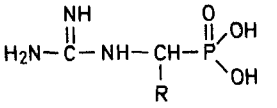
Guanidinophosphonic Acids

Józef Oleksyszyn, Roman Tyka*, Przemysław Mastalerz

Institute of Organic and Physical Chemistry, Technical University (Politechnika), 50-370 Wrocław, Wyb. Wyspiańskiego 27, Poland

In continuation of our research program concerned with the synthesis[1], chemical reactivity[2], biochemistry[3], and chelating properties[4] of aminophosphonates, it was desirable to prepare a series of guanidinophosphonic acids **1**.

A few years ago there was described[5] a phosphonic analogue of creatine **2**, and more recently, the compounds **3** were prepared by French workers interested in biochemical properties of guanidinophosphonates[6]. However, the details of preparation and properties of **3** were not described, except for microanalysis and chromatographic data.



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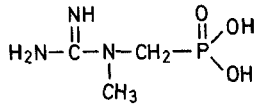

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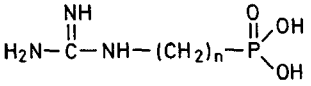
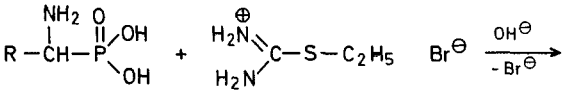


3 n = 1, 2, 3

In this communication we describe two general procedures for the preparation of 1-guanidinophosphonic acids. The first one, (Method A) starting from 1-aminophosphonic acids (**4**) and involving standard amidination with *S*-ethylisothiouronium bromide affords good yields of **1** but requires prior synthesis of **4**.



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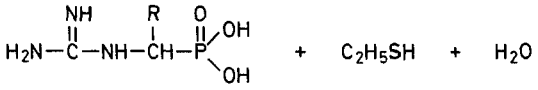

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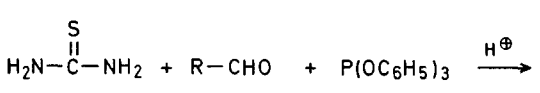
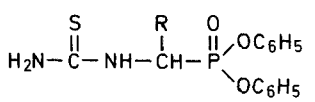
To avoid this difficulty we have developed a procedure (Method B) starting from simple substrates such as thiourea, aldehydes, and triphenyl phosphite which condense readily to give 1-thioureidophosphonates **5** and diphosphonates **6**.





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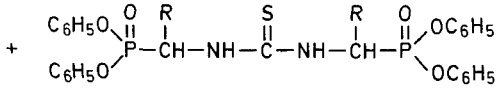
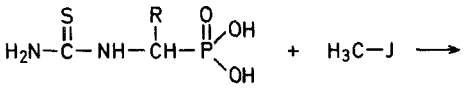


6

Only one example of similar condensation has been described by Birum[7].

The crude intermediates **5** were isolated as the free acids **7** from the mixture of **5** and **6** after hydrolysis. Treatment of **7** with methyl iodide gave the *S*-methylated products **8** which were reacted with ammonia to give **1**.



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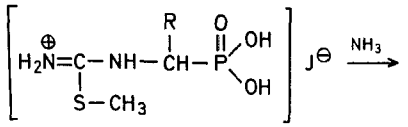

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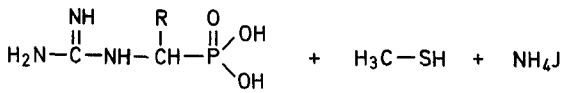

1

Although the yields of **5** are low, the whole procedure is rapid and cheap because of the availability of the substrates. Another advantage is that the products are readily isolated in the pure state.

Our attempts to obtain **1** from 1-hydroxy- or 1-chlorophosphonates and guanidine met with little success. The hydroxyphosphonates did not give the desired product, while the yields obtained from chlorophosphonates were low and the products difficult to isolate.

Preparation of Guanidinophosphonic Acids 1:

Method A: A stirred solution of an aminophosphonic acid (**4**: 0.1 mol) in aqueous 4 normal sodium hydroxide (75 ml) is kept at 45–55°, and *S*-ethylisothiouronium bromide (37.2 g, 0.2 mol) in water (20 ml) is added over 4 h. Stirring is continued at 45–55° for 1 h and then the mixture is left for crystallisation in a refrigerator. After 2–4 days, the resultant crystals are separated, dissolved in a small amount of hot water, and acidified with acetic acid. The resultant product is filtered, washed with alcohol, and air-dried. For yields and characteristic data see Table.

Method B: A stirred mixture of thiourea (15.2 g, 0.2 mol), triphenyl phosphite (62.2 g, 0.2 mol), glacial acetic acid (2 ml), and toluene (30 ml) is warmed to 80° and freshly distilled aldehyde (0.2 mol) is added dropwise during 0.5 h (exothermic reaction). After addition of all the aldehyde, the mixture is heated for 15 min under reflux. Then water (15 ml) and acetonitrile (20 ml) are added and the mixture is refluxed. After 2 h another portion of water (50 ml) is added, the mixture is boiled for 15 min, and allowed to cool. The organic layer is removed and the water evaporated at reduced pressure. The residual oil (**7**) is treated with methyl iodide (12.5 ml) and methanol (50 ml) and refluxed for 6 h. After cooling (ice-bath) an additional portion of methanol (50 ml) is added and gaseous ammonia is passed for 4 h through the solution. The resultant precipitate is dissolved in water (100 ml) and methanol (30 ml), acidified with acetic acid, and left for crystallisation. The product is filtered, washed with alcohol, and air-dried. The results are summarised in the Table.

Table. 1-Guanidinoalkanephosphonic Acids (**1**)

R	Method	Yields [%]	M.p. (dec.)	Molecular formula[a]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($D_2O + D_2SO_4$) δ [ppm]
H	A	75	321–322°	$C_2H_8N_3O_3P \cdot 1.5H_2O$ (180.1)	3620–2100 (broad); 1750–1550 (broad); 1460; 1440; 1300; 1250; 1230; 1150; 1080; 1030; 960; 920	3.68 (d, 2H, J_{P-H} = 12 Hz)
CH_3	A	42	286–287°	$C_3H_{10}N_3O_3P$ (167.1)	3560–2200 (broad); 1750–1550 (broad); 1470; 1450; 1385; 1330; 1255; 1210; 1170; 1140; 1075; 1000; 890	1.82 (dd, 3H, J_{H-H} = 7 Hz, J_{P-H} = 17 Hz); 4.05–4.50 (m, 1H)
	B	13				
C_2H_5	A	27	296–298°	$C_4H_{12}N_3O_3P$ (181.2)	3620–2200 (broad); 1760–1500 (broad); 1455; 1385; 1330; 1270; 1230; 1160; 1140; 1060; 1035; 1015; 950; 930; 910	1.37 (t, 3H, J_{H-H} = 7 Hz); 1.68–2.50 (m, 2H); 3.88–4.30 (m, 1H)
	B	18				
i-C_3H_7	A	25	302–303°	$C_5H_{14}N_3O_3P$ (195.2)	3620–2100 (broad); 1740–1550 (broad); 1460; 1390; 1370; 1310; 1240; 1200; 1130; 1095; 1070; 1030; 960; 955; 935; 920	1.38 (d, 3H, J_{H-H} = 7 Hz); 1.43 (d, 3H, J_{H-H} = 7 Hz); 2.38–2.75 (m, 1H); 4.02 (dd, 1H, J_{H-H} = 7 Hz, J_{P-H} = 17 Hz)
	B	21				
n-C_3H_7	B	22	295–296°	$C_5H_{14}N_3O_3P$ (195.2)	3600–2200 (broad); 1750–1500 (broad); 1465; 1390; 1210; 1160; 1075; 1010; 970; 915	1.27 (t, 3H, J_{H-H} = 7 Hz); 1.63–2.43 (m, 4H); 3.99–4.37 (m, 1H)
C_6H_5	A	24	296–299°	$C_8H_{12}N_3O_3P \cdot H_2O$ (247.2)	3560–2120 (broad); 1780–1520 (broad); 1500; 1455; 1235; 1190; 1145; 1105; 1050; 945; 920	5.35 (d, 1H, J_{P-H} = 22 Hz); 7.70 (s, 5 H_{arom})
	B	11				
2-$H_3C-C_6H_4$	B	11	314–315°	$C_9H_{14}N_3O_3P$ (243.2)	3500–2100 (broad); 1730–1540 (broad); 1495; 1460; 1385; 1335; 1225; 1150; 1075; 985; 910	2.69 (s, 3H); 5.47 (d, 1H, J_{P-H} = 20 Hz); 7.25–7.87 (m, 4 H_{arom})
3-$H_3CO-C_6H_4$	B	19	325–326°	$C_9H_{14}N_3O_4P$ (259.2)	3500–2200 (broad); 1750–1530 (broad); 1495; 1455; 1440; 1300; 1255; 1215; 1180; 1150; 1085; 1040; 1000; 935; 905	4.08 (s, 3H); 5.36 (d, 1H, J_{P-H} = 22 Hz); 7.00–7.73 (m, 4 H_{arom})

[a] The microanalyses showed the following maximum deviations from the calculated values: N, ±0.34; P, ±0.42.

Received: March 22, 1977

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