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Physiologically Active Bis(dialkylamides) of Phosphoryl-Substituted α,ω-Dicarboxylic Acids

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Abstract—Bis(dialkylamides) of phosphoryl-substituted α,ω-dicarboxylic acids were synthesized and their biological activity was studied.

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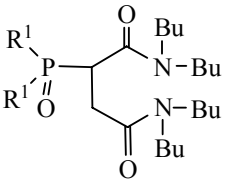
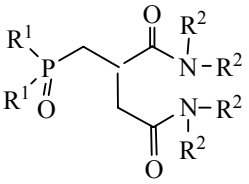
Glutamatergic neuromediator system plays an important role in the central nervous system both for the normal development of neurophysiological processes (signaling, memory consolidation, cognitive functioning) and in the pathogenesis of several neurodegenerative diseases. The system includes a family of eight types of metabotropic glutamate receptors (mGluR1 to mGluR8) from a group of 3G-protein-coupled receptors (GPCRs), and a family of three types of ligand-operated ionotropic receptors, namely NMDA (N-methyl-D-aspartate), AMPA [2-amino-3-(3-hydroxy-5-methylisoxazole-4-yl)propionic acid] and kainate (KA, kainic acid) receptors [1–3]. Although a large number of compounds are known that are active against these receptors [4], the search for new, especially highly selective receptor agonists and antagonists is an important task in the problem of treating neurodegenerative diseases.

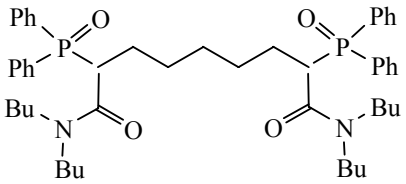
In this paper we synthesized and studied phosphoryl-substituted bis(dialkylamides) of 1,4-dicarboxylic acids (**I, II**) and 2,8-bis(diphenylphosphinoyl)-substituted nonane-1,9-dioic acid bis(dibutylamide) (**III**).



I



II



III

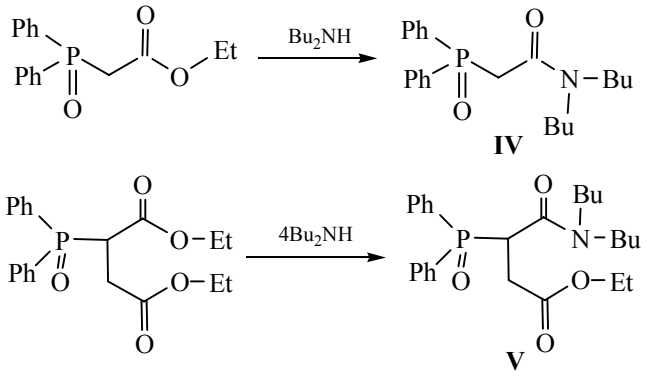
I, R^1 = Et (**a**), Bu (**b**), Ph (**c**), 2-$CH_3C_6H_4$ (**d**), 2,5-$(CH_3)_2C_6H_3$ (**e**), 4-$(CH_3)_2NC_6H_4$ (**f**), 4-ClC_6H_4 (**g**), 4-$CH_3OC_6H_4$ (**h**);
II, R^2 = Et, R^1 = Ph (**a**), R^2 = Bu, R^1 = 4-$CH_3OC_6H_4$ (**b**), 2,5-$(CH_3)_2C_6H_3$ (**c**).

The prerequisites for this choice were two factors. First, derivatives of 1,4-dicarboxylic acids demonstrate different types of biological activity [5]. Second, based on the concept of bioisosterism [6, 7], the introduction of phosphorus-containing groups was expected to improve the pharmacological properties of the leading compounds.

Although we had previously described [8] the synthesis of 2-(diphenylphosphinoyl)succinic acid 1,4-bis(dibutylamide) **Ic**, the reaction conditions were not optimized. The synthesis resulted in a mixture of substances, requiring separation by column chromatography (yield 42%). In this paper we applied the same method for the synthesis of compounds **I** and **II**, but

the reaction was carried out under milder conditions (40–80°C) and the results were acceptable.

Another convenient method commonly used for the synthesis of α-phosphoryl-substituted monoamides **IV** that consists in the direct amidation of the corresponding esters of secondary amines, proved to be unsuitable for the preparation of diamides of type **I, II**. Only the ester group located in the α-position to the phosphoryl substituent reacts readily, while the β-ethoxycarbonyl remains unchanged even in the rigid conditions of the reaction with an excess of amine: the reaction resulted in a phosphoryl-substituted amidoether **V**:



All the synthesized compounds were tested with respect to their effect on glutamate receptors by two methods.

The study of the ability of compounds to affect the influx of calcium ions mediated by glutamate receptors allowed us the estimation of their overall biological potential as presumable neuroprotectors (in the case of inhibition) or stimulants (in the case of activation) of cognitive functions. For the preliminary evaluation of biological activity of the synthesized compounds, we have studied the effect of the substances on the glutamate-induced calcium ion uptake using preparations of the synaptosomes of the rat brain cortex P_2 fraction, which contains NMDA, kainate and metabotropic glutamate receptor of I type [9]. Probably, glutamic acid activates all subtypes of glutamate receptors of P_2 fraction of the rat brain cortex synaptosomes. In the primary screening of the compounds their cumulative effect on all presynaptic glutamate receptors present in the P_2 fraction is determined.

Using other methods, it is possible to reveal the subtypes of glutamate receptors that are affected by the tested substances. In particular, the method of radioligand binding to the NMDA receptors allows quantifying the effect of compounds on the NMDA receptors, which play a key role in the mechanisms of neuroprotection and neurotoxicity.

The table presents results demonstrating the effect of structure of the synthesized compounds on the

Effect of compounds **I–V** on the $^{45}Ca^{2+}$ uptake into synaptosomes of the rat cerebral cortex by stimulation with glutamate (method *a*), and on the binding of [^{3}H]MK-801 with NMDA receptors in the rat cerebral cortex (method *b*).

Comp. no.	Method *a*		Method *b*	
	$^{45}Ca^{2+}$ uptake, % of control (control is 100%) at 100 μM	IC_{50}, μM	Binding of [^{3}H]MK-801, % of control (control is 100%) at 100 μM	IC_{50}, μM
Ia	101.7±6.3	–	–	–
Ib	0	44.7	100	–
Ic	0	14.1	100	–
Id	6.6±3.3	9.3	42±6.2	21.37
Ie	7.7±6.4	18.6	25±4.1	22.91
If	0	7.9	38±5.5	61.47
Ig	11.7±7.0	4.8	61±6.8	79.08
Ih	7.2±1.3	17.0	74±6.9	90.82
IIa	63.8±12	–	–	–
IIb	0	15.5	67±6.0	65.74
IIc	4.9±4.9	5.1	29±2.7	44.31
III	1.9±0.4	12.6	25±2.2	17.25
IV	77.2±11.4	–	–	–
V	96.2±2.9	–	–	–

calcium ions uptake into the rat brain cortex synaptosomes (method *a*) and binding with NMDA receptors (method *b*). Our own initial screening has identified certain patterns of structure–biological activity for the studied compounds.

The compounds **IV** and **V**, which do not belong to the series of diamides, show no appreciable biological activity. In a series of phosphoryl-substituted 1,4-dicarboxylic acids **I, II** bis-dialkylamides only 2 compounds which have short alkyl substituents at either phosphorus or nitrogen atom (**Ia** and **IIa**) show weak net effect on glutamate receptors, and therefore were excluded from further study. The compounds that had a significant inhibitory effect on the $^{45}Ca^{2+}$ uptake into synaptosomes of the cerebral cortex were examined in more detail to determine the concentration (IC_{50}), at which the 50% inhibition of the $^{45}Ca^{2+}$ uptake into synaptosomes occurred. The inhibitors were additionally investigated by the radioligand *b* method to determine their binding to the glutamate receptors (NMDA receptors) in the concentration range of 10^{-9} to 10^{-4} mol l^{-1} *in vitro*. The eight of the ten studied substances showed comparable ability of compete moderately with [^{3}H]MK-801 in binding to the same sites. From the results of inhibition IC_{50} values which fall to the range 10–90 μM were calculated using GraphPad Prism 4 Demo software.

Inhibition of NMDA receptors significantly affects the overall inhibition in the case of the compounds containing alkyl and dimethylamino substituents in the aromatic ring (compounds **Id–If** and **IIc**). The NMDA receptors are inhibited significantly also by the bis-phosphine oxide **III** whose amido groups are more conformationally independent. In other cases the contribution of NMDA receptor stimulation in the total effect on the presynaptic glutamate receptors of the P_2-fraction is less significant (compounds **Ig**, **Ih**, **IIb** containing Cl and MeO substituents at the aryl rings) or zero (compounds **Ib** and **Ic** with the alkyl and phenyl substituents at the phosphorus atom).

Summing up the results, we conclude that among the investigated bis(dialkylamido)phosphoryl-substituted α,ω-dicarboxylic acids **I**–**III** substances are found capable of simultaneously inhibiting several types of glutamate receptors, as well as the substances that act mainly on NMDA receptors, which means that further study of this class of compounds as potential neuroprotectors is quite promising.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Bruker instrument CHR-200 (Germany), reference Me_4Si. Melting points were determined on a Boetius PHMK heating table (Germany). Prior to the biological research the substances were additionally purified by recrystalliza-tion or by chromatography on an L 100/160 silica gel column, eluent chloroform, hexane–isopropanol 10:1, and dried in a vacuum.

Determination of the $^{45}Ca^{2+}$ uptake into the rat brain synaptosomes was performed according to the method described in [9], the synaptosomes were obtained by the standard Hajos method [10].

The study of binding to the receptors of NMDA subtypes was carried out by the method [11] with modifications. We used the tritium-labeled MK-801 (dizocilpine) with specific activity 79 Ci $mmol^{-1}$. The membrane samples for the radioligand analysis were prepared by the described method [12].

The initial 1,4-dicarboxylic acids were obtained from secondary phosphine oxides and 1,4-unsaturated dicarboxylic acids by the method of [13] or by acidification of salts [14], compounds **III, IV** were synthesized by a known method [15]. The synthesis of compounds **I, II, V** is given in this paper.

2-(Diethylphosphinoyl)succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ia). A solution of 1.25 g (0.003 mol) of hexabutyltriamidophosphite $(Bu_2N)_3P$ in 2 ml of anhydrous benzene was added dropwise to a suspension of 1.00 g (0.0045 mol) of 2-(diethylphosphinoyl)-succinic acid in 15 ml of anhydrous benzene, and the mixture was heated for 1 h at mild boiling of the solvent . The reaction mixture was washed with water (3×7 ml), dried over Na_2SO_4, and the solvent was removed in a vacuum. We obtained 1.95 g of compound **Ia**, yield 98%. The product was purified by chromatography on a column with silica gel L 100/160 μm. Elution with chloroform afforded 1.78 g (89%) of compound **Ia** as an oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.83–1.00 m (12H, $4CH_3$), 1.10–1.95 m (26H, $4CCH_2CH_2CN + CH_3CH_2PCH_2CH_3$), 2.46 m, 1H and 3.15 m, 1H (CH_2CP), 3.20–3.60 m (8H, $2CH_2NCH_2$), 4.00 m (1H, CHP). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 5.92 d ($\underline{C}H_3CH_2P$, $^2J_{CP}$ 5.6 Hz), 6.10 d ($\underline{C}H_3CH_2P$, $^2J_{CP}$ 5.6 Hz), 14.18 s, 14.25 s, 14.28 s ($2\underline{C}H_3CH_2CH_2CH_2NCH_2CH_2CH_2\underline{C}H_3$), 19.66 d ($CH_2P$, $^1J_{CP}$ 65.8 Hz), 20.11 d (CH_2P, $^1J_{CP}$ 65.8 Hz), 20.47 s, 20.49 s, 20.59 s, 20.75 s ($2\underline{C}H_2CH_2CH_2NCH_2$· $CH_2\underline{C}H_2$), 30.00 s, 30,27 s, 31.11 s ($2\underline{C}H_2CH_2N$·

$CH_2\underline{C}H_2$), 31.53 d ($\underline{C}H_2CHP$, $^2J_{CP}$ 4.0 Hz), 39.95 d (CHP, $^1J_{CP}$ 55.5 Hz), 46.45 s, 47.01 s, 48.17 s, 49.14 s ($2CH_2NCH_2$), 169.02 d [$\underline{C}$(O)CHP, $^2J_{CP}$ 2.3 Hz], 169.78 d [$\underline{C}$(O)CH_2CHP, $^3J_{CP}$ 13.2 Hz]. ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 53.08.

2-(Di-*n*-butylphosphinoyl)succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ib) was synthesized similarly to compound **Ia** from 0.43 g (0.0012 mol) of $(Bu_2N)_3P$ and 0.33 g (0.0012 mol) of 2-(di-*n*-butylphosphinoyl) succinic acid. We obtained 0.59 g of compound **Ib**, yield 98%, mp 46°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.80 m (18H, $6CH_3$), 1.20–1.80 m (28H, $6CCH_2CH_2CN + CH_2PCH_2$), 2.50 m, 1H and 4.00 m, 1H (CH_2CP), 3.10–3.60 m (9H, $2CH_2NCH_2$ + CHP). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 50.60.

2-(Diphenylphosphinoyl)succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ic) was synthesized similarly to compound **Ia** from 1.08 g (0.0026 mol) of $(Bu_2N)_3P$ and 0.96 g (0.0030 mol) of 2-(diphenylphosphinoyl) succinic acid. We obtained 1.45 g of compound **Ib**, yield 90%, oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.84 m (12H, $4CH_3$), 1.20 m (8H, $4CCH_2CCN$), 1.36 m (8H, $4CCCH_2CN$), 2.60 m, 1H and 3.00 m, 1H (CH_2CP), 3.16 m (8H, $2CH_2NCH_2$), 4.32 m (1H, CHP), 7.50 m ($6H_{arom.}$), 7.86 m ($2H_{arom.}$), 8.06 m ($2H_{arom.}$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.02 s, 14.12 s, 14.28 s, 14.31 s ($2\underline{C}H_3CH_2CH_2CH_2NCH_2CH_2\cdot CH_2\underline{C}H_3$), 20.28 s, 20.48 s, 20.54 s, 20.61 s ($2\underline{C}H_2CH_2\cdot CH_2NCH_2CH_2\underline{C}H_2$), 29.84 s, 30.27 s, 30.68 s, 31.27 s ($2\underline{C}H_2CH_2N\cdot CH_2\underline{C}H_2$), 32.86 s ($\underline{C}H_2CHP$), 42.56 d (CHP, $^1J_{CP}$ 62.8 Hz), 46.46 s, 47.18 s, 48.11 s, 48.93 s ($2CH_2NCH_2$), 168.48 d [$\underline{C}$(O)CHP, $^2J_{CP}$ 2.2 Hz], 169.76 d [$\underline{C}$(O)CH_2CHP, $^3J_{CP}$ 15.2 Hz]. ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.97.

2-[(2-Methylphenyl)phosphinoyl]succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Id) was synthesized similarly to compound **Ia**) from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 1.04 g (0.003 mol) of 2-[(2-methylphenyl)phosphinoyl]succinic acid. We obtained 1.55 g of compound **Id**, yield 91%, oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.94 m (12H, $4CH_3$), 1.28 m (8H, $4CCH_2CCN$), 1.44 m (8H, $4CCCH_2CN$), 2.48 s, 3H and 2.56 s 3H ($2CH_3$-Ar), 3.04 m (4H, CH_2NCH_2) and 3.40 m (4H, CH_2NCH_2), 3.18 m, 1H and 3.62 m, 1H (CH_2CP), 4.72 m (1H, CHP), 7.10–7.90 m ($8H_{arom.}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 38.96.

2-[Bis(2,5-dimethylphenyl)phosphinoyl]succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ie) was synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 0.86 g (0.0023 mol) of 2-[bis(2,5-dimethylphenyl)phosphinoyl]succinic acid. We obtained 1.30 g of compound **Ie**, yield 95%, oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.82 m (12H, $4CH_3$), 1.20 m (8H, $4CCH_2CCN$), 1.36 m (8H, $4CCCH_2CN$), 2.22 s, 3H, 2.30 s, 6H, and 2.38 s, 3H ($4CH_3$-Ar), 2.50 m, 1H and 3.50 m, 1H (CH_2CP), 2.96 m (4H, CH_2NCH_2) and 3.32 m (4H, CH_2NCH_2), 4.65 m (1H, CHP), 7.10–7.60 m ($6H_{arom.}$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.13 s, 14.17 s, 14.40 s, 14.40 s ($2\underline{C}H_3CH_2\cdot CH_2CH_2NCH_2CH_2CH_2\underline{C}H_3$), 20.41 s, 20.51 s, 20.60 s, 20.70 s ($2\underline{C}H_2CH_2CH_2NCH_2CH_2\underline{C}H_2$), 30.04 s, 30.35 s, 30.49 s, 31.54 s ($2\underline{C}H_2CH_2NCH_2\underline{C}H_2$), 32.86 s ($\underline{C}H_2CHP$), 40.89 d (CHP, $^1J_{CP}$ 61.9 Hz), 46.48 s, 47.22 s, 48.23 s, 48.86 s ($2CH_2NCH_2$), 167.97 d [$\underline{C}$(O)CHP, $^2J_{CP}$ 3.3 Hz], 170.33 d [$\underline{C}$(O)CH_2CHP, $^3J_{CP}$ 14.8 Hz]. ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 38.05.

2-[Bis(4-dimethylaminophenyl)phosphinoyl]-succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (If) was synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 0.97 g (0.0024 mol) of 2-[bis(4-dimethylaminophenyl)phosphinoyl]succinic acid. We obtained 1.25 g of compound **Ic**, yield 83%, mp 92°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 m (12H, $4CH_3$), 1.25 m (8H, $4CCH_2CC$), 1.50 m (8H, $4CCCH_2C$) 2.60 m, 1H and 2.90 m, 1H (CH_2CP), 3.00 s, (12H, $2CH_3NCH_3$), 3.20 m (8H, $2CH_2NCH_2$), 4.24 m (1H, CHP), 6.70 m ($4H_{arom.}$), 7.72 m ($4H_{arom.}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 33.44.

2-[Bis(4-chlorophenyl)phosphinoyl]succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ig) was synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 0.97 g (0.0025 mol) of 2-[bis(4-chlorophenyl)phosphinoyl]succinic acid. We obtained 1.40 g of compound **Ig**, yield 92%, mp 60°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.86 m (12H, $4CH_3$), 1.20 m (8H, $4CCH_2CCN$), 1.40 m (8H, $4CCCH_2CN$), 2.65 m, 1H and 2.95 m, 1H (CH_2CP), 3.08 m (4H, CH_2NCH_2), 3.26 m (4H, CH_2NCH_2), 4.30 m (1H, CHP), 7.45 m ($4H_{arom.}$), 7.78 m ($2H_{arom.}$), 8.10 m ($2H_{arom.}$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.03 s, 14.21 s, 14.34 s, 14.38 s ($2\underline{C}H_3CH_2CH_2CH_2NCH_2CH_2\cdot CH_2\underline{C}H_3$), 20.36 s, 20.54 s, 20.61 s, 20.64 s ($2\underline{C}H_2CH_2\cdot CH_2NCH_2CH_2\underline{C}H_2$), 29.83 s, 30.30 s, 31.01 s, 31.30 s ($2\underline{C}H_2CH_2NCH_2\underline{C}H_2$), 33.02 s ($CH_2CHP$), 43.00 d (CHP, $^1J_{CP}$ 63.8 Hz), 46.55 s, 47.33 s, 48.14 s, 49.13 s ($2CH_2NCH_2$), 168.65 d $\underline{C}$(O)CHP, $^2J_{CP}$ 1.8 Hz], 169.32 d [$\underline{C}$(O)CH_2CHP, $^3J_{CP}$ 15.5 Hz]. ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 30.73.

2-[Bis(4-methoxyphenyl)phosphinoyl]succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (Ih) was

synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 0.95 g (0.0025 mol) of 2-[bis(4-methoxyphenyl)phosphinoyl]succinic acid. We obtained 1.21 g of **Ih**, yield 81%, oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.83 m (12H, $4CH_3$), 1.18 m (8H, $2CCH_2CH_2C$), 1.32 m (8H, $2CCH_2CH_2C$) 2.58 m, 1H and 3.12 m, 1H (2H, CH_2CP), 3.18 m (8H, $2CH_2NCH_2$), 3.85 m (6H, $2CH_3O$), 4.26 m (1H, CHP), 6.95 m ($4H_{arom.}$), 7.75 m ($2H_{arom.}$), 7.96 m ($2H_{arom.}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.96.

2-(Diphenylphosphinoylmethyl)succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetraethyldiamide (IIa) was synthesized similarly to compound **Ia** from 0.49 g (0.002 mol) of $(Et_2N)_3P$ and 0.65 g (0.002 mol) of 2-(diphenylphosphinoylmethyl)succinic acid. We obtained 0.81 g of compound **IIa**, yield 91%, mp 116°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.90–1.10 m (12H, $4CH_3$), 2.40–2.70 m and 2.85 m (4H, CH_2P+CH_2CO), 3.06–3.42 m (8H, $2CH_2NCH_2$), 3.60 m (1H, CHCP), 7.52 m ($6H_{arom.}$), 7.80 m ($4H_{arom.}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.08.

2-[Bis(4-methoxyphenyl)phosphinoylmethyl]-succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (IIb) was synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 1.18 g (0.003 mol) of 2-[bis(4-methoxyphenyl)phosphinoylmethyl]succinic acid. We obtained 1.70 g of compound **IIb**, yield 92%, mp 65°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.85 m (12H, $4CH_3$), 1.00–1.58 m (16H, $4CCH_2CH_2C$), 2.24–2.90 m (4H, CH_2P+CH_2CO), 3.20 m (8H, $2CH_2NCH_2$), 3.56 m (1H, CHCP), 3.80 s (6H, $2CH_3O$), 6.90 m ($4H_{arom.}$), 7.68 m ($4H_{arom.}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.38.

2-[Bis(2,5-dimethylphenyl)phosphinoylmethyl]-succinic acid *N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetrabutyldiamide (IIc) was synthesized similarly to compound **Ia** from 0.83 g (0.002 mol) of $(Bu_2N)_3P$ and 0.78 g (0.002 mol) of 2-[bis(2,5-dimethylphenyl)phosphinoylmethyl]succinic acid. We obtained 1.04 g of compound **IIb**, yield 85%, oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.85 m (12H, $4CH_3$), 1.28 m (8H, $4CCH_2CCN$), 1.42 m (8H, $4CCCH_2CN$), 2.20 s, 2.22 s, 2.34 s and 2.36 s (12H, $4CH_3$-Ar), 2.60–3.00 m (4H, CH_2P+CH_2CO), 3.18 m (4H, CH_2NCH_2), 3.58 m (1H, CHCP), 7.08 m ($2H_{arom}$), 7.22 m ($2H_{arom}$), 7.68 m ($2H_{arom}$). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.28.

Ethyl *N*,*N*-dibutyl-3-(diphenylphosphinoyl) succinamate (V). A mixture of 1.87 g (0.005 mol) of diethyl(2-diphenylphosphinoyl)succinate and 2.59 g (0.02 mol) of Bu_2NH was heated in an evacuated ampule for 4 h at 180°C. The excess amine was removed in vacuo, the residue was purified by chromatography on a column, 1.98 g of compound **V** was isolated, yield 73%, mp 38–40°C (ether–pentane). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.84 m (6H, $2CH_3$), 1.18 t [3H, $CH_3C(O)$], 1.24 m (8H, $2CCH_2CH_2CN$), 2.84 m (2H, CH_2CP) 3.20 m (4H, CH_2NCH_2), 4.08 m [3H, $CH_2P+CH_2C(O)$], 7.50 m ($6H_{arom}$), 7.90 m ($2H_{arom}$), 8.16 m ($2H_{arom.}$) ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 29.79.

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