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LETTERS TO THE EDITOR

Synthesis of Imines with *N*-Containing Substituents and Their Reactions with Dialkylphosphorous Acids

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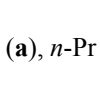
The addition of hydrophosphoryl compounds to the double C=N bond of imines is one of the main methods of synthesis of the phosphorus-containing amino compounds [1]. The latter, possessing such useful properties as biological activity, can be obtained via modifying carbonyl and amine components of the imine. The analysis of publications shows that imines with *N*-containing substituents were not virtually used in these reactions, since they were little known. The aim of this work is the synthesis of new substituted imines and the study of their reactions with dialkylphosphorous acids.

The triazole fragment is a part of the biologically active compounds, which are widely used in medicine, pharmacology, microbiology, agriculture, photography and textile industries [2]. So one of the selected amines was 1,2,4-triazol-4-ylamine **Ia**. In recent years, the alkylamino- and dialkylamino-substituted aldehydes have become readily available [3]. We used 2,2-dimethyl-3-(ethylamino)propanal **IIa** as the carbonyl component. Since 1,2,4-triazol-4-ylamine is readily soluble in organic solvents, it was used as a diluted solution in ethanol. Sulfuric acid was used as a catalyst. The reaction of aldehyde **IIa** with the unsubstituted propan-1-amine **Ib** was carried out in the solvent-free conditions in the presence of solid potassium hydroxide. The structure of compounds **III** was confirmed by the ^{1}H NMR spectra.

$$\underset{\mathbf{I}}{R^1NH_2} + \underset{\mathbf{II}}{R^2CHO} \xrightarrow[KOH]{H_2SO_4,\ \Delta} \underset{\mathbf{III}}{R^1N{=}CHR^2} + H_2O$$

I, R^1 =  (**a**), *n*-Pr (**b**); **II**, $R^2 = CMe_2CH_2NHEt$ (**a**), *i*-Pr (**b**); **III**, R^1 =  , R^2 = *i*-Pr (**a**), CMe_2CH_2NHEt (**b**), R^1 = *n*-Pr, $R^2 = CMe_2CH_2NHEt$ (**c**).

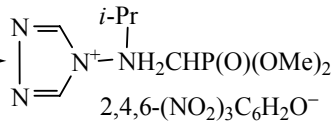
The reaction of imine **IIIa** with dimethylphosphorous acid **IVa** was carried out under the Pudovik reaction conditions. To a mixture of the starting compounds 5–6 drops of a sodium methoxide solution in methanol were added. The reaction mixture slightly warmed. After keeping the reaction mixture at room temperature for 3 days and processing it using common technique compound **Va** was isolated as crystals.

The reactions of imines **III** with dimethyl phosphite **IVa** was carried out without a catalyst by stirring the reactants. The reaction mixture warmed. Obviously, the ethylamino group plays the role of a nucleophilic catalyst. The reaction mixture was kept at room temperature for 5 days. Dimethyl [2,2-dimethyl-1-(*n*-propylamino)-3-(ethylamino)propyl]phosphonate **Vb** was isolated by the vacuum distillation.

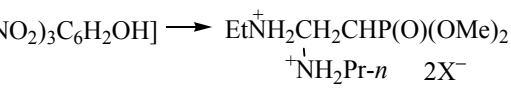
Imine **IIIb** was the least active in the reactions with dialkylphosphorous acids. The reaction was activated by metallic sodium: To a benzene solution of acid **IVb** were added imine **IIIb** and 2–3 very small pieces of sodium

$$R^1N{=}CHR^2 + (R^3O)_2PHO \longrightarrow R^1NHCHR^2P(O)(OR^3)_2O$$
III **IV** **V**

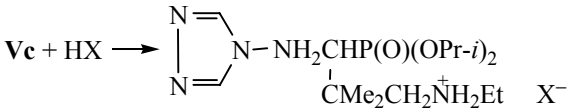
IV, R^3 = Me (**a**), *i*-Pr (**b**); V, R^1 =  , R^2 = *i*-Pr, R^3 = Me (**a**); R^1 = *n*-Pr, R^2 = CMe_2CH_2NHEt, R^3 = Me (**b**); R^1 =  , R^2 = CMe_2CH_2NHEt, R^3 = *i*-Pr (**c**).



VIa



VIb



VIc, VId

VI, X = 2,4,6-$(NO_2)_3C_6H_2O^-$ (**b, c**), ClO_4 (**d**).

metal. A slight self-heating was observed. The mixture was kept at room temperature for several days. After the removal of benzene the residue was recrystallized to give diisopropyl [2,2-diemethyl-1-(1,2,4-trazol-4-ylamino)-3-(ethylamino)propyl]phosphonate **Vc**.

The composition and structure of compounds **V** were confirmed by the elemental analysis data, ^1H and ^{31}P NMR spectroscopy, as well as by their transformation into the corresponding picrates **VIa**–**VIc** and perchlorate **VId**.

Diaminoalkylphosphonate **Vb** reacts with picric acid to form dipicrate **VIb**. At the same time phosphonate **Vc** with two amino groups reacts with perchloric and picric acids to give monosalts **VId** and **VIc**, even when using a two-fold excess of these acids. Obviously, the 1,2,4-triazole group in compound **Vc** creates more steric hindrances at the N(III) atom than *n*-propyl moiety in phosphonate **Vb**.

***N*-(1,2,4-Triazol-4-yl)-2-methylpropanimine (IIIa).** To a solution of 4.72 g (0.0561 mol) of 1,2,4-triazol-4-ylamine **Ia** in 45 ml of ethanol was added in small portions 6.6 g (0.0561 mol) of methylpropanal **IIb**. The reaction mixture slightly warmed. Then one drop of sulfuric acid was added, and the mixture was heated for 5 h. After the removal of the solvent in a high vacuum the residue was recrystallized from an ether–hexane mixture. Yield 4.78 g (62%), mp 47°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 d (6H, CMe_2, $^3J_{HH}$ 7.0 Hz), 2.86 m (1H, CH), 8.16 d (1H, CH=N, $^3J_{HH}$ 4.9 Hz), 8.61 s (2H, $C_2H_2N_3$).

***N*-(1,2,4-Triazol-4-yl)-2,2-dimethyl-3-(ethylamino)-propanimine (IIIb)** was prepared similarly from 7.69 g (0.0914 mol) of 1,2,4-triazol-4-ylamine **Ia** in 45 ml of ethanol and of 11.81 g (0.0914 mol) of 2,2-dimethyl-3-(ethylamino)propanal **IIa**. Yield 11.87 g (67%), mp 83°C (diethyl ether–hexane, 1:2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 t (3H, $NHCH_2\underline{Me}$, $^3J_{HH}$ 7.5 Hz), 1.36 s (6H, CMe_2), 1.41 s (1H, NH), 2.78 q (2H, $NH\underline{CH_2}Me$, $^3J_{HH}$ 7.5 Hz), 2.84 s (2H, $\underline{CH_2}NH$), 8.20 s (1H, CH=N), 8.61 s (2H, $C_2H_2N_3$).

***N*-Propyl-2,2-dimethyl-3-(ethylamino)propanimine (IIIc).** To 5.3 g (0.0886 mol) of propylamine **Ib** with stirring at –4 to –5°C was added dropwise 11.58 g (0.0886 mol) of 2,2-dimethyl-3-(ethylamino)propanal **IIa**. The reaction mixture slightly warmed. The mixture was stirred for 15 min with cooling and then warmed to room temperature. The solid KOH was added till separation of the mixture into two layers. The organic layer was separated, dried over KOH, and distilled. Yield 8.80 g (58%), bp 70–71°C (10 mm Hg), n_D^{20} 1.4352. ^1H NMR spectrum ($CDCl_3$ + CCl_4), δ, ppm: 0.78 t (3H, $NCH_2\underline{Me}$, $^3J_{HH}$ 7.5 Hz), 0.90 t (3H, $NCH_2CH_2\underline{Me}$, $^3J_{HH}$ 7.0 Hz, the signal is partially overlapped with the signals of CMe_2), 0.96 s and 1.03 s

(6H, CMe_2), 0.96 s (1H, NH), 1.50 m (2H, $MeCH_2$·CH_2N=), 2.46 s (2H, CH_2NCH_2Me), 2.50 q (2H, NCH_2Me, $^3J_{HH}$ 7.5 Hz), 3.21 t (2H, $MeCH_2CH_2N$, $^3J_{HH}$ 3.35 Hz), 7.37 s (1H, N=CH).

Dimethyl [2-methyl-1-(1,2,4-triazol-4-ylamino)-propyl]phosphonate (Va). To 3.15 g (0.0228 mol) of *N*-(1,2,4-triazol-4-yl)-2-methylpropanimine **IIIa** was added dropwise under argon 2.63 g (0.0239 mol) of dimethylphosphorous acid **IVa**. To this mixture 3–4 times was added 5–6 drops of sodium alcoholate. The reaction mixture slightly warmed. The mixture was kept at room temperature for 3 days. Then the solvent was removed, and the residue was precipitated from an ethyl acetate–toluene mixture. Yield 2.5 g (44%), mp 103–104°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 d and 1.30 d (6H, CMe_2, $^3J_{HH}$ 7.0 Hz), 2.24 m (1H, $CHMe_2$), 3.29 d.d (1H, PCH, $^2J_{PH}$ 15.0, $^2J_{HH}$ 4 Hz), 3.91 d [6H, $P(OMe)_2$, $^3J_{PH}$ 10.8 Hz], 6.00 br.s (1H, NH), 8.47 s (2H, $C_2H_2N_3$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.0 ppm. Found, %: C 38.85; H 6.65; N 22.54; P 12.25. $C_8H_{17}PO_3N_4$. Calculated, %: C 38.71; H 6.9; N 22.57; P 12.48.

Dimethyl [2,2-dimethyl-1-(propylamino)-3-(ethyl-amino)propyl]phosphonate (Vb). To 3.68 g (0.0216 mol) of *N*-propyl-2,2-dimethyl-3-(ethylamino)propanimine **IIIc** was added dropwise under argon 2.38 g (0.0216 mol) of dimethylphosphorous acid **IVa**. The reaction mixture slightly warmed. The mixture was kept at room temperature for 5 days and distilled in a vacuum. Yield 3.23 g (55%), bp 84–85°C (0.05 mm Hg), n_D^{20} 1.4582. ^{1}H NMR spectrum ($CDCl_3$ + CCl_4), δ, ppm: 1.20–1.70 m (6H, CMe_2, 3H, NCH_2Me, 3H, CH_2CH_2Me and NHEt), 1.75–2.10 m (2H, NCH_2CH_2Me and 1H, NHPr), 2.60–3.30 m. (1H, PCH, 2H, $NHCH_2Et$, 2H, CCH_2NH, 2H, $NHCH_2Me$), 3.75 m (6H, MeOP). ^{31}P NMR spectrum (CCl_4): δ_P 30.9 ppm.

Diisopropyl [2,2-dimethyl-1-(1,2,4-triazol-4-yl-amino)-3-(ethylamino)propyl]phosphonate (Vc). To a solution of 6.98 g (0.0421 mol) of isopropylphosphorous acid **IVb** in 40 ml of benzene was added under argon with stirring 8.21 g (0.0421 mol) of *N*-(1,2,4-triazol-4-yl)-2,2-dimethyl-3-(ethylamino)propanimine **IIIb**. To this mixture were added few small pieces of metallic sodium. The reaction mixture slightly warmed. The mixture was kept at room temperature for 2–3 days. The reaction mixture was treated with ether and filtered from the small amount of crystalline product. After the removal of the solvent in a high vacuum the residue was recrystallized from ether. Yield 9.12 g (60%), mp 88°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10–1.60 m (12H, Me_2CHO, 6H, Me_2C, 3H, the signals of $MeCH_2N$ are partially overlapped), 2.64–3.08 m (4H, CH_2NHCH_2Me), 3.44 d.d (1H, PCH, $^2J_{PH}$ 13.7, $^3J_{HH}$ 4.0 Hz), 4.89 heptet (2H, $POCH^3Me^1Me^2$, $^3J_{PH^3} = {}^3J_{H^1H^3} = {}^3J_{H^2H^3}$ = 6.3 Hz), 6.97 d.d (1H, NHN, $^3J_{PH}$ 17.0, $^3J_{HH}$ 4.0 Hz), 8.47 s (2H, $C_2N_3H_2$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 22.1 ppm.

Dimethyl [2-methyl-1-(1,2,4-triazol-4-ylamino) propyl]phosphonate picrate (VIa). To a solution of 0.65 g (0.0026 mol) of dimethyl [2-methyl-1-(1,2,4-triazol-4-ylamino)propyl]phosphonate **Va** in 5.5 ml of ethanol was added in small portions a solution of 0.6 g (0.0026 mol) of picric acid in 5.13 ml of ethanol. The mixture was kept at room temperature for 24 h. The precipitated crystals were filtered off and dried in a vacuum. Yield 0.86 g (70%), mp 140–142°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.23 d and 1.28 d (6H, CMe_2, $^3J_{HH}$ 7.0 Hz), 2.34 m (1H, $CHMe_2$), 3.83 d and 3.85 d [6H, $P(OMe)_2$, $^3J_{PH}$ 10.7 Hz], 3.86 d [1H, PCH, $^2J_{PH}$ 13.6 Hz, the signal is partially overlapped with the signals of $P(OMe)_2$], 7.41 br.s (2H, $^+NH_2$), 8.87 s (2H, $C_2H_2N_3$), 9.56 s (2H, C_6H_2). ^{31}P NMR spectrum (acetone-d_6): δ_P 25.3 ppm. Found, %: C 35.77; H 4.11; N 20.83; P 6.75. $C_{14}H_{20}PO_{10}N_7$. Calculated, %: C 35.38; H 4.02; N 20.59; P 6.5.

Dimethyl [2,2-dimethyl-1-(propylamino)-3-(ethyl-amino)propyl]phosphonate dipicrate (VIb). To a solution of 2.62 g (0.0114 mol) of picric acid in 15 ml of ethyl acetate was added in small portions 1.42 g (0.0057 mol) dimethyl [2,2-dimethyl-1-(propylamino)-3-(ethylamino)propyl]phosphonate **Vb** in 8 ml of ethyl acetate. The reaction mixture slightly warmed. The mixture was kept at room temperature for 24 h. The precipitated crystals were filtered off, recrystallized from ethanol, and dried in a vacuum. Yield 3.65 g (87%), mp 125°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.94 t (3H, $^+NCH_2CH_2Me$, $^3J_{HH}$ 7.0 Hz), 1.35 t (3H, $^+NCH_2Me$, $^3J_{HH}$ 7.0 Hz), 1.37 s and 1.40 s (6H, Me_2), 1.69 m (2H, $^+NCH_2CH_2Me$), 3.03 sextet and 3.23 м (2H, $^+NCH_2CH_2Me$), 3.30 q (2H, $^+NCH_2Me$, $^3J_{HH}$ 7.0 Hz), 3.40 d and 3.54 d (2H, CH_2N^+Et, $^2J_{HH}$ 13.2 Hz), 3.62 d (1H, PCH, $^2J_{PH}$ 17.7 Hz), 3.90 d (6H, 2MeOP, $^3J_{PH}$ 11 Hz), 4.70–6.10 br.s (4H, 2^+NH_2), 8.80 s (4H, 2ArO). ^{31}P NMR spectrum ($C_4H_8O_2$): δ_P 29.2 ppm. Found, %: C 38.70; H 4.72; N 15.09; P 4.45. $C_{24}H_{35}$·$PO_{17}N_8$. Calculated, %: C 39.03; H 4.77; N 15.17; P 4.19.

Diisopropyl [2,2-dimethyl-1-(1,2,4-triazol-4-yl-amino)-3-(ethylamino)propyl]phosphonate picrate (VIc). To a solution of 1.34 g (0.0037 mol) diisopropyl

[2,2-dimethyl-1-(1,2,4-triazol-4-ylamino)-3-(ethylamino)-propyl]phosphonate **Vc** in 10 ml of dioxane was added in small portions with stirring a solution of 1.70 g (0.0074 mol) of picric acid in 10 ml of dioxane at 13–16°C. The reaction mixture slightly warmed. The mixture was kept at room temperature for 24 h. The precipitated crystals were filtered off and dried in a vacuum. Yield 1.97 g (65%), mp 114°C. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.25–1.70 m (12H, $\underline{Me}_2CHO$, 6H, Me_2C, 3H, $\underline{Me}CH_2N$, the signals are partially overlapped), 3.10–3.50 m (4H, $\underline{CH_2}^+NH_2\underline{CH_2}Me$), 3.7 d.d (1H, PCH, $^2J_{PH}$ 17.8, $^3J_{HH}$ 5.0 Hz), 5.02 heptet (2H, $POCH^3Me^1Me^2$, $^3J_{PH^3} = {}^3J_{H^1H^3} = {}^3J_{H^2H^3}$ = 6.3 Hz), 6.07 d.d (1H, NH, $^3J_{PH}$ 12.6, $^3J_{HH}$ 5.0 Hz), 8.56 s (2H, C_6H_2), 8.97 s (2H, $C_2H_2N_3$), 9.24 br.s and 9.5 br.s (2H, $^+NH_2$). ^{31}P NMR spectrum (CD_3CN): δ_P 21.4 ppm. Found, %: C 42.21; H 5.65; N 18.15; P 5.4. $C_{21}H_{35}PO_{10}N_8$. Calculated, %: C 42.73; H 5.98; N 18.98; P 5.25.

Diisopropyl [2,2-dimethyl-1-(1,2,4-triazol-4-ylamino)-3-(ethylamino)propyl]phosphonate perchlorate (VId). To a solution of 1.30 g (0.0036 mol) [2,2-dimethyl-1-(1,2,4-triazol-4-ylamino)-3-(ethylamino)-propyl]phosphonate **Vc** in 15 ml of dioxane was added at 13°C in small portions with stirring a solution of 1.7 g (0.0072 mol) of perchloric acid. The reaction mixture slightly warmed. The mixture was kept at room temperature for 24 h. The precipitated crystals were filtered off, washed with dioxane and dried in a vacuum. Yield 1.68 g (83%), mp 174–175°C. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.24–1.66 m (12H, $\underline{Me}_2CHO$, 6H, Me_2C, 3H, $\underline{Me}CH_2N$, the signals are partially overlapped), 3.12–3.48 m (4H, $\underline{CH_2}^+NH_2\underline{CH_2}Me$), 3.64 d.d (1H, PCH, $^2J_{PH}$ 14.8, $^3J_{HH}$ 7.1 Hz), 5.02 heptet (2H, $POCH^3Me^1Me^2$, $^3J_{PH^3} = {}^3J_{H^1H^3} = {}^3J_{H^2H^3}$ = 7.1 Hz), 6.59 d.d (1H, NH, $^3J_{PH}$ 12.4, $^3J_{HH}$ 7.1 Hz), 7.03 br.s and 8.06 br.s (2H, $^+NH_2$), 9.02 s (2H, $C_2H_2N_3$). ^{31}P NMR spectrum (CD_3CN): δ_P 20.6 ppm.

The ^{1}H NMR spectra were recorded on a Tesla BS-567A and Bruker Avance-600 instruments operating at 100 and 600 MHz, respectively, relative to internal TMS. The ^{31}P NMR spectra were recorded on a Bruker Avance-600 instrument operating at 242.88 MHz relative to external 85% H_3PO_4.

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