Phosphohomocysteine Derivatives

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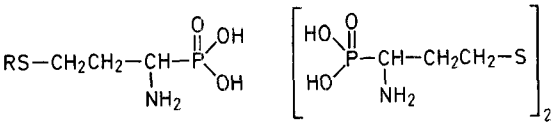
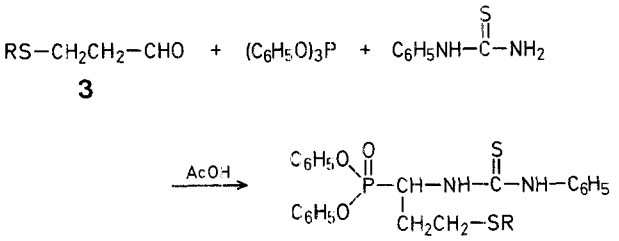
During the last few years a number of aminoalkanephosphonates, phosphonic analogs of naturally occurring amino acids, has been synthesised[1]. The discovery of the antibacterial activity of Alaphosphin (L-alanyl-L-1-aminoethanephosphonic acid)[2] prompted further activity by several research groups on the synthesis of new aminoalkanephosphonates[3]. In this communication we present the synthesis of *S*-substituted derivatives of phosphohomocysteine (**1**) and phosphohomocystine (**2**).



1 **2**

R = alkyl, acyl, trialkoxysilyl

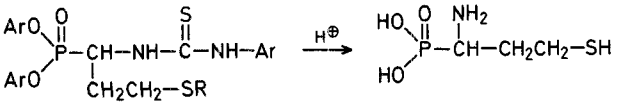
The intermediate *O,O*-diphenyl thioureido-3-substituted-thiopropanephosphonates **4** were obtained according to Ref.[4]; the starting material, *S*-substituted 3-mercaptopropanals **3** were prepared according to Ref.[5]. Treatment of **3** with triphenyl phosphite and phenylthiourea in acetic acid medium gave **4** in high yields; physical constants are given in Table 1.



3 **4**

Hydrolysis of compounds **4** (with the exception of **4f, g, h**) by hydrochloric acid gave the 1-amino-3-alkylthiopropanephosphonic acid **1** in satisfactory yields (Table 2).

Compounds **1** were also prepared by a one-pot procedure through hydrolysis of unisolated **4**. In both approaches, the hydrolysis of compounds **4f, g,** or **h** was accompanied by cleavage of the R—S bond.



4 (Ar = C_6H_5) **5**

Attempts to isolate pure **5** were not successful. For this reason the oxidation of unisolated **5** by means of iodine has been performed and phosphohomocystine **2** was isolated in satisfactory yield. The biological activities of compounds **1**, **2**, and **4** are under investigation.

Melting points were determined on a Böetius apparatus and are not corrected. ^{31}P-N.M.R. spectra were recorded with a Jeol C-60H spectrometer equipped with Heterospin Decoupler SNH-SP-HC at 24.3 MHz with external H_3PO_4 as the reference. Negative chemical shift values are reported for compounds absorbing at higher fields

Table 1. Diphenyl 1-(Thioureido)-3-substituted-thiopropanephosphonates **4**

Product No.	R	Yield [%]	m.p. [°C][a]	Molecular formula[b]	T.L.C.[c] [R_f]	^{31}P-N.M.R. δ [ppm] (AcOH)	(CHCl$_3$)	M.S. *m/e* (relative intensity %)
4a	CH_3	85	175–177°	$C_{23}H_{25}N_2O_3PS_2$ (472.6)	0.68	16.20	17.02	472 (M^+, 19); 457 (3.5); 425 (55); 379 (35); 235 (100)
4b	C_2H_5	80	160–162°	$C_{24}H_{27}N_2O_3PS_2$ (486.6)	0.66	16.20	17.22	486 (M^+, 7); 457 (10.5); 425 (14); 393 (17); 235 (100)
4c	*n*-C_3H_7—	78	90–91°	$C_{25}H_{29}N_2O_3PS_2$ (500.6)	0.68	16.42	17.02	500 (M^+, 2); 457 (3); 425 (4.5); 407 (8.3); 235 (100)
4d	*n*-C_4H_9—	72	91–92°	$C_{26}H_{31}N_2O_3PS_2$ (514.6)	0.68	16.32	16.90	514 (M^+, 9.5); 457 (14); 425 (11); 421 (12); 235 (100)
4e	$C_6H_5CH_2$—	90	99–100°	$C_{29}H_{29}N_2O_3PS_2$ (548.7)	0.70	16.20	17.20	455 (32); 235 (100)
4f	*t*-C_4H_9—	90	134–135°	$C_{26}H_{31}N_2O_3PS_2$ (514.6)	0.63	—	16.52	457 (11); 425 (1); 421 (9); 365 (100)
4g	H_3C—CO—	83	161–163°	$C_{24}H_{25}N_2O_4PS_2$ (500.5)	0.67	15.90	16.70	500 (M^+, 1); 457 (22.5); 425 (10); 407 (33); 365 (100)
4h	(*t*-$C_4H_9O)_3Si$—	76	147–150°	$C_{34}H_{49}N_2O_6PS_2$ (704.9)	0.70	16.22	18.62	704 (M^+, 4); 611 (0.6); 443 (100); 425 (37)

[a] Recrystallized twice from methanol/chloroform.

[b] Microanalysis (C, H, N, P, S) agreed within ±0.3% with the theoretical values; exception: **4e**, C ± 0.57.

[c] Chromatography: Silica-gel 60, F_{254}, developer: iodine, solvent system: chloroform/methanol (9:1).

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Table 2. 1-Amino-3-alkylthiopropanephosphonic Acids **1a–e**

Product	Yield [%] by Method A	Yield [%] by Method B	m.p. [°C][a]	Molecular formular[b]	T.L.C. [R_f][c] solvent I	T.L.C. [R_f][c] solvent II	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CF_3COOH) δ [ppm]	^{31}P-N.M.R. δ [ppm] (CF_3COOH)	^{31}P-N.M.R. δ [ppm] (KOH/H_2O)
1a	70	80	270–272°	$C_4H_{12}NO_3PS$ (185.2)	0.50	0.77	3700–2000, 1640, 1600, 1440, 1240, 1180, 1030, 1000, 925	2.35 (s, 3H, SCH_3); 2.4–2.7 (m, 2H, $CH_2CH_2SCH_3$); 2.99 (t, 2H, CH_2SCH_3); 3.9–4.5 (m, 1H, CH); 7.4–8.9 (br, 3H, NH_3)	16.03	20.34
1b	70	75	261–263°	$C_5H_{14}NO_3PS$ (199.2)	0.55	0.85	3300–2100, 1640, 1600, 1450, 1240, 1170, 1025, 1005, 920	1.33 (t, 3H, SCH_2CH_3); 2.3–3.3 (m, 6H, $CH_2SCH_2CH_2$); 7.4–7.9 (br, 3H, NH_3)	16.17	20.14
1c	57	64	276–278°	$C_6H_{16}NO_3PS$ (213.2)	0.60	0.88	3600–2000, 1645, 1615, 1455, 1240, 1175, 1030, 1020, 930	0.99 (t, 3H, $SCH_2CH_2CH_3$); 1.7 (m, 2H, $SCH_2CH_2CH_3$); 2.0–3.3 (m, 6H, $CH_2CH_2SCH_2$); 3.8–4.4 (m, 1H, CH); 7.3–8.0 (br, 3H, NH_3)	15.89	20.14
1d	60	69	273–275°	$C_7H_{18}NO_3PS \cdot 1/8\ H_2O$ (229.5)	0.73	0.92	3240–2200, 1645, 1610, 1535, 1465, 1220, 1175, 1020, 930	0.95 [t, 3H, $S(CH_2)_3CH_3$]; 1.5 (m, 4H, $SCH_2CH_2CH_2CH_3$); 2.0–3.3 (m, 6H, $CH_2CH_2SCH_2$); 3.8–4.5 (m, 1H, CH); 7.3–8.0 (br, 3H, NH_3)	16.09	20.14
1e	66	64	270–272°	$C_{10}H_{15}NO_3PS$ (260.3)	0.80	0.94	3700–2000, 1650, 1610, 1540, 1230, 1180, 1025, 925	1.5–3.0 (m, 4H, CH_2CH_2S); 3.8–4.3 (m, 3H, $SCH_2C_6H_5$ + CH); 7.35 (s, 5H_{arom}); 7.1–7.8 (br, 3H, NH_3)	—	20.14

[a] Recrystallized twice from ethanol/water.

[b] Microanalysis (C, H, N, P, S) agreed within ±0.3% with theoretical values; exception: **1d** P ± 0.43.

[c] Chromatography: Cellulose plates DC, developer 0.5% ethanolic solution of ninhydrin. Solvent I: n-butanol/acetic acid/water (12:3:5); solvent II: pyridine/acetic acid/water (10:7:3).

than H_3PO_4. ^{1}H-N.M.R. spectra were taken at 80 MHz on a Tesla BS-487 spectrometer. Mass spectra were obtained on a LKB-2091 Spectrometer at 15 eV ionizing energy. Samples were introduced via a direct inlet system. I.R. spectra were measured with Zeiss-Jena UR-10 spectrometer. Product purities were determined from integrated N.M.R. spectra or T.L.C. Tris[*t*-butoxy]silylthiol was obtained according to Ref.[6]. Other thiols, triphenyl phosphite, and acrolein were commercial products. Compounds **3** were distilled before use. *N*-Phenylthiourea was obtained from benzoyl isothiocyanate and aniline[7].

3-(Tris[*t*-butoxy]silyl)-propanal [3; R = (*t*-$C_4H_9O)_3Si$]:
A mixture of tris[*t*-butoxy]silylthiol (14 g, 0.05 mol), acrolein (8.4 g, 0.15 mol), and copper(II) acetate (0.15 g), is stirred at 30 °C for 3 days. Excess acrolein is evaporated in vacuo and the residue is distilled under reduced pressure to give a viscous oil; yield: 7.1 g (44%); b.p. 103–110 °C/0.2 torr.

G.L.C. (OV-101, 10%, 2 m, 150 °C): purity: 95%.

M.S.: *m/e* = 336 (M^+, 2.1%).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.33 (s, 27H, *t*-C_4H_9); 1.55 (t, 2H, SCH_2CH_2CHO); 2.8 (m, 2H, SCH_2CH_2CHO); 9.73 ppm (t, 1H, CHO).

p-Nitrophenylhydrazone: m.p. 114–115 °C.

Diphenyl 1-(Thioureido)-3-alkylthiopropanephosphonates 4:
Into the solution of triphenyl phosphite (0.02 mol) and aldehyde **3** (0.025 mol) in glacial acetic acid (10 ml), powdered *N*-phenylthiourea (0.02 mol) is added in one portion. The reaction mixture is stirred at room temperature for 0.5 h and for 0.5 h at 80 °C (oil bath temperature). After cooling of the reaction mixture to room temperature, water (5 ml) is added and the solution is maintained at room temperature for 10 h. The precipitate is filtered off, washed with 1:1 acetic acid/water (5 ml), dried with potassium hydroxide in an evacuated dessicator and recrystallised from chloroform/methanol. The purity was checked by T.L.C., developing system 9:1 chloroform/methanol, and by means of mass-spectrometry and ^{31}P-N.M.R. spectrometry. The yields and physical constants of all **4** obtained are given in Table 1.

1-Amino-3-alkylthiopropanephosphonic Acids 1:
Method A: Compound **4** (0.010 mol) is dissolved in glacial acetic acid (5 ml) and hydrochloric acid (36%, 20 ml) and the mixture is heated under reflux for 7–8 h. The solvents are evaporated under reduced pressure and the residue is dissolved in ethanol (20 ml). The solution is treated with propylene oxide until pH 6 is reached. The precipitated aminoalkanephosphonic acid **1** is filtered off, washed with ethanol, and dried under vacuum over potassium hydroxide. Recrystallisation from ethanol/water gives the desired aminoalkanephosphonic acid **1**, which was identified by ^{31}P-N.M.R., ^{1}H-N.M.R., I.R. spectrometry, and paper chromatography. The yields and analytical data are collected in Table 2.

One-Pot Method B: A mixture of triphenyl phosphite (3.1 g, 0.01 mol), aldehyde **3** (0.012 mol), and *N*-phenylthiourea (1.52 g, 0.01 mol) in glacial acetic acid (10 ml) is stirred for 1 h at 70 °C (oil bath) and crude **4**, without isolation, is treated with 36% hydrochloric acid (20 ml) and refluxed for 7–8 h. Product **1** is isolated analogously as described in Method A.

Phosphohomocystine (2):
To a solution of **4f**, **g**, or **h** (0.01 mol) in glacial acetic acid (10 ml) aqueous hydrobromic acid (d = 1.38 g/ml, 20 ml) is added and the mixture is heated under reflux for 14 h. The solvents are evaporated under reduced pressure. The residue is dissolved in ethanol (10 ml) and treated with a solution of iodine (1.4 g, 0.052 mol) in ethanol (10 ml). The mixture is stirred for 15 min and propylene oxide is added until pH 6 is reached. The precipitated crude phosphohomocystine **(2)** is filtered off, washed with ethanol (10 ml) and water (10 ml), and dissolved in ethanol/water/36% hydrochloric acid (10:10:1.5). The amino acid is again precipitated with propylene oxide. Phosphohomocystine is filtered off, washed with ethanol and water, and dried in vacuum over potassium hydroxide; yield: 64–77%; m.p. 271–273 °C.

$C_6H_{18}N_2O_6P_2S_2 \cdot 1/8\ H_2O$
(342.5)

calc.	C 20.90	H 5.41	N 8.13	P 17.99	S 18.63
found	21.13	5.43	7.85	18.10	18.22

^{31}P-N.M.R. (CF_3COOH): δ = 16.03, 16.34 ppm; (2 normal KOH): δ = 20.04 ppm.

^{1}H-N.M.R. (CF_3COOH): δ = 2.0–3.5 (m, 4H, $CHCH_2CH_2S$); 3.8–4.8 (m, 1H, CH); 7.0–8.0 ppm (broad s, 3H, NH_3).

I.R. (KBr): ν = 3640–2100, 1640, 1540 (broad), 1440, 1260, 1190, 1065, 905 cm^{-1}.

This project was financially assisted by Polish Academy of Sciences, Grant no. MR-1-12.1.7.10.

Received: May 19, 1980

[1] D. Redmore, in *Topics in Phosphorous Chemistry*, E. J. Griffith, H. Grayson, Eds., Vol. 8, John Wiley & Sons, New York, 1976.
[2] F. Atherton et al., *Nature, London* **272**, 56 (1978).
F. Atherton et al., *Antimicrob. Agents Chemother.* **15**, 677 (1979).
[3] P. Mastalerz, J. Zygmunt, *Pol. J. Chem.* **52**, 2271 (1978).
A. Dehanel, G. Lavielle, *Bull. Soc. Chim. Fr.* **1978**, II-95.
J. Spitzmeller et al., *Tetrahedron Lett.* **1979**, 4929.
[4] Z. H. Kudzin, W. J. Stec, *Synthesis* **1978**, 469.
[5] F. Pearson et al., *J. Am. Chem. Soc.* **70**, 1450 (1948).
[6] W. Woynowski, R. Piękoś, *Z. Anorg. Allg. Chem.* **314**, 189 (1962).
[7] K. L. Frank, U. P. Smith, *Org. Synth.* **28**, 89 (1948).

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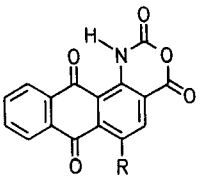
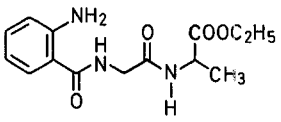
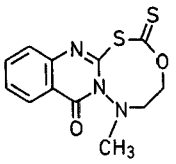
G. M. Coppola, *Synthesis* **1980** (7), 505–536;
The structures of compounds **43** (p. 511), **122** (p. 520), and **241** (p. 533) should be as shown below:



43

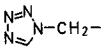


122



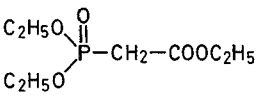
241

J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, A. Zugaza-Bilbao, *Synthesis* **1980** (7), 547–551;
The substitutent R^1 in Table 1 entries 2 and 20 and Table 2, entry 1 should be:



A more correct name for reagent **4** (as used in index) is **3,3'-(Chlorophosphinylidene)-bis[2-oxo-1,3-oxazolidine].**

J. Becher, *Synthesis* **1980** (8), 589–612;
The structure of compound **36** (p. 593) should be:



36

H. Paulsen, F. R. Heiker, J. Feldmann, K. Heyns, *Synthesis* **1980** (8), 636–638;
The correct name for reagent **1** is **3-methyl-2-selenoxo-2,3-dihydro-1,3-benzothiazole.**

G. Sosnovsky, J. A. Krogh, *Synthesis* **1980** (8), 654–656;
The first line of the text should read:
In 1978, Olah and Vankar reported[1] the conversion of

D. A. Walsh, *Synthesis* 1980 (9), 677–688;
The correct name for compound **39** (p. 680) is ***N'*-(2-Carboxyphenyl)-*N,N*-dimethylformamidine.**

M. A. Smoczkiewicz, J. Jasiczak, *Synthesis* **1980** (9), 739–740;
Compounds **2** should be named as **20,21-dioxo derivatives**; the name for compound **1a** (p. 740, Table 1) should be **21-hydroxy-3,20-dioxopregn-4-ene.**

Abstract 5878, *Synthesis* **1980** (9), 759;
The title should be: **Hydrofluorination, Halofluorination, and Nitrofluorination of Alkenes and Alkynes by Pyridinium Poly(Hydrogen Fluoride).**

Abstract 5885, *Synthesis* **1980** (9), 761;
The title should be: **Alkylation of *S*-Methyl 3-Oxoalkanethioates.**

T. Wagner-Jauregg, *Synthesis* **1980** (10), 769–798;
The name of compounds **552a** and **b** (p. 772) should be ***cis*-** and ***trans*-1-methyl-3-phenylindan.**
The heading for Table 2 (p. 784) should be:
Tabelle 2. Herstellung von 1-Arylacenaphthen-Derivaten durch Photocyclisierung von 1-(1-Arylethenyl)-naphthalin-Derivaten in Abwesenheit von Oxidationsmitteln[441].
The structures of the products in this Table should be of the type:

The first paragraph on p. 785 (right-hand side) should read:
Aus den konjugierten 1,2-Diiminen **667** und Phenyl-isocyanaten oder Benzoyl-isocyanat entstehen criss-cross-Addukte (**668**, Schema **2.2.1.-E**)[480,481].

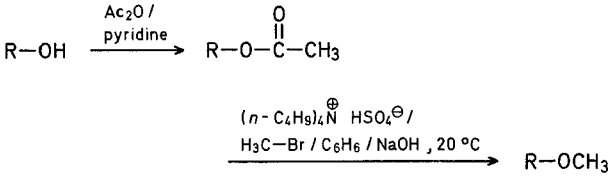
The last line on p. 794 should read:
und der Hydroxamsäuren[552] deutlich gesteigert[553].

Reference 441 (p. 796) should be:
[441] R. Lapougade, R. Koussini, H. Bouas-Laurent, *J. Am. Chem. Soc.* **99**, 7374 (1977).

H. Alper, D. E. Laycock, *Synthesis* **1980** (10), 799;
The last structure for R^1-R^2 in the Table should be:

T. Takajo, S. Kambe, *Synthesis* **1980** (10), 833–836;
Products designated as **4a,b,c,d** in Table 1 (p. 834) and Table 2 (p. 835) should be designated as **4a,b,f,g,** respectively.

P. Di Cesare, P. Duchaussoy, B. Gross, *Synthesis* **1980** (11), 953–954;
The first formula scheme (p. 954) should be:



Z. H. Kudzin, W. J. Stec, *Synthesis* **1980** (12), 1032–1034;
The heading for the first procedure (p. 1033) should be: **3-(Tris-[*t*-butoxy]silylthio)-propanal [3; R = (*t*-$C_4H_9O)_3Si$].**

R. E. Zipkin, N. R. Natale, I. M. Taffer, R. O. Hutchins, *Synthesis* **1980** (12), 1035–1036;
The substituents R^1-R^2 in the Table for product **4e** should be:
$-(CH_2)_2-C[=C(CH_3)_2]-CH_2-$

Abstract 5948, *Synthesis* **1980** (12), 1040;
Compounds **2** should be named **carboximidium dichlorides.**

Abstract 5963, *Synthesis* **1980** (12), 1045;
The title should be: **Acyl Fluorides, Chlorides, Bromides, and Iodides from Carboxylic Acids.**

Abstract 5973, *Synthesis* **1980** (12), 1047;
The title should be: **Acetoxylation-Arylselenylation of Alkenes.**