Synthesis of Phosphomethionine and Related Compounds

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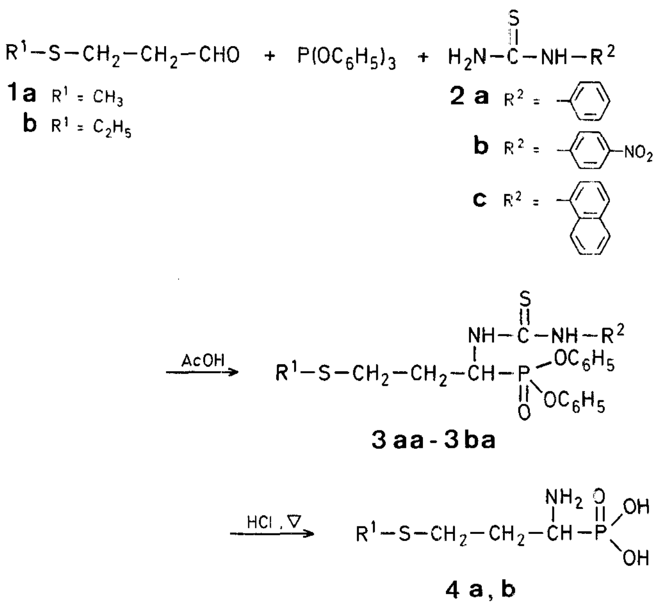
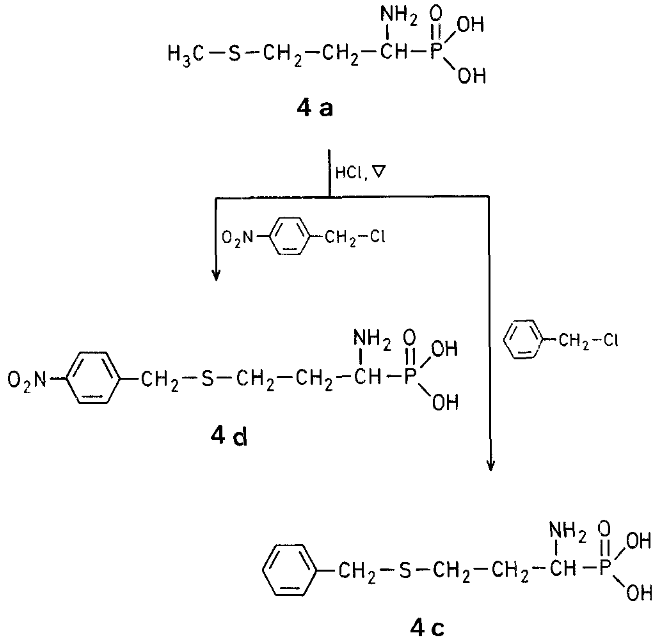
A number of phosphonic analogs of essential amino acids have been synthesized in the last decade[1,2] and recent publications have indicated that some aminoalkanephosphonic acids and peptides containing them are biologically active[3]. In a program designed to synthesize a number of α-aminoalkanephosphonic acids by various methods[4], and to extend our knowledge of their biological properties, we have synthesized the phosphonic analogs of methionine, ethionine, and a number of related compounds. A very recent publication on a related study[5] prompted us to report our results at this time.

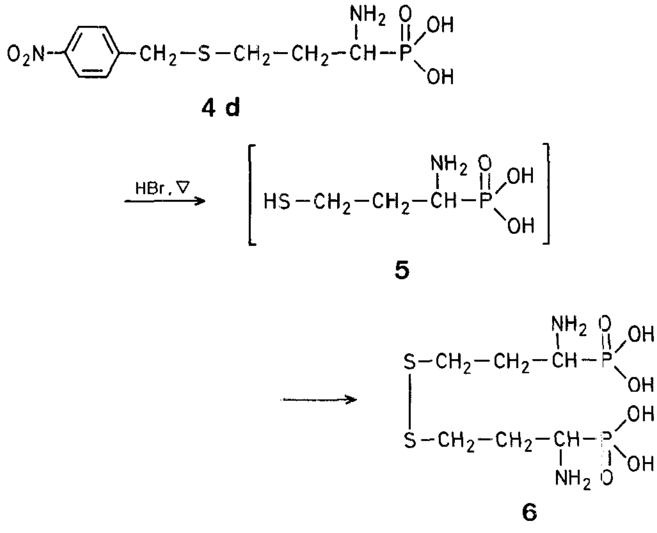
We chose to synthesize phosphomethionine (**4a**) and to prepare some related derivatives from it by starting with 3-methylthiopropanal (**1a**) since the latter is manufactured industrially as an intermediate in the production of DL-methionine and "methionine hydroxyanalog". Both compounds are used commercially in the fortification of animal feeds[6]. Phosphoethionine (**4b**) was also synthesized but from 3-ethylthiopropanal (**1b**) which we prepared from acrolein and ethylmercaptan[7]. Both aldehydes, **1a** and **1b**, were converted into their respective aminoalkanephosphonic acids **4a** and **4b** by treatment with triphenyl phosphite and phenylthiourea (**2a**) in acetic acid, followed by hydrolysis of the resulting thioureide **3** in hydrochloric acid[2]. This sequence worked elegantly and successfully lent itself to large scale laboratory production starting with over two mol of **1a**. The first reaction in this sequence proceeded smoothly with other arylthioureas, **2b** and **2c**, although the yields were lower.



The *S*-benzyl derivative **4c** was prepared from **4a** in moderate yield by refluxing with benzyl chloride in hydrochloric acid. Since **4a** can be prepared in large quantities and in high yields from readily available reagents, this method provides for a convenient synthesis of **4c**, and thus eliminating the preparation of 3-benzylthiopropanal as a starting material required by the method of Ref.[5]. Similarly, **4d** was prepared from **4a** and *p*-nitrobenzyl chloride in good yield.



Our procedure for the synthesis of phosphohomocystine (**6**) is also different from that reported[5]. Various attempts to prepare **5** or **6** by treatment of **4c** or **4d** with sodium in liquid ammonia or in refluxing butanol[8], or with hydrogen bromide gas in acetic acid solution failed. However, refluxing a solution of **4d** in 48% hydrobromic acid provided, after neutralization, a yellow solid (possibly **5**) which rapidly air-oxidized to **6** in good yield. Under these conditions, *p*-nitrobenzyl bromide was obtained as the by-product.



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We have also prepared the sulfoxide, the sulfone, and the methylsulfonium iodide derivatives of phosphomethionine. Treatment of **4a** with a slight excess hydrogen peroxide[9] in glacial acetic acid gave the sulfoxide **7** in 87% yield while treatment of **4a** with two equivalents of hydrogen peroxide gave the sulfone **8** in 67% yield. The methylsulfonium iodide derivative **9** was readily formed by treating phosphomethionine with excess methyl iodide.

Phosphoethionine and the sulfoxide and sulfone of phosphomethionine were prepared for biological studies since the corresponding analogs in the amino acid series are enzyme inhibitors[10]. The methylsulfonium iodide salt of phosphomethionine is of interest because the corresponding methylsulfonium halide of methionine has been reported to be present in cabbage leaves and is thought to have anti-ulcer activity[11].

Physical and spectral data of all products are shown in the Table. Melting points were determined on a Mel-Temp apparatus and are corrected. ^{1}H-N.M.R. spectra were taken at 200 MHz with a Varian XL-200 spectrometer.

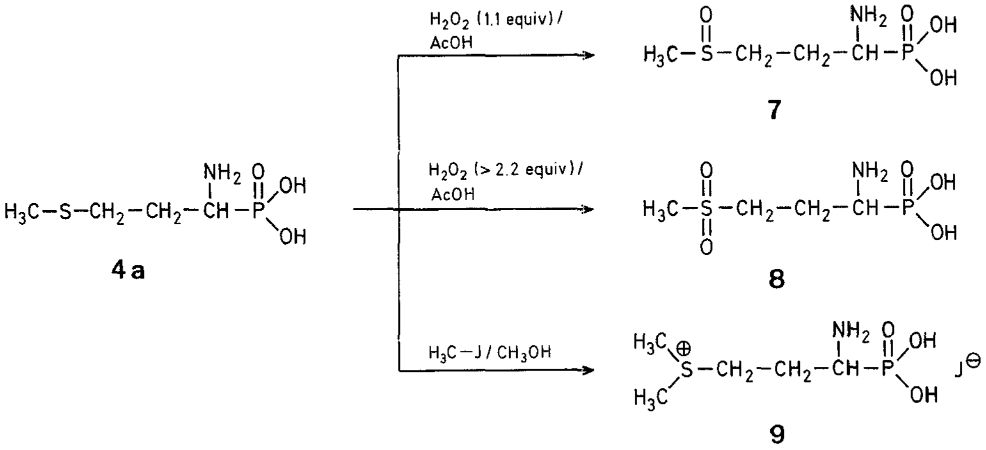

Table. 1-Amino-3-substituted-thiopropanephosphonic Acids and Derivatives

Product No.	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	^{1}H-N.M.R. (solvent)[b] δ [ppm]
3aa	CH_3	C_6H_5	86	175–176° ($CHCl_3$)	$C_{23}H_{25}N_2O_3PS_2$ (472.6)	2.02 (m, 1H); 2.08 (s, 3H); 2.35 (m, 1H); 2.70 (t, 2H, J=8 Hz); 5.88 (m, 1H); 6.79 (br d, 1H, J=9 Hz); 7.28 (m, 15H); 8.18 (br s, 1H)
3ab	CH_3	4-O_2N—C_6H_4	56	186–187° (2-butanone)	$C_{23}H_{24}N_3O_5PS_2$ (517.6)	2.00 (m, 1H); 2.12 (s, 3H); 2.36 (m, 1H); 2.69 (t, 2H, J=8 Hz); 6.05 (m, 1H); 7.03 (br d, 1H, J=8 Hz); 7.30 (m, 10H); 7.44 (d, 2H, J=10 Hz); 8.06 (d, 2H, J=10 Hz); 9.25 (br s, 1H)
3ac	CH_3	1-naphthyl	41	153–155° (C_6H_6 or CCl_4)	$C_{27}H_{27}N_2O_3PS_2$ (522.6)	1.92 (m, 1H); 2.00 (s, 3H); 2.30 (m, 1H); 2.66 (t, 2H, J=8 Hz); 5.85 (m, 1H); 6.38 (br, 1H); 6.92–8.02 (m, 17H); 8.14 (br, 1H)
3ba	C_2H_5	C_6H_5	88	157–158° ($CHCl_3$)	$C_{24}H_{27}N_2O_3PS_2$ (486.6)	1.22 (t, 3H, J=7 Hz); 1.98 (m, 1H); 2.32 (m, 1H); 2.54 (q, 2H, J=7 Hz); 2.72 (t, 2H, J=8 Hz); 5.91 (m, 1H); 6.97 (br d, 1H, J=9 Hz); 7.28 (m, 15H); 8.36 (br s, 1H)
4a	CH_3	—	95	274–275°	$C_4H_{12}NO_3PS$ (185.2)	2.12 (s, 3H); 2.15 (m, 2H); 2.74 (m, 2H); 3.44 (m, 1H)
4b	C_2H_5	—	64	272–273°	$C_5H_{14}NO_3PS$ (199.2)	1.23 (t, 3H, J=7 Hz); 2.03 (m, 1H); 2.22 (m, 1H); 2.64 (q, 2H, J=7 Hz); 2.78 (m, 2H); 3.42 (m, 1H)
4c	$C_6H_5CH_2$	—	32	245–247°	$C_{10}H_{16}NO_3PS$ (261.3)	2.12 (m, 2H); 2.59 (m, 2H); 3.82 (m, 1H); 3.84 (s, 2H); 7.44 (m, 5H)
4d	4-O_2N—C_6H_4—CH_2	—	66	246–248°	$C_{10}H_{15}N_2O_5PS$ (274.3)	2.13 (m, 2H); 2.74 (m, 2H); 3.68 (m, 1H); 3.94 (s, 2H); 7.66 (d, 2H, J=8 Hz); 8.26 (d, 2H, J=8 Hz)
6	—	—	65	272–274°	$C_6H_{18}N_2O_6P_2S_2$ (340.3)	2.18 (m, 2H); 2.26 (m, 2H); 2.92 (m, 4H); 3.42 (m, 2H)
7	—	—	87	188–190°	$C_4H_{12}NO_4PS$ (201.2)	2.28 (m, 2H); 2.77 (s, 3H); 3.16 (m, 2H); 3.40 (m, 1H)
8	—	—	67	258–260°	$C_4H_{12}NO_5PS$ (217.2)	2.37 (m, 2H); 3.18 (s, 3H); 3.44 (m, 1H); 3.52 (m, 2H)
9	—	—	76	287–289° (dec)	$C_5H_{15}JNO_3PS$ (327.1)	2.34 (m, 2H); 2.98 (s, 6H); 3.42 (m, 1H); 3.56 (t, 2H, J=7 Hz)

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.42, N ±0.22.

[b] Spectra of **3** were taken in $CDCl_3$ using tetramethylsilane as internal standard; **4d** was taken in 10% DCl/D_2O, and **4a–4c**, **6**, **7**, **8**, and **9** were taken in D_2O using sodium trimethylsilylpropanoate as internal standard.

Diphenyl 1-(N-Arylthioureido)-3-alkylthiopropanephosphonates 3:
A mixture of aldehyde **1a** or **1b** (0.10 mol), triphenyl phosphite (24.8 g, 0.08 mol), and N-arylthiourea **2a, 2b,** or **2c** (0.08 mol) in glacial acetic acid (40 ml) is stirred at room temperature for 2 and 10 h for **3aa** and **3ba**, respectively. For cases **3ab** and **3ac**, the mixtures are heated at 60–100 °C for 0.5 h to effect solution, before cooling to room temperature and stirring for an additional 3 h. The precipitates that result in all cases are filtered, washed successively with acetic acid and ethanol, and air-dried. Analytical samples are recrystallized from appropriate solvents.

1-Amino-3-alkylthiopropanephosphonic Acids 4a and 4b:
Thioureide **3aa** (30.5 g, 65 mmol) is suspended in glacial acetic acid (50 ml) and concentrated hydrochloric acid (50 ml) and the mixture is heated to reflux with stirring for 7 h. After cooling, the solution is diluted with water (25 ml) and extracted with dichloromethane (3 × 25 ml). The aqueous layer is concentrated under reduced pressure and the crystalline residue dissolved in ethanol (150 ml) and concentrated hydrochloric acid (10 ml). The hot solution is filtered, cooled, and treated with propylene oxide (20 ml). Filtration followed by washing with ethanol and air-drying affords white crystalline phosphomethionine **(4a)**. Phosphoethionine **(4b)** is obtained similarly from **3ba**.

1-Amino-3-benzyl- and 1-Amino-3-p-nitrobenzylthiopropanephosphonic Acids (4c and 4d):
To a solution of **4a** (7.1 g, 38 mmol) in concentrated hydrochloric acid (150 ml) is added benzyl chloride (4.8 g, 38 mmol). The mixture is refluxed for 15 h, cooled, and washed with ether (3 × 50 ml). The aqueous layer is brought to dryness, the residue is taken up in water (25 ml), and triturated until a white solid is formed. Filtration followed by washing successively with water, ethanol, and ether affords pure **4c.**

A similar reaction of **4a** (1.42 g, 7.6 mmol) and p-nitrobenzyl chloride (1.31 g, 7.6 mmol) in hydrochloric acid (150 ml) gives **4d**. In the latter case, the crude product is washed with dichloromethane (3 × 20 ml) instead of ether before bringing down to dryness as before.

Phosphohomocystine (6)[12]:
A solution of **4d** (3.0 g, 9.8 mmol) in concentrated hydrobromic acid (40 ml) is refluxed overnight, cooled, and washed with chloroform (4 × 25 ml). The aqueous layer is brought to dryness and the residue is dissolved in methanol (35 ml). Propylene oxide is added until pH 6 is reached and a yellow solid appears, which is filtered and washed successively with methanol and ether. The yellow solid obtained is rapidly air-oxidized to a brown crust, which is dissolved in water/methanol/concentrated hydrobromic acid, brought to neutral pH by addition of propylene oxide and filtered to give **6** as a beige solid.

Phosphomethionine Sulfoxide (7):
To a suspension of **4a** (10.0 g, 54 mmol) in glacial acetic acid (100 ml) at 0 °C is added aqueous hydrogen peroxide (30%, 7 ml, 62 mmol) carefully. After stirring for 10 min, the solution is concentrated under reduced pressure and diluted with water (5 ml) and methanol (50 ml). Acetone (75 ml in total) is slowly added to the warm solution until it becomes cloudy. On cooling to room temperature, white solids appear, which are filtered and recrystallized from water/methanol/acetone to give pure sulfoxide **7.**

Phosphomethionine Sulfone (8):
To a mixture of **4a** (2.0 g, 10.8 mmol) in glacial acetic acid (25 ml) is added hydrogen peroxide (30%, 2.4 ml, 21.1 mmol) portionwise and the mixture is stirred at room temperature for 3 days. Methanol (30 ml) and acetone (100 ml) are added. The precipitate is filtered, washed with acetone and ether, and recrystallized from water/methanol to give sulfone **8.**

Phosphomethionine Methylsulfonium Iodide (9):
A stirred suspension of **4a** (1.8 g, 10 mmol) in methanol (30 ml) containing methyl iodide (6 ml, 0.1 mol) is boiled under reflux for 24 h during which time the starting solid goes into solution and the nicely crystalline product separates. Essentially pure **9** is separated by filtration and washed copiously with methanol.

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[12] For large scale preparation of **6**, we have recently found that the procedure of Kudzin and Stec[5] is superior to the one we have reported here.

