Russian Journal of General Chemistry, Vol. 71, No. 11, 2001, pp. 1823–1824. Translated from Zhurnal Obshchei Khimii, Vol. 71, No. 11, 2001, pp. 1928–1929.

LETTERS TO THE EDITOR

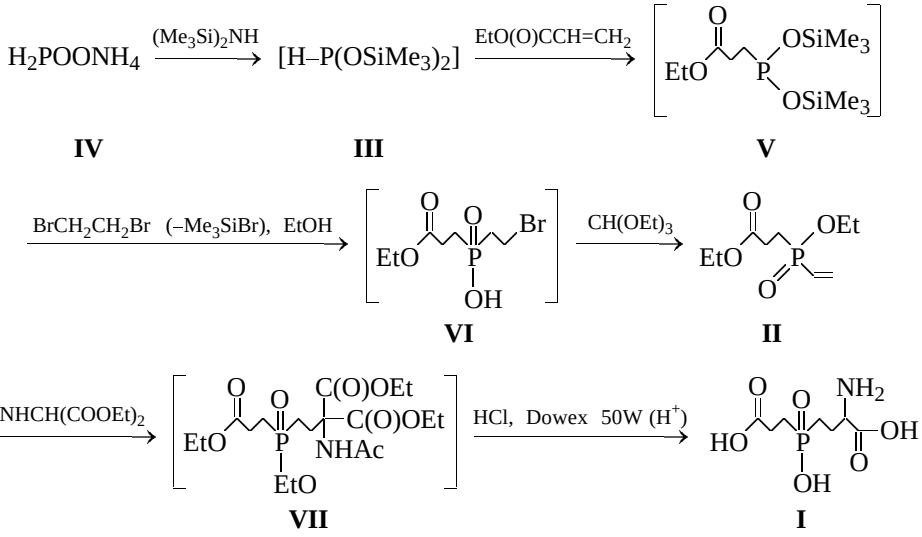
Synthesis of Phosphine Analog of Glutamylglycine

V. V. Ragulin

Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Moscow oblast, Russia

Received December 29, 2000

Synthesis of phosphoryl analogs of natural compounds is a promising route to new physiologically active compounds [1]. In this connection, development of procedures for preparing phosphine analogs of peptides, the potential inhibitors of natural enzymes [2, 3], is an urgent problem. Using the procedure developed by us previously for preparing functionalized phosphinic acids [4, 5], we suggest a convenient two-stage synthesis of pseudopeptide, the phosphine analog of glutamylglycine, 2-(hydroxycarbonyl)ethyl-3-amino-3-(hydroxycarbonyl)propylphosphinic acid **I** according to the following scheme:



The first stage is the synthesis of ethyl 2-(ethoxycarbonyl)ethylvinylphosphinate **II**. Bis(trimethylsilyl) hypophosphite **III** formed *in situ* from ammonium hypophosphite **IV** and hexamethyldisilazane [6, 7] adds to the double bond of ethyl acrylate to form bis-(trimethylsilyl)-2-(ethoxycarbonyl)ethylphosphonite **V** [8]. The latter reacts, also *in situ*, with an excess of dibromoethane by the scheme of the Arbuzov reaction. Subsequent alcoholysis gives 2-ethoxycarbonylethyl-2-bromoethylphosphinic acid **VI** which without isolation was treated with triethyl orthoformate. Esterification with the simultaneous dehydrobromination according to the previously developed procedures [9, 10] gives vinylphosphinate **II**, which was isolated and characterized.

The second stage of the synthesis includes the Michael addition of diethyl acetamidomalonate to vinylphosphinate **II**, the acid hydrolysis of the resulting phosphinate **VII** without its isolation, the subsequent ion-exchange chromatography of the reaction mixture on cation exchanger, and isolation of the target amino acid **I**.

Ethyl (2-ethoxycarbonylethyl)vinylphosphinate II. A mixture of 4.0 g of ammonium hypophosphite and 15 ml of hexamethyldisilazane was stirred for 2 h at 120–130°C. Then the reaction mixture was cooled to room temperature, and 5.3 ml of freshly distilled ethyl acrylate was added dropwise. The resulting mixture was stirred for an additional 2 h at 40–50°C. Then the mixture was cooled to room temperature, 20 ml

1070-3632/01/7111-1823 $25.00

of 1,2-dibromoethane was added in one portion, and the mixture was stirred for 5 h at 120°C. The formed trimethylbromosilane and excess 1,2-dibromoethane were removed in a vacuum, and 50 ml of aqueous ethanol (1 : 1) was added dropwise to the residue. The mixture was refluxed for 0.5 h, and the solvent was evaporated in a vacuum. The residue was treated with 100 ml of ethyl acetate and 50 ml of water, and the aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic layers were evaporated in a vacuum, the residue was treated with 40 ml of triethyl orthoformate, and the mixture was refluxed with a Dean–Stark trap to remove ethanol and ethyl formate. Excess triethyl orthoformate was removed in a vacuum, and the residue was distilled to give 4.2 g (40%) of vinylphosphinate **II** as an oil with bp 125–129°C/3 mm Hg, n_D^{20} 1.4600. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (3H, CH_3), 1.34 t (3H, CH_3), 2.07 m (2H, PCH_2), 2.60 m [2H, $C(O)CH_2$], 4.03 m (2H, CH_2OC), 4.15 m (2H, CH_2OP), 6.00–6.50 m (3H, $CH{=}CH_2$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 41.3 ppm. Found, %: C 49.14, 49.33; H 7.97, 8.11. $C_9H_{17}O_4P$. Calculated, %: C 49.09; H 7.78.

2-(Hydroxycarbonyl)ethyl-3-amino-3-(hydroxycarbonyl)propylphosphinic acid I. A mixture of 6.8 g of diethyl acetamidomalonate, 7.5 g of vinylphosphinate **II**, 8.6 g of potassium carbonate, and 0.5 g of tetrabutylammonium bromide in 20 ml of THF was refluxed with stirring for 11–13 h until diethyl acetamidomalonate was completely consumed (TLC monitoring, elution with (4–5) : 1 chloroform–acetone, R_f 0.5 (Silufol). The reaction mixture was treated with 50 ml of chloroform and 25 ml of water, and the aqueous phase was neutralized and treated with chloroform (2 × 25 ml). The combined organic extracts were evaporated in a vacuum. The oily residue (about 14 g) was treated with 70 ml of 8 N HCl, and the mixture was refluxed for 13–15 h. Then the reaction mixture was cooled and washed with diethyl ether (3 × 20 ml), the solvent was evaporated in a vacuum, and the residue was chromatographed on a Dowex 50W(H^+) column, elution with 0.5–0.7 N HCl. The fractions with the positive ninhydrin test were concentrated, dissolved in 20 ml of aqueous ethanol (1 : 4), and treated with an excess of propylene oxide to isolate the target amino acid. After the additional crystallization of the product from aqueous ethanol, 5.3 g of **I** was obtained (71% based on diethyl acetamidomalonate). Total yield 28% based on ammonium hypophosphite; mp 205–207°C with decomposition. ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 1.70 m (2H), 1.88 m (4H), 2.36 d.t (2H, J_{HP} 12 Hz), 3.92 t (1H). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 26.4 d (P–*C*H_2–C, *J* 91.4 Hz), 27.3 d (P–*C*H_2–C, *J* 90.2 Hz), 28.9 d (C–*C*H_2–CH, *J* 2.4 Hz), 31.4 d [C–*C*H_2–C(O), *J* 3.1 Hz], 57.5 d (CH, *J* 15.8 Hz), 183.3 d [*C*(O)CH_2, *J* 17.1 Hz), 183.6 s [*C*(O)CH]. ^{31}P NMR spectrum: δ_P 50.0 (D_2O), 44.0 (D_2O + NaOD, pH 10). Found, %: C 34.06, 33.93; H 6.07, 6.08; N 5.89, 5.86. $C_7H_{14}NO_6P \cdot 0.5H_2O$. Calculated, %: C 33.88; H 6.09, N 5.64.

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer relative to internal TMS and external 85% phosphoric acid.

TLC analysis was performed on glass plates (Merck), eluent 1-butanol–acetic acid–water (5 : 1 : 1).

ACKNOWLEDGMENTS

The work was supported by Nippon Chemical Industrial Co. [11].

REFERENCES

1. Collinsova, M. and Jiracek, J., *Curr. Med. Chem.*, 2000, vol. 7, no. 6, pp. 629–647.
2. Chen, H., Noble, F., Mothe, A., Meudal, H., Coric, P., Danascimento, S., Roques, B.P., George, P., and Fournie-Zaluski, M.-C., *J. Med. Chem.*, 2000, vol. 43, no. 7, pp. 1398–1408.
3. Burchardt, J., Ferreras, M., Krog-Jensen, C., Delaisse, J.-M., Fored, N.T., and Meldal, N., *Chem. Eur. J.*, 1999, vol. 5, no. 10, pp. 2877–2884.
4. Ragulin, V.V. and Tsvetkov, E.N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, no. 11, p. 2652.
5. Kurdyumova, N.R., Rozhko, L.F., Ragulin, V.V., and Tsvetkov, E.N., *Zh. Obshch. Khim.*, 1997, vol. 67, no. 12, pp. 1970–1973.
6. Voronkov, M.G. and Marmur, L.Z., *Zh. Obshch. Khim.*, 1970, vol. 40, no. 9, pp. 2135–2136.
7. Issleib, K., Mogelin, W., and Balszuweit, A., *Z. Anorg. Allg. Chem.*, 1985, vol. 530, no. 1, pp. 16–21.
8. Kurdyumova, N.R., Rozhko, L.F., Ragulin, V.V., and Tsvetkov, E.N., *Zh. Obshch. Khim.*, 1997, vol. 67, no. 12, pp. 1965–1969.
9. Kurdyumova, N.R., Ragulin, V.V., and Tsvetkov, E.N., *Zh. Obshch. Khim.*, 1996, vol. 66, no. 5, pp. 769–771.
10. Kurdyumova, N.R., Ragulin, V.V., and Tsvetkov, E.N., *Mendeleev Commun.*, 1997, no. 2, pp. 69–70.
11. JPN Patent B2000-18568, January 27, 2000.