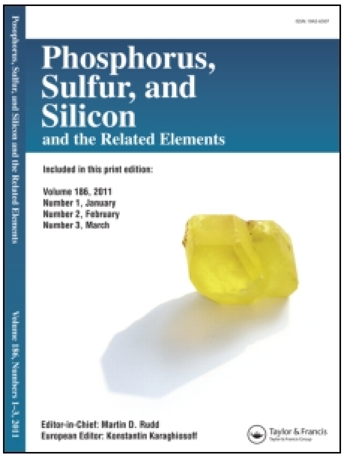

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SYNTHESIS OF PHOSPHORUS-CONTAINING CARBOXYLIC ACIDS BASED ON BIS(TRIMETHYLSILYL)HYPOPHOSPHITE

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SYNTHESIS OF PHOSPHORUS-CONTAINING CARBOXYLIC ACIDS BASED ON BIS(TRIMETHYLSILYL)HYPOPHOSPHITE

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Silylation of ammonium hypophosphite (**1**) with hexamethyldisilasane (HMDS) followed by alkylation of the intermediate bis(trimethylsilyl)hypophosphite (**2**) with methylchloroacetate in the presence of HMDS gives O-trimethylsilylbis(methoxycarbonylmethyl)phosphinate (**3**) and O,O-bis(trimethylsilyl)-methoxycarbonylmethylphosphonite (**4**). Methanolysis of phosphinate **3** gives bis(methoxycarbonylmethyl)phosphinic acid (**5**), the hydrolysis of which leads to bis(hydroxycarbonylmethyl)phosphinic acid (**6**). Treatment of the acids **5** and **6** with sodium hydroxide gives trisodium salt (**7**).

Key words: bis(hydroxycarbonylmethyl)phosphinic acid, bis(trimethylsilyl)hypophosphite, alkylation, O-trimethylsilylbis(methoxycarbonylmethyl)phosphinate, O,O-bis(trimethylsilyl)methoxycarbonylmethylphosphonite, methanolysis, hydrolysis.

In search for analogues of the physiologically active phosphonoacetic acid[1-3] we have synthesized various derivatives of phosphorus-containing carboxylic acids.[4] The synthesis of bis(hydroxycarbonylmethyl)phosphinic acid and its derivatives by silylation of ammonium hypophosphite (**1**) with hexamethyldisilasane (HMDS)[5] followed by alkylation of the resultant bis(trimethylsilyl)hypophosphite (**2**) with methylchloroacetate is described. The reaction was carried out in one stage[6] without isolation of hypophosphite **2** (scheme).

Depending on the ratio of the starting reagents and alkylation conditions either O-trimethylsilylbis(methoxycarbonylmethyl)phosphinate (**3**) or O,O-bis(trimethylsilyl)methoxycarbonylmethylphosphonite (**4**) are obtained. Thus heating hypophosphite **2** with two moles of methylchloroacetate at 125°C gives the crystalline phosphinate **3** in high yield. It should be noted that this temperature in the reaction mixture can only be attained after the resultant trimethylchlorosilane has been distilled off. The presence of the latter prevents the temperature from being raised over 100°C. These conditions lead to a two-fold decrease in the yield of phosphinate **3**. Moreover the reaction should be run in an excess of HMDS as shown by the study of interaction between hypophosphite **2** and ethylchloroformiate.[5] Readily crystallizable phosphinate **3** is isolated by distillation. P. Majewsky[7] synthesized

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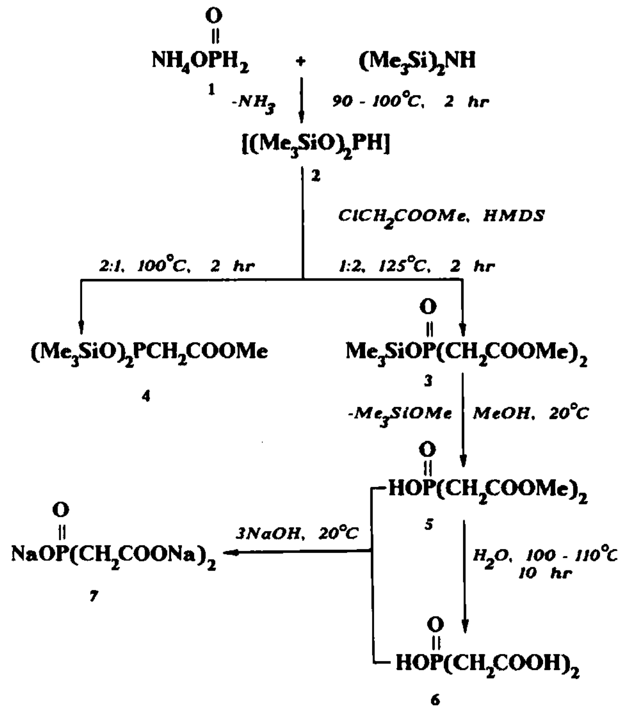

this compound from hypophosphite **2** and methylchloroacetate in the presence of trimethylchlorosilane and triethylamine in benzene and isolated it as an oil. The purity of this product was apparently affected by the low reaction temperature (80°C).

The reaction of hypophosphite **2** with one mole of methylchloroacetate at 100°C gives a mixture of the esters **3** and **4**, the latter is isolated in a low yield. A two-fold excess of hypophosphite **2** allows to obtain phosphonite **4** in 47% yield.

Treatment of phosphinate **3** with dry methanol at 20°C gives crystalline bis(methoxycarbonylmethyl)phosphinic acid (**5**). The ^{31}P NMR spectrum of phosphinate **3** in dry methanol exhibits only one signal which corresponds to acid **5** (36.2 ppm). It should be pointed out that alcoholysis of phosphinate **3** with ethanol at room temperature leads to a partial transesterification of the methoxycarbonyl groups. Thus in the ^{31}P NMR spectrum of phosphinate **3** in dry ethanol there are three signals (32.7 ppm, 32.9 ppm and 33.2 ppm, with ratio 3:4:1), whereas in the ^{1}H NMR spectrum of the ethanolysis product[8] the ethyl protons signals are observed. This fact probably did not permit Majewsky to isolate acid **5** in a crystalline form by refluxing phosphinate **3** in ethanol.

Methoxycarbonylmethyl groups are hydrolyzed under more rigid conditions. A pure bis(hydroxycarbonylmethyl)phosphinic acid (**6**) was obtained by refluxing acid **5** in aqueous solution (pH 1.05) for 10 hr and subsequent evaporation in vacuo. Treatment of acids **5** and **6** with three moles of sodium hydroxide at 20°C gives the trisodium salt of bis(hydroxycarbonylmethyl)phosphinic acid (**7**).

The yields, physical constants and spectroscopy data of compounds **3–7** are listed in Table 1.

TABLE I

Physical properties of the Phosphorus-containing carboxylic acid derivatives **3–7**

	Yield (%)	Bp (°C)/mmHg or mp. (°C) (solvent)	Lit. bp. (°C)/mmHg or molecular formula[a]	^{31}P-NMR δ (ppm) (solvent/H_3PO_4 $_{ext}$)	^{1}H-NMR (solvent, δ ppm/TMS_{ext})
3	74	130–132/1 50–54 (in mass)	110/0.6[7]	25.2 (C_6H_6)	0.16 (18H, *s*, CH_3Si); 2.53 (2H, *d*, J_{PCH_2} 6.3 Hz, CH_2P); 3.68 (3H, *s*, CH_3O)
4	47	75–77/1	$C_9H_{23}O_4PSi_2$ (282.43)	140.9	C_6H_6, 0.10 (9H, *s*, CH_3Si); 2.95 (4H, *d*, J_{PCH_2} 20.7 Hz, CH_2P); 3.22, (6H, *s*, CH_3O)
5	76	63–64 (MeCOOEt)	$C_6H_{11}O_6P$[b] (210.12)	28.2 (H_2O)	$(CD_3)_2CO$, 3.20 (4H, *d*, J_{PCH_2} 18.3 Hz, CH_2P); 3.70 (6H, *s*, CH_3O)
6	97	108–110	$C_4H_7O_6P$ (182.07)	34.5 (H_2O)	D_2O, 3.15 (4H, *d*, J_{PCH_2} 17.4 Hz, CH_2P)
7	97	>300	$C_4H_4Na_3O_6P$ (248.02)	31.3 (D_2O)	D_2O, 2.85 (4H, *d*, J_{PCH_2} 17.8 Hz, CH_2P)

[a] Satisfactory microanalysis obtained: C ± 0.38, H − 0.25, P ± 0.50.

[b] Lit.: oil.[7]

EXPERIMENTAL

All operations with the phosphorus (III) compounds and trimethylsilyl esters of phosphorus acids were carried out under argon. Melting points were measured with Anschütz thermometers. The ^{31}P- {^{1}H} and ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer, using 85% H_3PO_4 and Me_4Si as external standards, respectively.

O-Trimethylsilylbis(methoxycarbonylmethyl)phosphinate **(3)**. Methylchloroacetate (51.8 g, 480 mmol) was added dropwise at 100°C to hypophosphite **2**, that had been obtained by stirring ammonium hypophosphite **1** (20.0 g, 240 mmol) with HMDS (96.6 g, 600 mmol) for 3 hr at 90–100°C.[5] The mixture obtained was heated at 100°C with resulting trimethylchlorosilane being distilled off (vapour temperature 57–70°C), until the temperature in the mixture attained 125°C (for ca. 2 hr). After addition of methylchloroacetate (12.9 g, 120 mmol) the mixture was refluxed for 2 hr and distilled in vacuo. Yield 50.5 g (74%).

O,O-Bis(trimethylsilyl)methoxycarbonylmethylphosphonite **(4)**. Methylchloroacetate (13.0 g, 120 mmol) was added dropwise at 100°C to stirred hypophosphite **2** obtained from ammonium hypophosphite **1** (20.0 g, 240 mmol) and HMDS (57.9 g, 360 mmol). The mixture was heated at 100°C for 2 hr and distilled in vacuo. Yield 15.9 g (47%).

Bis(methoxycarbonylmethyl)phosphinic acid **(5)**. The phosphinate **3** (46.2 g, 160 mmol) was dissolved in dry methanol (20 ml) at 20–25°C, the solution was evaporated in vacuo and the precipitate recrystallized. Yield 26.0 g (76%).

Bis(hydroxycarbonylmethyl)phosphinic acid **(6)**. The solution of acid **5** (4.1 g, 19 mmol) in water (15 ml) was refluxed for 10 hr and evaporated in vacuo. Yield 3.4 g (97%).

Trisodium salt of bis(hydroxycarbonylmethyl)phosphinic acid **(7)**. Acid **5** (2.4 g, 11 mmol) was dissolved in 20% aqueous sodium hydroxide (1.3 g, 33 mmol), the solution was evaporated in vacuo. The residue was dried at 100°C (1 mmHg) for 4 hr. Yield 2.6 g (97%). Analogously, salt **7** was obtained from acid **6**. Yield 98%.

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8. Phosphinate **3** was dissolved in dry ethanol at 20°C, the solution was evaporated in vacuo, the residue was heated at 100°C (1 mmHg) for 15 min.