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## LETTERS TO THE EDITOR

# Synthesis of 1,3,4-Thiazaphosphols Containing Aminocarboxylic Acid Fragments in the Molecule

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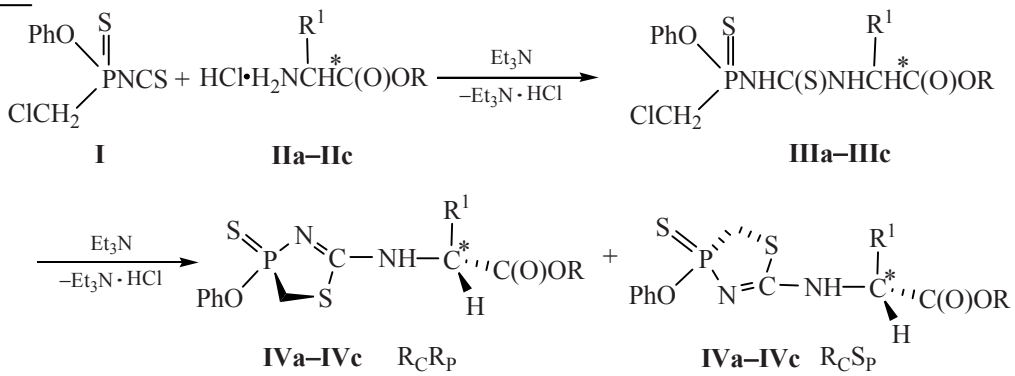
Amino acids, their derivatives, and phosphorus analogs exhibit biological activity of a broad spectrum [1, 2]. In this connection linear and cyclic derivatives of the tetracoordinated phosphorus involving aminocarboxylic acid fragments are of undoubted interest. Recently we have shown that the reaction of amine hydrochlorides with chloromethylthiophosphonylated isothiocyanates in the presence of a base gives rise to 1,3,4-thiazaphosphols [3]. We used this approach to synthesize the ring structures containing phosphorus atom and the fragments of optically active aminocarboxylic acids.




**II–IV**, R = $R^1$ = Me (**a**); R = Et, $R^1$ = $CH_2Ph$ (**b**); R = Me, $R^1$ = $CHMe_2$ (**c**).

The optically pure aminocarboxylate hydrochlorides **IIa–IIc** were involved into the reaction with isothiocyanatothiophosphonate. Reaction occurs through intermediate formation of thioureas **IIIa–IIIc**, which rapidly undergo ring closure into 1,3,4-thiazaphosphols **IVa–IVc** in the presence of a base. Since in the end product molecules there are two chiral centers, they are formed as pairs of diastereomers. In the case of alanine and phenylalanine derivatives diastereomers **IVa** and **IVb** are formed in equal amount that indicates a low stereospecificity of these processes. When *L*-valine methyl ester **IIc** containing rather bulky isopropyl group was used in the reaction with isothiocyanate **I**, the diastereomers ratio in a crude mixture was 65:35%. The prevailing diastereomer was isolated by fractional recrystallization from solution. Recently we have shown that in the reaction of chiral isothiocyanate **I** with optically active phenylethylamine the binding of enantiomer having inverse configuration of chiral centre is preferred [4]. Based on these data it is likely that the isolated enantiomer **IVc** contains chiral centers with the configuration $R_CS_P$ . Its rotation angle equals 120°.

**4-Phenoxy-4-thioxo-2-(methylmethoxycarbonylmethyl)amino-1,3,4-thiazaphosphol (IVa).** To a solu-

tion of 0.85 g of hydrochloride of *L*-alanine methyl ester **IIa** in 25 ml of anhydrous methylene chloride was added a mixture of 1.22 g of triethylamine and 1.61 g of isothiocyanate **I** under stirring and cooling to 0°C. After 2 days the solvent was removed and to the residue was 10 ml of benzene was added. The precipitate of triethylamine hydrochloride was separated and benzene solution was washed with distilled water thrice by 10 ml and dried over anhydrous sodium sulfate. After 12 h the solid component was separated and benzene was removed under a water-jet pump vacuum. Yield 1.1 g (55%), pale yellow viscous liquid (diastereomers mixture in a ratio 53:47%). $^1$H NMR spectrum [$(CD_3)_2CO$], δ, ppm: (dominant isomer) 1.48 d (3H, $CH_3C$, $^3J_{HH}$ 7.65 Hz), 3.54 d.d (1H, $PCH_A$, $^2J_{PH}$ 9.45 Hz, $^2J_{HH}$ 13.10 Hz), 3.72 s (3H, $CH_3O$), 3.92 d.d (1H, $PCH_B$, $^2J_{PH}$ 3.15 Hz, $^2J_{HH}$ 13.10 Hz), 4.68 q (1H, CHN, $^3J_{HH}$ 7.20 Hz), 7.18–7.38 m (5H, Ph), 8.12 br.s (1H, NH); (minor isomer) 1.46 d (3H, $CH_3C$, $^3J_{HH}$ 7.20 Hz), 3.55 d.d (1H, $PCH_A$, $^2J_{PH}$ 9.46 Hz, $^2J_{HH}$ 13.51 Hz), 3.71 s (3H, $CH_3O$), 3.89 d.d (1H, $PCH_B$, $^2J_{PH}$ 3.15 Hz, $^2J_{HH}$ 13.51 Hz), 4.74 q (1H, CHN, $^3J_{HH}$ 7.20 Hz), 7.18–7.38 m (5H, Ph), 8.12 br.s (1H, NH). $^{31}$P NMR spectrum [$(CD_3)_2CO$], $\delta_P$, ppm: 117.99. Found, %: C 43.98; H 4.17; N 8.10; P 9.00; S 19.01. $C_{12}H_{15}N_2O_3PS_2$. Calculated, %: C 43.62; H 4.58; N 8.48; P 9.38; S 19.41.

**4-Phenoxy-4-thioxo-2-(benzylethoxycarbonylmethyl)amino-1,3,4-thiazaphosphol (IVb)** was prepared similarly from 1.26 g of *L*-phenylalanine **IIb** hydrochloride, 1.10 g of triethylamine, and 1.46 g of isothiocyanate **I**. Yield 1.2 g (52%), pale yellow viscous liquid (diastereomers mixture in a ratio 52:48%). $^1$H NMR spectrum [$(CD_3)_2CO$], δ, ppm: (dominant isomer) 1.22 t (3H, $CH_3C$, $^3J_{HH}$ 7.20 Hz), 3.19 m (2H, $CH_2Ph$), 3.53 d.d (1H, $PCH_A$, $^2J_{PH}$ 4.05 Hz, $^2J_{HH}$ 5.40 Hz), 3.89 d.d (1H, $PCH_B$, $^2J_{PH}$ 3.50 Hz, $^2J_{HH}$ 5.40 Hz), 4.13 q (2H, $CH_2O$, $^2J_{HH}$ 6.85 Hz), 4.92 t (1H, CHN, $^3J_{HH}$ 7.20 Hz), 7.14–7.35 m (5H, Ph); (minor isomer) 1.18 t (3H, $CH_3C$, $^3J_{HH}$ 7.20 Hz), 3.19 m (2H, $CH_2Ph$), 3.52 d.d (1H, $PCH_A$, $^2J_{PH}$ 4.05 Hz, $^2J_{HH}$ 13.52 Hz), 3.86 d.d (1H, $PCH_B$, $^2J_{PH}$ 5.97 Hz, $^2J_{HH}$ 13.51 Hz), 4.17 q (2H, $CH_2O$, $^2J_{HH}$ 7.20 Hz), 4.99 t (1H, CHN, $^3J_{HH}$ 6.30 Hz), 7.14–7.35 m (5H, Ph). $^{31}$P NMR spectrum [$(CD_3)_2CO$], $\delta_P$, ppm: 117.88. Found, %: C 54.50; H 5.16; N 6.71; P 7.21; S 14.95. $C_{19}H_{21}N_2O_3PS_2$. Calculated, %: C 54.26; H 5.04; N 6.66; P 7.37; S 15.25.

**4-Phenoxy-4-thioxo-2-(isopropylmethoxycarbonylmethyl)amino-1,3,4-thiazaphosphol (IVc).** To a solution of 0.93 g of *L*-valine hydrochloride **IIc** in 20 ml anhydrous methylene chloride was added a mixture of 1.2 g of triethylamine and 1.47 g of isothiocyanate **I** under stirring and cooling to 0°C . After 2 days the solvent was removed under water-jet pump vacuum and to the residue was 10 ml of benzene added. The precipitate of triethylamine hydrochloride was separated, benzene was removed and the precipitated product was separated. Yield 0.21 g (11%, optically pure compound), mp 163–165ºC, $[\alpha]_D^{20}$ –125.5º (*c* 0.8, $CH_3CN$). IR spectrum, ν, $cm^{-1}$: 698 (P=S), 1218 (POPh), 1566 (C=N), 1593 (Ph), 1735 (C=O), 3349 (NH). $^1$H NMR spectrum [$(CD_3)_2CO$], δ, ppm: 1.02 d (6H, $CH_3C$, $^3J_{HH}$ 6.74 Hz), 2.24 m (1H, C*H*$CH_3$), 3.54 d.d (1H, $PCH_A$, $^2J_{PH}$ 9.45 Hz, $^2J_{HH}$ 13.64 Hz), 3.73 s (3H, $CH_3O$), 3.90 d.d (1H, $PCH_B$, $^2J_{PH}$ 3.15 Hz, $^2J_{HH}$ 13.64 Hz), 4.59 d (1H, CHN, $^3J_{HH}$ 4.44 Hz), 7.17–7.36 m (5H, Ph), 8.11 br.s (1H, NH). $^{31}$P NMR spectrum [$(CD_3)_2CO$], $\delta_P$, ppm: 117.96. Found, (%): C 47.13; H 5.53; N 8.15; P 8.53; S 17.63. $C_{14}H_{19}N_2O_3PS_2$. Calculated, (%): C 46.90; H 5.35; N 7.82; P 8.64; S 17.89. By the $^1$H NMR spectrum data, the rest part of product, yellow viscous liquid, is a diastereomers mixture in the ratio 56:44%.

The IR spectra were registered on a UR-20 spectrometer in the range of 400–3600 $cm^{-1}$ (mineral oil). The $^1$H NMR spectra were measured on a Bruker AVANCE-600 spectrometer (600 MHz). The $^{31}$P NMR spectra were taken on a Bruker MSL-400 NMR-Fourier spectrometer (100.62 MHz).

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