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Synthesis and Biological Activity of Dialkylamino-Substituted Phosphine Oxides

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Abstract—A series of dialkylamino-substituted phosphine oxides was synthesized and their physiological activity was studied.

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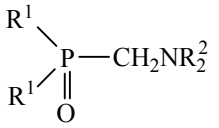
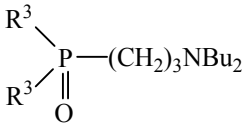
The amino-containing phosphine oxides are of interest as potential physiologically active substances, since they contain two types of coordinating centers in a single molecule with the properties largely dependent on the nature of the substituents at the heteroatoms. However, the methods of their synthesis are insufficiently developed which hampers wide screening of these compounds. In this connection it is interesting to synthesize the amino-containing phosphine oxides, differing primarily by the substituents at the phosphorus atom and the length of the hydrocarbon bridge between the coordinating sites, in order to study the effect *in vitro* of these factors on the biological activity of the compounds, their efficiency and selectivity toward different receptors.

In this work for the synthesis of dialkylamino-substituted phosphine oxides containing $P(O)(CH_2)_nN$ fragment we used a reaction of nucleophilic substitution of the halogen atom in the substituted haloalkylphosphine oxides $R_2P(O)(CH_2)_nHlg$ by the secondary amines. The choice of the synthesis conditions was performed considering the data on the reactivity of the synthesized and previously studied halomethylphosphine oxides [1–3].

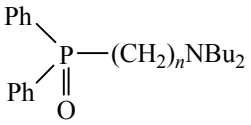
The application of the most reactive haloalkyl component allows performing the reaction in nonpolar solvents (benzene, toluene). The transformation of the resulting HBr (HCl) into an amine hydrohalide insoluble in these solvents at the use of the 2–3-fold excess of a secondary amine also promotes this reaction. This approach made it possible to obtain a wide range of compounds **I–IV** distinguished by the substituents at the phosphorus and nitrogen atoms, the distance between the functional groups, and the number of amino groups in the phosphine oxide molecule.



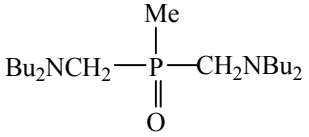
Ia–Ii



IIIa–IIId



IIa, IIb

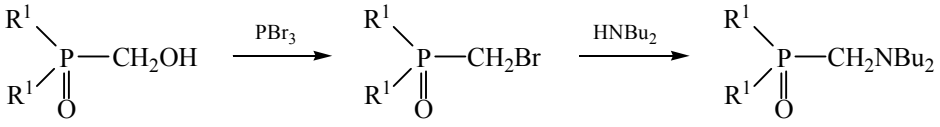


IV

I, R^2 = Bu, R^1 = Me (**a**), Ph (**b**), *p*-$CH_3C_6H_4$ (**c**), *p*-$CH_3OC_6H_4$ (**d**), *p*-ClC_6H_4 (**e**), *m*-$O_2NC_6H_4$ (**f**); $R^2_2 = (CH_2)_5$, R^1 = Ph (**g**), *p*-$CH_3C_6H_4$ (**h**); R^2 = cyclo-C_6H_{11}, R^1 = *p*-$CH_3C_6H_4$ (**i**); **II**, *n* = 2 (**a**), 5 (**b**); **III**, R^3 = Ph (**a**), *p*-$CH_3C_6H_4$ (**b**), *p*-ClC_6H_4 (**c**), *p*-BrC_6H_4 (**d**).

For the reactions with amines we used both the most active chloro derivatives and the more reactive diaryl(bromomethyl)phosphine oxides **VIb–VId** synthesized specially from the corresponding diaryl(hydroxymethyl)phosphine oxides **Vb–Vd** and PBr_3.

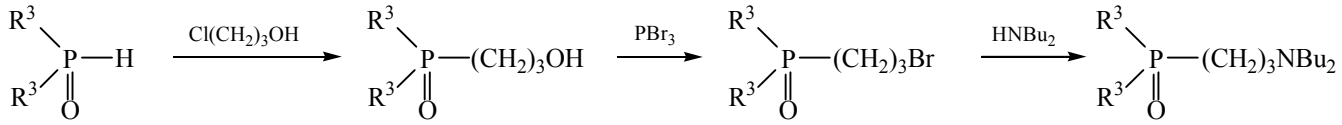
The diaryl(bromoalkyl) phosphine oxides **VIIa–VIId** were prepared by the bromination of the corresponding alcohols, obtained by the method [4] starting from the secondary phosphine oxides and 3-chloropropanol in a two-phase system (method *a*). Compound **IX** was prepared in a one step similar to



Vb–Vd **VIb–VId** **Ib–Id**

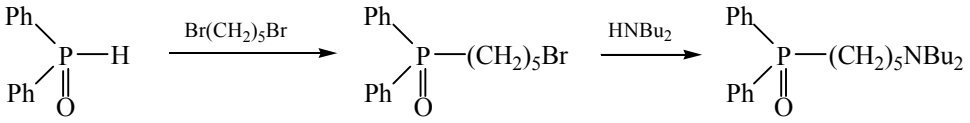
the method [5] starting from the diphenylphosphine oxide and 1,5-dibromopentane (method *b*). Compounds **VIIa–VIId** and **IX** were transformed into the corresponding amines **IIIa–IIId** and **IIb**.

a



VIIa–VIId **VIIIa–VIIId** **IIIa–IIId**

b



IX **IIb**

For the initial evaluation of the biological activity of the synthesized compounds we investigated their effect on the glutamate-induced uptake of calcium ions into synaptosomes of the P_2-fraction of the rat brian [6]. It is known that the glutamate receptors play an important role in the central nervous system in the development of the normal neurophysiologic processes and in the pathogenesis of several neurodegenerative diseases [7]. In this regard, the evaluation of the ability of these compounds to influence the calcium flows mediated by glutamate receptors allows the estimation of their overall biological potential as a possible neuroprotectors (for inhibition) or cognitive functions stimulants (in the case of the activation).

Effect of the structure of phosphine oxides **I–IV** on a glutamate-induced $^{45}Ca^{2+}$ uptake

Comp. no.	Amount of $^{45}Ca^{2+}$ % relative to the control	IC_{50}, μM
Ia	81.7±2.0	–
Ib	18.5±5.4	53.8
Ic	4.6±4.6	14.5
Id	19.9±9.4	57.5
Ie	0.45±0.15	8.3
If	70.6±13.1	–
Ig	72.9±3.3	–
Ih	79.2±3.1	–
Ii	6±3.7	19.1
IIa	71.3±6.5	–
IIb	55.6±1.5	–
IIIa	76.2±3.5	–
IIIb	63.4±1.6	–
IIIc	40.4±13.5	39.8
IIId	32.8±3.7	61.7
IV	0	31.6

The initial screening revealed some structure–biological activity regularities for this set of compounds. Almost all studied dialkylamino-sub-stituted phosphine oxides inhibit $^{45}Ca^{2+}$ uptake into the synaptosomes, which makes it possible to consider this class of compounds as a perspective object for the study and creation on its basis of new neuroprotective drugs.

The screening results are presented in the table. Compounds that have a significant inhibitory effect on $^{45}Ca^{2+}$ uptake into the cortical synaptosomes, were examined in detail to determine their concentration (IC_{50}), at which inhibition of the a 50% $^{45}Ca^{2+}$ ions takes place.

In the (dibutylamino)methyl-substituted phosphine oxides **Ia–Ie** series only two compounds with the least (**Ia**) and the most (**Ie**) sterically hindered conformations at the phosphorus atom exhibit a low

activity. The other compounds of this group inhibit significantly the $^{45}Ca^{2+}$ uptake into the synaptosomes. Depending on the substituents in the phenyl group, this effect increases as follows: $CH_3O < H < CH_3 < Cl$. The decrease in the size of the amino group in compounds **Ih** and **Ii** owing to the conformationally rigid piperidine fragment prevents inhibition of $^{45}Ca^{2+}$ uptake, while the replacement of butyl substituents at the amino group by the cyclohexyl moiety of the roughly equal size has virtually no effect on the activity of compounds **Ib** and **Ig**.

As expected, the distance between the coordinating sites is the determining factor for the manifestation of the biological activity. Comparison of compounds **Ib, Ic, Ie** and **IIIa–IIIc**, which differ only in the alkylene bridge length, shows a marked decrease in the activity of the compounds of III series. The general character of the effect of substituents in the phenyl group in this case is the same as for compounds containing one methylene group. The effect of inhibiting $^{45}Ca^{2+}$ uptake increases depending on the substituents in the phenyl group as follows: $H < CH_3 < Cl < Br$. The halogen-substituted compounds **IIIc** and **IIId** are the most active.

Attention is drawn to the fact that among the amines **Ia, IIa, IIIa**, and **IIb** the activity of compounds **IIa** and **IIIa** are first decreases while the substituent includes 2 and 3 methylene units, and then increases slightly (n = 5) for **IIb** as the distance between the coordinating sites $Ph_2P(O)$ and NBu_2 sequentially increases. Bis(dialkylaminomethyl)-substituted phosphine oxide **IV** is a more effective inhibitor of the $^{45}Ca^{2+}$ ions uptake.

Thus, the studied dialkylamino-substituted phosphine oxides are a convenient model for the identification of the main regularities of the influence of the functional groups on the biological activity. The new high-active inhibitors of a glutamate-induced $^{45}Ca^{2+}$ ions uptake were found in a series of the multifunctional amine-containing phosphine oxides. It makes these compounds promising for further study as alternative neuroprotectors.

EXPERIMENTAL

The ^1H and ^{31}P NMR spectra were recorded on a Bruker CHR-200 spectrometer (Germany) relative to internal Me_4Si. The melting points were determined on a Boetius PHMK instrument (Germany).

Before the biological screening, the substances were additionally purified by the recrystallization or chromatography on a silica gel column (L 100/160, eluents chloroform, hexane–isopropanol, 10:1) and dried in a vacuum.

General procedure for the synthesis of diaryl (bromomethyl)phosphine oxides (VIb–VId). A mixture of 0.015 mol of diaryl(hydroxymethyl)phosphine oxide **VIb–VId** and 0.006 mol of PBr_3 in 10 ml of anhydrous benzene was refluxed for 1–3 h. Then the reaction mixture was diluted with an equal volume of chloroform. The organic solution was washed with water, $NaHCO_3$ saturated solution, water, and dried over Na_2SO_4. The solvent was removed in a vacuum, and the substances were crystallized on standing.

Bromomethyl(diphenyl)phosphine oxide (VIb). Yield 80%, mp 169.5–170.5°C (methylethylketone). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.82 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.54 m (6H, Ph), 7.81 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 28.41 ppm.

Bromomethyl(di-*p*-tolyl)phosphine oxide (VIc). Yield 83%, mp 61–63°C (CCl_4). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.79 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.29 m ($4H_{Ar}$), 7.64 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 28.00 ppm.

Bromomethyl(di-*p*-anisyl)phosphine oxide (VId). Yield 98%, mp 121–123°C (benzene–hexane). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.75 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 3.88 s (6H, $2CH_3O$), 7.00 m ($4H_{Ar}$), 7.70 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.73 ppm.

Bromomethyl(di-*p*-chlorophenyl)phosphine oxide (VIe). Yield 91%, mp 138–140°C (benzene). ^1H NMR spectrum (acetone-d_6), δ, ppm: 4.32 d (2H, CH_2P), 7.62 m ($4H_{Ar}$), 7.94 m ($4H_{Ar}$). ^{31}P NMR spectrum (acetone-d_6): δ_P 24.78 ppm.

3-[Bis(4-chlorophenyl)phosphinoyl]propanol (VIIc). To a solution of 0.90 g (0.0033 mol) of p-$(ClC_6H_4)_2$·P(O)H and 0.31 g (0.0033 mol) of $Cl(CH_2)_3OH$ in 10 ml of DMSO was added dropwise 50% aqueous solution of 0.37 g (0.0065 mol) of KOH. The reaction mixture was stirred for 2 h at 55–60°C. Then the mixture was cooled, poured into 150 ml of water, and extracted with chloroform (5×30 ml). The organic extract was washed with water, dried with Na_2SO_4, and concentrated. Yield 83% (0.90 g), mp 167–169°C (benzene–acetone). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.84 m (2H, CH_2CP), 2.40 m (2H, CH_2P), 3.70 m (2H, CH_2OH), 7.46 m ($4H_{Ar}$), 7.66 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 34.20 ppm.

3-[Bis(4-bromophenyl)phosphinoyl]propanol (VIId) was obtained similarly. Yield 88%, mp 173–175°C (ethyl acetate–hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.80 m (2H, CH_2CP), 2.40 m (2H, CH_2P), 3.68 m (2H, CH_2OH), 7.60 m ($8H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 34.48 ppm.

1-Bromo-3-(diphenylphosphinoyl)propane (VIIIa). A solution of 2.44 g (0.009 mol, 0.85 ml) of PBr_3 in 10 ml of anhydrous benzene was added dropwise with stirring to a suspension of 6.30 g (0.024 mol) of VIIa [4] in 20 ml of anhydrous benzene. The reaction mixture was slightly refluxed for 1.5 h while stirring. An equal volume of chloroform was added to the reaction mixture. The organic solution was washed with a $NaHCO_3$ saturated solution and water, dried with Na_2SO_4, and concentrated in a vacuum. The substance crystallizes on standing. Yield 88% (6.82 g), mp 94–96°C (benzene–hexane, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.20 m (2H, CH_2CP), 2.42 m (2H, CH_2P), 3.50 t (2H, CH_2Br), 7.56 m (6H, Ph), 7.81 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.97 ppm.

1-Bromo-3-[bis(*p*-tolyl)phosphinoyl]propane (VIIIb) was obtained similarly from alcohol VIIb [4]. Yield 86%, mp 110–112°C (benzene–hexane, 1:3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 m (2H, CH_2CP), 2.38 m (2H, CH_2P), 2.42 s (6H, $2CH_3$), 3.48 t (2H, CH_2Br), 7.30 m ($4H_{Ar}$), 7.64 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.40 ppm.

1-Bromo-3-[bis(4-chlorophenyl)phosphinoyl]-propane (VIIIc) was obtained similarly from alcohol **VIIc**. Yield 74%, mp 106–107.5°C (benzene–hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 m (2H, CH_2CP), 2.44 m (2H, CH_2P), 3.50 t (2H, CH_2Br), 7.48 m ($4H_{Ar}$), 7.72 m ($4H_{Ar}$). Спектр ЯМР ^{31}P ($CDCl_3$): δ_P 31.30 ppm.

1-Bromo-3-[bis(4-bromophenyl)phosphinoyl]-propane (VIIId) was obtained similarly from alcohol **VIId**. Yield 83%, mp 141–143°C (benzene–hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 m (2H, CH_2CP), 2.42 m (2H, CH_2P), 3.52 t (2H, CH_2Br), 7.62 m ($8H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.35 ppm.

1-Bromo-5-(diphenylphosphinoyl)pentane (IX). A solution of 2.02 g (0.01 mol) of $Ph_2P(O)H$ in 10 ml of anhydrous THF was added dropwise to a mixture of 4.83 g (0.021 mol) of $Br(CH_2)_5Br$ and 4.89 g (0.015 mol) Cs_2CO_3 in 10 ml of anhydrous THF under stirring, which was continued for another 20 h at 20°C. The precipitate was filtered off, washed with THF on a filter. The combined organic solution was concentrated in a vacuum. The residue was chromatographed on a silica gel column. A dibromide excess was eluted with hexane, then the target compound was eluted with a hexane–isopropanol mixture (10:1). Yield 87% (3.11 g), mp 72.5–73.5°C (diethyl ether). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.60 m (4H), 1.82 m (2H), 2.30 m (2H, $CH_2CH_2CH_2CH_2P$), 3.32 t (2H, CH_2Br), 7.46 m (6H, Ph), 7.76 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.97 ppm.

(Dimethylphosphinoylmethyl)dibutylamine (Ia). A mixture of 2.52 g (0.02 mol) of $Me_2P(O)CH_2Cl$ [9] and 6.46 g (0.05 mol) of Bu_2NH in 20 ml of anhydrous benzene was slightly refluxed for 15 h. After cooling the reaction mixture, $Bu_2NH{\cdot}HCl$ was filtered off. The solvent and an amine excess were removed in a vacuum on a rotary evaporator. The residue was distilled in a vacuum. Yield 84% (3.67 g), bp 140–142°C (1 mm Hg), hygroscopic. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (6H, $2CH_3$), 1.36 m (8H, $2CH_2CH_2$), 1.51 d (6H, CH_3PCH_3, $^2J_{HP}$ 12 Hz), 2.54 t (4H, CH_2NCH_2), 2.75 d (2H, CH_2P, $^2J_{HP}$ 6 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 44.19 ppm.

(Diphenylphosphinoylmethyl)dibutylamine (Ib). A solution of 0.89 g (0.003 mol) of bromide **VIb** and 1.52 g (0.009 mol) of Bu_2NH in 10 ml of anhydrous benzene was slightly refluxed for 25 h. After cooling the reaction mixture, $Bu_2NH{\cdot}HCl$ was filtered off. The organic solution was washed with water and dried with Na_2SO_4. The solvent was removed in a vacuum on a rotary evaporator. Yield 89%, (0.92 г), mp 75–76°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.80 t (6H, $2CH_3$), 1.10 m (4H), 1.30 m (4H, $CH_2CH_2{\cdot}CNCCH_2CH_2$), 2.60 t (4H, CH_2NCH_2), 3.34 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.46 m (6H, Ph), 7.84 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.85 ppm.

[Bis(4-methylphenyl)phosphinoylmethyl]dibutylamine (Ic) was obtained similarly from bromide **VIc**. Yield 84%, mp 64–65°C (pentane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.80 t (6H, $2CH_3$), 1.14 m (4H, $CH_2CCNCCCH_2$), 1.34 m (4H, CH_2CNCCH_2), 2.36 s (6H, $2CH_3$), 2.58 t (4H, CH_2NCH_2), 3.36 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.28 m (4H, Ph), 7.70 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 28.40 ppm.

[Bis(4-methoxyphenyl)phosphinoylmethyl]dibutylamine (Id) was obtained similarly from bromide **VId**. Yield 68%, mp 53–55°C (cyclohexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 t (6H, CH_3), 1.14 m (4H), 1.32 m (4H, $CH_2CH_2CNCCH_2CH_2$), 2.56 m (4H, CH_2NCH_2), 3.30 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 3.82 s (6H,

CH_3O), 7.00 m (4H, Ph), 7.74 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 28.72 ppm.

[Bis(4-chlorophenyl)phosphinoylmethyl]dibutylamine (Ie) was obtained similarly from bromide **VIe**. Yield 90%, mp 54–55°C (hexane). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.84 t (6H, $2CH_3$), 1.16 m (4H), 1.32 m (4H, $CH_2CH_2CNCCH_2CH_2$), 2.56 t (4H, CH_2NCH_2), 3.36 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.48 m ($4H_{Ar}$), 7.78 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.10 ppm.

[Bis(3-nitrophenyl)phosphinoylmethyl]dibutylamine (If). A mixture of 0.42 g (0.0012 mol) of (*m*-$O_2NC_6H_4)_2P(O)CH_2Cl$ [9] and 0.48 g (0.60 ml, 0.0036 mol) of Bu_2NH in 10 ml of anhydrous toluene was slightly refluxed for 8 h. After cooling the reaction mixture, $Bu_2NH{\cdot}HCl$ was filtered off. The organic solution was washed with water and dried with Na_2SO_4. The solvent was removed in a vacuum on a rotary evaporator. The oily residue, which crystallizes on standing, was chromatographed on a column with silica gel eluting with a hexane–isopropanol mixture (10:1). Compound **If** (0.33 g) crystallizes at the grinding with hexane. Yield 63%, mp 89–92°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.81 t (6H, $2CH_3$), 1.15 m (4H), 1.33 m (4H, $CH_2CH_2CNCCH_2CH_2$), 2.65 t (4H, CH_2NCH_2), 3.50 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.75 m ($2H_{Ar}$), 8.20 m ($2H_{Ar}$), 8.42 m ($2H_{Ar}$), 8.70 m ($2H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 25.20 ppm.

1-Diphenylphosphinoylmethylpiperidine (Ig). A mixture of 1.48 g (0.005 mol) of bromide **VIb** and 1.88 g (0.022 mol) of piperidine in 15 ml of anhydrous benzene was slightly refluxed for 4 h. The reaction mixture was cooled, and piperidine hydrobromide was filtered off. The organic layer was washed with water and dried with Na_2SO_4. The solvent and piperidine excess were removed on a rotary evaporator. The residue was recrystallized from hexane. Yield 82% (1.23 g), mp 120.0–121.5°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 m (2H, CH_2CCN), 1.52 m (4H, CH_2CNCCH_2), 2.54 m (4H, CH_2NCH_2), 3.23 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.44 m (6H, Ph), 7.83 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.10 ppm.

1-[Bis(4-methylphenyl)phosphinoylmethyl]piperidine (Ih). A mixture of 0.65 g (0.002 mol) of bromide **VIc** and 0.34 g (0.004 mol) of piperidine in 5 ml of anhydrous benzene was slightly refluxed for 1 h. The reaction mixture was cooled, and piperidine hydrobromide was filtered off. The solvent was removed on a rotary evaporator. Yield 85% (0.55 g), mp 137–139°C (benzene–pentane). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 m (2H, CH_2CCN), 1.56 m (4H, CH_2CNCCH_2), 2.40 s (6H, $2CH_3$), 2.70 m (4H, CH_2NCH_2), 3.32 d (2H, CH_2P, $^2J_{HP}$ 6 Hz), 7.24 m (H_{Ar}), 7.74 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.40 ppm.

[Bis(4-methylphenyl)phosphinoylmethyl]dicyclohexylamine (Ii). A mixture of 0.80 g (0.0025 mol) of bromide **VIc** and 0.1.36 g (0.0075 mol, 1.49 ml) of *cyclo*-Hex_2NH in 10 ml of anhydrous toluene was refluxed for 45 h with stirring. After cooling the reaction mixture, the precipitate of *cyclo*-$Hex_2NH{\cdot}HBr$ (0.57 г, 86%) was filtered off. The filtrate was washed with water, dried with Na_2SO_4, and concentrated. The oily residue was chromatographed on a column with silica gel eluting with benzene. Yield 74% (0.78 g), mp 93–95°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.04 m (12H, $6CH_2$), 1.60 m [8H, $2CH_2(C–N)CH_2$], 2.40 s (6H, $2CH_3$), 2.70 m (2H, CH–N–CH), 3.46 d (2H, CH_2P, $^2J_{HP}$ 5 Hz), 7.24 m ($4H_{Ar}$), 7.68 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 29.50 ppm.

[(2-Diphenylphosphinoyl)ethyl]dibutylamine (IIa). A mixture of 1.00 g (0.0044 mol) of vinyl(diphenyl) phosphine oxide, 0.65 g (0.005 mol, 0.84 ml) of Bu_2NH, 2.00 ml of water and 0.5 ml of DMSO was stirred at 90°C for 4 h. After cooling, to the reaction mixture was added 10 ml of chloroform and 5 ml of water. The organic layer was separated, washed with water (3×5 ml), and dried with Na_2SO_4. Then the solvent was removed, and the residue crystallized. Yield 94% (1.47 g). Then compound **IIa** was recrystallized with charcoal from hexane. Yield 72% (1.10 g), mp 62.5–63.5°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.84 t (6H, $2CH_3$), 1.28 m [8H, $(CCH_2CH_2C)_2N$], 2.36 t (4H, CH_2NCH_2), 2.46 m (2H, NCH_2CP), 2.84 m (2H, CH_2P), 7.48 m (6H, Ph), 7.76 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.04 ppm.

[(5-Diphenylphosphinoyl)pentyl)]dibutylamine (IIb). A mixture of 0.50 g (0.0014 mol) of $Ph_2P(O){\cdot}(CH_2)_5Br$ (**IX**) and 0.78 g (0.0059 mol) of Bu_2NH in 5 ml of anhydrous toluene was slightly refluxed for 4 h. Then the reaction mixture was cooled, and the precipitated $Bu_2NH{\cdot}HBr$, was filtered off. The organic solution was washed with water, dried with Na_2SO_4, and concentrated. The dark-yellow oily residue was chromatographed on a column with silica gel eluting with chloroform. Yield 71% (0.40 g). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 t (6H, $2CH_3$), 1.36 m (12H, $3CH_2CH_2CN$), 1.67 m (2H, CH_2CP), 2.40 m [8H, $(CH_2)_3N + CH_2P$], 7.45 m (6H, Ph), 7.76 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.82 ppm.

[(3-Diphenylphosphinoyl)propyl)]dibutylamine (IIIa). A mixture of 3.88 g (0.012 mol) of $Ph_2P(O)\cdot(CH_2)_3Br$ (**VIIIa**) and 4.65 g (6.06 ml, 0.036 mol) of Bu_2NH in 20 ml of anhydrous benzene was slightly refluxed for 5 h. After cooling, the precipitated $Bu_2NH\cdot HBr$ was filtered off. The organic solution was washed with water, dried with Na_2SO_4, and concentrated in a vacuum. The residue crystallizes. Yield 96% (4.30 g), mp 37–39°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 t (6H, CH_3), 1.28 m [8H, $(CCH_2CH_2C)_2N$], 1.76 t (2H, CH_2CP), 2.16–2.40 m (6H, $3CH_2N$), 2.50 t (2H, CH_2P), 7.46 m (6H, Ph), 7.76 m (4H, Ph). ^{31}P NMR spectrum ($CDCl_3$): δ_P 33.37 ppm.

[3-Bis(4-methylphenyl)phosphinoylpropyl]dibutylamine (IIIb) was obtained similarly from bromide **VIIIb**. Yield 86%, mp 73–74.5°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (6H, CH_3), 1.30 m [8H, $(CCH_2CH_2C)_2N$], 1.72 m (2H, CH_2CP), 2.17–2.48 and 2.62 two m (8H, $3CH_2N+CH_2P$), 2.36 s (6H, $2CH_3$), 7.24 m ($4H_{Ar}$), 7.60 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 33.73 ppm.

[3-Bis(4-chlorophenyl)phosphinoylpropyl]dibutylamine (IIIc) was obtained similarly from bromide **VIIIc**. Yield 67%, mp 86–87.5°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (6H, $2CH_3$), 1.30 m [8H, $(CCH_2CH_2C)_2N$], 1.70 m (2H, CH_2CP), 2.22–2.40 m (6H, $3CH_2N$), 2.50 t (2H, CH_2P), 7.42 m ($4H_{Ar}$), 7.66 m ($4H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.10 ppm.

[3-Bis(4-bromophenyl)phosphinoylpropyl]dibutylamine (IIId) was obtained similarly from bromide **VIIId**. Yield 69%, mp 93–94.5°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 t (6H, $2CH_3$), 1.34 m [8H, $(CCH_2CH_2C)_2N$], 1.78 m (2H, CH_2CP), 2.26–2.46 m (6H, $3CH_2N$), 2.52 t (2H, CH_2P), 7.64 m ($8H_{Ar}$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 32.70 ppm.

Methyl[bis(*N*,*N*-dibutylaminomethyl)]phosphine oxide (IV). A mixture of 2.61 g (0.016 mol) of $MeP(O)(CH_2Cl)_2$ [10] and 8.27 g (0.064 mol, 10.78 ml) of Bu_2NH in 10 ml of anhydrous toluene was slightly refluxed for 3 h. After cooling, the precipitated $Bu_2NH\cdot HCl$ (4.87 g, 91%) was filtered off. The organic solution was washed with water, dried with Na_2SO_4, and concentrated in a vacuum. The oily residue (3.97 g, 72%) crystallized on standing. The product was distilled in a vacuum. Yield 57% (3.15 g), bp 174–178°C (0.5 mm Hg), hygroscopic. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 t (12H, $4CH_3$), 1.36 m (16H, $2CCH_2CH_2CNCCH_2CH_2C$), 1.48 d (3H, CH_3P, $^2J_{HP}$ 14 Hz), 2.55 m (8H, $2CH_2NCH_2$), 2.79 m (4H, CH_2PCH_2). ^{31}P NMR spectrum ($CDCl_3$): δ_P 48.10 ppm.

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REFERENCES

1. Patsanovskii, I.I., Ishmaeva, E.A., Sundukova, E.N., Yarkevich, A.N., and Tsvetkov, E.N., *Zh. Obshch. Khim.*, 1986, vol. 56, no. 3, p. 567.
2. Tkachenko, S.E., Yarkevich, A.N., Timofeev, S.V., and Tsvetkov, E.N., *Zh. Obshch. Khim.*, 1988, vol. 58, no. 3, p. 531.
3. Tkachenko, S.E., Yarkevich, A.N., Tsvetkov, E.N., Galkin, V.I., Sayakhov, R.D., Cherkasov, R.A., and Pudovik, A.N., *Dokl. Akad. Nauk SSSR*, 1990, vol. 315, no. 3, p. 628.
4. Tsvetkov, E.N., Bondarenko, N.A., Malakhova, I.G., and Kabachnik, M.I., *Zh. Obshch. Khim.*, 1985, vol. 55, no. 5, p. 11.
5. Bondarenko, N.A., Yarkevich, A.N., Bovin, A.N., and Tsvetkov, E.N., *Izv. Akad. Nauk, Ser. Khim.*, 1991, no. 8, p. 1933.
6. Petrova, L.N. and Bachurin, S.O., *Bull. Eksp. Biol. i Med.*, 2006, vol. 142, no. 7, p. 51.
7. Kew, J.N. and Kemp, J.A., *Psychopharmacology*, 2005, vol. 179, no. 1, p. 4.
8. Tsvetkov, E.N., Kron, T.E., and Kabachnik, M.I., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, no. 3, p. 669.
9. Tsvetkov, E.N., Malevannaya, R.A., and Kabachnik, M.I., *Zh. Obshch. Khim.*, 1969, vol. 39, no. 7, p. 1520.
10. Tsvetkov, E.N., Borisov, G., Sivriev, Kh., Malevannaya, R.A., and Kabachnik, M.I., *Zh. Obshch. Khim.*, 1970, vol. 40, no. 2, p. 285.