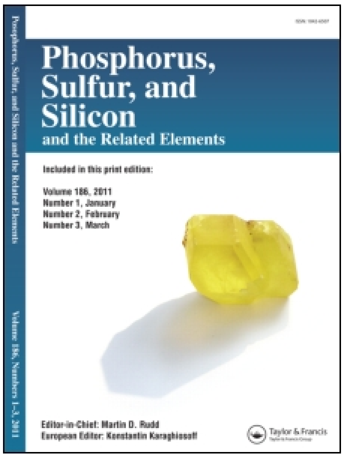

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ORGANIC PHOSPHORUS COMPOUNDS 95.[1] A SIMPLE METHOD FOR THE PREPARATION OF N-DIHYDROXYPHOSPHONYLMETHYL-GLYCINE (GLYPHOSATE)

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Interaction of N-benzylglycine, formaldehyde and phosphorous acid in 30% HCl-solution produces N-benzyl-N-dihydroxyphosphonylmethyl-glycine **1**, in 90% yield. Debenzylation of **1**, dissolved in water with H_2 in the presence of 5% Pd/C as catalyst gives glyphosate **2** in quantitative yield.

Key words: Mannich reaction; debenzylation; N-benzyl-N-dihydroxyphosphonylmethyl-glycine; N-dihydroxyphosphonylmethyl-glycine (glyphosate).

INTRODUCTION

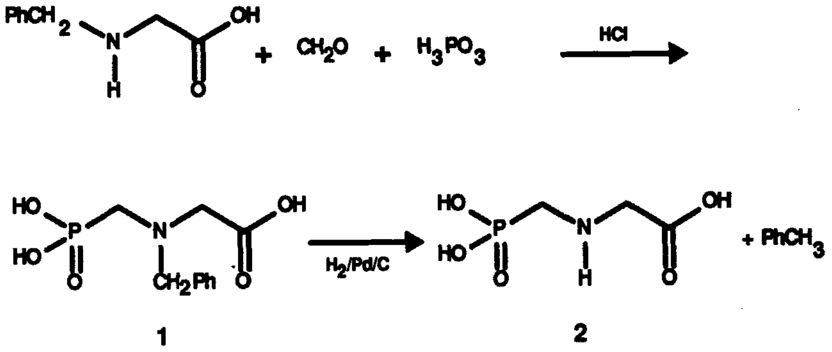
In the past twenty years the N-phosphonylmethyl- and N-alkylphosphinylmethyl-glycines were intensively investigated, since some of these compounds such as for example glyphosphate,[2] glyphosine,[3] N-alkylphosphinylmethyl-glycines[4,5,6] and some others[7,8,9] possess herbicidal or plant growth regulating properties. Among these the isopropylamine salt of glyphosate has achieved enormous importance and is the world's largest selling herbicide.[10] In addition to the many methods[11] known for the preparation of glyphosate we report here on a simple, two steps procedure[12] which is particularly suitable for the preparation of very pure glyphosate.

RESULTS AND DISCUSSION

It is well known that glycine reacts with formaldehyde and phosphorous acid with the formation of N,N-bis(phosphonylmethyl)-glycine[13] which can be converted by oxidation or electrolytically[11] into N-phosphonomethyl-glycine. However, the work-up is difficult and the yield is not particularly high.

To overcome these difficulties, it has been suggested[14] to react N-benzylethyl-glycinate with formaldehyde and phosphorous acid and treat the formed N-benzyl-N-phosphonomethyl-glycine with 48% hydrobromic acid at reflux temperature. This effects cleavage of the N-benzyl bond and produces glyphosate but only in a yield of about 40%. In addition this process produces the lacrimatory benzyl bromide as a by-product and is therefore not advantageous.

We observed that high yields of N-benzyl-N-phosphonomethyl-glycine **1** are obtained, when phosphorous acid and benzylglycine are dissolved in conc. HCl and treated with 35% aqueous formaldehyde at reflux temperature (Scheme). Small amounts of N-benzyl-N-methyl glycine were detected as a by-product. In contrast



SCHEME

to the literature[14] which reports a m.p. of about 35°C for **1**, our product was highly crystalline and had a melting point of 203–206°C (with decomposition). Debenzylation of **1** with H_2 in the presence of 5% Pd on charcoal in aqueous solution produced toluene and glyphosate **2** in 99% yield (Scheme). Work-up is easy and the product is obtained in a pure state. If softened at 213–217°C with loss of water to form N,N'-diphosphonomethyl-2,5-diketopiperazine which melted with decomposition at 309–312°C (Literature[11], softening point between 200 and 230°C and m.p. 316° (dec.)).

EXPERIMENTAL

Phosphorus NMR-spectra were recorded using a Bruker WP 80 spectrometer at 32.28 MHz (ref. 85% H3PO4), and ^{1}H-NMR-spectra were recorded with a Varian EM 360 spectrometer at 60 MHz or a Bruker WM 250/250 MHz spectrometer (ref. $(CH_3)_4Si$). The chemical shifts are reported in ppm, with negative values being upfield of the standard, and positive downfield.

1. N-Benzyl-N-phosphonomethyl-glycine, **1**. 101.0 g (0.5 mol) of N-benzylglycine hydrochloride and 41.0 g of phosphorous acid are dissolved in 500 ml of concentrated hydrochloric acid and 100 ml of water in a reaction vessel provided with stirrer and reflux condenser. The reaction mixture is then heated to reflux temperature, and 160 ml of 35% aqueous formaldehyde solution are added dropwise, with stirring, in the course of 30 minutes, stirring being maintained for 4 hours at reflux temperature. The cloudy solution is afterwards filtered, and evaporated to dryness in a rotary evaporator. The resinous residue (149 g) is crystallised from 1000 ml of water to yield 93.5 g of N-benzyl-N-phosphonomethyl-glycine, m.p. 203–206°C (decomposition). A further 23.3 g of **1** are obtained from the filtrate by concentration in vavuo and crystallisation of the resinous residue from water. The total yield is thus 116.8 g (90.1% of theory).

^{1}H-NMR (in D_2O/NaOD) δ: 2.17 (d, J 12 Hz, PCH_2); 2.8 (s, CH_2CO); 3.4 (s, CH_2Ph); 4.8 (s, OH); 7.01 (s, C_6H_5)

^{31}P (in D_2O/NAOD, pH 11) δ: + 10.7

$C_{10}H_{14}NO_5P \times 0.1\ H_2O$ (261.0)

calc.:	C 46.01	H 5.52	N 5.37	P 11.86	H_2O 0.72%
found:	C 45.93	H 5.52	N 5.46	P 12.01	H_2O 0.72%

Aequiv. weight found 259; $pK_1 = <2$; $pK_2 = 2.2$; $pK_3 = 5.63$; $pK_4 = 10.5$

2. N-phosphonomethyl-glycine, **2**. In a hydrogenating vessel, a solution of 51.8 g (0.2 mol) of N-benzyl-N-phosphonomethyl-glycine in 500 ml of water is treated, after the addition of 5.0 g of palladium on charcoal (5%), at room temperature with hydrogen. The amount of hydrogen absorbed during 45 hours is 4.89 litres (109% of theory). The catalyst is filtered off, and extracted twice by boiling with 500 ml of water each time. Concentration of the combined filtrates in vacuo yields 33.5 g (99% of theory) of N-phosphonomethyl-glycine as a white powder, which softens at 213–217°C, loses water to form the diketopiperazin[11] which melts at 309–312°C (dec.).

^{1}H-NMR (in D_2O/NaOD) δ: 3.05 (d, J 11.6 Hz, CH_2P); 3.73 (s, CH_2CO); 4.87 (s, OH, NH)

^{31}P (in D_2O/NAOD, pH ~ 5) δ: + 8.46 (Literature[11] 8.9)

$C_3H_9NO_5P$ (169.07)

calc.:	C 21.31	H 4.77	N 8.28	P 18.32%
found:	C 21.29	H 4.74	N 8.31	P 18.46%

ACKNOWLEDGEMENT

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