiphosphonium tetrafluoroborate (1.32 g, 85.0% yield), viscous pale yellow substance. Found, %: C 47.98, H 7.71, P 9.32. Calcd. for $C_{13}H_{24}BF_4N_2P$, %: C 47.86, H 7.43, P 9.50. ^{31}P NMR ($CHCl_3$): δ = 66.

2-Pyridiniumaminodiisopropylphosphine chloride 6. Diisopropylchlorophosphine (3.05 g, 20 mmol) was added with stirring the solution of 2-aminopyridine (1.88 g, 20.0 mmol) in chloroform (8 ml) at 20°C. Chloroform was evaporated in vacuum, the residue was washed with benzene (3 times in 3 ml) and dried in vacuum (1 mm Hg) at 40°C for 2 hrs to obtain 2-pyridiniumaminodiisopropylphosphine chloride (4.44 g, 90.0% yield), hygroscopic crystals, m.p. 48–52°C. Found, %: C 53.25, H 8.32,

P 12.67. Calcd. for $C_{11}H_{20}ClN_2P$, %: C 53.55, H 8.17, P 12.55. ^{31}P NMR ($CHCl_3$): δ = 56, $^2J_{PNH}$ 29.1 Hz.

2-Pyridineethylaminodiisopropylphosphine 7. The solution of diisopropylchlorophosphine (3.05 g, 20.0 mmol), 2-(N-ethylamino) pyridine (2.44 g, 20.0 mmol), triethylamine (2.43 g, 24.0 mmol) in benzene (45 ml) was refluxed for 30 hrs. The residue was filtered off, the solvent was evaporated under reduced pressure and the residue was distilled in vacuum to receive 2-pyridineethylaminodiisopropylphosphine (1.91 g, 40.0% yield), b.p. 85–88°C at 1 mm Hg. Found, %: C 65.71, H 9.81, P 12.82. Calcd. for $C_{13}H_{23}N_2P$, %: C 65.50, H 9.75, P 13.00. ^{31}P NMR (C_6H_6): δ = 82.

2-(2-Pyridineethylamino)-5,5-dimethyl-1,3,2-dioxaphosphorinane 8. By analogy with aminophosphine 1, from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (5.43 g, 32.0 mmol), 2-(N-ethylamino) pyridine (3.95 g, 32.0 mmol) and triethylamine (3.85 g, 38.0 mmol) in benzene (50 ml) 2-(2-pyridineethylamino)-5,5-dimethyl-1,3,2-dioxaphosphorinane (6.43 g, 79.0% yield) was obtained, b.p. 113–115°C at 1 mm Hg. Found, %: C 56.91, H 7.83, P 12.00. Calcd. for $C_{12}H_{19}N_2O_2P$, %: C 56.67, H 7.55, P 12.18. ^{31}P NMR (C_6H_6): δ = 136.

1,2-Dihydropyridine-1-ethyl-2-iminodiisopropylphosphine 9. By analogy with aminophosphine 1, from diisopropylchlorophosphine (3.94 g, 25.8 mmol), 1-ethyl-2-imino-1,2-dihydropyridine (3.15 g, 25.8 mmol) and triethylamine (2.73 g, 27.0 mmol) in benzene (25 ml) 1,2-dihydropyridine-1-ethyl-2-iminodiisopropylphosphine (4.61 g, 75.0% yield) was obtained, b.p. 101–102°C at 1 mm Hg. Found, %: C 65.25, H 9.53, P 13.50. Calcd. for $C_{13}H_{23}N_2P$, %: C 65.50, H 9.75, P 13.00. ^{31}P NMR (C_6H_6): δ = 58.

2-(1,2-Dihydropyridine-1-ethyl-2-imino)-5,5-dimethyl-1,3,2-dioxaphosphorinane 10. By analogy with aminophosphine 1, from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (7.30 g, 43.0 mmol), 1-ethyl-2-imino-1,2-dihydropyridine (5.25 g, 43.0 mmol) and triethylamine (5.06 g, 50.0 mmol) in benzene (60 ml) 2-(1,2-dihydropyridine-1-ethyl-2-imino)-5,5-dimethyl-1,3,2-dioxaphosphorinane (7.98 g, 73.0% yield) was obtained, b.p. 135–136°C at 1 mm Hg, m.p. 63–64°C. Found, %: C 56.87, H 7.93, P 11.72. Calcd. for $C_{12}H_{19}N_2O_2P$, %: C 56.67, H 7.55, P 12.18. ^{31}P NMR (C_6H_6): δ = 121.

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