Chemistry of Heterocyclic Compounds, Vol. 40, No. 1, 2004

SYNTHESIS AND STUDY OF THE PROPERTIES OF 7,8-POLYMETHYLENEIMIDAZO[4,5-*d*]-1,3,2-DIAZAPHOSPHORIN-2-THIONES

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In thionation of cyclic N-cyanoamidines, a four-step process occurs that leads to derivatives of novel heterocyclic systems: 7,8-polymethyleneimidazo[4,5-d]-1,3,2-diazaphosphorin-2-thiones. We have studied the chemical and spectral properties of the compounds obtained.

Keywords: imidazo[4,5-*d*]-1,3,2-diazaphosphorins, phosphorus pentasulfide, N-cyanoamidines, thionation, Thorpe–Ziegler cyclization.

In the course of studying the chemical and biological properties of derivatives of 1-carbamidomethyl-2-pyrrolidone (piracetam) and its analogs [1-3], it has been established that converting the amide groups to thioamide groups leads to a sharp enhancement of the antihypoxic and nootropic activity of the compounds [4, 5]. Continuing this research, we attempted to convert the carbamoyl group of 1-carbamidomethyl-2-cyanoiminopyrrolidine (**1a**), which also exhibits nootropic and anticonvulsive action [6] to thiocarbamoyl group. However, in a study of the reaction product of carbamide **1a** and phosphorus pentasulfide in pyridine, we found that the reaction did not stop at the thionation step but rather proceeded all the way to formation of a tricyclic system containing annelated pyrrole, imidazole, and 1,3,2-diazaphosphorin rings. In fact, in the IR spectrum of the product **2a** obtained (isolated as a pyridine solvate), there was no absorption band from the CN group. In the ^{1}H NMR spectrum of compound **2a** in DMSO-d_6, we observed the following proton signals at δ, ppm (*J*, Hz): 2.50 (2H, m, 7-CH_2); 2.84 (2H, t, 8-CH_2); 4.30 (2H, t, 6-CH_2); 9.30 (1H, br. d, ^2J = 15.3, NH, NH–P), and 9.38 (1H, br. s, NH), and pyridine protons at 7.79 (2H, t, β-H); 8.26 (1H, t, γ-H); 8.79 (2H, d, α-H).* In the mass spectrum of tricycle **2a**, we observe a molecular ion peak (*m*/*z*) $[M]^+$ 276 and ion peaks 243 [M^+ - SH], 184 [M^+ - SH, - $CSNH_2$], 148 [M^+ - SH, - PS_2], 123 [M^+ - CS - NH - PS_2], 95 [PS_2^+]. An SH proton signal is not clearly seen in the ^{1}H NMR spectrum, which is consistent with the data in [8] concerning a study of the spectra for such compounds.

Based on all the results obtained, the isolated compound was assigned the structure of 7,8-trimethyleneimidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-thione (**2a**). Similarly, 1-carbamidomethyl-2-cyano-iminopiperidine (**1b**) and 1-carbamidomethyl-2-cyanoiminohexahydroazepine (**1c**), when reacted with P_2S_5 in pyridine, are converted to 7,8-tetra- and 7,8-pentamethyleneimidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-thiones **2b,c**. The proposed scheme for these irreversible conversions is shown below:

* The tendency of 1,3,2-diazaphosphorin derivatives to form pyridine solvates of variable composition has been described in [7-12].

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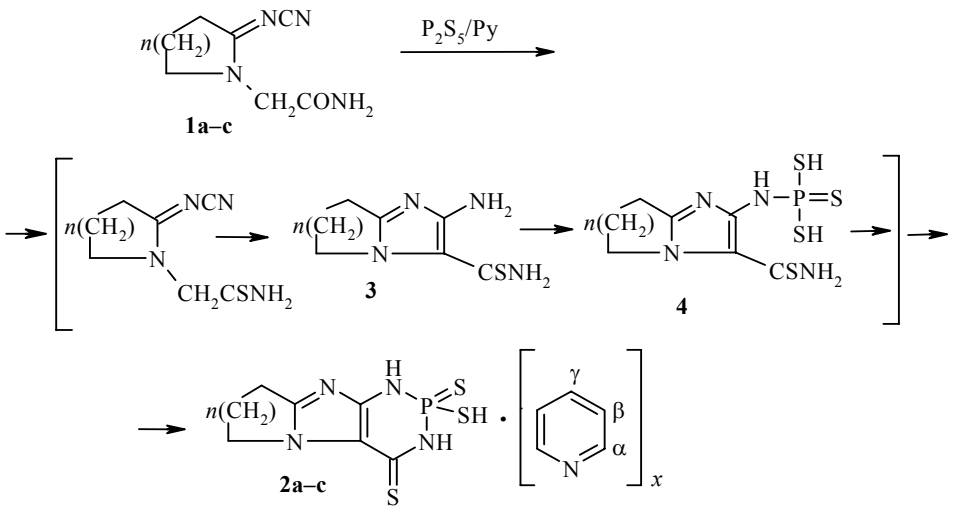
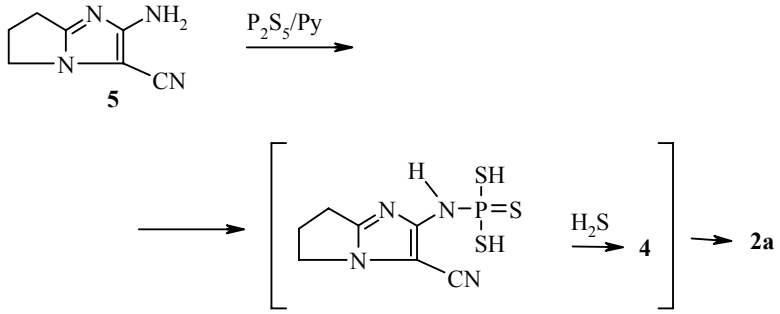


1a, **2a** n = 1; **1b**, **2b** n = 2; **1c**, **2c** n = 3

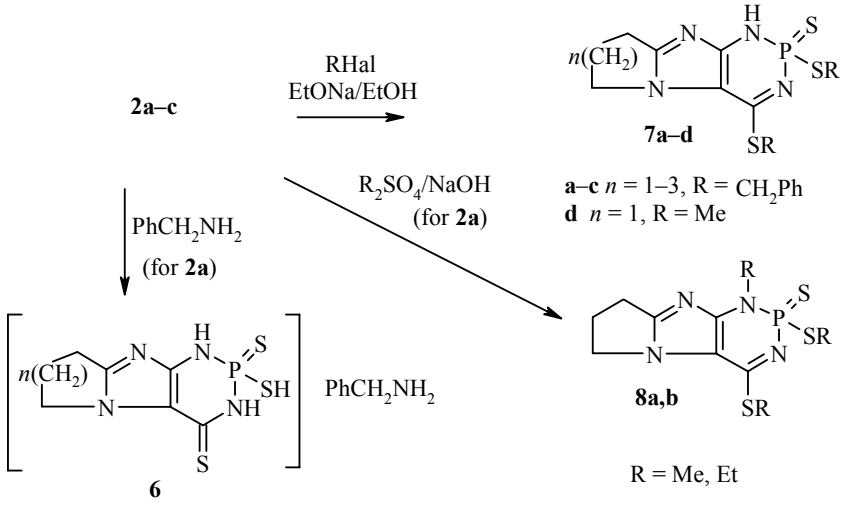
In the first step, conversion of amide to thioamide occurs (as is usual under these conditions), where significant activation of the methylene unit occurs [14], making possible a Thorpe–Ziegler cyclization [15] with participation of this unit and the N-cyano group. 1,2-Polymethylene-4-amino-5-carbamidoimidazoles **3** formed in this case are acylated by the phosphorus pentasulfide at the primary 4-amino group, followed by cyclization of the derivative **4** obtained to tricyclic diazaphosphorins **2**.

We carried out an analogous cyclization within this work based on 1,2-trimethylene-4-amino-5-cyanoimidazole (**5**) [16, 17]. In this case, as the reaction product we isolated the tricycle **2a** (the reaction probably occurs *via* intermediate **4**).

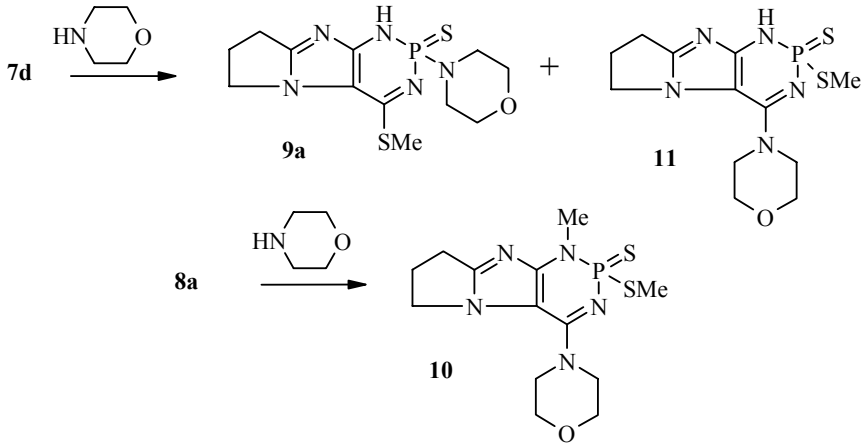


We must reiterate that in this work, as in the papers cited above [7-12], depending on the conditions under which the reaction products are isolated and the conditions under which the solvent is removed, the pyridine content (%) in the solvates fluctuates in rather broad limits (from 6 to 50 mole %, according to ^{1}H NMR spectral data). Nevertheless, a stable compound was obtained upon heating pyridine solvate **2a** with benzylamine. The high basicity of the latter makes it possible to synthesize a stable compound **6**, for which we obtained not only clear spectral data but also satisfactory elemental analysis results (see Experimental).

The presence of thiol and thiocarbamoyl moieties in compounds **2a-c** makes possible alkylation of their anions by both alkyl halides and dialkyl sulfates. In this case, using alkyl halides we can obtain dialkyl derivatives **7a-d.** When compound **2a** reacts with dimethyl and diethyl sulfates, the alkylation occurs not only at the sulfur atoms but also at the NH group in the position 1, and as a result tris-alkyl derivatives **8a,b** are formed:



The next step in this work was to study the reactions of compounds **7** and **8** with nucleophilic reagents, as which we selected various amino derivatives. When compounds **7d** and **8a** reacted with amines, we observed an interesting fact: while diallyl derivative **7d** yields 2-morpholide **9a** as the major product when reacted with morpholine (the other bis-alkyl substituted derivative **7a** reacts analogously, to form the derivative **9b)**, the reaction of tris-alkyl derivative **8a** with morpholine leads to substitution at the position 4 and formation of compound **10**. To refine these results using ^{1}H NMR spectroscopy, we studied the reaction mixtures (after driving off the excess morpholine) obtained as a result of the indicated reactions. We found that after reaction of compounds **7d** and morpholine, the mixture contained morpholide **9a**, the starting compound **7d**, and 4-morpholino derivative **11** (~6:2:1). Only 4-morpholino derivative **10** and starting **8a** (24:1) were present in the reaction mass obtained when compound **8a** was heated with morpholine.



The compounds **9a,b** and **10** were isolated in pure form. A series of reactions carried out with other amines, including aromatic amines (the mixtures thus obtained were analyzed using ^{1}H NMR spectra) shows that for reaction of 1-unsubstituted 2,4-dialkylthiodiazophosphorins **7a,d** with amines, formation of 2-phosphamides is typical (upon reaction with amines under harsher conditions (180-190°C), a mixture of 2,4-diamino derivatives is formed), while for the 1-substituted compounds **8** the process of substitution at the position 4 predominates (this tendency has already been noted in the literature [18]). From our standpoint, such a direction for the change in the course of the reaction with amines is due to the fact that the presence of the

substituent in the position 1 of the diazaphosphorin ring leads to steric hindrances in the transition state upon attack at the phosphorus atom in the position 2, which in this case promotes the substitution process occurring exclusively at the position 4.

The structure of all the synthesized compounds was studied in detail using ^{1}H and ^{13}C NMR spectra (most of them are given in Experimental). Here we compare the ^{13}C NMR spectra (in DMSO-d_6) of compound **2a** [δ, ppm (*J*, Hz): 24.1 ($C_{(7)}$); 24.6 ($C_{(8)}$); 49.8 ($C_{(6)}$); 113.2 ($C_{(4a)}$, ^{3}J = 7.6, $C_{(4a)}$–P); 141.8 ($C_{(9a)}$); 177.1 ($C_{(4)}$, d, ^{2}J = 11.4, C–P)] and compound **7a** [δ, ppm (*J*, Hz): 23.8 ($C_{(7)}$); 25.0 ($C_{(8)}$); 32.2 (4-C–S–$\underline{CH_2}$, ^{4}J = 1.8, C–P); 37.7 (P–S–$\underline{CH_2}$, ^{2}J = 4.4, C–P); 46.9 ($C_{(6)}$); 108.9 ($C_{(4a)}$, ^{4}J = 33.0, C–P); 155.4 ($C_{(9a)}$); 159.4 ($C_{(8a)}$); 160.9 ($C_{(4)}$, ^{4}J = 17.0, C–P)].* Comparison of the chemical shifts for the $C_{(4)}$ atom of both compounds allows us to say that tricycle **2a** exists in the thione tautomeric form. For compounds **2a, 7a, 9b**, and **12** (isolated from reaction of compound **7a** and benzylamine at 180-190°C, see Experimental), we also obtained data from ^{31}P NMR spectra (DMSO-d_6, external standard 85% H_3PO_4). In diazaphosphorin **2a**, the ^{31}P signal is observed at 75 ppm; in 2-S- and 4-S-dibenzyl derivative **7a**, the ^{31}P signal is shifted upfield to 63.3 ppm, while for compound **11** we observe further shift of the signal to 55.8 ppm. These results also are evidence in favor of thione structure for compound **2a**.

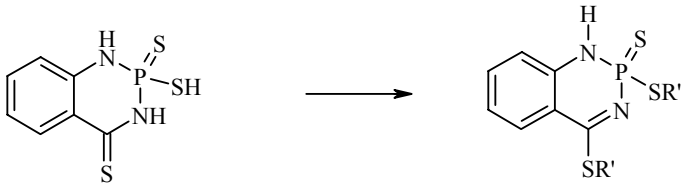
In conclusion, we need to focus on some features of the ^{1}H NMR spectra of the synthesized compounds.

1. The signals from protons of the 2-S–CH_2Ph group in compounds **8a-c** are nonequivalent, which is due to their spatial proximity to the asymmetric phosphorus atom: $\Delta\delta = \delta_{SCHaPh} - \delta_{SCHbPh}$ = 0.07-0.08 ppm. These protons are represented by two triplets of equal intensity at 3.74-3.79 ppm and 3.83-3.88 ppm ($^{2}J_{HaHb} = {}^{3}J_{CHa\text{-}P} \sim$ 14 Hz).

2. The protons of the 4-thiobenzyl moiety in compounds **7a-c** are spatially distant from the P atom (no spin–spin coupling with the phosphorus atom appears) and form two doublets of equal intensity in the 4.26-4.35 ppm region with $^{2}J_{HaHb} \sim$ 13.5 Hz.

3. The most unexpected feature was the appearance of nonequivalence of the cyclic methylene protons in the position 6, which formally are quite distant from the phosphorus atom. This nonequivalence is even observed for the seven-membered compound **7c** and is ~0.1 ppm. For compounds **9b** and **8**, the nonequivalence of the 6-H protons is 0.04 ppm and 0.10 ppm respectively (two symmetric 1H multiplets each). For these compounds, the nonequivalence of the 4-S–CH_2Ph protons is Δδ = 0.06 ppm and 0.18 ppm respectively, while for the diamino derivative **12** that was isolated in pure form we have $\Delta\delta_{6\text{-}CHa,CHb}$ = 0.20 ppm (two symmetric ^{1}H multiplets each that are far apart from each other). For this compound, we also observe nonequivalence for the methylene protons of the 4-S–CH_2Ph moiety ($\Delta\delta_{CH_2}$ = 0.11 ppm).

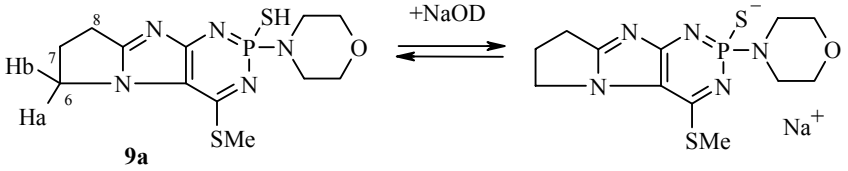
The observed nonequivalence of the 4-S–CH_2Ph and 6-CH_2 protons undoubtedly is connected with the spatial structure of the studied systems. It has been shown [8] that when benzo-1,3,2-diazaphosphorin-4-thiones are converted to S,S-dialkyl derivatives, the heterocycle becomes markedly flatter.



In the case of the studied compounds, the transition of the heterocycle to a more planar structure also should lead to the substituent at the 4 position coming appreciably closer to the 6-CH_2 group. In order to assess to what extent such flattening may affect the appearance of nonequivalence of the protons of this methylene

* The signals from the carbon atoms of the two phenyl rings were: 127.4, 127.6, 128.7 (2C), 128.8 (4C), 129.5 (2C), 137.4, 137.7 ppm.

group, we studied the spectra of compound **9a** in DMSO in the presence of NaOD. This transition of the heterocyclic system to a flatter state, connected with formation of the anion, led to appreciable divergence of the signals for the 6-CHa and 6-CHb protons, and $\Delta\delta_{6\text{-}CHa,CHb}$ (before addition of the base, ~0.02 ppm) increased up to 0.1 ppm.



9a

Thus we can conclude that namely specifically spatial and conformational effects are responsible for the appreciable nonequivalence of the 4-S–CH_2R and 6-CH_2 protons observed in the ^{1}H NMR spectra of the studied compounds.

EXPERIMENTAL

The NMR spectra were recorded on XL-200 and Unity 400+ (Varian) spectrometers (400 MHz for ^{13}C, 163 MHz for ^{31}P), internal standard TMS. The mass spectra were recorded on a MAT-112 (Varian) and an SSQ-710 (Finnigan) spectrometer with electron impact ionization energy 70 eV. The IR spectra were recorded on a Perkin-Elmer 599 spectrometer. The melting points were determined on a Boetius heating stage. Thin layer chromatography was run on Silufol UV-254 plates, methanol as the eluent, visualization in iodine vapors.

1-Carbamidomethyl-2-cyanoiminopiperidine (1b). A stream of dry ammonia was passed through suspension of 2-cyanoimino-1-ethoxycarbonylmethylpiperidine (2.1 g, 10 mmol) in methanol (30 ml) for 2 h at room temperature. Then the reaction mass was cooled down to 0-5°C and the precipitate was filtered off. Yield 1.3 g (72%); mp 222-224°C (EtOH–water, 5:1). Found, %: C 53.31; H 6.69: N 31.27. $C_{18}H_{12}N_4O$. Calculated, %: C 53.31; H 6.71; N 31.09.

Compound **1c** was obtained similarly. Yield 79%; mp 215-217°C (EtOH–water, 5:1). Found, %: C 55.79; H 7.48; N 28.66. $C_9H_{14}N_4O$. Calculated, %: C 55.65; H 7.27; N 28.85.

7,8-Trimethylene-1H-imidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-mercapto-2,4-dithione, Pyridine Solvate (2a). A. Dry pyridine (30 ml) was added slowly and carefully with stirring to carefully ground and stirred mixture of 1-carbamidomethyl-2-cyanoiminopyrrolidine **1a** (10 g, 60 mmol) and phosphorus pentasulfide (20 g, 90 mmol). The mixture was heated and changed to an oil. After addition of pyridine, the mixture was boiled for 5 min and then washed with boiling benzene (2 × 100 ml); water (200 ml) was added and this was boiled for 2 min and then cooled down. The precipitate was filtered off and carefully washed with water and ethanol. Yield 12.4 g (63%)*; mp > 300°C (DMF–water, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.50 (2H, m, 7-CH_2); 2.84 (2H, t, 8-CH_2); 4.30 (2H, t, 6-CH_2); 9.30 (1H, br. d, ^2J = 15.3, NH-P), and 9.38 (1H, br. s, NH); pyridine: 7.85 (2H, m, β-H); 8.26 (1H, t, γ-H), 8.79 (2H, d, α-H); SH does not appear; ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 24.1 ($C_{(7)}$); 24.6 ($C_{(8)}$); 49.8 ($C_{(6)}$); 113.2 ($C_{(4a)}$), d, ^3J = 7.6, $C_{(4a)}$–P); 141.8 ($C_{(9a)}$); 153.1 ($C_{(8a)}$); 177.1 ($C_{(4)}$, d, ^2J = 11.4, $C_{(4)}$–P). Mass spectrum: $[M]^{+\cdot}$ 276, 243 [M^+ - SH], 184 [M^+ - SH, - $CSNH_2$], 148 [M^+ - SH, –PS_2], 123 [M^+ - CS–NH–PS_2], 95 (PS_2^+).

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* Here and in other cases, to calculate the product yields we assumed that the average pyridine content in the solvates was 2/3 mol/liter of pyridine per 1 mol/liter of diazaphosphorin.

B. Dry pyridine (3 ml) was added slowly with stirring to mixture of 1,2-trimethylene-4-amino-5-cyanoimidazole **5** (1.48 g, 10 mmol) and phosphorus pentasulfide (3.33 g, 15 mmol), then the procedure was continued as in Method A. Yield 1.02 g (31%).

Homologs of Compound 2a were obtained similarly.

Compound 2b. Yield 45%; mp > 300°C (DMF–water, 3:1), $[M]^{+\cdot}$ 374.

Compound 2c. Yield 54%; mp > 300°C (DMF–water, 3:1), $[M]^{+\cdot}$ 388.

7,8-Trimethylene-2,4-dibenzylthio-1H-imidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-thione (7a). Pyridine solvate **2a** (1.65 g, 5 mmol) was dissolved in sodium ethoxide solution prepared from Na (0.28 g, 12 mmol) and ethanol (20 ml). Then benzyl chloride (1.5 ml, 12 mmol) was added; this was boiled for 5 min and then poured into cold water (40 ml). The mixture obtained was acidified with HCl down to pH 2-3, the precipitate was filtered off and then washed with water and ethanol. Yield 1.73 g (76%); mp 187-189°C (DMF–water, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (2H, m, 7-CH_2); 2.78 (2H, t, 8-CH_2); 4.07 (2H, t, 6-CH_2); 3.77 (1H, t, $^2J_{CHaCHb}$ = 14.0, $^3J_{CHa\text{-}P}$ = 14.0, 2-CHaPh), and 3.85 (1H, t, $^3J_{CHb\text{-}P}$ = 14.0, 2-CHbPh); 4-CH_2 protons: 4.30 (1H, d, $^2J_{CHaCHb}$ = 13.5, CHa) and 4.31 (1H, d, CHb); 10.26 (1H, d, $^2J_{1NH\text{-}P}$ = 8.5, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz); 23.8 ($C_{(7)}$); 25.0 ($C_{(8)}$); 32.2 ($C_{(4)}$–S–CH_2, $^4J_{avg}$ = 1.8); 37.7 (P–S–CH_2, $^2J_{avg}$ = 4.6); 46.9 ($C_{(6)}$); 108.9 ($C_{(4a)}$, $^4J_{avg}$ = 33.0); 155.4 ($C_{(9a)}$); 159.4 ($C_{(8a)}$); 160.9 ($C_{(4)}$, $^4J_{avg}$ = 16.7), signals from the two phenyl rings are observed at 127.4 (1C), 127.6 (1C), 128.7 (2C), 128.8 (4C), 129.5 (2C), 137.4 (1C, $^3J_{avg}$ = 5.1), 137.7 (1C), mass spectrum: $[M]^+$ 456, fragmentation: 333 [M^+ - SCH_2Ph], 301 [M^+ - SCH_2Ph, - S], 211 [M^+ - SCH_2Ph - SCH_2Ph], 124 [$HSCH_2Ph^+$], 91 [CH_2Ph^+]. Found, %: C 55.00; H 4.65; N 12.25. $C_{21}H_{21}N_4PS_3$. Calculated, %: C 55.25; H 4.64; N 12.27.

Compound 7b was obtained similarly. Yield 62%; mp 214-218°C (DMF–water). $[M]^{+\cdot}$ 470. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.77, 1.90 (4H, m, 7-CH_2, 8-CH_2); 2.71 (2H, t, 9-CH_2); 4.07 (2H, t, 6-CH_2); 3.74, 3.83 (2H, t, $^2J_{CHaCHb}$ = 14.1, $^3J_{CHa\text{-}P}$ = 14.1, $^3J_{CHb\text{-}P}$ = 14.1, P–CHaHb); 4.26, 4.35 (2H, d, $^2J_{CHaCHb}$ = 13.6, 4-C–S–CHaHb); 7.15-7.45 (10H, m, 2Ph); 10.16 (1H, d, $^2J_{NH\text{-}P}$ = 8.8, 1-NH). Found, %: C 55.73; H 5.07; N 11.95; S 19.98. $C_{22}H_{23}N_4PS_3$. Calculated, %: C 56.15; H 4.93; N 11.91; S 20.44.

Compound 7c was obtained similarly. Yield 38%; mp 182-186°C (DMF–water, 3:1), $[M]^{+\cdot}$ 484. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.45-1.85 (6H, m, 7-, 8-, 9-CH_2); 2.82 (2H, m, 10-CH_2); 4.22, 4.32 (2H, m, 6-CH_2); 3.79 (1H, t, $^2J_{CHaCHb}$ = 14.0, $^3J_{CHa\text{-}P}$ = 14.0, P–SCHa); 3.88 (1H, br. t, $^3J_{CHb\text{-}P}$ = 14.4, P–SCHb); 4.27, 4.35 (2H, d, $^2J_{H\text{-}H}$ = 13.6, 4-C–S–$\underline{CH_2}$–Ph); 7.15-7.50 (10H, m, 2Ph); 10.20 (1H, d, $^2J_{1\text{-}NH\text{-}P}$ = 9.1, 1-NH). Found, %: C 56.72; H 5.14; N 11.50; S 19.68. $C_{23}H_{25}N_4PS_3$. Calculated, %: C 57.00; H 5.20; N 11.56; S 19.85.

Compound 7d was obtained similarly. Yield 47%; mp 249-251°C (DMF), $[M]^{+\cdot}$ 304. ^{1}H NMR spectrum (DMSO-d_6, 90°C), δ, ppm (*J*, Hz): 2.11 (3H, d, $^3J_{Me\text{-}P}$ = 15.7, P–S–Me); 2.51 (3H, s, 4-C–SMe); 2.54 (2H, m, 7-CH_2); 2.80 (2H, t, 8-CH_2); 4.14 (2H, t, 6-CH_2); ~10 (1H, br. s, 1-NH). Found, %: C 35.65; H 4.38; N 18.47; S 31.35. $C_9H_{13}N_4PS_3$. Calculated, %: C 35.52; H 4.31; N 18.41; S 31.61.

1-Methyl-7,8-trimethylene-2,4-dimethylthio-1H-imidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-thione (8a). Pyridine solvate **2a** (3.29 g, 10 mmol) was dissolved in aqueous (1 mol/l) solution of NaOH (80 ml). The solution obtained was washed twice with benzene and cooled down to 0-5°C, and then dimethyl sulfate (5 ml) was added. The reaction mixture was stirred for 30 min, the precipitate was filtered off and washed with water and ethanol. Yield 1.96 g (62%); mp 144-147°C (DMF–water, 3:1). $[M]^{+\cdot}$ 318, fragments 271 [M^+ - SCH_3], 255 [M^+ - PS], 239 [M^+ - SCH_3 - SCH_3], 198 [M^+ - N=C–CH_3 - CH_3], 79 (P–SCH_3^+), 63 (PS^+). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.99 (3H, d, $^3J_{Me\text{-}P}$ = 15.7, P–SCH_3); 2.52 (2H, m, 7-CH_2); 2.52 (3H, s, 4-C–SCH_3); 2.83 (2H, t, 8-CH_2); 3.22 (3H, d, $^3J_{Me\text{-}P}$ = 10.1, 1-N–CH_3), 4.16 (2H, m, 6-CH_2). Found, %: C 37.65; H 4.94; N 17.46; S 30.12. $C_{10}H_{15}N_4PS_3$. Calculated, %: C 37.72; H 4.75; N 17.60; S 30.21.

Compound 8b was obtained similarly. Yield 54%; mp 131-134°C (DMF–water, 3:1). Found, %: C 43.13; H 6.24; N 15.54; S 26.77. $C_{13}H_{21}N_4PS_3$. Calculated, %: C 43.32; H 5.87; N 15.54; S 26.69.

Reaction of 7,8-Trimethylene-1H-imidazo[4,5-*d*]-1,3,2-diazaphosphorin-2-thiones with Amines. General Method. Mixture of diazaphosphorin **2a, 8a,** or **7d** (10 mmol) and 5-fold excess of the corresponding amine was boiled for 10-30 min. 2-Propanol (50 ml) was added, the mixture was boiled for 1 min and cooled down. The precipitate was filtered off and washed with 2-propanol and hexane.

Compound 6. Yield 37%; mp 236-239°C (decomp., DMF–water, 3:1), $[M]^{+\cdot}$ 276. ^{1}H NMR spectrum (DMS-d_6), δ, ppm (*J*, Hz): 2.43 (2H, m, 7-CH_2); 2.70 (2H, t, 8-CH_2); 4.19 (2H, t, 6-CH_2); 8.66 (2H, br. d, $^2J_{NH-P}$ = 16.4, NH); 8.92 (1H, br. d, $^2J_{NH-P}$ = 13.6, NH); 4.05 (2H, s, $\underline{CH_2}$Ph); 7.43 (5H, m, Ph); 8.13 (2H, br. s, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 23.9 ($C_{(7)}$); 24.9 ($C_{(8)}$); 47.1 ($C_{(6)}$); 115.5 ($C_{(4a)}$, $^3J_{C4a-P}$ = 6.8); 151.2 ($C_{(9a)}$); 158.8 ($C_{(8a)}$); 175.8 ($C_{(4)}$, $^2J_{C4-P}$ = 12.5); 42.7 ($\underline{CH_2}$Ph); 128.8, 129.0, 129.2, 134.3 (Ph). Found, %: C 43.85; H 4.80; N 18.17; S 25.50. $C_{14}H_{18}N_5PS_3$. Calculated, %: C 43.85; H 4.73; N 18.27; S 25.09.

Compound 9a. Yield 74%; mp 243-246°C (DMF), $[M]^{+\cdot}$ 343. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.44 (3H, s, 4-C–SCH_3); 2.50 (2H, m, 7-CH_2); 2.76 (2H, t, 8-CH_2); 3.10 (4H, m, $^3J_{CH2-P}$ = 8.3, α,α'-N–CH_2); 3.52 (4H, t, β,β'-OCH_2); 4.10 (2H, m, 6-CH_2); 9.36 (1H, d, $^3J_{NH-P}$ = 6.8, NH). Found, %: C 41.98; H 5.36; N 20.40; S 18.64. $C_{12}H_{18}N_5OPS_2$. Calculated, %: C 41.97; H 5.28; N 20.40; S 18.68.

Compound 9b. Yield 36%; mp 240-242°C (DMF–water, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (2H, m, 7-CH_2); 2.75 (2H, t, 8-CH_2); 4.07 (2H, m, 6-CH_2); 3.08 (4H, m, $^3J_{CH2-P}$ = 8.5, α,α'-NCH_2); 3.51 (4H, m, β,β'-OCH_2); 4.32 and 4.42 (2H, d, $^2J_{CHaCHb}$ = 13.6, S–CH_2); 9.45 (1H, d, $^2J_{1-NH-P}$ = 6.8, NH); 7.15-7.45 (5H, m, Ph). Found, %: C 51.23; H 5.32; N 16.69; S 15.52. $C_{18}H_{22}N_5OPS_2$. Calculated, %: C 51.54; H 5.29; N 16.70; S 15.29.

Compound 10. Yield 46%; mp 194-197°C (DMF–water, 2:1), $[M]^{+\cdot}$ 357. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.98 (3H, d, $^2J_{Me-P}$ = 14.9, P–S–Me); 2.47 (2H, m, 7-CH_2); 2.83 (2H, t, 8-CH_2); 3.15 (3H, d, $^3J_{Me-P}$ = 10.7, 1-N–Me); 3.53 (4H, t, α,α'-N–CH_2); 3.65 (4H, t, β,β'-OCH_2); 4.09 (2H, m, 6-CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 23.7 ($C_{(7)}$); 25.1 ($C_{(8)}$); 31.7 (S–CH_2); 45.4 (2C, $^2J_{NCH2-P}$ ~ 1, N–CH_2); 46.8 ($C_{(6)}$); 66.7 (2C, $^3J_{OCH2-P}$ = 6.4, OCH_2); 108.3 ($C_{(4a)}$, $^3J_{C4a-P}$ = 23.9); 155.4 ($C_{(9a)}$); 158.4 ($C_{(4)}$, $^3J_{C4-P}$ = 10.9); 158.7 ($C_{(8a)}$); aromatic carbon atoms of the SCH_2Ph moiety give signals at 127.4 (1C), 128.7 (2C), 129.4 (2C), 138.3 (1C). Found, %: C 43.31; H 5.71; N 19.43; S 18.13. $C_{13}H_{20}N_5OPS_2$. Calculated, %: C 43.69; H 5.64; N 19.60; S 17.94.

Compound 12. Yield 69%; mp 225-227°C (DMF–water, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.48 (2H, m, 7-CH_2); 2.71 (2H, t, 8-CH_2), and 4.05 and 4.25 (two symmetric multiplets 1H each, 6-CH_2, $\Sigma^2J_{6\text{-}CHa,6\text{-}CHb} + {}^3J_{6\text{-}CH2,7\text{-}CH2}$ = 24); 8.55 (1H, d, NH, $^2J_{NH-P}$ = 6.0); 3.75 (Ha) and 3.83 (Hb) (two doublets 1H each, P–NH–$\underline{CH_2}$Ph, $^2J_{CHaCHb}$ = 14.3, $^3J_{NH\text{-}CHa} = {}^3J_{CHb\text{-}NH}$ = 7.4); 5.11 (1H, m, J_{NH-P} = 14.2); 4.46 (Ha) and 4.58 (Hb) (two q 1H each, 4-C–NH–CH_2-Ph, $^2J_{HaHb}$ = 15.2, $^3J_{NHCHb}$ = 6.2); 7.12-7.36 (10H, m, 2Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 23.4 ($C_{(7)}$); 25.1 ($C_{(8)}$); 43.1 ($C_{(4)}$–N$\underline{CH_2}$–Ph); 45.5 (P–NH–$\underline{CH_2}$–Ph, ^3J = 2.7); 46.0 ($C_{(6)}$); 100.8 ($C_{(4a)}$, $^3J_{C4b,P}$ = 19.9); 151.1 ($C_{(9a)}$); 155.6 ($C_{(4)}$, $^2J_{C4,P}$ = 4.4); 155.7 ($C_{(8a)}$); 126.5, 126.8, 127.4 ($C_{(4)}$); 128.1 ($C_{(2)}$); 128.4 ($C_{(2)}$); 140.2, 141.3 ($^3J_{avg}$ = 6.2, 2Ph). Found, %: C 59.52; H 5.66; N 19.78; S 7.38. $C_{21}H_{23}N_6PS$. Calculated, %: C 59.70; H 5.49; N 19.89; S 7.32.

REFERENCES

1. T. M. Bargar and C. M. Riley, *Synth. Commun.*, 479 (1980).
2. T. V. Stezhko, V. G. Granik, R. G. Glushkov, L. E. Roshchina, A. I. Polezhaeva, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 290 (1984).
3. T. A. Gudasheva, R. I. Ostrovskaya, F. V. Maksimova, A. V. Chupin, S. S. Trofimov, V. P. Lezina, T. A. Voronina, and A. P. Skoldinov, *Khim.-Farm. Zh.*, 276 (1989).
4. V. G. Granik, T. V. Golovko, R. G. Glushkov, M. D. Mashkovskii, L. E. Roshchina, A. I. Polezhaeva, R. B. Parimbetova, Yu. G. Bobkov, A. S. Losev, and I. A. Ivanova, *Khim.-Farm. Zh.*, 1186 (1989).

5. A. V. Kadushkin, T. V. Golovko, V. G. Granik, R. G. Glushkov, R. B. Parimbetova, V. A. Parshin, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 1193 (1989).
6. D. B. Nilov, A. V. Kadushkin, V. G. Granik, N. P. Solov'eva, V. V. Asnina, R. B. Parimbetova, V. A. Parshin, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, No. 1, 35 (1993).
7. W. Walter, T. Fleck, J. Voss, and M. Gerwin, *Liebigs Ann. Chem.*, 275 (1975).
8. R. M. Acheson, C. T. Lines, M. R. Bryce, Z. Dauter, C. D. Reynolds, and A. Schmidpeter, *J. Chem. Soc., Perkin Trans. 2*, 1913 (1985).
9. K. Nagarajan, S. J. Shenoy, H. Fritz, O. Hosang, and W. J. Richter, *Helv. Chim. Acta*, **68**, 900 (1985).
10. B. R. Shinde, S. J. Shenoy, and N. R. Pai, *Indian J. Chem.*, **29B**, 711 (1990).
11. R. Chen and J. Wang, *Gaodeng Xuexiao Huaxue Xuebao*, 923 (1992); *Chem. Abstr.,* **118**, 102089 (1992).
12. D. B. Nilov, N. P. Solov'eva, I. S. Nikolaeva, V. V. Peters, L. Yu. Krylova, T. A. Gus'kova, and V. G. Granik, *Khim.-Farm. Zh.*, No. 7, 16 (1998).
13. D. B. Nilov, A. V. Kadushkin, N. P. Solov'eva, and V. G. Granik, *Mendeleev Commun.*, 67 (1995).
14. A. S. Fissyuk, M. A. Vorontsova, and D. V. Temnikov, *Tetrahedron Lett.*, **37**, 5203 (1996).
15. V. G. Granik, A. V. Kadushkin, and J. Liebsher, *Adv. Het. Chem.*, **72**, 79 (1998).
16. D. B. Nilov, A. V. Kadushkin, S. G. Kalistratov, A. S. Sokolova, I. S. Nikolaeva, V. V. Peters, L. Yu. Krylova, and V. G. Granik, *Khim.-Farm. Zh.*, No. 9-10, 63 (1992).
17. E. N. Dozorova, A. V. Kadushkin, G. A. Bogdanova, N. P. Solov'eva, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 754 (1991).
18. B. R. Shinde, S. J. Shenoy, and N. R. Pai, *Indian J. Chem.*, **29B**, 721 (1990).