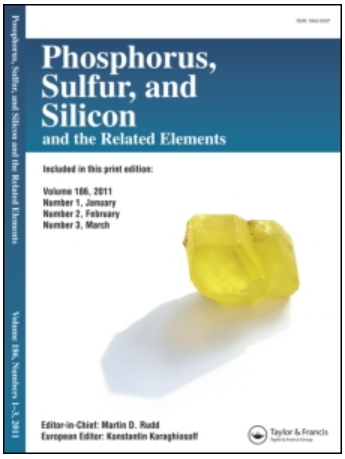


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# PHOSPHORUS-CONTAINING AMINOCARBOXYLIC ACIDS. COMMUNICATION IV.[1] A CONVENIENT METHOD OF PHOSPHONIC ACIDS SYNTHESIS

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# PHOSPHORUS-CONTAINING AMINOCARBOXYLIC ACIDS. COMMUNICATION IV.[1] A CONVENIENT METHOD OF PHOSPHONIC ACIDS SYNTHESIS

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The communication is concerned with the synthesis of phosphonic aminocarboxylic acids by phosphorylation of diethyl ω-halogen alkyl acetamidomalonates with tris(trimethylsilyl) phosphite, followed by alcoholysis and acid hydrolysis of the resulting intermediate esters.

*Key words:* Phosphonic aminocarboxylic acids; tris(trimethylsilyl) phosphite; ω-halogenalkyl acetamidomalonates; phosphorylation; alcoholysis, hydrolysis



Phosphorus-containing aminocarboxylic acids (PAA) exhibit a variety of physiological activities such as anticonvulsive,[2,3] herbicidal[4,5] and antitumor,[6] which fact is responsible for the interest displayed by the researchers to this type of compounds.

The PAA molecules with general formula $(HO)_2P(O)$-A-$CH(NH_2)COOH$ **(I)** are usually constructed by phosphorylation of a hydrocarbon-containing fragment (A) with subsequent addition of an aminoacid function.[4–10] The literature also contains description of a reverse construction of the PAA molecule, consisting in bonding the hydrocarbon fragment to the aminoacid function, phosphorylation of the resulting compounds and acid hydrolysis.[1,11–13] The latter method may be convenient when there is a need for modifying the phosphorus part of the molecule.

This work offers a new version of this method suitable for PAA synthesis. It is distinguished by the fact that the phosphorylation of diethyl-ω-halogenalkyl acetamidomalonates **(II)** and synthesis of a phosphorylating agent occur in a single process: tris(trimethylsilyl)phosphite resulting from hexamethyldisilazane and phosphorous acid is alkylated in the reaction mixture with ester **(II)** by Arbuzov's reaction. The resulting bis(trimethylsilyl)phosphonates **(III)** are converted by alcoholysis to diethyl dihydroxyphosphonyl alkyl acetamidomalonates **(IV)**. The latter are converted to the desired PAA **(I)**, which are also isolated in the form of dimethyl esters **(V)** or diethylammonium salts **(VI)**.

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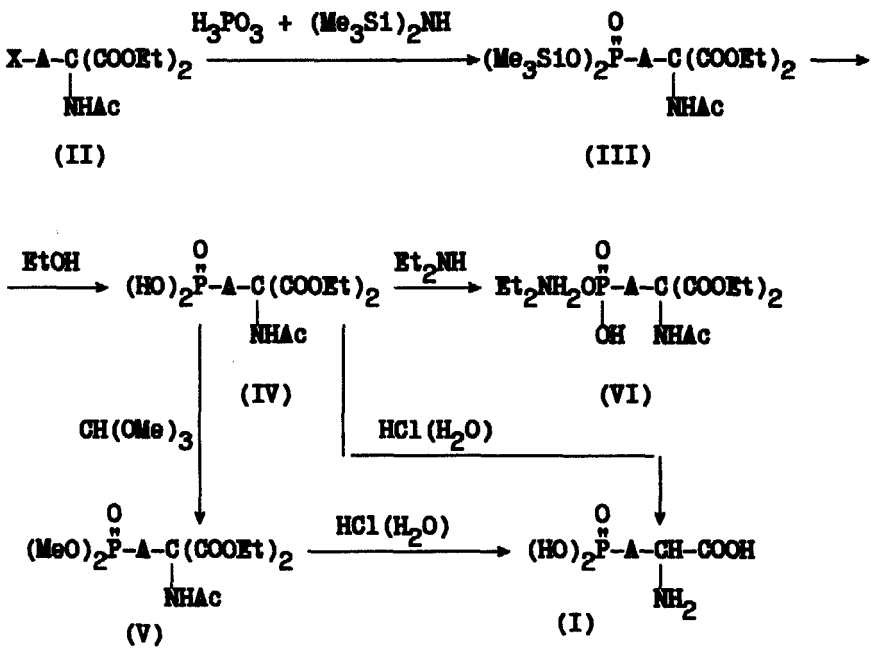


A : $(CH_2)_n$; n = 4(a), 5(b), 6(c), 7(d), 10(e);

$CH_2CH_2OCH_2CH_2$(f); o-$CH_2$-$C_6H_4$-$CH_2$(g)

X: Br, Cl

SCHEME

## EXPERIMENTAL

The PMR and $^{31}P$ NMR spectra were recorded on a Bruker CXP 200 Fourier spectrometer with TMS standards (internal), 85% $H_3PO_4$ (external), and $CDCl_3$ as solvent. The spectra of acids (**I**) were recorded in $D_2O$ while controlling the pH of the solution (Table III) by adding NaOH for improving the solubility

TABLE I

Yields of acids $(HO)_2P(O)$-A-$CH(NH_2)COOH$ (**I**)[a]

| A | Yield (%) |
|---|---|
| **Ia** $(CH_2)_4$ | 62 |
| **Ib** $(CH_2)_5$ | 75 |
| **Ic** $(CH_2)_6$ | 74 |
| **Id** $(CH_2)_7$ | 61 |
| **Ie** $(CH_2)_{10}$ | 58 |
| **If** $CH_2CH_2OCH_2CH_2$[b] | 64 |
| **Ig** o-$CH_2$-$C_6H_4$-$CH_2$[c] | 66 |

[a] From the corresponding ester (**II**); [b] m.p. 236–240°C (with decomp.). Found (%): C 32.1; H 6.6; N 6.3; P 13.3. $C_6H_{14}NO_6P$. Calc. (%): C 31.7; H 6.2; N 6.2; P 13.5; [c] m.p. 238–244°C (with decomp.). Found (%): C 43.1; H 6.1; N 5.3; P 10.8. $C_{10}H_{14}NO_5P \cdot H_2O$. Calc. (%): C 43.3; H 5.8; N 5.1; P 11.1.

TABLE II

Yields, constants and averaged analytical data for compounds **X-A-C(NHAc) $(COOEt)_2$ (II) and (IV–VI)**

| Number of compound | X | A | Yield (%) | M.p. or (°C) ($n_D^{20}$) | Found (%) | | | | Calculated (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | P | Formula | C | H | N | P |
| **IId** | Br | $(CH_2)_7$ | 52[a] | 38 | 48.5 | 7.3 | 3.5 | 19.8[b] | $C_{16}H_{28}BrNO_5$ | 48.7 | 7.2 | 3.6 | 20.3[b] |
| **IIf** | Br | $CH_2CH_2OCH_2CH_2$ | 54[a] | 1.4670 | 42.7 | 5.9 | 4.1 | 21.4[b] | $C_{13}H_{22}BrNO_6$ | 42.4 | 6.0 | 4.0 | 21.7[b] |
| **IIg** | Cl | o-$CH_2C_6H_4CH_2$ | 55[a] | 78–80 | 57.5 | 6.2 | 4.0 | 9.8[c] | $C_{17}H_{22}ClNO_5$ | 57.4 | 6.2 | 3.9 | 10.0[c] |
| **IVa** | $(HO)_2P(O)$ | $(CH_2)_4$ | 84 | 110–112 | 44.2 | 6.8 | 4.0 | 8.7 | $C_{13}H_{24}NO_8P$ | 44.5 | 7.0 | 4.3 | 8.4 |
| **Vb** | $(MeO)_2P(O)$ | $(CH_2)_5$ | 58 | 1.4640 | 48.2 | 7.8 | 3.3 | 7.5 | $C_{16}H_{30}NO_8P$ | 48.6 | 7.6 | 3.5 | 7.8 |
| **Vd** | $(MeO)_2P(O)$ | $(CH_2)_7$ | 63 | 1.4655 | 50.9 | 8.3 | 3.1 | 7.1 | $C_{18}H_{34}NO_8P$ | 51.1 | 8.1 | 3.3 | 7.3 |
| **Vf** | $(MeO)_2P(O)$ | $(CH_2CH_2)_2O$ | 60 | 1.4635 | 45.1 | 6.8 | 3.8 | 7.7 | $C_{15}H_{28}NO_9P$ | 45.3 | 7.1 | 3.5 | 7.8 |
| **Vg** | $(MeO)_2P(O)$ | o-$CH_2C_6H_4CH_2$ | 53 | 105–108 | 52.8 | 6.7 | 3.1 | 6.9 | $C_{19}H_{29}NO_8P$ | 53.1 | 6.6 | 3.3 | 7.2 |
| **VIa** | $Et_2NH_2OP(O)(OH)$ | $(CH_2)_4$ | 57 | 115–118 | 47.7 | 8.1 | 6.3 | 7.0 | $C_{17}H_{35}N_2O_8P$ | 48.0 | 8.2 | 6.6 | 7.1 |
| **VIb** | $Et_2NH_2OP(O)(OH)$ | $(CH_2)_5$ | 48 | 131–134 | 48.7 | 8.5 | 6.4 | 6.6 | $C_{18}H_{37}N_2O_8P$ | 49.2 | 8.4 | 6.4 | 6.9 |
| **VIc** | $Et_2NH_2OP(O)(OH)$ | $(CH_2)_6$ | 50 | 110–112 | 50.1 | 8.5 | 6.0 | 6.4 | $C_{19}H_{39}N_2O_8P$ | 50.3 | 8.6 | 6.2 | 6.7 |
| **VIe** | $Et_2NH_2OP(O)(OH)$ | $(CH_2)_{10}$ | 52 | 104–106 | 53.8 | 8.9 | 5.2 | 5.8 | $C_{23}H_{47}N_2O_8P$ | 54.2 | 9.2 | 5.5 | 6.0 |

[a] From the corresponding $\alpha,\omega$-dihalogenalkane[12]; [b] Br; [c] Cl.

TABLE III

PMR and $^{31}P$ NMR spectra for compounds (I, II, IV–VI)

| Number of compound | δ (ppm) | | | | | | | δ P(ppm) (pH of solution) |
|---|---|---|---|---|---|---|---|---|
| | NH | $CH_2O$ | $CH_3O$ (*j*PH, Hz) | $CH_2CN$ | Ac | $CH_2C$ | $\underline{CH_3}CH_2$ | |
| **If** | 3.88t[a] | 3.58m | — | 2.00m[b] | — | — | — | 23.5(2) |
| **Ig** | 4.00t[a] | 7.20m[c] | — | — | — | 3.30m | 3.02d[d] (16.0) | 20.8(5) |
| **IId** | 6.89s | 4.24m | 1.84m[e] | 2.31m[f] | 2.03s | (1.05 ÷ 1.50)m | 1.27t | — |
| **IIf** | 7.05s | 4.16m | 3.61t[g] | 2.55t | 2.00s | 3.35t[f] | 1.26t | — |
| **IIg** | 6.90s | 4.24m | 7.22m[c] | 3.80s | 1.96s | 4.59s[h] | 1.24t | — |
| **IVa** | — | 4.20m | — | 2.16m | 2.00s | (1.20 ÷ 1.75)m | 1.20t | 32.6(1); 24.5(7) |
| **IVb** | — | 4.12m | — | 2.20m | 1.91s | (1.20 ÷ 1.80)m | 1.14t | 33.4 |
| **IVc** | — | 4.20m | — | 2.30m | 2.06s | (1.30 ÷ 1.90)m | 1.27t | 34.3 |
| **IVe** | — | 4.26m | — | 2.32m | 2.06s | (1.10 ÷ 1.70)m | 1.26t | 30.0 |
| **Vb** | 6.82s | 4.25m | 3.74d (11.0) | 2.33m | 2.06s | (1.05 ÷ 1.80)m | 1.27t | 35.3 |
| **Vd** | 6.81s | 4.25m | 3.73d (11.0) | 2.31m | 2.05s | (1.05 ÷ 1.80)m | 1.28t | 35.7 |
| **Vf**[i] | 7.44s | 4.20m | 3.74d (11.2) | 2.58t | 2.07s | 2.05dt[d] | 1.25t | 31.8 |
| **Vg**[k] | 6.70s | 4.27m | 3.64d (11.0) | 3.76s | 2.10s | 3.18d (22.0) | 1.28t | 29.2 |
| **VIa** | 6.95s | 4.25m | 2.92q[l] | 2.30m | 2.05s | (1.10 ÷ 1.60)m | 1.26m | 25.4 |
| **VIb** | 6.92s | 4.20m | 2.90q[l] | 2.30m | 2.05s | (1.00 ÷ 1.70)m | 1.27m | 25.2 |
| **VIc** | 6.92s | 4.26m | 2.94q[l] | 2.32m | 2.06s | (1.00 ÷ 1.60)m | 1.32m | 26.2 |
| **VId** | 6.90s | 4.24m | 2.92q[l] | 2.28m | 2.06s | (1.00 ÷ 1.60)m | 1.26m | 26.0 |

[a] CHN; [b] $CH_2P$ + $CH_2CN$; [c] $C_6H_4$; [d] $CH_2P$(*j*PH, Hz); [e] $\underline{CH_2}CH_2CN$; [f] δ $CH_2Br$ 3.39t; [g] δ $CH_2OCH_2$ 3.48t; [h] $CH_2Cl$; [i] δ $PCH_2\underline{CH_2}$ 3.56 dt(*j*PH 13.0 Hz); [k] δ $C_6H_4$ 7.20m; [l] $CH_2\underline{N}$.

of the substances. The melting points were measured with a Boetius PHMK instrument. A 100–250 $\mu$ silica gel was used for column chromatography. Esters (**II**) were synthesized as described elsewhere.[1,11] The structure of the new esters (**IId, f, g**) was proved by PMR spectroscopy and confirmed by elementary analysis. Yields, constants, NMR spectroscopic evidence and averaged analytical data for compounds (**I, II, IV–VI**) are listed in Tables I–III.

*General method for the synthesis of acids* (**I**). Ester (**II**) (0.10 mol),[1] $H_3PO_3$ (0.12 mol) and $(Me_3Si)_2NH$ (0.18 mol) were stirred for 4–5 hr under argon at 100–120°C. After cooling the mixture alcohol (70–100 ml) was added. After 12–24 hr (20°C) the mixture was evaporated in vacuo, the residue dissolved in $CHCl_3$ and washed with water to remove excess $H_3PO_3$. The chloroform solution was evaporated in vacuo, the residue dissolved in water (100 ml) and the unreacted compound (**II**) extracted with ether (2–4) × 15 ml) (the process was controlled by TLC, $R_f$ of ester (**II**) 0.7–0.8; chloroform: acetone = 2–4:1). The aqueous solution was evaporated in vacuo and then to the residue were added conc. HCl (120–150 ml) and activated charcoal (1 g). The mixture was boiled for 15 hr. After cooling and filtration the solution was extracted with ether (2 × 15–30 ml) and evaporated in vacuo. HCl was removed by multiple (3–4 times) addition of water with its subsequent evaporation. The residue was dried by azeotropic water distillation with benzene or toluene. The dry residue was dissolved in alcohol (30–50 ml) and dropwise propylene oxide (0.15–0.20 mol) added. The resulting precipitate was washed with alcohol and dried in vacuo at 90°C. The constants of the previously described acids (**Ia–e**) were found to be identical with the published ones.[1,8–12] The structure of the new acids (**If, g**) was proved by PMR and $^{31}P$ NMR spectroscopy and confirmed by elementary analysis (Tables I–III). With another method acids (**I**) were obtained from esters (**V**) (see below). Esters (**IV**) were characterized by PMR and $^{31}P$ NMR spectroscopy (Table III). They represent thick oils, except for compound (**IVa**) which was isolated in crystalline form (Table II).

*General method for the synthesis of esters* (**V**) *and salts* (**VI**). To the phosphonic acid (**IV**) obtained from (**III**) by alcoholysis in the form of an oil was added $CH(OMe)_3$ (50 ml). Excess $H_3PO_3$ was removed by water extraction of the chloroform solution of the reaction mixture (see gen. method for the synthesis of acids (**I**)). The mixture was boiled for 3 hr and the alcohol formed was distilled off. After removal of excess $CH(OMe)_3$ the residue was chromatographed on silica gel to obtain ester (**V**) (eluent-$CHCl_3$).

Esters (**V**) were converted to PAA (**I**) by acid hydrolysis as described above. The yields of (**I**) were 68–73%, based on esters (**V**).

To obtain salt (**VI**), a crude acid (**IV**) produced after alcoholysis and removal of the unreacted $H_3PO_3$, as described above, was treated with $Et_2NH$ in alcohol. Salts (**VI**) was purified by recrystallization from aceton. Their structure was confirmed by NMR spectra and by elementary analysis (Tables II, III).



## REFERENCES

1. V. V. Ragulin, M. E. Bofanova and E. N. Tsvetkov, *Izv. AN SSSR, Ser. Khim.*, **11,** 2590 (1989).
2. J. L. M. Campbell, R. Burtel, H. S. Freidman and D. D. Bigner, *J. Neurochem.*, **45,** 1186 (1985).
3. Z. Kleinrok, K. Kolasa, P. Mastalerz and P. Kafarski, *Pol. J. Pharmacol. Pharm.*, **38,** 435 (1986).
4. L. Maier, *Phosphorus and Sulfur*, **14,** 295 (1983).
5. L. Maier and G. Rist, *Phosphorus and Sulfur*, **17,** 21 (1983).
6. J. Davies and J. S. Watkins, *Brain Res.*, **235,** 378 (1982).
7. J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29,** 832 (1964).
8. P. L. Ornstein, *Org. Prep. Proc. Int.*, **20,** 371 (1988).
9. E. W. Logusch, D. M. Walker, J. F. McDonald, G. C. Leo and J. E. Franz, *J. Org. Chem.*, **53,** 4069 (1988).
10. K. Matoba, H. Yonemoto, M. Fukui and T. Yamazaki, *Chem. Pharm. Bull.*, **32,** 3918 (1984).
11. E. Aboujaoude, N. Collignon, P. Savignac and J. Bensoam, *Phosphorus and Sulfur*, **34,** 93 (1987).
12. E. W. Logusch, *Tetrahedron Lett.*, **27,** 5935 (1986).
13. D. M. Walker, J. F. McDonald and E. W. Logusch, *J. Chem. Soc., Chem. Commun.*, 1710 (1987).