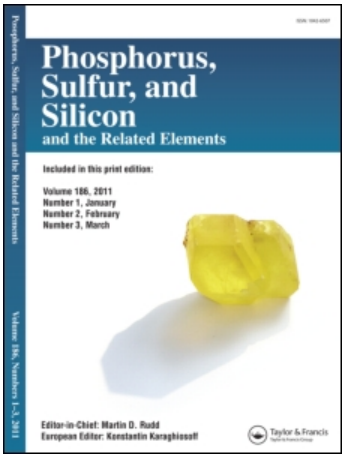

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PHOSPHORUS CONTAINING AMINOCARBOXYLIC ACIDS. COMMUNICATION V.[1] METHOD FOR SYNTHESIS OF PHOSPHINIC ACIDS

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A facile method for the synthesis of phosphinic aminocarboxylic acids containing a lypophilic β-phenylethyl radical at the phosphorus atom has been suggested. Bis(trimethylsilyl)hypophosphite, prepared from ammonium hypophosphite, is added to styrene, the phosphonite formed is further alkylated by the corresponding diethyl ω-bromoalkylacetoamidomalonate. Subsequent hydrolysis of β-phenylethylphosphinylalkylacetoamidomalonates leads to the desired aminoacids.

Key words: Phosphorus containing aminocarboxylic acids; bis(trimethylsilyl)hypophosphite; diethyl ω-bromoalkylacetoamidomalonate; styrene; alcoholysis; hydrolysis.

Phosphorus containing aminocarboxylic acids of the general formula $R(HO)P(O)(CH_2)_nCH(NH_2)COOH$ (**I**) possess various physiological activity. Phosphinic and phosphonic analogs of glutamic acid (**I**, n = 2; R = Me, HO) inhibit glutamine synthetase and display herbicide activity.[2–5] Phosphonic aminocarboxylic acids with a longer hydrocarbon chain (**I**, n = 3, 5; R = HO) are selective antagonists of N-methyl-D-aspartic receptors and possess anticonvulsant properties.[6–8] Permeability of the acids (**I**) through the blood-brain barrier is possibly one of the major factors that determine their physiological activity.[9] From this point of view phosphinic aminocarboxylic acids (**I**) containing a lypophilic radical at the phosphorus atom may be of interest.

In the present work a method for synthesis of similar phosphinic acids, containing a β-phenylethyl radical as a lypophilic substituent, is suggested. The method is a modification of the technique developed by us for the preparation of dialkylphosphinic acids on the basis of ammonium hypophosphite (**II**).[10]

Bis(trimethylsilyl)hypophosphite (**III**), which is prepared from salt (**II**) and hexamethyldisilazane,[11] was added to styrene at the activated carbon-carbon double bound[12] to form the bistrimethylsilyl ester of phosphonous acid (**IV**). The latter further undergoes the Arbuzov reaction with diethyl ω-bromoalkylacetoamidomalonate (**V**).

This one-pot synthesis is carried out without isolation of the intermediate compounds (**III**), (**IV**) and (**VI**). Alcoholysis of the silyl ester (**VI**) leads to phosphinic acids (**VII**), which are transformed into methyl esters (**VIII**) in an excess of trimethylorthoformate. The latter are isolated chromatographically easier than the acids (**VII**). Phosphinic aminocarboxylic acids (**I**) containing a lypophilic β-phen-

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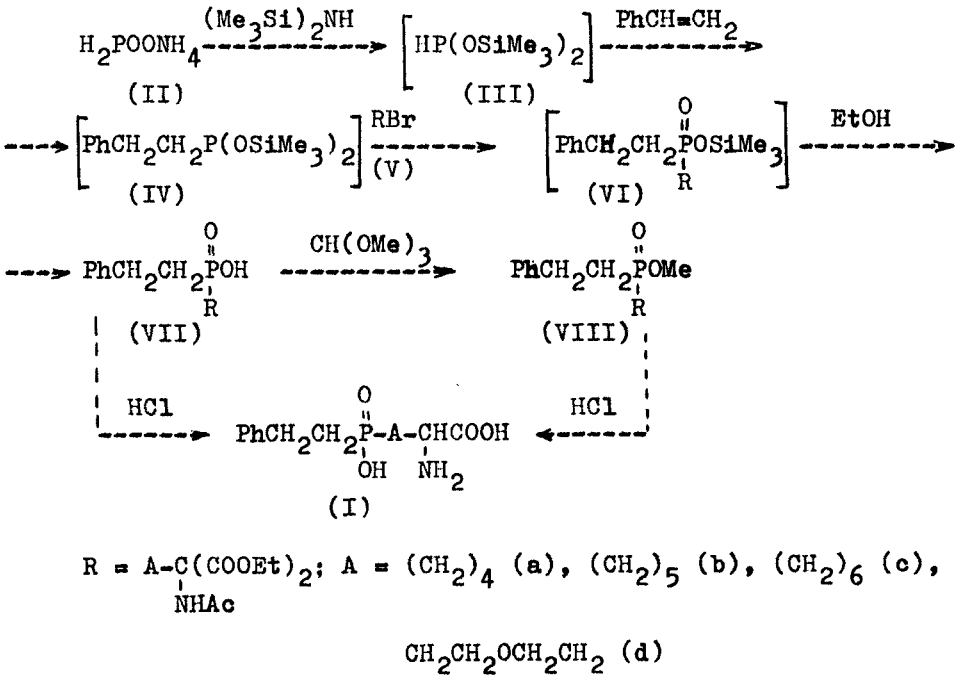

R = A-C(COOEt)$_2$; A = $(CH_2)_4$ (a), $(CH_2)_5$ (b), $(CH_2)_6$ (c),

$CH_2CH_2OCH_2CH_2$ (d)

ylethyl radical at the phosphorus atom are obtained via acidic hydrolysis of phosphinic acids (**VII**) or their esters (**VIII**).

EXPERIMENTAL

^1H and ^{31}P NMR spectra were recorded on a Fourier spectrometer "Bruker CXP 200" using TMS and 85% H_3PO_4 as internal and external standards, respectively. The spectra of acids (**I**) were taken in D_2O with addition of NaOH to improve solubility of the compounds (Table II). Melting points of the compounds were recorded on a "Boetius PHMK" instrument. Column chromatography was carried out on silica gel L 100-250μ. Diethyl ω-bromoalkylacetoamidomalonates (**V**) were synthesized by the earlier described technique.[13] Yields, constants, average elemental analysis and NMR spectroscopic data are listed in Tables 1 and II.

General method for the synthesis of phosphinic acids (**I**). A mixture of 0.10 mol of H_2POONH_4, 0.12 mol of $(Me_2Si)_2NH$ and 0.12 mol of styrene was stirred under argon for 5 h at 120°C. Then 0.10 mol of ester (**V**) and 0.06 mol $(Me_3Si)_2NH$ was added to the reaction mixture under stirring. The mixture was stirred for 4 h at 100–120°C. 50 ml of ethanol was added to the reaction mixture after cooling. The solution was refluxed for 1 h and evaporated in vacuo. The residue was dissolved in 100 ml of $CHCl_3$. The solution was washed with water (3 × 25 ml) dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel (eluent-$CHCl_3$: iso-C_3H_7OH= 10:1) to give the acids (**VII**). According to another technique, 30 ml of $CH(OMe)_3$ were added to the residue. The mixture was refluxed for 3 h and the methanol formed distilled off. Then the excess of $CH(OMe)_3$ was removed, and the obtained residue was chromatographed on silica gel (eluent-$CHCl_3$) to give the methyl esters (**VIII**). The latter operation requires smaller amounts of eluent than the chromatographic isolation of acids (**VII**) and this is preferable.

A mixture of 0.01 mol of phosphinic acid (**VII**) or its methyl esters (**VIII**) and 15 ml of 6N HCl was refluxed for 12–15 h. The reaction mixture was extracted with ether (2 × 10 ml) and the residue evaporated in vacuo; HCl was removed by multifold (3–4 times) addition of distilled water (10 ml each) followed by azeotropic distillation with benzene or toluene. After cooling the residue was dissolved in 10 ml of alcohol. Then 0.02 mol of propylene oxide was added dropwise to the solution. The obtained crystals were separated and washed with alcohol and dried in vacuo at 110°C.

TABLE 1

Yields, constants and elemental analysis data for compounds $PhCH_2CH_2P(O)(OH)—A—CH(NH_2)COOH$ (**Ia–d**), $PhCH_2CH_2P(O)(OH)—A—C(NHAc)(COOEt)_2$ (**VIIa–c**) $PhCH_2CH_2P(O)(OMe)—A—C(NHAc)(COOEt)_2$ (**VIIIb–d**)

N	A	Yield (%)	M.p. (°C)	Found (%) C	H	N	P	Formula	Calculated (%) C	H	N	P
Ia	$(CH_2)_4$	67[a]	271-276	56.0	7.6	4.5	10.1	$C_{14}H_{22}NO_4P$	56.2	7.4	4.7	10.4
Ib	$(CH_2)_5$	62[a]	260-266	57.3	7.9	4.4	10.0	$C_{15}H_{24}NO_4P$	57.5	7.7	4.5	9.9
Ic	$(CH_2)_6$	66[a]	263-267	58.8	8.2	4.6	9.5	$C_{16}H_{26}NO_4P$	58.7	8.0	4.3	9.5
Id	$CH_2CH_2OCH_2CH_2$	61[b]	237-240	47.7	7.6	3.6	8.7	$C_{14}H_{22}NO_5P\times 2H_2O$	47.9	7.5	4.0	8.8
VIIa	$(CH_2)_4$	56[c]	67-68	56.7	7.0	3.2	6.6	$C_{21}H_{32}NO_7P$	57.1	7.3	3.2	7.0
VIIb	$(CH_2)_5$	51[c]	oil	55.8	7.3	3.0	6.7	$C_{22}H_{34}NO_7P\times H_2O$	55.8	7.7	3.0	6.5
VIIc	$(CH_2)_6$	54[c]	oil	56.9	7.4	3.2	5.9	$C_{23}H_{36}NO_7P\times H_2O$	56.7	7.8	2.9	6.3
VIIIb	$(CH_2)_5$	62[c]	oil	58.4	7.8	2.8	6.3	$C_{23}H_{36}NO_7P$	58.8	7.7	3.0	6.6
VIIIc	$(CH_2)_6$	65[c]	oil	59.4	8.3	2.6	6.3	$C_{24}H_{38}NO_7P$	59,6	7.9	2.9	6.4
VIIId	$CH_2CH_2OCH_2CH_2$	63[c]	oil	50.2	7.3	2.4	5.9	$C_{22}H_{34}NO_8P\times 3H_2O$	50.3	7.6	2.6	5.9

[a] Based on the corresponding acid (**VII**); [b] Based on the ester (**VIIId**); [c] Based on the ammonium hypophosphite (**II**).

TABLE II

^1H and ^{31}P NMR Spectroscopic data for compounds (**I**), (**VII**) and (**VIII**)

N	POOH (s)[a]	Ph (m)	NH (s)[a]	CHN	CH_2O	MeO (J_{PH},Hz)	$PhCH_2$ (m)	$PhCH_2CH_2$ (m)	CH_2 (m)	CH_2CN	Ac (s)	CH_3 (t)	δP[e] (ppm) (pH)
Ia	-	7.20	-	3.13t	-	-	2.70	1.70	1.35	-	-	-	46.1(11)
Ib	-	7.30	-	3.15t	-	-	2.70	1.72	1.35	-	-	-	46.3(11)
Ic	-	7.10	-	3.06t	-	-	2.60	1.62	1.25	-	-	-	46.2(10)
Id	-	7.30	-	3.20t	3.50[b]	3.62dt[c] (8.0)	2.80	1.85	1.85	-	-	-	41.6(10)
VIIa	10.30	7.10	6.80	1.98m[b]	4.13q	-	2.88	1.60[d]	1.20	2.27m	1.98	1.20	54.9
VIIb	11.80	7.25	6.95	2.02m[b]	4.20q	-	2.95	1.60[d]	1.25	2.32m	2.02	1.23	56.6
VIIc	9.80	7.25	6.80	2.04m[b]	4.24q	-	2.95	1.64[d]	1.35	2.30m	2.04	1.28	58.6
VIIIb	-	7.50	7.05	2.11m[b]	4.35q	3.80d (10.8)	3.00	1.65[d]	1.30	2.37m	2.11	1.28	58.0
VIIIc	-	7.50	7.10	2.10m[b]	4.30q	3.85d (10.8)	3.00	1.70[d]	1.30	2.40m	2.15	1.25	58.3
VIIId	-	7.45	7.20	3.44t[b]	4.20q	3.72d (10.0)	2.92	2.00[d]	3.58dt[c] (13.2)		2.62t	2.04	1.23	55.2

[a] Broad; [b] $NCCH_2\underline{CH_2}$; [c] $PCH_2\underline{CH_2}O$, (J_{PH},Hz); [d] CH_2PCH_2; [e] Solvents: D_2O (**Ia–Id**) and $CDCl_3$(**VIIa–VIIc,VIIIb–VIIId**).

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