Aminophosphonic Acids; XVI[1]. A New and Facile Synthesis of Phosphinothricine and 2-Amino-4-phosphonobutanoic Acid

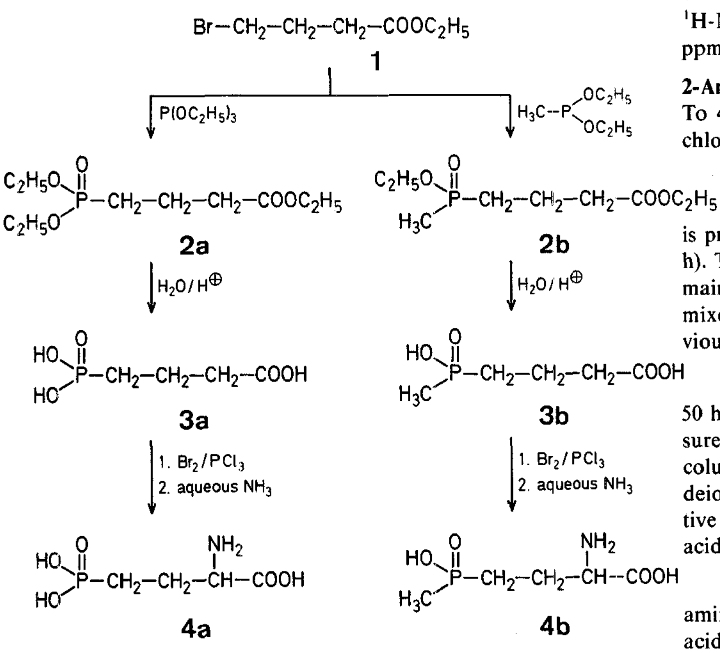
Czesław WASIELEWSKI*, Kazimierz ANTCZAK

Department of Organic Chemistry, Institute of Organic and Food Chemistry and Technology, Technical University, 80-952 Gdańsk, ul. Majakowskiego 11/12, Poland

An example of a natural compound containing the carbon-phosphorus bond is phosphinothricine, 2-amino-4-(methylphosphino)-butanoic acid (**4b**), a methylphosphinic glutamic acid analog. Phosphinothricine and its peptide derivatives, which are produced by the Streptomyces viridochromogenes[2] and Streptomyces hydroscopicus[3] strains, exhibit antibiotic properties. They inhibit the growth of some bacteria and fungi. 2-Amino-4-phosphonobutanoic acid (**4a**), a phosphonic analog of glutamic acid whose structure is similar to that of phosphinothricine, demonstrates its biologic activity by inhibiting some enzymatic processes[4,5].

Phosphinothricine (**4b**) was first synthesized on a milligram scale[2]. Further studies on phosphinothricine synthesis have been reported[6,7]. The acetamidomalonic method applied gave low total yields. 2-Amino-4-phosphonobutanoic acid (**4a**) has been described[8,9]. A general method for the synthesis of phosphinothricine (**4b**) and 2-amino-4-phosphonobutanoic acid (**4a**) using 2-bromopropanal as substrate in Arbusov and Strecker reactions has been reported[10].

We present here a simple preparation of phosphinothricine (**4b**) and 2-amino-4-phosphonobutanoic acid (**4a**) from easily available substrates as illustrated below.



The triethyl ester of 4-phosphonobutanoic acid (**2a**)[11] and the diethyl ester of 4-(methylphosphino)-butanoic acid (**2b**) were obtained in a simple manner and in good yields by the Arbusov reaction of ethyl 4-bromobutanoate (**1**) and the appropriate phosphorus substrates. On acid hydrolysis, **3a** and **3b** were obtained from **2a** and **2b**, respectively, in high yields. The products of bromination of acids **3a** and **3b** were, without isolation and purification, subjected to ammonolysis with aqueous ammonia solution to give 2-amino-4-phosphonobutanoic acid (**4a**) and phosphinothricine (**4b**). Because of its good crystallizability[7] phosphinothricine was isolated as the hydrochloride.

4-Phosphonobutanoic Acid Triethyl Ester (2a):

Prepared according to Ref.[11] from ethyl 4-bromobutanoate (**1**) and triethyl phosphite; yield: 82%; b.p. 120-121 °C/0.4 torr.

4-(Methylphosphino)-butanoic Acid Diethyl Ester (2b):

Diethyl methanephosphonite (44.5 g, 0.33 mol) and ethyl 4-bromobutanoate (**1**; 58.5 g, 0.3 mol) are heated at 130 °C under dry argon for 2 h. 4-(Methylphosphino)-butanoic acid diethyl ester (**2b**) is isolated by distillation; yield: 47.1 g (71%); b.p. 124-126 °C/0.8 torr.

$C_9H_{19}O_4P$	calc.	C 48.64	H 8.62
(222.2)	found	48.3	8.4

^{1}H-N.M.R. (CCl_4): $\delta = 1.1$-1.6 (m, 9 H); 1.6-2.0 (m, 4 H); 2.30 (t, 3 H, $J = 6$ Hz); 3.8-4.3 ppm (m, 4 H).

4-Phosphonobutanoic Acid (3a):

4-Phosphonobutanoic acid triethyl ester (**2a**; 126 g, 0.5 mol) is refluxed with concentrated hydrochloric acid (300 ml) for 20 h. The solution is evaporated to dryness under reduced pressure. The residue is treated with water (100 ml) and reevaporated under vacuum. This procedure is repeated several times until hydrogen chloride is removed. The crude product is crystallized from tetrahydrofuran/chloroform to give 4-phosphonobutanoic acid; yield: 80 g (95%); m.p. 121-122 °C.

$C_4H_9O_5P$	calc.	C 28.58	H 5.39
(168.1)	found	28.3	5.6

^{1}H-N.M.R. (D_2O): $\delta = 2.1$-2.9 (m, 4 H); 2.30 ppm (t, 2 H).

4-(Methylphosphino)-butanoic Acid (3b):

Obtained from 4-(methylphosphino)-butanoic acid diethyl ester (**2b**; 44.5 g, 0.2 mol) by the method described for **3a**, the hydrolysis period is reduced to 8 h. The product is crystallized from tetrahydrofuran to give 4-(methylphosphino)-butanoic; yield: 31.2 g (94%); m.p. 93-95 °C.

$C_5H_{11}O_4P$	calc.	C 36.15	H 6.68
(166.1)	found	36.0	6.8

^{1}H-N.M.R. (D_2O): $\delta = 2.15$ (d, 3 H, $J = 17$ Hz); 2.4-2.8 (m, 4 H); 3.27 ppm (t, 2 H, $J = 7$ Hz).

2-Amino-4-phosphonobutanoic Acid (4a):

To 4-phosphonobutanoic acid (**3a**; 16.8 g, 0.1 mol), phosphorus trichloride (0.5 ml) and bromine (16.0 g, 0.1 mol) are added. The mixture is protected against moisture and refluxed until total decoloration (~3 h). The hydrogen bromide residue is removed under vacuum, the remaining oil is dissolved in a small amount of water/ice, the solution is mixed with concentrated aqueous ammonia solution (600 ml) previously cooled to 0 °C, and the mixture is left at room temperature for 50 h. The solution is then evaporated to dryness under reduced pressure. The residue is dissolved in water, the solution is passed through a column of Dowex 50W-X8 H$^\oplus$ resin, and the column washed with deionized water. The first eluate is strongly acidic but ninhydrin negative and is discarded. Continued washing with water elutes the amino acid as a slightly acidic, ninhydrin positive solution. Evaporating the amino acid eluate to dryness leaves 2-amino-4-phosphonobutanoic acid which is recrystallized from water/ethanol; yield: 8.8 g (48%); m.p. 229-231 °C.

$C_4H_{10}NO_5P$	calc.	C 26.24	H 5.51	N 7.65
(183.1)	found	26.0	5.8	7.5

I.R. (KBr): $\nu = 1740$ (C=O); 1630, 1550 ($NH_3^\oplus$); 1260 cm^{-1} (P=O).

^{1}H-N.M.R. (D_2O): $\delta = 2.1$-2.8 (m, 4 H); 4.47 ppm (t, $J = 6$ Hz, 1 H).

Paper chromatography[12]: S_1: $R_f = 0.21$; S_2: $R_f = 0.19$.

2-Amino-4-(methylphosphino)-butanoic Acid Hydrochloride (Phosphinothricine Hydrochloride; 4b):

Obtained from 4-(methylphosphino)-butanoic acid (**3b**; 8.3 g, 0.05 mol) according to the method described for 2-amino-4-phosphonobu-

0039-7881/81/0732-0540 $ 03.00

tanoic acid. The ammonolysis product is evaporated to dryness under vacuum and applied to a column of Dowex-1 OH$^{\oplus}$ resin. Basic impurities are eluted with water and the residue is eluted with 0.5 normal hydrochloric acid. The acidic eluate is concentrated under reduced pressure and applied to a column of Dowex 50W-X8 H$^{\oplus}$ resin. The column is washed with water. The first strongly acidic eluate is discarded. The ninhydrin positive fraction is eluted with 0.5 normal hydrochloric acid and then evaporated to dryness under vacuum. The residue, after recrystallization from ethyl alcohol/ethyl ether, is 2-amino-4-(methylphosphino)-butanoic acid hydrochloride (**4b**; phosphinothricine hydrochloride); yield: 7.2 g (66%); m.p. 202–204 °C.

$C_5H_{13}ClNO_4P$	calc.	C 27.60	H 6.02	N 6.44
(217.6)	found	27.3	6.1	6.5

I.R. (KBr): $\nu = 1740$ (C=O); 1630, 1510 ($NH_3^{\oplus}$); 1300 (P—CH_3); 1250 cm^{-1} (P=O).

^{1}H-N.M.R. (D_2O): $\delta = 1.87$ (d, 3H, $J = 15$ Hz); 2.1–2.8 (m, 4H); 4.47 ppm (t, 1H, $J = 6$ Hz).

Paper chromatography[12]: S_1: $R_f = 0.31$; S_2: $R_f = 0.35$.

The authors acknowledge financial support for this work by a grant MR-I.12.1. from Polish Academy of Sciences.

Received: December 31, 1980

---

* Author to whom correspondence should be addressed.

[1] Aminophosphonic acids; Part XV. J. Szewczyk, C. Wasielewski, *Polish J. Chem.*, in press.

[2] E. Bayer et al., *Helv. Chim. Acta* **55**, 224 (1972).

[3] Y. Kondo et al., *Meiji Seika Kenkyu Nempo* **1973**, 34; *C. A.* **81**, 89705 (1974).

[4] S. G. Cull-Candy, J. F. Donnellan, R. W. James, G. G. Lunt, *Nature* **262**, 408 (1976).

[5] Wu Chung, *Can. J. Biochem.* **55**, 332 (1977).

[6] Y. Ogawa, H. Yoshida, S. Inoue, T. Niida, *Meiji Seika Kenkyu Nempo* **1973**, 49; *C. A.* **81**, 37788 (1974).

[7] H. Gross, Th. Gnauk, *J. Prakt. Chem.* **318**, 157 (1976).

[8] P. Mastalerz, *Acta Biochim. Polon.* **4**, 19 (1957).

[9] J. R. Chambers, A. F. Isbell, *J. Org. Chem.* **29**, 832 (1964).

[10] E. Gruszecka, P. Mastalerz, M. Soroka, *Roczn. Chem.* **49**, 2127 (1975).

[11] J. Falbe, R. Paatz, F. Korte, *Chem. Ber.* **98**, 2312 (1965).

[12] The purity of the amino acids was evaluated on the basis of paper chromatography: ascending technique, Whatman No. 1 paper, developer 0.5% ninhydrin solution in ethanol; solvent systems:
S_1: *i*-propyl alcohol : 20% aqueous ammonia : water = 8 : 1 : 1;
S_2: *n*-butyl alcohol : acetic acid : water = 2 : 1 : 1.

0039-7881/81/0732-0541 $ 03.00