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Synthesis of Phosphorus-substituted Dialkylamides of Organophosphorus Acids, Containing PCH_2NP Fragments

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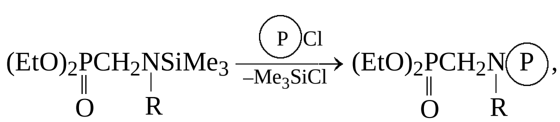
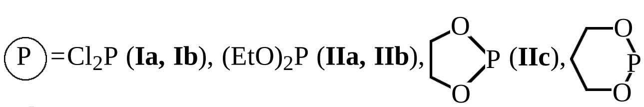
Abstract—Reactions of [*N*-(trimethylsilyl)aminomethyl]phosphonates with organophosphorus acid chlorides was studied, which allowed to develop convenient synthetic approaches to novel phosphorus-substrituted dialkylamides of organophosphorus acids, including a PCH_2NP fragment. Certain properties of the resulting compounds are presented.

Organophosphorus acid amides of various structure are widely used in organic synthesis as highly reactive synthons [1] and ligands in a series of catalytic systems. They are also of interest as biologically active compounds [3]. In the present work we have developed convenient methods for preparing novel organophosphorus acid amides containing PCH_2NP fragments. It was previously shown that easily available *N*-(trimethylsilyl)aminomethylphosphonates (**A**) [4] are convenient synthons for preparing promising phosphorus-containing carboxamides and sulfonamides containing $PCH_2NC(O)$ and PCH_2NSO_2 fragments [5]. We found that the reaction of phosphonates **A** with chlorides of three- and four-coordinate organophosphorus acids in methylene chloride leads to phosphorus-substituted amides **I**–**VI** in high yields.

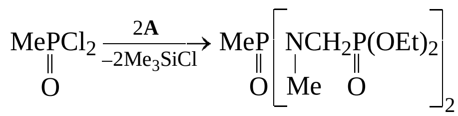


A **I–VI**



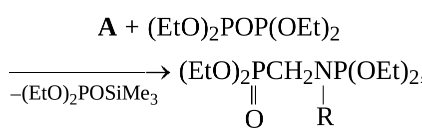
(**IId**), Et_2P (**III**), Bu_2P (**IV**), $(EtO)_2P(O)$ (**V**), $Bu_2P(O)$ (**VI**); R = Me (**Ia, IIa, IV–VI**), Et (**Ib, IIb–IId, III**).

Phosphorus-substituted methylphosphonic diamide **VII** was prepared by the reaction of an excess of phosphonate **A** with methylphosphonic dichloride under mild conditions.



VII

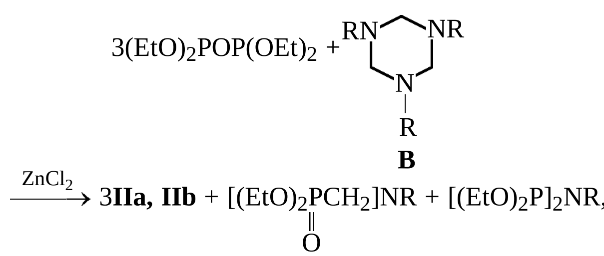
Amides **IIa** and **IIb** were also prepared from tetraethyl pyrophosphite, but the latter proved to be less reactive in analogous transformations. Thus its reaction with phosphonates **A** could only be effected on heating at 130°C in the presence of a catalyst, zinc chloride. As a result, amides **IIa** and **IIb** were obtained in high yields.



IIa, IIb

R = Me (**a**), Et (**b**).

The reaction of tetraethyl pyrophosphite with symmetrical hexahydrotriazines **B** under similar conditions leads to amides **IIa** and **IIb** in high yields. Along with these products, bis(phosphonomethyl)amines **VIII** were isolated in low yields (10–15%), and the ^{31}P NMR spectra of low-boiling fractions displayed signals of amides **IX**.



VIIIa, VIIIb **IXa, IXb**

R = Me (**a**), Et (**b**).

Hence, under conditions of this reactions, ring cleavage in compounds **B** occur mainly by a symmetric pathway (cf. [4]).

Substituted amidophosphorous dichlorides **I** were prepared in quantitative yields, but, unlike amides **II**–**VII**, they are thermally unstable. They can be stored for a long time at 20°C but polymerize on distillation. Treatment of amidochlorides **I** with a mixture of ethanol and triethylamine gives phosphoroamidites **IIa** and **IIb** in high yields.

The reaction of amidochloride **Ia** with an excess of triethyl orthoformate involves cleavage of the P–N bond. Subsequent reactions of the intermediates and triethyl orthoformate lead to *N*-formylaminomethylphosphonate **X** and diethoxymethylphosphonate **XI**.

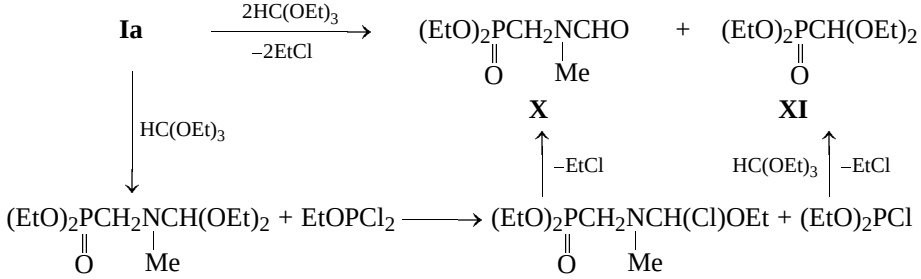
$$(EtO)_2P(O)CH_2NPCl_2(R)$$

Ia, Ib

$$\xrightarrow[2Et_3N\cdot HCl]{2EtOH,\ 2Et_3N} (EtO)_2P(O)CH_2NP(OEt)_2(R),$$

IIa, IIb

R = Me (**a**), Et (**b**).



The presented reaction scheme agrees with data in [6]. Amides **II**–**IV** containing a three-coordinate phosphorus atom were used by us to prepare novel four-coordinate phosphorus compounds with a PCH_2NP fragment.

Amides **IIb**–**IV** smoothly take up sulfur in benzene to form thio derivatives **XII**.

$$\textbf{IIb, III, IV} \xrightarrow{S} (EtO)_2P(O)CH_2NP(R)X_2(S),$$

XIIa–**XIIc**

X = EtO (**a**), Et (**b**), Bu (**c**): R = Et (**a, b**), Me (**c**).

Amide **IIb** reacts with an excess of methyl iodide under mild conditions by an Arbuzov reaction scheme, yielding amidophosphonate **XIII**.

$$\textbf{IIb} \xrightarrow[-EtI]{MeI} (EtO)_2P(O)CH_2NP(Et)(Me)(OEt)(O),$$

XIII

The novel phosphorus-substituted organophosphorus acid amides **I**–**VII, XII**, and **XII** present interest as promising ligands and biologically active compounds. Their structure was confirmed by the ^1H, $^{12}{}^3C$, and ^{31}P NMR spectra containing characteristic signals of the $P^1C^1H_2N(C^2H_n)P^2$ fragments (see table). The ^{31}P NMR signals of the obtained compounds are located in the ranges characteristic of their simplest analogs with the same coordination of the phosphorus atoms. The elemental analyses of a series of the obtained compounds, confirmatory of their composition, were also presented in the preliminary publication [7].

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were obtained on a Varian VXR-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ (15–20% solutions) against TMS (^1H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P).

All reactions were carried out under argon in anhydrous solvents.

Diethyl [*N*-(dichlorophosphino)-*N*-methylamino]methylphosphonate (Ia). To a solution of 10 g of diethyl [*N*-methyl-*N*-(trimethylsilyl)amino]-methylphosphonate in 40 ml of methylane chloride, a solution of 6.5 g of phosphorus trichloride in 20 ml of methylene chloride was added dropwise with stir-

Physicochemical characteristics of compounds **I**–**XIII**[a] and NMR spectral data for the $P^1C^1H_2N(C^2H_n)P^2$ fragments (δ, ppm, *J*, Hz)

Comp. no	Yield, %	bp, °C (*p*, mm Hg)	n_D^{20}	δ(C^1H_2)	$^2J_{PH}$	$^3J_{PH}$	δ(C^1)	$^1J_{PC}$	$^2J_{PC}$	δ(C^2)	$^2J_{PC}$	δ(P^1), d	δ(P^2)	$^2J_{PP}$
Ia	98	–	–	3.4–3.5 m	–	–	46.54 d.d	160.5	28.1	37.43 d	14.3	18.54	162.49 d	12.9
Ib	98	–	–	3.4–3.5 m	–	–	41.92 d.d	159.4	22.9	43.81 d	19.7	18.90	163.13 d	8.5
IIa	84	111 (1)	1.4472	2.98 t	8.0	8.0	42.97 d.d	159.3	24.1	32.17 d	13.7	22.29	142.72d	18.3
IIb	86	115 (1)	1.4485	3.01 d.d	8.4	6.8	37.86 d.d	157.9	17.3	38.80 d	20.5	22.59	143.19 d	12.2
IIc	81	129 (1.5)	1.4742	3.03 t	8.6	8.6	39.09 d.d	158.3	22.6	39.35 d	16.7	21.24	141.25 d	9.7
IId	74	123 (1)	1.4735	2.9–3.1 m	–	–	37.95 d.d	158.0	15.7	39.54 d	23.5	21.85	142.37 d	8.6
III	85	108 (1)	1.4672	2.90 t	8.0	8.0	44.47 d.d	156.0	15.1	43.83 d	11.3	23.02	67.89 d	7.0
IV	83	128 (1)	1.4680	2.87 t	8.0	8.0	51.28 d.d	157.1	28.4	34.88 s	–	22.54	63.71 d	23.8
V	81	139 (1)	1.4418	3.06 t	9.2	9.2	44.05 d.d	159.7	4.8	34.34 s	–	20.97	6.96 d	19.5
VI	81	168 (1)	1.4630	3.02 t	8.0	8.0	41.31 d	160.6	–	33.35 s	–	21.10	48.23 d	15.3
VII	78	202 (1)	1.4705	3.05 t	8.8	8.8	42.29 d	159.9	–	32.83 s	–	21.19	34.41 t	18.5
XIIa	89	138 (1)	1.4718	3.34 d.d	12.0	9.2	40.57 d.d	158.6	6.6	40.54 s	–	21.23	73.60 d	12.9
XIIb	87	160 (2)	1.5018	3.35 t	9.2	9.2	39.09 d.d	157.8	3.1	40.63 s	–	21.83	84.55 d	8.3
XIIc	85	169 (1)[b]	–	3.30 t	8.6	8.6	43.75 d	160.8	–	34.87 s	–	21.44	81.16 d	14.7
XIII	74	152 (2)	1.4498	2.9–3.1 m	–	–	38.26 d.d	156.2	4.5	39.11 d	4.6	21.69	30.79 d	8.5

[a] Fragment C^2H_3. ^1H NMR spectrum, δ, ppm (*J*, Hz): **IIa**: 2.37 d.d ($^3J_{PH}$ 7.6, $^4J_{PH}$ 1.2); **IV**: 2.54 d.d ($^3J_{PH}$ 5.2, $^4J_{PH}$ 1.6); **V**: 2.40 d.d ($^3J_{PH}$ 9.2, $^4J_{PH}$ 1.2); **VI**: 2.35 d.d ($^3J_{PH}$ 9.2, $^4J_{PH}$ 1.2); **VII**: 2.43 d.d (^3J_P4dH 9.6, $^4J_{PH}$ 2.8); **XIIb**: 2.52 d ($^2J_{PH}$ 10.4); the signals of the C^2H_2 fragments of the other compounds appear as multiplets in the range 2.6–3.1 ppm. Fragment PCH_3, δ, ppm (*J*, Hz): **VII**: δ_H 1.25 d ($^2J_{PH}$ 15.2), δ_C 9.37 d ($^1J_{PC}$ 116.3); **XIII**: δ_H 1.32 d ($^2J_{PH}$16.8), δ_C 11.40 d ($^1J_{PC}$ 134). [b] mp 43°C.

ring at 0°C. The solvent was removed at 20°C, and the residue was kept in a vacuum (1 mm Hg) at 20°C to give 10.9 g of phosphonate **Ia**.

Phosphonate **Ib** was obtained analogously.

Diethyl [*N*-(diethoxyphosphino)-*N*-methylamino]methylphosphonate (IIa). *a*. To a solution of 6.5 g of diethyl [*N*-methyl-*N*-(trimethylsilyl)amino]-methylphosphonate in 10 ml of methylane chloride, a solution of 4.1 g of diethyl phosphorochloridite in 5 ml of methylene chloride was added dropwise with stirring at 10°C. The solvent was removed, and the residue was distilled in a vacuum to give 6.5 g of phosphonate **IIa**. Found, %: C 39.65; H 8.26; P 20.28. $C_{10}H_{25}NO_5P_2$. Calculated, %: C 39.87; H 8.36; P 20.56.

Compounds **IIb, IIc, IId**–**VII** were obtained analogously.

b. A mixture of 5.1 g of diethyl [*N*-methyl-*N*-(trimethylsilyl)amino]methylphosphonate, 5.4 g of tetraethyl pyrophosphite, and 0.2 g of zinc chloride was heated at 130°C for 1 h and then distilled to give 4.9 g of phosphonate **IIa**, yield 81%.

Phosphonate **IIb** was obtained analogously, yield 83%.

c. A mixture of 6.3 g of tetraethyl pyrophosphite, 1 g of 1,3,5-trimethylhexahydrotriazine, and 0.2 g of zinc chloride was heated at 135°C for 1 h and then distilled to give 5.2 g of phosphonate **IIa**, yield 74%. Repeated distillation of the high-boiling fraction gave 0.5 g of *N*,*N*-bis(diethoxyphosphinoylmethyl)-*N*-methylamine (**VIIIa**). Yield 20%, bp 155°C (1 mm Hg), n_D^{20} 1.4530. $PC^1H_2NC^2H_3$ fragment: ^1H NMR spectrum, δ, ppm: 3.01 d (C^1H_2, $^2J_{PH}$ 9.6 Hz); ^{13}C NMR spectrum, δ_C, ppm: 54.02 d.d (C^1, $^1J_{PC}$ 157.5, $^3J_{PC}$ 10.4 Hz), 46.22 t (C^2, $^3J_{PC}$ 7.9 Hz); ^{31}P NMR spectrum, δ, ppm: 21.55 s (cf. [8]). The ^{31}P NMR spectrum of the low-boiling fraction [bp 75–85°C (1 mm Hg)] contains, together with the signal of the starting tetraethyl pyrophosphite (δ_P 125.5 ppm), a signal of *N*,*N*-bis(diethoxyphosphino)-*N*-methylamine (**IXa**), δ_P 143.22 ppm (cf. [9]).

Phosphonate **IIb** (yield 72%) and *N*,*N*-bis(diethoxyphosphinoylmethyl)-*N*-ethylamine (**VIIIb**) were obtained analogously, yield 15%, bp 159°C (1 mm Hg), n_D^{20} 1.4480. $PC^1H_2NC^2H_2$ fragment: ^1H NMR spectrum, δ, ppm: 3.10 d (C^1H_2, $^2J_{PH}$ 9.2 Hz); ^{13}C NMR spectrum, δ_C, ppm: 49.00 d.d (C^1, $^1J_{PC}$

156.9, $^3J_{PC}$ 7.5 Hz), 49.97 t (C^2, $^3J_{PC}$ 7.8 Hz). ^{31}P NMR spectrum, δ_P, ppm: 22.01 s (cf. [8]). The ^{31}P NMR spectrum of the low-boiling fraction contains a signal of *N*,*N*-bis(diethoxyphosphino)-*N*-ethylamine (**IXb**), δ_P 143.72 ppm (cf. [9]).

d. To a solution of 10.9 g of phosphonate **Ia** in 50 ml of diethyl ether, a solution of 3.6 g of ethanol and 8.2 g of triethylamine in 30 ml of ether was added dropwise with stirring at 0°C. The resulting mixture was left for a day at 20°C, the triethylamine hydrochloride was filtered off, the solvent was removed, and the residue was distilled to give 8.9 g of phosphonate **IIa**, yield 76%.

Phosphonate **IIb** was obtained analogously, yield 78%.

Reaction of phosphonate Ia with triethyl orthoformate. To a solution of 10.9 g of phosphonate **Ia** in 20 ml of methylene chloride, a solution of 12.6 g of triethyl orthoformate in 20 ml of methylene chloride was added dropwise with stirring at 0°C. The resulting mixture was left for a day at 20°C, the solvent was removed, and the residue was distilled to give 6.3 g (78%) of diethyl [(*N*-formyl-*N*-methyl)amino]-methylphosphonate (**X**), bp 125°C (1 mm Hg), n_D^{20} 1.4570. According to NMR data, phosphonate **X** is a 4 : 1 ratio of two stereoisomers. First isomer. $PC^1H_2N\cdot(C^2H_3)C^3(O)H$ fragment: ^1H NMR spectrum, δ, ppm: 3.25 d (C^1H_2, $^2J_{PH}$ 11.3 Hz), 2.65 s (C^2H_3), 7.56 s (C^3H); ^{13}C NMR spectrum, δ_C, ppm: 38.40 d (C^1, $^1J_{PC}$ 155.2 Hz), 34.35 s (C^2), 161.20 s (C^3); ^{31}P NMR spectrum, δ_P, ppm: 18.61 s. Second isomer. $PC^1H_2N\cdot(C^2H_3)C^3(O)H$ fragment: ^1H NMR spectrum, δ, ppm: 3.15 d (C^1H_2, $^2J_{PH}$ 10.0 Hz), 2.45 s (C^2H_3), 7.53 s (C^3H); ^{13}C NMR spectrum, δ_C, ppm: 43.95 d (C^1, $^1J_{PC}$ 158.0 Hz), 30.10 s (C^2), 162.00 s (C^3); ^{31}P NMR spectrum, δ, ppm: 18.20 s (cf. [10]). Repeated distillation of the low-boiling fraction gave 6.7 g of diethyl (diethoxymethyl)phosphonate (**XI**), yield 72%, bp 79°C (1 mm Hg), n_D^{20} 1.4255. PCH fragment: ^1H NMR spectrum, δ, ppm: δ 4.55 d ($^2J_{PH}$ 5.0 Hz); ^{13}C NMR spectrum, δ_C, ppm: 98.19 d ($^1J_{PC}$ 207.0 Hz); δ_P 11.15 ppm (cf. [11]).

Diethyl [*N*-(diethoxyphosphinothioyl)-*N*-ethylamino]methylphosphonate (XIIa). A mixture of 3.2 g of phosphonate **IIb**, 0.4 g of sulfur, and 10 ml of benzene was heated on a water bath for 1 h and then cooled. The residual sulfur was then filtered off, the solvent was removed, and the residue was distilled to give 2.9 g of phosphonate **XIIa**. Found, %: C 37.89; H 7.72; P 17.68. $C_{11}H_{27}NO_5P_2S$. Calculated, %: C 38.04; H 7.83; P 17.83.

Compounds **XIIb** and **XIIc** were obtained analogously.

Diethyl [*N*-[ethoxy(methyl)phosphinoyl]-*N*-ethylamino]methylphosphonate (XIII). To a solution of 4.2 g of phosphonate **IIb** in 15 ml of ether, a solution of 6 g of methyl iodide in 5 ml of ether was added dropwise with stirring at 10°C. The resulting mixture was refluxed for 1 h, the solvent was removed, and the residue was distilled to give 3 g of phosphonate **XIII**. Found, %: C 39.69; H 8.22; P 20.30. $C_{10}H_{25}NO_5P_2$. Calculated, %: C 39.67; H 8.36; P 20.56.

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