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New Phosphonic Analogs of Aspartic and Glutamic Acid by Aminoalkylation of Trivalent Phosphorus Chlorides with Ethyl Acetyloacetate or Ethyl Levulinate and Benzyl Carbamate

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Preparation of the phosphonic analogs of α-methylaspartic (**4a–d**), glutamic (**7a–b**) and α-methylpyroglutamic (**5a–b**) acids by aminoalkylation of trivalent phosphorus chlorides with ethyl esters of oxoalkyloacids and benzyl carbamate is described. The phosphonic analogs of pyroglutamic acid (**8a–b**) was obtained by the cyclization of the corresponding esters (**9a–b**). The stability of the phosphonic analogs of pyroglutamic acid in acidic and alkaline media was also studied.

(Keywords: Aminoalkylation; Aminophosphonates; Aspartic acid analogs; Glutamic acid analogs)

Die Herstellung von neuen Phosphonanalogen der Asparagin- und Glutaminsäure in der Reaktion von trivalenten Phosphorchloriden mit Ethyl-acetyloacetat oder Ethyl-lävulinat bzw. Benzylcarbaminat

Es wurde die Darstellung der Phosphonanalogen der α-Methylasparaginsäure (**4a–d**), Glutamin- (**7a–b**) und α-Methylpyroglutaminsäure (**5a–b**) in der Reaktion der trivalenten Phosphorchloride und der Oxoalkansäureethylester sowie des Benzylcarbaminats beschrieben. In der Ringschlußreaktion der Ester (**9a–b**) erhält man Phosphonanaloge der Pyroglutaminsäure. Die Stabilität der Analogen der Pyroglutaminsäure wurde in sauren und alkalischen Medien geprüft.

Biological activity of a variety of aminophosphonates[1] stimulates interest in the synthesis of phosphonic analogs of carboxylic amino acids. Especially interesting are the glutamic and aspartic acid analogs

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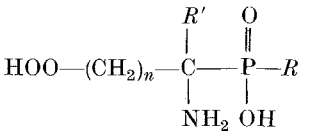
Table 1. *Phosphonic analogs of glutamic and aspartic acids*



Compound	M.p. [°C]	Yield [%]	^{1}H-n.m.r. (D_2O, or D_2O + D_2SO_4/*HMDS*) δ [ppm]
4a	236-237	54	2.08 (d, J^3_{PH} = 14.0 Hz, 3 H, C**H**$_3$); 3.55-3.30 (m, 2 H, HOOCC**H**$_2$)
4b	254-255	55	1.91 (d, J^3_{PH} = 14.0 Hz, 3 H, C**H**$_3$); 3.1-3.4 (m, 2 H, C**H**$_2$); 8.05 (m, 5 H, arom.)
4c	172-174	42	1.76 (d, J^2_{PH} = 14.0 Hz, 3 H, PC**H**$_3$); 1.93 (d, J^2_{PH} = 11.0 Hz, 3 H, PCC**H**$_3$); 3.10-3.4 (m, 2 H, C**H**$_2$)
4d	214-215	51	1.44 (t-t, J^3_{PH} = 17.0 Hz, J^3_{HH} = 7.0 Hz, 3 H, P—CH_2C**H**$_3$); 1.85 (d, J^3_{PH} = 12.0 Hz, 3 H, P—C—C**H**$_3$); 1.8—2.0 (m, 2 H, PC**H**$_2$); 3.1—3.4 (m, 2 H, C**H**$_2$COOH)
4e	250-251.5	22	2.2-3.1 (m, 6 H, 3 × C**H**$_2$); 3.5-4.0 (m, 1 H, C**H**)
7a	167-169	36 72[a]	2.30-2.85 (m, 2 H, —CH_2—C**H**$_2$CH—); 3.13 (t, 2 H, J_{HH} = 7.0 Hz, HOOCC**H**$_2$—); 4.01 (dt, 1 H, J_{PH} = 18,0 Hz, J_{HH} = 9.0 Hz, —C**H**)
7b	185-186.5	25 80[a]	2.03-2.57 (m, CH_2C**H**$_2$CH); 2.83 (t, 2 H, J_{HH} = 7.0 Hz, HOOCC**H**$_2$—); 4.00 (dt, 1 H, J_{PH} = 18 Hz, J_{HH} = 9.0 Hz, —C**H**—); 8.00 (m, 5 H, arom.)
14a	149-152	53[a] 52[e]	1.69 (d, J^2_{PH} = 13.0 Hz, 3 H, PC**C**H$_3$); 2.0 3.2 (m, 4 H, 2 × CH_2)

13a[f]	semisolid[c]		1.70 (d, J^3_{PH} = 14.5 Hz, 3 H, CH_3); 1.85-2.8
	300 °C <	90	(m, 4 H, 2 × CH_2)
14b	167 168	43[e]	1.73 (d, J^2_{PH} = 14.0 Hz, 3 H, PCC**H**$_3$); 2.0 2.6 (m, 2 H, PCC**H**$_2$); 2.6 3.0 (m, C**H**$_2$COOH); 7.75-8.0 (m, 5 H, arom.)
13b	300 °C <[c]	92	1.38 (d, J^3_{PH} = 14.0 Hz, 3 H, CH_3); 1.85 2.6 (m, 4 H, 2 × CH_2); 7.8 8.2 (m, 5 H, H arom.)

[a] By acid hydrolysis.
[b] From sodium salt.
[c] Very hygroscopic.
[d] Contains 1.5 equiv. of water in crystal.
[e] By alkaline hydrolysis followed by acidification.
[f] **14** as trisodium salt.

4e:

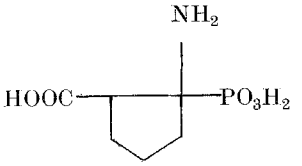
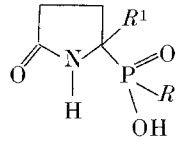


Table 2. *Phosphonic analogs of pyroglutamic acid*



Compound	Yield	M.p.	^{1}H-n.m.r. (D_2O or D_2O + D_2SO_4, *HMDS*) δ [ppm]
8a	86[a]	238–241	2.37–3.03 (m, 4H, —C**H**$_2$C**H**$_2$); 4.03–4.45 (m, 1H, C**H**)
8b	81[a]	c d	2.03–2.5 (m, 2H, —CH$_2$C**H**$_2$CH—); 2.63 (t, 2H, J_{HH} = 7.0 Hz, HOOCC**H**$_2$—); 3.38 (dt, 1H, J_{PH} = 17.0 Hz, J_{HH} = 8.0 Hz, —C**H**—); 7.87 (m, 5H, arom.)
5a	53[b]	244–245.5	1.75 (d, J^3_{PH} = 14.5 Hz, 3H, CH_3); 2.0–3.1 (m, 4H, 2 × CH_2)
5b	50[b]	227.5–229	1.72 (d, J^3_{PH} = 13.0 Hz, 3H, CH_3); 2.0–2.9 (m, 2H, CH, C**H**$_2$CP); 2.6–3.4 (m, 2H, C**H**$_2$CONH$_2$); 7.8–8.6 (m, 5H, H arom.)

[a] By cyclization reaction.
[b] From ethyl levulinate.
[c] Very hygroscopic.
[d] Contains ethanol as impurity.

for which strong neuroactive[2–6], antibiotic[7,8] and antiviral[9] and an other[10,12] activity has been demonstrated.

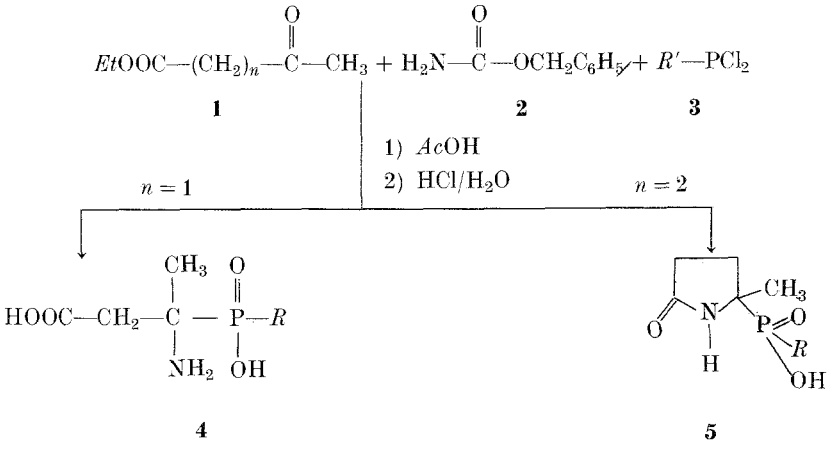
Syntheses of several phosphonic analogs of aspartate and glutamate have been described[13–16] except for glutamic acid analogs in which phosphonic group replaces the α-carboxylic function. Also unknown so far are the phosphonic analogs of α-methylaspartic and pyroglutamic acids.

We found that α-phosphonic analogs of α-methylaspartic, glutamic and pyroglutamic acids can be obtained readily by the general procedure developed in our laboratory for the preparation of 1-aminoalkanephosphonates from carbonyl compounds, amides and trivalent phosphorus chlorides[17].

Thus the reaction of ethyl acetoacetate (**1**, $n = 1$) with benzyl carbamate (**2**) and phosphorus trichloride or dichlorophosphines (**3**) gave the analogs of α-methyl aspartic acid (Table 1).

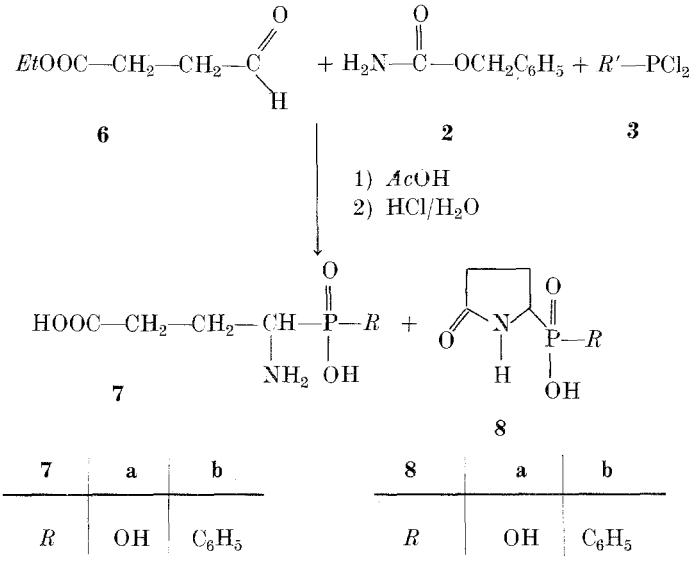
To provide samples for biological studies these analogs were converted to carboxylic esters and amides by standard methods.

Similar reaction with ethyl levulinate (**1**, $n = 2$) gave unexpectedly, cyclic products (**5**) representing the phosphonic analogs of α-methyl-pyroglutamic acid (Table 2).



4	a	b	c	d
R	OH	C_6H_5	CH_3	C_2H_5

5	a	b
R	OH	C_6H_5

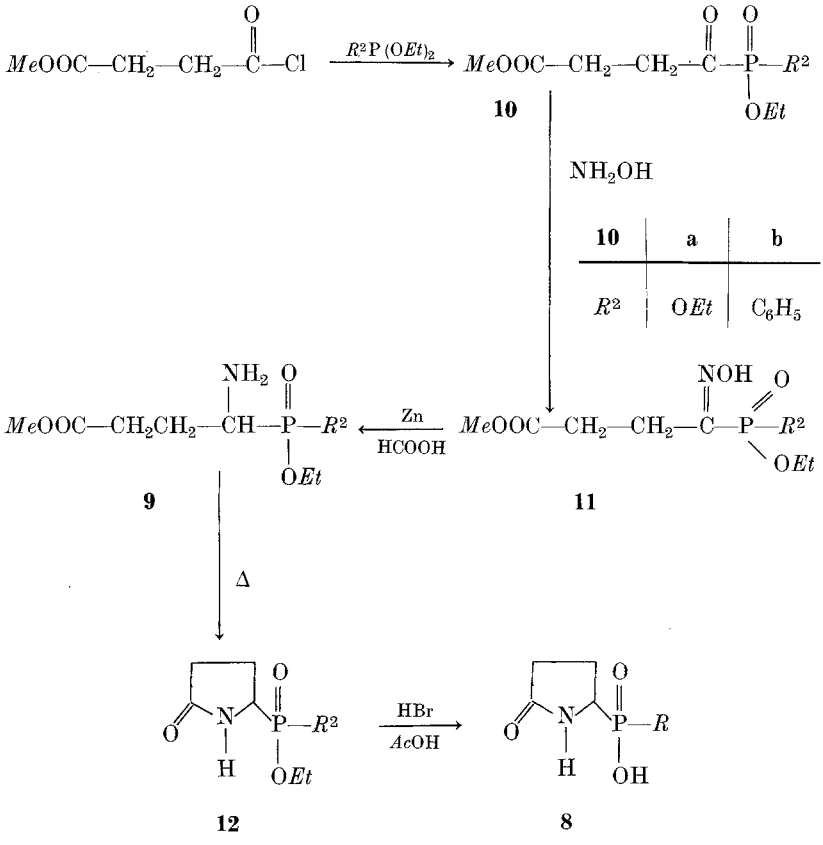


7	a	b
R	OH	C_6H_5

8	a	b
R	OH	C_6H_5

Cyclisation was not expected because an analogous reaction of ethyl succinate semialdehyde (**6**) produced in a moderate yield, the open chain product (**7**) (Table 1) with only traces of the cyclic one (**8**).

We were able to prepare the pyroglutamic acid analogs **8** (Table 2) by cyclisation of the ester **9**. The synthesis of ester **9** was accomplished from the corresponding oxophosphonate **10** which was converted to the oxime **11** and then reduced with zinc in formic acid.

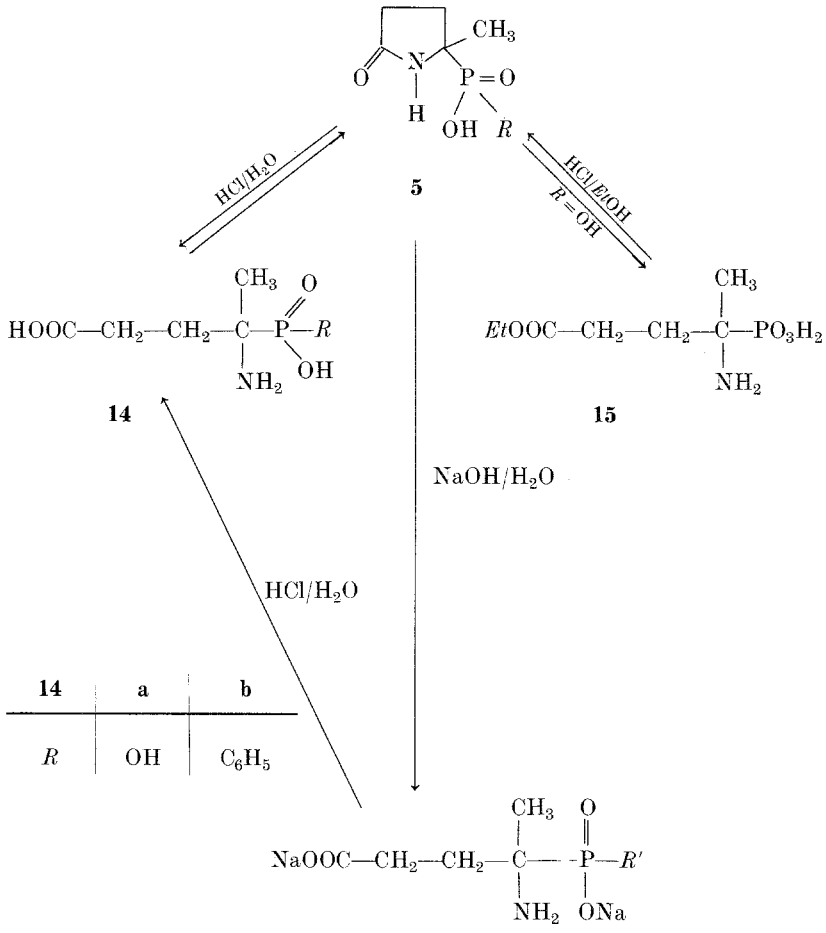


Phosphonic analogs of pyroglutamic acid **5** were hydrolysed in sodium hydroxide solution yielding salts of the open chain product **13** (Table 1).

In acidic media, the α-methylpyroglutamic acid analogs **5**, are in equilibrium with open chain compounds **14**. Thus after prolonged heating of **5** in hydrochloric acid there were obtained mixtures of cyclic and open chain products.

Ring opening with ethyl alcohol and hydrogen chloride yielded C-ester **15** (Table 3), and unchanged substrate. Similar mixture was obtained upon esterification of open chain product **14**.

No such equilibria were observed in the case of pyroglutamic acid analogs **8**. We were unable to cyclise the open chain compound **7** or its C-ethyl ester by heating in acidic media and acid hydrolysis of the cyclic to open chain product was complete.



14	a	b
R	OH	C_6H_5

13	a	b
R'	ONa	C_6H_5

Experimental

Melting points are uncorrected. ^{1}H-n.m.r. spectra were recorded with a Tesla 80 MHz spectrometer, with hexamethyldisiloxane as standard. Structure of the all obtained compounds were additionally proved by means of ^{13}C-n.m.r.; i.r. spectrocopy elemental analyses and potentiometric titration.

Preparation of phosphonic and phosphinic analogs of α-methylaspartic acid; 3-amino-3-phosphonobutyric acid (**4a**); *3-amino-3-phosphino-butyric acids* **4b-e**

Ethyl acetoacetate (**1**, $n = 1$) (0.3 mol, 38 ml) was added dropwise, to a stirred mixture of benzyl carbamate (**2**) (0,2 mol, 30.6 g), phosphorus trichloride (**3**, $R' = Cl$) (0,2 mol, 18 ml) and glacial acetic acid (40 ml). Addition was complete within 20 min. Exothermic reaction with evolution of hydrogen chloride gas occurred. The resulting mixture was refluxed for 30 min, then treated with concentrated hydrochloric acid (80 ml) and refluxed again for 3 h. After cooling the organic layer was removed and the aqueous solution was evaporated, in vacuo to dryness. The obtained residue was dissolved in methanol (60-100 ml) and left for crystallization. After 1-3 h the crystalline product was collected by filtration. Yield of the product and spectral analyses are summarized in Table 1.

α-Phosphonic and phenylphosphinic analogs of glutamic acid; 4-amino-4-phosphonobutyric acids (**7a-b**)

Ethyl succinate semialdehyde (**6**) (0.15 mol, 19.5 g) was added dropwise to a stirred mixture of benzyl carbamate (**2**) (0.1 mol, 15.3 g), phosphorus trichloride or phenyldichlorophosphine (0,1 mol) and glacial acetic acid (20 ml). The addition was complete within 5 min. The resulting mixture was refluxed for 30 min, treated with concentrated hydrochloric acid (20 ml) and refluxed again for 0.5 h. After cooling, the organic layer was removed and the aqueous solution was purified by boiling with charcoal (2 g). After filtering the solution was evaporated to dryness and obtained residue was dissolved in methanol (30 ml) and treated with propene oxide. The precipitated product was filtered out, washed with ethanol and dried. Phenylphosphinic acid required more time for precipitation.

Yields based on trivalent phosphorus chlorides and spectral data of the obtained compounds (**7a-b**) are given in Table 1.

α-Phosphonic and phenylphosphinic analogs of α-methylpyroglutamic acid (**5a-b**)

Ethyl levulinate (**1**, $n = 2$) (0,3 mol, 43 g) was added dropwise, during 20 min, to a stirred mixture of benzyl carbamate (**2**) (0.2 mol, 30.6 g) phosphorus trichloride or phenyldichlorophosphine (0.2 mol) and glacial acetic acid (40 ml). The obtained mixture was refluxed for 30 min, treated with concentrated hydrochloric acid (40 ml) and refluxed again for 0.5 h. After cooling, the organic layer was removed and the aqueous solution was evaporated in vacuo to dryness. The obtained residue was then dissolved in methanol (60-80 ml) and left for crystallization. The precipitated product was collected by filtration, washed with the mixture of methanol and acetone (1 : 1) and dried. Yields based on the trivalent phosphorus chlorides and spectral data of the products are given in Table 2.

C-alkyl esters of 3-amino-3-phosphonobutyric acids

3-amino-3-phosphonobutyric acid (**4a, b** or **d**) (0.04 mol) was added to a chilled solution of thionyl chloride (15 ml) in alcohol (60-100 ml) and the mixture was shaken vigrously for a few minutes, until most of the solid dissolved. The reaction mixture was then permitted to stand overnight at room temperature, the solvent was evaporated in vacuo. The oily residue was dissolved in ethanol (50 ml) and dry pyridine was added until *pH* reached of about 6. The mixture was then permitted to stand at room temperature until the product precipitated. Alkyl 3-amino-3-phosphonobutyrates were crystallized from the mixture of water and acetone.

For example: Methyl 3-amino-3-phosphonobutyrate: 88% yield, m.p. = 231-232 °C dec.; ^{1}H.-n.m.r. ($D_2O + D_2SO_4$, *HMDS*) δ, pp,: 1.99 (d, $J^3_{PH} = 14.0$ Hz; 3H, CH_3); 3.2-3.5 (m, 2H, CH_2CO); 4.40 (s, 3H, OCH_3). Ethyl 3-amino-3-(P-ethylphosphino)butyrate: 85% yield, oil ^{1}H-n.m.r. ($D_2O + D_2SO_4$, *HMDS*) δ, ppm: 1.92 (t, $J^3_{PH} = 12.5$ Hz, 3H, CCH_3); 3.1-3.4 (m, 2H, CH_2CO); 1.25-2.45 (m, 5H, $PC\mathbf{H}_2C\mathbf{H}_3$); 1.63 (t, $J^3_{HH} = 7.5$ Hz. 3H, $OCH_2C\mathbf{H}_3$); 4.60 (g, $J^3_{HH} = 7.5$ Hz, 2H, OCH_2).

C-amides of 3-amino-3-phosphonobutyric acids

Ethyl 3-amino-3-phosphonobutyrate (0.03 mol) was dissolved in 25% aq. ammonia (100 ml) and the obtained solution was permitted to stand for five days at room temperature. Then the solution was evaporated in vacuo to dryness, dissolved in dilute hydrochloric acid and evaporated again. The oily residue was dissolved in ethanol (50 ml) and pyridine to *pH* of about 6 was added. After several hours the product precipitated off, then was filtered and recrystallized from water—acetone.

For example: 3-amino-3-phosphonobutyramide: 96.5% yield, m.p. = 235-237 °C, dec. ^{1}H-n.m.r. ($D_2O + D_2SO_4$, *HMDS*) δ, ppm: 2.11 (d, $J^3_{PH} = 14.0$ Hz, 3H, C—CH_3); 3.3-3.6 (m, 2H, CH_2CO).

C-alkyl esters of 4-amino-4-phosphonobutyric acid

The standard procedure for esterification, given for alkyl 3-amino-3-phosphonobutyrates was used. The alkyl 4-amino-4-phosphonobutyrates were obtained.

For example: Methyl 4-amino-4-phosphonobutyrate: 84% yield; m.p. = 174—175 °C; ^{1}H-n.m.r. ($D_2O + D_2SO_4$, *HMDS*) δ, ppm: 2.1-3.25 (m, 4H, OOC—$C\mathbf{H}_2C\mathbf{H}_2$); 3.71 (t-t, $J^3_{HH} = 7{,}0$ Hz, $J^2_{PH} = 15.0$ Hz, 1H, CH); 4.07 (s, 3H, $COOCH_3$).

Hydrolysis of phosphonic analog of α-methylpyroglutamic acid; 4-amino-4-phosphonovaleric acid (**14a**)

a) *Acid hydrolysis*

Compound **5a** (5.0 g, 0.028 mol) was dissolved in concentrated hydrochloric acid and the resulting solution was refluxed for 30 h. Then the aqueous solution was evaporated in vacuo to dryness and the oily residue was dissolved in methanol (30 ml), followed by addition of 2 ml propene oxide and 1 ml of pyridine. After few days the product precipitated and was collected by filtrate, washed with ethanol and dried. Pure open-chain product (**14a**) was obtained with 53% yield (Table 1).

The filtrate was evaporated in vacuo to dryness, the obtained residue was dissolved in methanol (15 ml) and acetone (10 ml) was added. After several hours the substrate (**5a**) crystallized out.

b) *Alkaline hydrolysis*

Compound **5a** (1.8 g, 0.01 mol) was dissolved in 2*M*-sodium hydroxide solution (20 ml, 0.04 mol) and refluxed for 20 h. Then the solvent was evaporated in vacuo and the oily residue was refluxed with ethanol (20 ml). The product was filtered, washed with ethanol and suspended in ethanol (20 ml) again, and then refluxed. This operation was repeated several times. Finally the product was suspended in acetone and refluxed again. Filtration yielded semisolid, very hygroscopic substance (**13a**) (Table 1).

Acidification of the alkaline reduction, after the hydrolysis, with concentrated hydrochloric acid to *pH* about 1, evaporation of the obtained solution in vacuo to dryness and dissolving the residue in ethanol, filtration off the sodium chloride and precipitation of the product with propene oxide and pyridine yielded the open chain acid **14a** (Table 1).

Hydrolysis of P-phenylphosphinic analog of α-methylpyroglutamic acid; 4-amino-4-(P-phenyl)phosphinovaleric acid (**14b**)

a) *Acid hydrolysis*

Acid hydrolysis of **5b** (2.4 g, 0.01 mol) in concentrated hydrochloric acid (50 ml) was unsuccessfull.

b) *Alkaline hydrolysis*

Compound **5b** (2.4 g, 0.01 mol) was dissolved in 2*M*-sodium hydroxide solution (20 ml, 0.04 mol) and was refluxed for 20 h. Then the solvent was evaporated in vacuo and the product was purified by refluxing of its ethanol and/or acetone suspensions. Then the product was filtered, washed with acetone and dried. The obtained disodium 4-amino-4-(P-phenyl)phosphinovalerate (**13b**) (Table 1) appeared to be hygroscopic substance.

Acidification of the alkaline solution, after hydrolysis, to *pH* of about 1 with concentrated hydrochloric acid followed by evaporation to dryness, dissolving the residue in ethanol, filtration off the sodium chloride and addition of propene oxide and pyridine yielded the open chain analog (**14b**) (Table 1).

Alcoholysis of phosphonic analog of α-methylpyroglutamic acid (**5a**); *Ethyl 4-amino-4-phosphonovalerate* (**15**)

Compound (**5a**) (1.8 g, 0.01 mol) was added to a chilled solution of thionyl chloride (5 ml) in ethanol (50 ml). The resulting mixture was refluxed for 2 h, cooled and next portion of thionyl chloride was added (5 ml). The reaction mixture was refluxed again for 2 h and the solvent was evaporated. The oily residue was dissolved in ethanol (30 ml) and pyridine (to *pH* of about 6) was added. After several hours the product precipitated. It was collected by filtration, washed with acetone and dried. The yield of the ester (**15**) was 22%.

^{1}H-n.m.r. (D_2O + D_2SO_4, *HMDS*) δ, ppm: 1.56 (t, J^3_{HH} = 7.5 Hz, 3H, $COOCH_2CH_3$); 1.91 (d, J^3_{PH} = 14.5 Hz, 1.5 H, P—C—CH_3); 1.93 (d, J^3_{PH} = 14.5 Hz, 1.5 H, P—CH_3); 2.25—3.25 (m, 4H, CH_2CH_2P); 4.08 (q, J^3_{HH} = 7.5 Hz, 2H, OCH_2); m.p. 136—137 °C dec.

To the filtrate acetone (40 ml) was added and the substrate precipitated. The yield of unreacted product (**5a**) was 74%.

Esterification of 4-amino-4-phosphonenvaleric acid (**14a**); *Ethyl 4-amino-4-phosphonovalerate* (**15**)

4-amino-4-phosphonovaleric acid (2.0 g, 0.01 mol) was added to a chilled solution of thionyl chloride (5 ml) in ethanol (30 ml). The mixture was shaken vigrously for a few minutes until most of the solid dissolved. The resulting solution was left overnight at room temperature and the solvent was evaporated in vacuo. The obtained yellow oil was dissolved in ethanol (50 ml) and pyridine added. After several hours the product precipitated. The yield of the ester was 30%.

To the filtrate acetone (40 ml) was added and the solution was permitted to stand at room temperature for several hours. The unchanged substrate precipitated with 67% yield.

C-methyl P,P-diethyl 4-phosphono-4-oxobutyrate (**10a**)

This compound was prepared by the procedure described by *Asano* et al.[18]. Yield of the product is 91%. The crude product was used to obtain oxime **11a**.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.38 (t, J^3_{HH} = 7.0 Hz, 6H, $POCH_2CH_3$); 2.62 (t, J^3_{HH} = 6.0 Hz, 2H, $—CH_2—CH_2—C$); 3.15 (t-t, J^3_{HH} = 6.0 Hz, $CH_2—CH_2—C$); 3.66 (s, 3H, CH_3OOC); 4.20 (q-q, J^3_{HH} = 7.0 Hz, J^3_{POH} = 7.0 Hz, 4H, $POCH_2$).

Oxime of C-methyl P,P-diethyl 4-phosphono-4-oxobutyrate (**11a**)

The oxime was obtained by the *Asano* method[18] with 93% yield of the crude product.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.34 (t, J^3_{HH} = 7.0 Hz, 6H, $POCH_2CH_3$); 2.45-2.97 (m, 4H, $CH_2—CH_2$); 3.68 (s, 3H, $COOCH_3$); 4.20 (q-q, J^3_{HH} = 7.0 Hz, J^3_{POH} = 7.0 Hz, $POCH_2$); 11.10 (s, 1H, NOH).

C-methyl P,P-diethyl 4-amino-4-phosphonobutyrate (**9a**)

C-methyl P,P-diethyl 4-amino-4-phosphonobutyrate was obtained by the procedure described by *Kowalik* et al.[19] with 49% yield, after purification by oxalic acid salt of **9a**.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.20 (t, J^3_{HH} = 7.0 Hz, 6H, $POCH_2CH_3$); 1.54-2.60 (m, 6H, CH_2CH_2, NH_2); 2.63-3.10 (m, 1H, CH); 3.55 (s, 3H, $COOCH_3$); 3.98 (q-q, J^3_{HH} = 7.0 Hz, J^3_{POH} = 7.0 Hz, 4H, $POCH_2$).

P-Ethyl ester of phosphonic analog of pyroglutamic acid (**12a**)

C-methyl P,P-diethyl 4-amino-4-phosphonobutyrate (**9a**) (12.65 g, 0.05 mol) obtained by the described procedure[19] was heated for 30 min on metal bath (150 °C). Reaction started at 110 °C giving the dense oil.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.27 (t, J^3_{HH} = 7.0 Hz, 3H, $POCCH_3$); 2.05-2.55 (m, 4H, $—CH_2CH_2—$); 3.55-4.4 (m, 5H, $POCH_2$, —CH—); 7.52 (s, 1H, NH).

Phosphonic analog of pyroglutamic acid (**8a**)

The product of cyclization reaction (**12a**) was added to 40% solution of hydrobromide in acetic acid (70 ml) and was permitted to stand at room temperature for 48 h. Then the mixture was evaporated to dryness and the

residue was mixed with ethanol and product solidified. The resulting solid was filtered and recrystallized from water.The yield of pure product was 9.5 g (86%) The analytical data are given in Table 2.

C-methyl P-ethyl 4-(P-phenyl)phosphino-4-oxobutyrate (**10 b**)

This compound was also obtained by the described procedure[18]. The yield of reaction of crude product was 92%.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.25 (t, $J^3_{HH} = 7.0$ Hz, 3H, $POCH_2C\mathbf{H}_3$); 2.48-2.99 (m, 4H, $C\mathbf{H}_2C\mathbf{H}_2$); 3.60 (s, 3H. $COC\mathbf{H}_3$); 3.99 (q-q, $J^3_{HH} = 7.0$ Hz, $J^3_{POH} = 7.0$ Hz, 2H, $POC\mathbf{H}_2$); 7.12-7.98 (m, 5H, phenyl ring).

Oxime of C-methyl-P-ethyl 4-(P-phenyl)phosphino-4-oxobutyrate (**11 b**)

The oxime (**11 b**) was obtained by the described procedure[18] with 93% yield, of the crude compound.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.18 (t, $J^3_{HH} = 7.0$ Hz, 3H, $POCH_2C\mathbf{H}_3$); 2.33-3.15 (m, 4H, $C\mathbf{H}_2C\mathbf{H}_2$); 3.62 (s, 3H, $COOC\mathbf{H}_3$); 3.97 (q-q, $J^3_{HH} = 7.0$ Hz, 2H, $POC\mathbf{H}_2$); 7.05-7.93 (m, 5H, phenyl ring); 11.05 (s, 1H, $NO\mathbf{H}$).

C-methyl P-ethyl 4-amino-4-(P-phenyl)phosphinobutyrate (**9 b**)

The aminoester **9 b** was obtained by the method described by *Kowalik* et al.[19] with 34% yield, after purification by via oxalate of **9 b**.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.23 (t, $J^3_{HH} = 7.0$ Hz, 3H, $POCH_2C\mathbf{H}_3$); 1.67-2.50 (m, 6H, $C\mathbf{H}_2C\mathbf{H}_2$, $N\mathbf{H}_2$); 2.60-3.20 (m, 1H, C**H**); 3.55 (s, 3H, $COOC\mathbf{H}_3$); 3.98 (q-q, $J^3_{HH} = 7.0$ Hz, $J^3_{POH} = 7.0$ Hz, 2H, P—$OC\mathbf{H}_2$); 7.18 8.00 (m, 5H, phenyl ring).

P-ethyl ester of (P-phenyl)phosphinic analog of pyroglutamic acid (**12 b**)

Compound **12 b** was obtained by cyclization of **9 b** (14.2 g, 0.05 mol) by the same procedure as for **12 a**. The product was not purified because it was already chemically pure.

^{1}H-n.m.r. ($CDCl_3$) δ, ppm: 1.23 (t, $J^3_{HH} = 7.0$ Hz, 3H, $POCH_3C\mathbf{H}_3$); 1.78-2.38 (m, 4H, $C\mathbf{H}_2C\mathbf{H}_2$); 3.45-4.27 (m, 5H, $POC\mathbf{H}_2$, C**H**); 7.22 7.93 (m, 6H, phenyl ring, NH).

(P-phenyl)phosphinic analog of pyroglutamic acid (**8 b**)

The ethyl ester **12 b** was acidolized by the means of hydrobromide in acetic acid. The obtained dense oil solidified. It was purified by washings by washings with ethyl ether. The obtained product was hygroscopic and slightly impure. The open-chain product appeared as impurity. It crystallized with ethanol. Data for cyclic **8 b** are given in Table 2.

Acid hydrolysis of phosphonic analog of pyroglutamic acid; 4-amino-4-phosphonobutyric acid (**7 a**)

Cyclic analog **8 a** (1,65 g, 0,01 mol) was dissolved in concentrated hydrochloric acid (50 ml) and refluxed for 8 h. Then the mixture was evaporated to dryness and the oily residue dissolved in ethanol (50 ml). Addition of pyridine was followed by precipitation. The product was filtered and air dried. Yield and physical data of the product are given in Table 1.

Acid hydrolysis of (P-phenyl)phosphinic analog of pyroglutamic acid: 4-amino-4-(P-phenyl-)phosphinobutyric acid (**7b**)

The reaction was carried out like for **7a** starting from cyclic analog **8b** (2.25 g, 0.01 mol). The yield and other data of the product obtained are given in Table 1. It contains traces of cyclic analog (checked by tlc.).

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