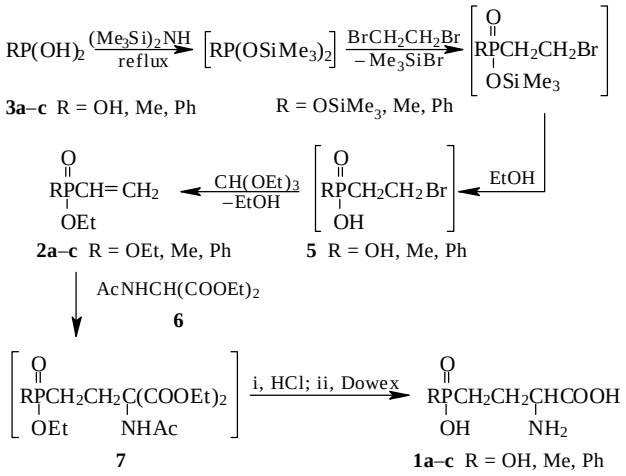
Synthesis of phosphinothricine and other phosphorylic analogues of glutamic acid

Nadezhda R. Kurdyumova, Valery V. Ragulin* and Eugene N. Tsvetkov

Institute of Physiologically Active Substances, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 095 913 2113

A new convenient synthesis of vinylphosphorylic derivatives was used to obtain phosphinothricine and other phosphorylic analogues of glutamic acid.

Phosphonic and phosphinic analogues of glutamic acid of general formula $R(OH)P(O)CH_2CH_2CH(NH_2)COOH$ **1** inhibit glutamine synthetase, an enzyme that plays a pivotal role in the ammonia metabolism of plants and bacteria.[1,2] The corresponding vinylphosphorylic derivatives $RP(O)(OEt)CH=CH_2$ **2** are convenient intermediates for the synthesis of **1**.[3]

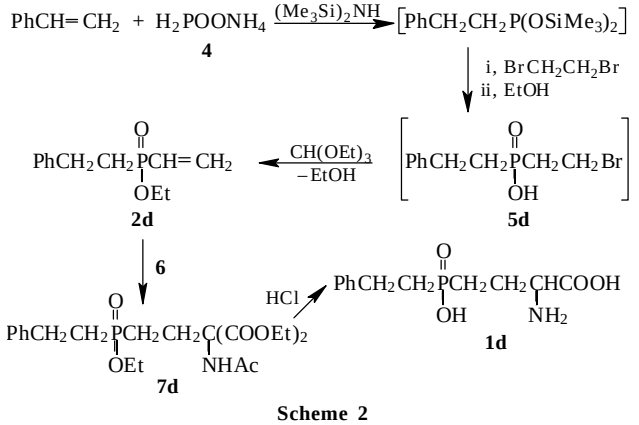


Scheme 1

The aim of this work was to develop a general method for the preparation of 2-amino-4-phosphonobutyric **1a** (R = OH) (AP4), 2-amino-4-(methylphosphino)butyric **1b** (R = Me) (phosphinothricine, PPT) acids and their analogues **1c**–**d** from phosphorous or the corresponding alkylphosphonous acids **3** (Scheme 1) or ammonium hypophosphite **4** (Scheme 2) as starting materials.†

We have found that triethyl orthoformate is an excellent reagent for synthesis of **2**. Dehydrobromination of β-bromoethylphosphorylic derivatives **5** at the same time as esterification gave the desired vinylphosphorylic compounds **2**.

Michael addition of diethyl acetamidomalonate **6** to vinylphosphorylic derivatives **2** in ethanol with sodium alcoholate leads to compounds **7** which were, without isolation, acidic hydrolysed to the amino acids **1** which were chromatographed on Dowex 50W(H^+) (Scheme 1).



Scheme 2

This convenient synthesis of vinylphosphorylic compounds leads to novel analogues of PPT, *e.g.* **1d**, by using styrene in a one-pot synthesis of phosphinic acids[4,5] (Scheme 2).

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† ^1H and ^{31}P NMR spectra were recorded on a Bruker CXP 200 Fourier spectrometer in $CDCl_3$ ($SiMe_4$ as internal standard or 85% H_3PO_4 as an external standard) and in D_2O (acids). The structure of all compounds was confirmed by ^1H and ^{31}P NMR spectra, the constants of previously described esters **2a**–**c**[6–9] and amino acids **1a**–**c**[9–13] were found to be identical with the published ones.

General synthesis of vinylphosphorylic compounds **2a**–**c**. A mixture of **3a**–**c** (0.4mol), hexamethyidisilazane (0.5–0.7mol) and 1,2-dibromoethane (1.8 mol) was stirred for 4h at 100–110 °C. Bromotrimethylsilane and an excess of 1,2-dibromoethane were removed *in vacuo* and ethanol was added to the residue. The solution was refluxed and concentrated *in vacuo*. The residue was treated with triethyl orthoformate (1.2 mol) and the resultant mixture heated under reflux to distill off the ethanol. The residue was purified by distillation to afford **2a**–**c**, 48–64%.

Ethyl (β-*phenylethyl*)*vinylphosphinate* **2d**. A mixture of **4** (0.3 mol), hexamethyldisilazane (0.4 mol) and styrene (0.3 mol) was stirred under an argon atmosphere for 5h at 120–130°C. After cooling 1,2-dibromoethane (1.5mol) was added to the reaction mixture which was then stirred for 5h at 120 °C. The excess of 1,2-dibromoethane and bromotrimethylsilane was removed *in vacuo* and ethanol was added to the residue. The solution was refluxed and evaporated *in vacuo* and the residue obtained treated with an excess of triethyl orthoformate as described above. Distillation afforded **2d**, 58%, oil, bp 153–155 °C/ 3mmHg, n_D^{20} 1.5090. Found: C 64.41; H 7.38; P 13.91. Calc. for $C_{12}H_{17}O_2P$: C 64.31; H 7.61; P 13.78%. ^1H NMR δ: 1.3 (t, 3H), 2.0 (m, 2H), 2.9 (m, 2H), 4.0 (m, 2H), 6.2 (m, 3H) and 7.2 (m, 5H). ^{31}PNMR δ: 41.6.

Phosphorus-containing aminocarboxylic acids **1a**–**d**. A mixture of diethyl acetamidomalonate **6** (0.09 mol) and an excess of the corresponding vinylphosphorylic compounds **2a**–**d** (0.10–0.11mol) in ethanol (20ml) with sodium alcoholate were heated with stirring until **6** disappeared (the process was controlled by TLC, R_f of **6** =0.5–0.6; chloroform: acetone = 4–5 : l). The mixture was dissolved in chloroform and washed with water. In the case of **d** ($R=PhCH_2CH_2$), the previously unknown ester **7d** was also isolated as an individual compound by using column chromatography: yield 62% (based on **2d**), oil, R_f =0.2; chloroform : acetone = 5 : l. ^1HNMR δ: 1.25 (t, 6H), 1.3 (t, 3H), 1.9 (m, 2H), 2.0 (s, 3H), 2.0 (m, 4H), 2.9 (m, 2H), 4.05 (dq, 2H), 4.18 (q, 4H), 7.2 (m, 5H) and 7.6 (s, 1H). ^{31}P NMR δ: 56.0. Usually **7a**–**d** were not isolated. The chloroform solution was evaporated *in vacuo*. HCl (6 M) was added to the residue and the solution was refluxed for 13–15 h. The reaction mixture was washed with ether, concentrated *in vacuo* and the residue purified by chromatography on Dowex 50W(H^+), (eluent HCl, 0.5–0.7 M). The eluate was concentrated and treated with an excess of propylene oxide in water–ethanol. The crystalline precipitate was filtered off and dried to afford compound **1**, 56–67% (based on **2a**–**d**). **1d**: yield 62%; mp 165–170°C (decomp.). Found: C 49.93: H 7.03; N 4.87; P 11.29. Calc. for $C_{12}H_{18}NO_4P\cdot H_2O$: C 50.09; H 6.93; N 4.67; P 10.76%. ^1H NMR δ: 1.3 (m, 2H), 1.6 (m, 2H), 1.8 (m, 2H), 2.5 (m, 2H), 3.5 (t,1H) and 7.1 (m, 5H). ^{31}PNMR δ: 43.9.

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