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Amidoalkylation of Hydrophosphoryl Compounds

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Abstract—A new mild procedure of the amidoalkylation of hydrophosphoryl compounds in a mixture of acetic anhydride and acetyl chloride was developed as a convenient method of constructing the α-aminophosphoryl fragment of the pseudo-α,α'-dipeptide molecule. The reaction intermediates *N,N'*-benzylidene- and *N,N'*-alkylidenebiscarbamates were detected, isolated, and identified. The report presents the results of studying the direct interaction of hydrophosphoryl compounds previously synthesized with biscarbamates in acetic anhydride and other solvents, the influence of the structure of phosphorus component and biscarbamate, and the effect of acid catalysis on the course of this two-component reaction. A new version of the mechanism of the three-component reaction of amidoalkylation of hydrophosphoryl compounds is suggested: it is regarded as a multistage process involving the stage of biscarbamate formation followed by the stage of Arbuzov-type reaction with the intermediate formation of acyliminium cation and P–OAc derivative with trivalent phosphorus.

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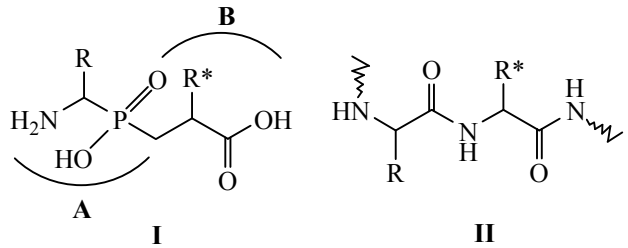
A suitable imitation of the substrate in the transition state of the reactions involving hydrolytic enzymes, Zn-metalloproteinases and aspartylproteinases is the replacement of the peptide bond with a non-hydrolized phosphinate fragment [1].

The known approach to constructing molecular phosphinic analogs **I** of α,α'-dipeptides **II** is the synthesis of *N*-protected aminoalkylphosphonic component of the pseudopeptide, phosphonic analog **A** of amino acid, followed by adding the latter to the appropriate α-substituted acrylate and the formation of pseudopeptide fragment **B** [2–4].



I Phosphinic acidic pseudo-{Ψ(P(O)(OH)CH_2}-α,α'-dipeptide

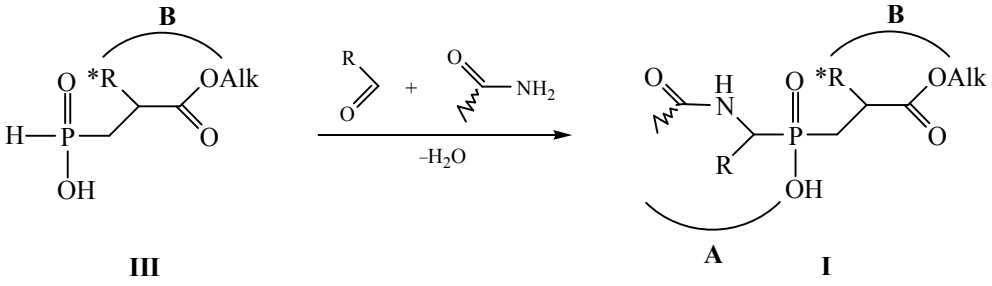
II Peptide fragment

In this case, the synthesis of an aminoalkylphosphoryl peptide fragment requires three or more stages [2–4], due to the incorporation and removal of the protective groups. Introduction of aminoalkylphosphonic component into the acrylates as a silyl ether [4] has a limitation in the construction of the complex aminoalkylphosphonic building-blocks. The attempts to obtain the phosphine pseudo-AspAla-dipeptide via the addition of trimethylsilyl ethers of aminophosphonic analog of aspartic acid to ethyl methacrylate failed [4].

In this regard, the development of alternative methods of constructing pseudopeptides is actual. Previously we have developed new synthesis methods of pseudo-γ-glutamylpeptides [5] and pseudo-γ-aminobutanoylpeptides [6] with the inverse order of constructing the target molecule: First adding hypophosphite to the corresponding acrylate to form phosphonic acids containing structural isostere of amino acids followed by the addition of amino acid function and the formation of pseudopeptide molecules [5, 6].

Further development of this methodology in the synthesis of phosphinic peptidomimetics, the promising pseudo-α,α'-dipeptide building-blocks **I** for combinatorial chemistry, includes finding a convenient procedure for constructing α-aminophosphoryl functions involving phosphonic acids **III** containing a structural isosteres of the corresponding amino acids [7, 8].

Scheme 1.

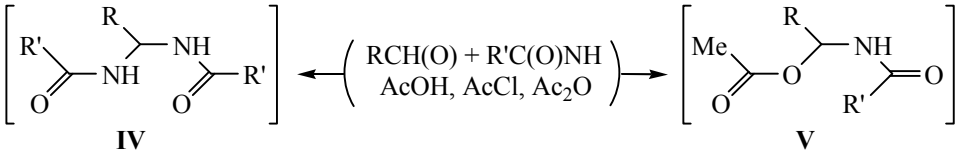


In this regard, the development of the amidoalkylation procedure of the trivalent phosphorus compounds via the Kabachnik–Fields type reaction using the carbonyl compounds and amides as an amino component of the synthesis [9, 10] may be a promising way to the construction of *N*-protected pseudopeptide molecule **I**.

The amidoalkylation reaction originally developed for the trivalent phosphorus chlorides in acetic acid (Oleksyszyn reaction) [9] was further modified into the procedure of dialkylphosphites amidoalkylation in acetyl chloride or in a mixture of acetic acid and thionyl chloride with aldehydes or ketones, amides or carbamates [10]. The use of benzyl carbamate in acetyl chloride medium allows to obtain the α-aminoalkylphosphoryl *N*-benzyloxycarbonyl derivatives, which are of interest for peptide synthesis [10]. The procedure of amidoalkylation of hydrophosphoryl compounds in a mixture of acetyl chloride and acetic acid has been used in the synthesis of phosphinic pseudopeptide blocks involving the prehydrolyzed phosphonous component [8], probably due to the partial dealkylation of alkoxyphosphoryl and alkoxycarboxyl fragments occuring in acetyl chloride medium. Our attempt to amidoalkylate dimethylphosphite and 2-(ethoxycarbonyl)propylphosphonic acid in the acetyl chloride medium resulted in a significant loss of ester groups in phosphoryl and carboxyl fragments of the target molecule, hampering the isolation of the target product. Typically, crude *N*-acylated α-aminophosphonic derivatives were subjected to the acid hydrolysis to isolate free α-aminoalkylphosphonic acids [9–11]. In this regard, a search for milder conditions for the synthesis of *N*-protected derivatives of α-aminoalkylphosphoryl compounds is urgent. The relatively mild amidoalkylation procedure has been developed for the phosphorous acid amides, which consists in adding the aldehyde to a preheated mixture of the reagents in acetic anhydride [11]. An attempt to further development of this synthetic approach to the pseudo-α,α'-dipeptides using acetamide as amino component and phosphonic acids containing the amino acid structural isosteres led to the satisfactory results only in the case of aromatic aldehydes [7]. However, this procedure can underlie a more efficient and mild procedure of amidoalkylation of the hydrophosphoryl compounds.

Earlier *N*,*N*'-alkylidenebisamides **IV** [11] and *O*,*N*-hemiaminals, 1-(acylamino)alkyl acetates **V**, have been suggested as possible intermediates in the amidoalkylation reaction of trivalent phosphorus compounds [12] (Scheme 2).

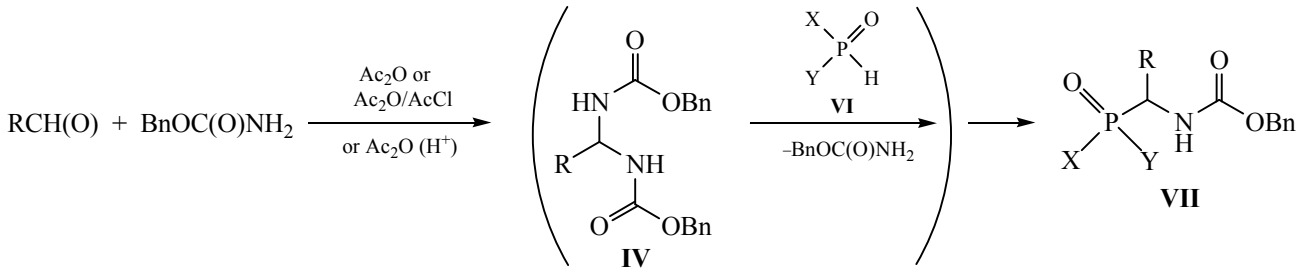
Scheme 2.



N,*N*'-Arylidene or *N*,*N*'-alkylidene bisamides **IV** were suggested in [11] as probable intermediates in the amidoalkylation reaction due to their easy formation from carbonyl compounds and amides [13], but they were not isolated from the reaction mixture [11]. The hemiaminals **V** have also been postulated as intermediates in this reaction, but these compounds also were not isolated from the reaction mixture [12].

This paper presents the results of the study of amidoalkylation of the hydrophosphoryl compounds in acetic anhydride medium. We have found that the milder Oleksyszyn modification of the procedure [11] allows to carry out the reaction of benzyl carbamate as amino component and aldehydes with various hydrophosphoryl compounds **VI** in acetic anhydride in the cold to form *N*-benzyloxycarbonyl-α-aminoalkylphosphoryl compounds **VII** in moderate yields (Scheme 3).

Scheme 3.



A mixture of acetic anhydride and acetyl chloride is a more effective medium for amidoalkylation of PH-compounds (Table 1), however, the search for the optimum mixture was not performed. The use of methyl and ethyl carbamates as amino components in acetic anhydride gives a positive result [14]. The attempts to use in these conditions phthalimide, acetamide, trifluoroacetamide, and *tert*-butyl carbamate proved to be unsuccessful or ineffective.

The mild conditions of amidoalkylation of hydrophosphoryl compounds **VI** in acetic anhydride using benzyl carbamate allowed us to isolate for the first time the reaction intermediates *N*,*N*'-benzylidene- and *N*,*N*'-alkylidenebis(benzyl carbamates) (**IV,** R' = OCH_2Ph). The initially formed biscarbamate **IV** rapidly accumulates and often crystallizes from the reaction solution, but then it dissolves again and interacts with the PH-component **VI** to give the target *N*-Cbz-α-aminoalkylphosphoryl compound **VII** (Scheme 3). The latter sometimes also crystallizes from the reaction solution.

When the three-component reaction was stopped at the early stages the isolated products contained a mixture of *N*-Cbz-α-aminoalkylphosphoryl compound

N-Benzyloxycarbonyl-α-aminoalkylphosphoryl compounds **VIIa**–**VIIn**

Comp. no.	X	Y	R	Yield, %
VIIa	OMe	OMe	Ph	63[a], 73б, 69[c], 56[d]
VIIb	Me	OH	Me	27[a,f], 67[c], 51[e], 62[a,e]
VIIc	Me	OH	Et	61[c], 31[d]
VIId	Me	OH	*i*-Pr	57[c], 30[d]
VIIe	Me	OH	*i*-Bu	46[b], 53[c], 33[d], 41д, 59[b,e]
VIIf	Me	OH	Ph	69б, 76[c], 61[d], 63[e], 69[a,e]
VIIg	$PhCH_2CH_2$	OH	Et	59[c], 35[d]
VIIh	$PhCH_2CH_2$	OH	*i*-Pr	63[c], 29[d]
VIIi	$PhCH_2CH_2$	OH	*i*-Bu	31[a], 68[c]
VIIj	$HOCH_2$	OH	*i*-Bu	33[a,g]
VIIk	$HOCH_2$	OH	Ph	42[a,g]
VIIl	$EtOOCCH(Me)CH_2$	OH	Me	33[a], 57[c]
VIIm	$EtOOCCH(Me)CH_2$	OH	Ph	54[a], 63[b], 69[c], 43[d]
VIIn	Et	Et	Ph	51[a], 67[c], 41[d]

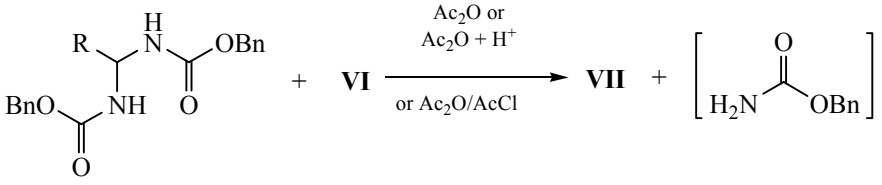
[a] Reaction was catalyzed with: Trifluoroacetic acid (10 mol %); [b] *p*-TsH (2 mol%). In the absence of a catalyst: [c] in the medium of AcCl/Ac_2O (1:4) or [d] Ac_2O. [e] Relative to PH-component for the two-component synthesis, the reaction of methylphosphonic acid with the corresponding biscarbamate **IV**. [f] Using acetaldehyde diethylacetal. [g] The amidoalkylation products of hydroxymethylphosphonic acid were hydrolyzed; the free aminophosphinic acids yields are given, calculated on benzyl carbamate.

VII and the corresponding biscarbamate **IV** in different ratios depending on the reagents reactivity and reaction time. Compounds **IV** and **VII** were isolated using chromatography on silica gel and were characterized by TLC and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.

These data are surprising because the more probable intermediates of the three-component reactions are acetates **V** (Scheme 2) [12]. They are more favorable, if we accept the reaction mechanism comprising the step of nucleophilic attack of PH-component phosphorus atom on the electrophilic carbon center of acetate **V** containing a good leaving acetoxy group. The results of the research suggest that the mixture of acetic anhydride and acetyl chloride is the optimum medium for the three-component reaction.

The data obtained are a good justification for the study of the two-component reaction between biscarbamates **IV** and hydrophosphoryl compounds **VI**. We found that the pre-synthesized biscarbamates **IV** are able to react in the cold with hydrophosphoryl compounds **VI** in acetic anhydride or a mixture of acetyl chloride and acetic anhydride (1:4) to give the target α-aminoalkylphosphoryl compounds **VII** (Scheme 4) .

Scheme 4.



R = Me, *i*-Bu, Ph; X = Me, OMe, Y = OH, OMe.

The amidoalkylation of the hydrophosphoryl compounds **VI** in a mixture of acetic anhydride and acetyl chloride (4:1) proceeds with a higher yield of target compounds **VII** than in acetic anhydride. The Ac_2O/AcCl mixture is a suitable medium for the three-component reaction. However, the focused search for the optimal ratio of acetic anhydride and acetyl chloride for the amidoalkylation of hydrophosphoryl compounds was not performed.

The amidoalkylation of 2-(ethoxycarbonyl)propylphosphonic acid containing the structural isostere of alanine is a way to phosphine pseudoalanine peptides. In this work 1-(benzyloxycarbonylamino)ethyl-2-(ethoxycarbonyl)propylphosphinic **VIIl** and α-(benzyloxycarbonylamino)benzyl-2-(ethoxycarbonyl)propylphosphinic **VIIm** acids were synthesized. These compounds are ethyl esters of *N*-Cbz-protected phosphinic acid analogs of alanylalanine *N*-Cbz-Ala-ψ{P(O)(OH)·CH_2}Ala and phenylglycylalanine *N*-Cbz-PhGly-ψ{P(O)(OH)CH_2}Ala peptides, respectively. Due to the presence of a chiral center in the molecule of 2-(ethoxycarbonyl)propylphosphonic acid along with the formation of the second chiral α-carbon of aminophosphoryl fragment in the course of amidoalkylation, the target compounds **VIIl** and **VIIm** are formed as mixtures of two diastereomers, which is manifested in the presence of the corresponding signals in the NMR spectra of these compounds.

Synthesis of 1-(benzyloxycarbonylamino)ethylmethylphosphinic acid **VIIb** was performed using acetaldehyde or its diethylacetal, or in a two-component reaction of methylphosphonic acid with the preliminary synthesized *N*,*N*'-ethylidenebis(benzyl carbamate) **IVa**. The use of aldehyde gives the desired product **VIIb** in high yield. An alternative way of synthesis of the target molecules could be the use of the preliminary synthesized biscarbamate (see the table). However, the use of acetaldehyde diethylacetal decreases significanty the yield of **VIIb**. Ethyl acetate, which was detected in the reaction mixture, probably causes a poor result, because its formation consumes acetyl chloride and (or) acetic anhydride, which affects significantly the catalytic properties of the reaction medium. Perhaps the reason for the yield decrease is more profound, and the use of aldehyde acetals in this reaction requires an additional investigation.

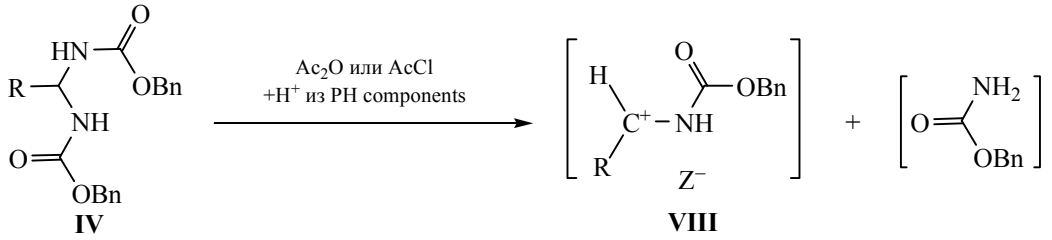
The reaction monitoring with the use of the ^{31}P NMR spectroscopy revealed a greater reactivity of benzylidenebiscarbamate compared with alkylidenebiscarbamate. In addition, we found that *N*,*N*'-benzylidenebis(benzyl carbamate) **IVe** (R = Ph) reacts with methylphosphonic acid to form compound **VIIf** in

higher yield than in the case of *N*,*N*'-isoamylidenebis(benzyl carbamate) **IVd** (R = *i*-Bu) in the reaction with methylphosphonic acid to form **VIIe** both in acetic anhydride medium and in Ac_2O/AcCl (4:1) mixture. These data indicate the electrophilic nature of biscarbamates **IV**. However, it should be noted that while studying hydrophosphoryl compounds **VI** of different structures and potentially different nucleophilicity (dimethyl phosphite–alkylphosphonic acid–diethylphosphinic acid) we found no explicit nucleophilic nature of the phosphorus components, both in three- and two-component versions of the synthesis.

The reaction of biscarbamate **IV** with PH-component in acetic anhydride medium was found to be acid-catalyzed, in contrast to the previously published negative data for the three-component reaction [11]. Adding trifluoroacetic acid or *p*-toluenesulfonic acid (*p*-TsOH) to a mixture of reactants in acetic anhydride or performing the reaction in a mixture of acetyl chloride and acetic anhydride (1:4) leads to a marked increase in the reaction rate, as confirmed by the increase in the reaction product yield. It is important to note that in benzene or toluene, ethanol, dioxane, and tetrahydrofuran the reaction of biscarbamate **IV** with hydrophosphoryl compounds fails. The reaction of biscarbamates **IV** with PH-compounds in acetic anhydride proceeds satisfactorily in the cold without a catalyst, better with acid catalyst (CF_3COOH or *p*-TsOH), and significantly better in a mixture of acetic anhydride and acetyl chloride or acetyl chloride medium. But in the last case there is a significant dealkylation of alkoxyphosphoryl and alkoxycarboxyl fragments.

The results obtained suggest that amidoalkylation of hydrophosphoryl compounds is a multistep process, and the rate-determining stage is probably the protonation of oxygen (C=O) or nitrogen atoms in the amide fragment of the biscarbamate **IV** intermediate, followed probably by the release of benzyl carbamate molecule (Schemes 4, 5) and the formation of a reactive intermediate *N*-(benzyloxycarbonyl)iminium cation **VIII** (Scheme 5). The conditions for the formation of similar acyliminium ions and their reactivity data were published earlier [13].

Scheme 5.



IV **VIII**

Z = OAc or Cl.

We assume that all subsequent stages of the amidoalkylation process are extremely fast and do not affect the overall reaction rate.

It is interesting to note that in an excess of acetic anhydride the formation is possible of the intermediate salts **VIII** (Z = OAc), a ionic analog of 1-(acylamino)alkyl acetate **V** (Scheme 2) suggested early [12] as an intermediate of the reaction. However, we believe that the formation of acetate **V** molecules does not occur, since in the course of the cation **VIII** formation the trivalent phosphorus atom having a lone electron pair attacks the positively charged carbon atom of *N*-(benzyloxycarbonyl)iminium cation **VIII** to give the desired phosphorus–carbon bond.

Study of the reaction of methylphosphonic acid with biscarbamates **IV** by means of the ^{31}P NMR spectroscopy showed greater reactivity of *N*,*N*'-benzylidenebiscarbamate **IVe** as compared with *N*,*N*'-alkylidenebiscarbamates **IVa**–**IVd** (the reaction progress was monitored observing the relative content of the target product **VII** in the reaction mixture). This is confirmed by the high yield of α-(benzyloxycarbonylamino)benzylmethylphosphinic acid **VIId** (63%) in the reaction of methylphosphonic acid with *N*,*N*'-benzylidenebiscarbamate **IVe** in comparison with the yield of *N*-protected α-aminoalkylmethylphosphinic acids **VIIb** (R = Me) (51%) and **VIIe** (R = *i*-Bu) (41%) (see the table).

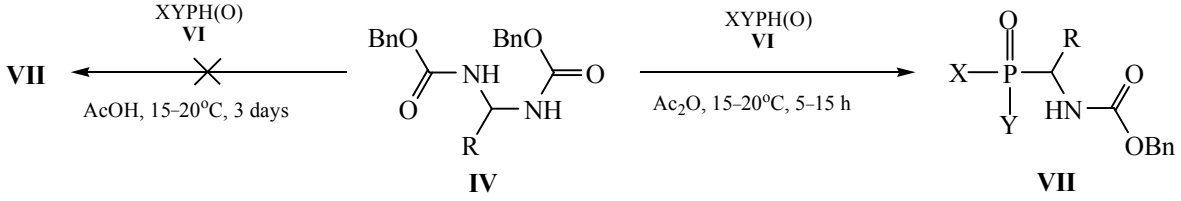
The addition of trifluoroacetic acid (TFA) (5–10 mol %) or *p*-toluenesulfonic acid (*p*-TSA) (2 mol%) into the acetic anhydride accelerated the two-component reaction (the process rate was assessed by the ^{31}P NMR spectroscopy) and increased the yields of the reaction products to 62% (**VIIb**), 59% (**VIId**), and 69% (**VIIe**) (see the table). A stronger effect of *p*-toluenesulfonic acid should be noted.

The reaction of biscarbamates **IV** with hydrophosphoryl compounds **VI** in a mixture of acetyl chloride and acetic anhydride gives good results, which is consistent with the results of the three-component reaction. However, the search for the optimal ratio of acetyl chloride and acetic anhydride, and the optimal contents of *p*-TSA and TFA in acetic anhydride for the two-component reaction was not performed.

The reaction of dimethylphosphite with biscarbamates **IV** in the acetyl chloride medium proceeds with a significant dealkylation of the ester frag-ments of the target molecule of dimethyl α-(benzyloxycarbonylamino)benzylphosphonate **VIIa**. Probably it affects the relative decrease in the yield of acid **VIIa** during the three-component reaction in a mixture of acetic anhydride and acetyl chloride (4:1) (see the table).

N-Benzyloxycarbonyl-α-aminoalkylphosphoryl compounds **VII,** the target products of the reaction of biscarbamates **IV** with methylphosphonic acid or dimethylphosphite, were not detected while carrying out reaction in benzene, toluene, ethanol, dioxane, or tetrahydrofuran medium. In this context, it is extremely important that biscarbamates **IV** react with methylphosphonic acid or dimethylphosphite in acetic anhydride in the cold and without any acid catalysis, whereas in acetic acid the formation of the corresponding α-amidoalkylphosphoryl compounds **VII** in the cold does not occur (Scheme 6).

Scheme 6.



R = *i*-Bu, Ph; X = Me, MeO; Y = MeO, OH.

Note that in both cases the same acid catalysis occurs by the acetic acid that is either used as a reaction medium or is formed during the reaction of PH-component with acetic anhydride.

This result may indicate the following:

(1) The starting PH-component **VI** and intermediate biscarbamate **IV** are not involved directly into the formation of the target phosphorus-carbon bond;

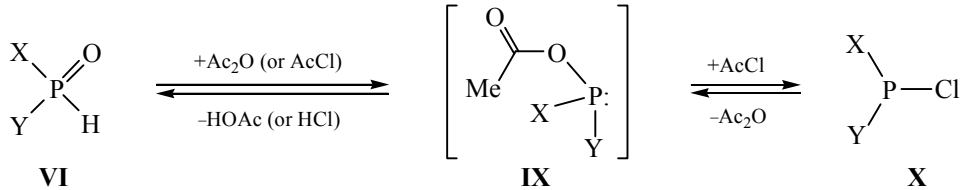
(2) The relatively weak acetic acid is able to provide formation of acyliminium intermediate cation **VIII** in accordance with Scheme 5;

(3) The initial phosphoric component in acetic anhydride medium can form a more reactive compoundwith respect to acyliminium cation **VIII**.

We assume that the trivalent phosphorus P–OAc derivative **IX** can interact directly with acyliminium cation **VIII** (Scheme 7).

Probably, in the acetyl chloride medium, the hydrophosphoryl compounds **VI** are converted into the corresponding trivalent phosphorus chlorides **X** with the initial formation of the P–OAc compounds **IX** (Scheme 7). The P–OAc form **IX** can be regarded as

Scheme 7.

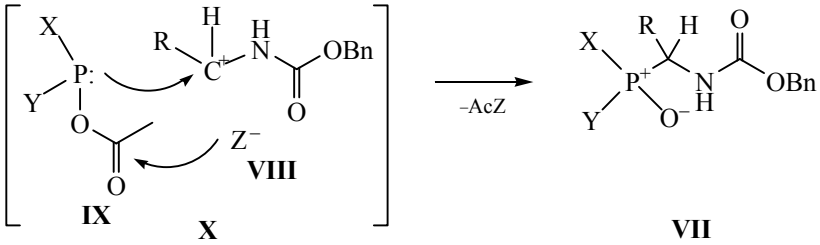


the intermediate between the PH and PCl forms participating in the equilibrium processes occurring in the AcOH–Ac_2O–AcCl medium (Scheme 7). The increase in acetyl chloride content in the mixture shifts the equilibrium toward the formation of trivalent phosphorus chlorides **X**, while increase in the acetic acid content in the mixture shifts the equilibrium toward the formation of hydrophosphoryl form **VI**. Perhaps, acetic anhydride is milder and the most convenient solvent-reagent for the formation of P–OAc derivatives **IX** (Scheme 7).

We found two ^{31}P signals in the region characteristic of the trivalent phosphorus compounds in the ^{31}P NMR spectrum of the solution of methylphosphonous acid in acetyl chloride, as well as in the ^{31}P NMR spectrum of methyldichlorophosphine solution in acetic anhydride. The signal at δ 198 ppm corresponds to the phosphorus atom of methyldichlorophosphine. Probably, the second signal at δ 185 ppm belongs to any of the two formally possible P–OAc derivatives of methylphosphonic acid, MeP(OAc)Cl or $MeP(OAc)_2$, and the formation of the latter in the acetic anhydride excess is more likely.

The acyl derivatives of trivalent phosphorus **IX** may be more reactive with respect to cations **VIII** in comparison with the starting PH-compounds **VI**, because they contain in the molecule both nucleophilic phosphorus atom and the electrophilic carbon atom of AcO-group, and therefore can easily participate in the Arbuzov-type transformations [15] (Scheme 8).

Scheme 8.



Z = Cl, OAc.

The nucleophilic phosphorus atom can attack the positively charged carbon atom of the formed iminium cation **VIII,** probably, with the simultaneous attack of the anion (Z^-) on the electrophilic carbon atom of AcO-fragment of the intermediately formed acylphosphite, acylphosphonite or acylphosphinite **IX** (Scheme 8).

Better understanding of the reaction mechanism requires further study, however, the formation of the reaction intermediate complex **X** is quite likely in the amidoalkylation reaction of hydrophosphoryl compounds (Scheme 8), and may explain the unique positive role of acetic anhydride (or acetic acid, trivalent phosphorus chlorides or acetylchloride in the case of hydrophosphoryl compounds) for the discussed reactions type.

Thus, in the reaction of amidoalkylation of the hydrophosphoryl compounds in acetic anhydride the *N*,*N*'-alkylidene biscarbamates **IV** were obtained, isolated and identified as intermediates; the two-component reaction of hydrophosphoryl compounds **VI** with the previously synthesized biscarbamates **IV** in acetic anhydride and other solvents was studied; the effect of the structure of biscarbamates **IV** and phosphate components **VI**, as well as acid catalysis in the course of a two-component reaction were examined.

The data obtained suggest the formation of iminium cation **VIII** as a result of protonation of the amide fragment of the intermediate biscarbamate **IV**, followed by probable release of benzyl carbamate molecule. Furthermore, we assume the intermediate formation of P–OAc derivatives **IX** of trivalent phosphorus as more reactive compounds than the original hydrophosphoryl compounds in the three-component reaction with the probable formation of the reaction complex **X** (Scheme 8).

The research results suggest a new version of the mechanism of the three-component reaction of the amidoalkylation of hydrophosphoryl compounds: This is a multistage process involving the stage of biscarbamates **IV** formation, and subsequent stages probably occurring through the Arbuzov type reaction involving the intermediately formed *N*-(benzyloxycarbonyl)iminium cation **VIII** and P–OAc derivative **IX** of trivalent phosphorus (Scheme 8).

We developed a new mild version of the amidoalkylation procedure of hydrophosphoryl compounds in a mixture of acetic anhydride and acetyl chloride in the cold using both aromatic and less reactive aliphatic aldehydes, which yielded *N*-protected α-aminophosphoryl compounds **VII** with retention of alkoxyphosphoryl and alkoxycarbonyl fragments in the target molecule.

EXPERIMENTAL

The ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer relative to TMS (internal standard) and 85% H_3PO_4 (external standard). Melting points of the compounds were determined on a Boetius PHMK device or in a block in an open capillary. The TLC analysis of the individual compounds and the reaction mixture was performed on Silufol plates, glass plates (Merck) with a layer of silica gel UV-254 0.2 mm thick (eluent chloroform–acetone, 4–5:1) as well as on Alufol plates (Kavalier) (neutral aluminum oxide on aluminum foil) detecting with the iodine vapor, UV irradiation, or with a solution of ninhydrin for amino acid analysis. The column chromatography was performed on silica gel Silpearl L100/160 (Chemapol) or Silica gel 60 (Alfa Aesar).

Benzyl carbamate, *tert*-butyl carbamate, acetic anhydride, acetic acid, trifluoroacetic acid, trifluoroacetamide, phthalimide, acetyl chloride, dimethyl phosphite were provided by Alfa Aesar company. Benzaldehyde, acetaldehyde diethyl acetal and isovaleric aldehyde were purchased from Acros Organics. Methylphosphonic, hydroxymethylphosphonic and diethylphosphinic acids were synthesized in accordance with the previously developed method [16]. The synthesis of 2-(ethoxycarbonyl)propylphosphonic and 2-phenylethylphosphonic acids was performed by adding *in situ* the bis(trimethylsilyl)hypophosphite formed in the reaction of a salt of hypophosphoric acid with hexamethyldisilazane, to ethylmethacrylate and styrene, respectively, followed by the mild hydrolysis of the formed bis(trimethylsilyl)-2-(ethoxycarbonyl) propylphosphonite or bis(trimethylsilyl)-2-phenylethylphosphonite according to the previously published procedures [7, 16].

General procedure of hydrophosphoryl compounds amidoalkylation in acetic anhydride. To a stirred solution of hydrophosphoryl compound **VI** (4.5 mmol) and benzyl carbamate (4.5 mmol) in acetic anhydride (4 ml) was added acetyl chloride or other catalyst[1] and then the corresponding aldehyde (5.0 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 10–50 h. The reaction progress was monitored using the ^{31}P NMR and TLC methods. The reaction mixture was diluted with toluene (5–10 ml) and evaporated in a vacuum. The residue was dissolved in chloroform (20–30 ml) and washed with water (3–5 ml), the organic phase was dried over sodium sulfate and evaporated in a vacuum. The residue was chromatographed on silica gel (eluent chloroform, chloroform–isopropanol (3–5%), and (or) was crystallized from diethyl ether or hexane and recrystallized from hexane–ethanol (7–10:1) or diethyl ether–alcohol mixture (10:1) to give *N*-benzyloxycarbonyl-α-aminoalkylphosphinic acids **VII**.

The exceptions are 1-(benzyloxycarbonilamino)-3-methylbutylhydroxymethylphosphinic (**VIIj**) and α-(benzyloxycarbonilamino)benzylhydroxymethylphosphinic (**VIIk**) acids isolated as oily substances, which according to the NMR data may contain an admixture of the *O*-acetylated derivatives, so that the compounds **VIIj** and **VIIk** were hydrolyzed to form the free amino acids **VIIj'** and **VIIk',** which were isolated and characterized.

Dimethyl α-(benzyloxycarbonylamino)benzylphosphonate (VIIa), mp 119–120°C (published data [7]: 120–121°C). ^{1}H NMR spectrum [$Me_2C(O)$-d_6], δ, ppm: 3.51 d (3H, CH_3O, $^{3}J_{PH}$ 10.6 Hz), 3.67 d (3H, CH_3O, $^{3}J_{PH}$ 10.6 Hz), 5.07 m (2H, CH_2Ph), 5.19 d.d (1H, CHN, $^{2}J_{PH}$ 20.5, $^{3}J_{HH}$ 7.3 Hz), 7.2–7.6 m (10H, 2Ph), 8.04 d (1H, NH, $^{3}J_{HH}$ 7.3 Hz). ^{1}H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 3.51 d (3H, CH_3O, $^{3}J_{PH}$ 10.6 Hz), 3.59 d (3H, CH_3O, $^{3}J_{PH}$ 10.6 Hz), 5.04 m (2H, CH_2Ph), 5.15 d.d (1H, CHN, $^{2}J_{PH}$ 21.6, $^{3}J_{HH}$ 10.1 Hz), 7.25–7.55 m (10H, 2Ph), 8.51 d (1H, NH, $^{3}J_{HH}$ 10.1 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 51.8 d ($^{1}J_{PC}$ 164.0 Hz), 53.1 d ($^{2}J_{PC}$ 7.0 Hz), 53.3 d ($^{2}J_{PC}$ 7.0 Hz), 66.0, 127.7, 127.8 (2C), 127.9, 128.1, 128.2 (2C), 128.4 (2C), 128.7, 135.6, 136.8, 155.9 d ($^{3}J_{PC}$ 8.5 Hz). ^{31}P NMR spectrum [$Me_2C(O)$-d_6]: δ_P 24.6 ppm. ^{31}P NMR spectrum (DMSO-d_6:CCl_4 = 1:3): δ_P 20.2 ppm.

1-(Benzyloxycarbonylamino)ethylmethylphosphinic acid (VIIb), mp 100–101°C. ^{1}H NMR spec-

[1] Catalyst is acetyl chloride (1ml) and trifluoroacetic acid (TFA) (0.45 mmol, 0.1 equiv) or *p*-toluenesulfonic acid (*p*-TSA) (0.09 mmol, 0.02 equiv).

trum (DMSO-d_6), δ, ppm: 1.19 d.d (3H, CH_3CH, $^3J_{HH}$ 7.5, $^3J_{PH}$ 10.2 Hz), 1.24 d ($^2J_{PH}$ 13.7 Hz), 3.69 m (1H, CHN), 5.04 AB (2H, CH_2O), 7.35 m (5H, Ph), 7.52 d (1H, NH, $^3J_{HH}$ 9.3 Hz). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 d.d (3H, CH_3CH, $^3J_{HH}$ 7.1, $^3J_{PH}$ 15.0 Hz), 1.42 d (3H, CH_3P, $^2J_{PH}$ 15.4 Hz), 3.99 m (1H, CHN), 5.09 AB (2H, CH_2Ph), 5.37 d (1H, NH, $^3J_{HH}$ 9.7 Hz), 7.32 m (5H, Ph), 10.56 br.s (1H, POOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 15.4 d ($^1J_{PC}$ 89.6 Hz), 16.4 d ($^2J_{PC}$ 5.5 Hz), 50.4 d ($^1J_{PC}$ 90.5 Hz), 65.7, 127.6, 127.7, 127.8, 128.4 (2C), 137.2, 155.6. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.4 d ($^1J_{PC}$ 93.3 Hz), 13.9, 46.0 d ($^1J_{PC}$ 107.6 Hz), 67.2, 128.1 (2C), 128.2, 128.5 (2C), 136.1, 155.9 d ($^3J_{PC}$ 5.1 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 47.0 ppm. ^{31}P NMR spectrum (CDCl3): δ_P 54.8 ppm. Found, %: C 51.21, 51.23; H 6.31, 6.37; N 5.37, 5.34. $C_{11}H_{16}NO_4P$. Calculated, %: C 51.36, H 6.27, N 5.45.

1-(Benzyloxycarbonylamino)propylmethylphosphinic acid (VIIc), mp 109–111°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.88 t (3H, CH_3CH_2), 1.22 d (3H, CH_3P, $^2J_{PH}$ 13.7 Hz), 1.43 m (1H, CH_2CH), 1.75 m (1H, CH_2CH), 3.47 m (1H, PCH), 5.05 AB (2H, $PhCH_2O$), 7.34 m (5H, Ph), 7.43 d (1H, NH, $^3J_{HH}$ 9.7 Hz). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 t (3H, CH_3CH_2), 1.42 d (3H, CH_3P, $^2J_{PH}$ 14.1 Hz), 1.55 m (1H, CH_2CH), 1.88 m (1H, CH_2CH), 3.82 m (1H, PCH), 5.11 AB (2H, $PhCH_2O$), 5.24 d (1H, NH, $^3J_{HH}$ 9.3 Hz), 7.32 m (5H, Ph), 10.71 br.s (1H, POOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.5 d ($^2J_{PC}$ 11.7 Hz), 12.7 d ($^1J_{PC}$ 93.0 Hz), 21.0, 52.0 d ($^1J_{PC}$ 107.6 Hz), 67.1, 127.9 (2C), 128.1, 128.5 (2C), 136.2, 156.4 d ($^3J_{PC}$ 4.0 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 46.6 ppm. ^{31}P NMR spectrum ($CDCl_3$): δ_P 54.6 ppm. Found, %: C 53.07, 52.95; H 6.73, 6.77; N 5.07, 5.11. $C_{12}H_{18}NO_4P$. Calculated, %: C 53.14, H 6.69, N 5.16.

1-(Benzyloxycarbonylamino)-2-methylpropylmethylphosphinic acid (VIId), mp 107–109°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 d (3H, CH_3CH, $^3J_{HH}$ 5.3 Hz), 0.93 d (3H, CH_3CH, $^3J_{HH}$ 5.3 Hz), 1.22 d (3H, CH_3P, $^2J_{PH}$ 13.7 Hz), 2.08 m (1H, CH), 3.50 m (1H, CHP), 5.05 AB (2H, CH_2O), 7.33 m (6H, Ph+NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.1 d ($^1J_{PC}$ 89.9 Hz), 18.7 d ($^3J_{PC}$ 5.5 Hz), 20.8 d ($^3J_{PC}$ 7.7 Hz), 27.6 ($^2J_{PC}$ 3.3 Hz), 56.3 d ($^1J_{PC}$ 105.0 Hz), 65.5, 127.5 (2C), 127.8, 128.4 (2C), 137.2, 156.7 d ($^3J_{PC}$ 5.2 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 46.5 ppm. Found, %: C 54.47, 54.53; H 7.01, 6.95; N 4.67, 4.83. $C_{13}H_{20}NO_4P$. Calculated, %: C 54.73, H 7.07, N 4.91.

1-(Benzyloxycarbonylamino)-2-methylbutylmethylphosphinic acid (VIIe), mp 167–168°C (published data [10]: 162–164°C). ^{1}H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 0.81 d (3H, CH_3CH, $^3J_{HH}$ 5.6 Hz), 0.87 d (3H, CH_3CH, $^3J_{HH}$ 6.5 Hz), 1.21 d (3H, CH_3P, $^2J_{PH}$ 13.0 Hz), 1.45 m (2H, CH_2CH), 1.60 m (1H, $CHCH_3$), 3.67 d.d (1H, CHN, $^2J_{PH}$ 16.8, $^3J_{HH}$ 9.3 Hz), 5.01 AB (2H, CH_2Ph), 7.3 m (5H, Ph), 7.44 d (1H, NH, $^3J_{HH}$ 9.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.5 d ($^1J_{PC}$ 89.5 Hz), 20.9, 23.3, 24.1 d ($^3J_{PC}$ 11.5 Hz), 35.9, 49.2 d ($^1J_{PC}$ 107.5 Hz), 65.5, 127.6, 127.7, 127.8, 128.4 (2C), 137.2, 156.2 d ($^3J_{PC}$ 3.6 Hz). ^{31}P NMR spectrum (DMSO-d_6:CCl_4 = 1:3): δ_P 47.2 ppm.

α-(Benzyloxycarbonylamino)benzylmethylphosphinic acid (VIIf), mp 191–192°C. (published data [10]: 193–194°C). ^{1}H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 1.22 d (3H, CH_3P, $^2J_{PH}$ 13.7 Hz), 4.87 d.d (1H, CHN, $^2J_{PH}$ 18.1, $^3J_{HH}$ 9.7 Hz), 5.04 br.s (2H, CH_2Ph), 7.36 m (10H, 2Ph), 8.25 d (1H, NH, $^3J_{HH}$ 9.7 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.5 d ($^1J_{PC}$ 92.3 Hz), 56.0 d ($^1J_{PC}$ 97.4 Hz), 65.8, 127.1, 127.7, 127.8, 127.85, 127.9, 128.0, 128.4 (2C), 128.6, 129.3, 136.8, 136.9 156.1 d ($^3J_{PC}$ 5.1 Hz). ^{31}P NMR spectrum (DMSO-d_6:CCl_4 = 1:3): δ_P 42.8 ppm.

1-(Benzyloxycarbonylamino)propyl-2-phenylethylphosphinic acid (VIIg), mp 101–103°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.89 t (3H, CH_3CH_2), 1.49 m (1H, CH_2CH), 1.80 m (3H, $CH_2CH + CH_2P$), 2.73 m (2H, CH_2Ph), 3.59 m (1H, CHP), 5.05 AB (2H, CH_2O), 7.25 m (10H, 2Ph), 7.49 d (1H, NH, $^3J_{HH}$ 8.8 Hz). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 t (3H, CH_3CH_2), 1.68 m (1H, CH_2CH), 2.14 m (3H, $CH_2CH + CH_2P$), 3.02 m (2H, CH_2CH_2P), 4.07 m (1H, CHP), 5.24 AB (2H, CH_2O), 7.37 m (11H, NH + 2Ph), 9.16 br.s (1H, POOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.5 d ($^3J_{PC}$ 11.4 Hz), 21.2, 27.2, 28.5 ($^1J_{PC}$ 89.3 Hz), 46.2 ($^1J_{PC}$ 104.3 Hz), 67.2, 126.3, 128.0 (3C), 128.2 (2C), 128.5 (4C), 136.2, 140.8 d ($^3J_{PC}$ 16.1 Hz), 156.4 ($^3J_{PC}$ 4.8 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 46.9 ppm. ^{31}P NMR spectrum ($CDCl_3$): δ_P 55.7 ppm. Found, %: C 63.07, 62.95; H 6.85, 6.81; P 8.43, 8.51. $C_{19}H_{24}NO_4P$. Calculated, %: C 63.15, H 6.69, P 8.57.

1-(Benzyloxycarbonylamino)-2-methylpropyl-2-phenylethylphosphinic acid (VIIh), mp 139–141°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.94 d (3H, CH_3CH, $^3J_{HH}$ 5.3 Hz), 0.96 d (3H, CH_3CH, $^3J_{HH}$ 5.3 Hz), 1.79 m (2H, CH_2P), 2.14 m (1H, $CHCH_3$),

2.74 m (2H, CH_2Ph), 3.65 m (1H, CHP), 5.04 AB (2H, CH_2O), 7.30 m (10H, 2Ph), 7.47 d (1H, NH, $^3J_{HH}$ 10.1). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 d (3H, CH_3CH, $^3J_{HH}$ 6.6 Hz), 1.18 d (3H, CH_3CH, $^3J_{HH}$ 6.6 Hz), 2.13 m (2H, CH_2P), 2.49 m (1H, CHCHP), 3.03 m (2H, CH_2CH_2P), 4.07 m (1H, CHP), 5.25 AB (2H, CH_2O), 7.45 m (10H, NH + 2Ph), 8.10 br.s (1H, POOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 17.7 d ($^3J_{PC}$ 2.9 Hz), 20.8 d ($^3J_{PC}$ 10.7 Hz), 27.3 d ($^2J_{PC}$ 3.3 Hz), 27.7, 29.7 d ($^1J_{PC}$ 88.8 Hz), 53.7 d ($^1J_{PC}$ 103.9 Hz), 67.3, 126.3, 128.0 (3C), 128.2, 128.6 (4C), 136.2, 140.7, 141.0, 156.5 d ($^3J_{PC}$ 6.3 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 47.1 ppm. ^{31}P NMR spectrum ($CDCl_3$): δ_P 56.3. Found, %: C 63.87, 63.75; H 6.95, 7.11; P 8.20, 8.11. $C_{20}H_{26}NO_4P$. Calculated, %: C 63.99, H 6.98, P 8.25.

1-(Benzyloxycarbonylamino)-3-methylbutyl-2-phenylethylphosphinic acid (VIIi), mp 161–163°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.82 d (3H, CH_3CH, $^3J_{HH}$ 6.2 Hz), 0.89 d (3H, CH_3CH, $^3J_{HH}$ 6.6 Hz), 1.49 m (3H, $CHCH_3$ + CH_2CH), 1.80 m (2H, CH_2P), 2.74 m (CH_2Ph), 3.70 m (1H, PCH), 5.05 AB (2H, CH_2O), 7.23 m (10H, 2Ph), 7.52 d (1H, NH, $^3J_{HH}$ 9.3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 d (6H, $2CH_3CH$, $^3J_{HH}$ 5.7 Hz), 1.68 m (3H, $CHCH_3$ + CH_2CH), 2.07 m (2H, CH_2P), 2.97 m (2H, CH_2CH_2P), 4.18 m (1H, CHP), 5.16 AB (2H, CH_2O), 7.30 m (11H, 2Ph + NH), 9.67 br.s (POOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.1, 23.5, 24.3 d ($^2J_{PC}$ 10.6 Hz), 27.2, 28.4 d ($^1J_{PC}$ 89.3 Hz), 36.2, 47.6 d ($^1J_{PC}$ 105.0 Hz), 67.2, 126.3, 128.0 (2C), 128.1 (3C), 128.5 (4C), 136.2, 140.8 d ($^3J_{PC}$ 16.5 Hz), 156.1. ^{31}P NMR spectrum (DMSO-d_6): δ_P 47.4 ppm. ^{31}P NMR spectrum ($CDCl_3$): δ_P 56.3 ppm. Found, %: C 64.64, 64.59; H 7.25, 7.31; P 8.03, 8.01. $C_{21}H_{28}NO_4P$. Calculated, %: C 64.77; H 7.25; P 7.95.

1-(Benzyloxycarbonylamino)-3-methylbutylhydroxymethylphosphinic acid (VIIj). Yield 44%, oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 d (3H, CH_3, $^2J_{HH}$ 7.2 Hz), 0.91 d (3H, CH_3, $^2J_{HH}$ 6.5 Hz), 1.37 m (2H, CH_2CH), 1.66 m (1H, $CHCH_3$), 3.39 m (2H, PCH_2O), 3.95 m (1H, CHN), 5.04 AB (2H, $PhCH_2O$), 7.30 m (Ph). ^{31}P NMR spectrum (CD_3OD): δ_P 44.8 ppm. (The ^1H NMR spectrum contains a singlet at ~2.0 ppm belonging probably to impurity PCH_2OAc-derivative). Compound **VIIj** was used further without purification.

1-Amino-3-methylbutylhydroxymethylphosphinic acid (VIIj'). A mixture of 0.63 g of crude **VIIj** and 8 ml of 6 M HCl was refluxed for 17 h. The cooled mixture was extracted with petroleum ether. The aqueous acidic phase was evaporated in a vacuum. The residue was dissolved in aqueous ethanol, treated with excess of propylene oxide to obtain amino acid. The product was recrystalled from aqueous ethanol. Yield 0.27 g (75%, 33% relative to benzyl carbamate), mp 243–244°C (published data [17]: 244–245°C). ^1H NMR spectrum (D_2O + DCl), δ, ppm: 0.83 d (3H, CH_3, $^2J_{HH}$ 5.6 Hz), 0.87 d (3H, CH_3, $^2J_{HH}$ 5.8 Hz), 1.61 m (3H, $CHCH_2CHN$), 3.36 d.t (1H, CHN, $^2J_{PH}$ 8.6, $^2J_{HH}$ 7.0 Hz), 3.75 ABX (2H, CH_2O, $^2J_{PH}$ 6.4 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 20.1, 22.4, 23.9 d ($^3J_{PC}$ 8.8 Hz), 35.8, 47.8 d ($^1J_{PC}$ 90.8 Hz), 59.1 d ($^1J_{PC}$ 114.5 Hz). ^{31}P NMR spectrum (D_2O): δ_P 33.9 ppm. Found, %: C 39.67, 39.59; H 9.07, 9.13, N 7.57, 7.59. $C_6H_{16}NO_3P$. Calculated, %: C 39.78; H 8.90; N 7.73.

α-(Benzyloxycarbonylamino)benzylhydroxymethylphosphinic acid (VIIk). Yield 53%, oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 4.30–4.50 m (2H, CH_2O), 4.80–5.00 m (2H, CH_2OPh), 5.10 m (1H, CHN), 7.2–7.5 (m, 10H, 2Ph). ^{31}P NMR spectrum (CD_3OD): δ_P 48.1 ppm. (The ^1H NMR spectrum contains a singlet at ~2.0 ppm belonging probably to impurity PCH_2OAc-derivative). Compound **VIIj** was used further without purification.

α-Aminobenzylhydroxymethylphosphinic acid (VIIk'). A mixture of 0.80 g of crude **VIIk** and 10 ml of 6 M HCl was refluxed for 15 h. The cooled mixture was extracted with toluene. The aqueous acidic phase was evaporated in a vacuum. The residue was dissolved in aqueous ethanol, treated with excess propylene oxide to obtain amino acid. The product was recrystallized from aqueous ethanol. Yield 0.38 g (80%, 42% relative to benzyl carbamate), mp 233–235°C (published data [8]: 235–237°C). ^1H NMR spectrum (D_2O), δ, ppm: 3.57 d (2H, CH_2, $^2J_{PH}$ 6.2 Hz), 4.42 d (1H, CH, $^2J_{PH}$ 10.6 Hz), 7.35 m (5H). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 54.3 d ($^1J_{PC}$ 85.1 Hz), 59.4 d ($^1J_{PC}$ 116.2 Hz), 128.1, 128.2, 129.3, 129.5 (2C), 132.2 d ($^2J_{PC}$ 3.6 Hz). ^{31}P NMR spectrum (D_2O + DCl): δ_P 34.5 ppm. Found, %: C 43.67, 43.59; H 6.51, 6.47, P 14.23, 14.17. $C_8H_{12}NO_3P \cdot H_2O$. Calculated, %: C 43.84; H 6.44, P 14.13.

1-(Benzyloxycarbonylamino)ethyl-2-(ethoxycarbonyl)propylphosphinic acid (VIIl), mp 113–115°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.10–1.25 m (9H, $2CH_3CH$ + CH_3CH_2), 1.60 m (1H, CH_2P), 2.00 m (1H, CH_2P), 2.71 m [1H, CHC(O)], 3.72 m (2H, CH_3CH_2O), 4.04 m (1H, CHN), 5.04 AB (2H, Ph

CH_2O), 7.34 m (5H, Ph), 7.53 d (1H, NH, $^3J_{HH}$ 8.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.8, 14.0, 18.6 d ($^2J_{PC}$ 7.0 Hz), 18.8* d ($^2J_{PC}$ 8.1 Hz), 29.3 d ($^1J_{PC}$ 88.6 Hz), 29.4* d ($^1J_{PC}$ 88.2 Hz), 33.4, 45.7 d ($^1J_{PC}$ 105.8 Hz), 46.0* d ($^1J_{PC}$ 105.8 Hz), 60.1, 65.6, 127.7 (2C), 127.8, 128.4 (2C), 137.1, 155.8 d ($^3J_{PC}$ 3.7 Hz), 175.1 d ($^3J_{PC}$ 9.5 Hz). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 46.6, 46.0* (signals of the second diastereomer are marked with asterisk, ~13%). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 55.0, 53.6*. Found, %: C 53.68, 53.57; H 6.79, 6.87; P 8.53, 8.43. $C_{16}H_{24}NO_6P$. Calculated, %: C 53.78, H 6.77, P 8.67.

α-(Benzyloxycarbonylamino)benzyl-2-(ethoxycarbonyl)propylphosphinic (VIIm), mp 153–155°C. ^{1}H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 1.17 t (6H, 2CH_3), 1.62 m (1H, CH_2P), 2.01 m (1H, CH_2P), 2.67 m [1H, CHC(O)], 4.03 q (2H, CH_2O), 4.88 d.d (1H, CHN, $^2J_{PH}$ 18.1, $^3J_{HH}$ 10.2 Hz), 5.04 AB (2H, OCH_2Ph), 7.33 m (10H, 2Ph), 8.16 d (1H, NH, $^3J_{HH}$ 10.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.0, 18.6, 18.7*, 29.7 d ($^1J_{PC}$ 91.4 Hz), 33.4, 33.7*, 55.7 d ($^1J_{PC}$ 96.2 Hz), 55.9* d ($^1J_{PC}$ 107.2 Hz), 60.1, 65.8, 127.2, 127.7 (2C), 127.9, 128.0 (2C), 128.1, 128.2, 128.4 (2C), 136.5, 137.0, 156.1 d ($^3J_{PC}$ 7.7 Hz), 175.1 d ($^3J_{PC}$ 10.3 Hz). ^{31}P NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ_P, ppm: 42.3, 41.5* (~7%). Found, %: C 60.09, 60.03; H 6.34, 6.27; P 7.30, 7.23. $C_{21}H_{26}NO_6P$. Calculated, %: C 60.14; H 6.25; P 7.38.

α-(Benzyloxycarbonylamino)benzyldiethylphosphine oxide (VIIn), mp 177–179°C. ^{1}H NMR spectrum [$Me_2C(O)$-d_6], δ, ppm: 0.89 d.t (3H, CH_3, $^3J_{PH}$ 16.1 Hz), 1.07 d.t (3H, CH_3, $^3J_{PH}$ 16.1 Hz), 1.54 m (d.q) (2H, CH_2P), 1.80 m (d.q) (2H, CH_2P), 5.03 d.d (1H, CHN, $^2J_{PH}$ 12.6 Hz, $^3J_{HH}$ 8.8 Hz), 5.10 m (2H, OCH_2), 7.20–7.60 m (11H, 2Ph + NH). ^{1}H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 0.88 d.t (6H, 2CH_3, $^3J_{PH}$ 15.9 Hz), 1.58 m (4H, 2CH_2), 5.04 br.s (2H, OCH_2), 5.10 d.d (1H, CHN, $^2J_{PH}$ 12.8, $^3J_{HH}$ 9.7 Hz), 7.20–7.50 m (10H, 2Ph), 8.39 d (1H, NH, $^3J_{HH}$ 9.7 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 5.1 d ($^2J_{PC}$ 4.8 Hz), 5.4 d ($^2J_{PC}$ 4.8 Hz), 17.7 d ($^1J_{PC}$ 63.8 Hz), 18.0 d ($^1J_{PC}$ 64.9 Hz), 53.5 d ($^1J_{PC}$ 67.1 Hz), 66.0, 127.4, 127.7 (2C), 127.9 (3C), 128.1 (2C), 128.4 (2C), 136.3, 136.8, 156.1 d ($^3J_{PC}$ 3.6 Hz). ^{31}P NMR spectrum (DMSO-d_6:CCl_4 = 1:3): δ_P 57.2 ppm. Found, %: C 66.03, 65.97; H 7.11, 7.13; N 3.93, 3.89. $C_{19}H_{24}NO_3P$. Calculated, %: C 66.08; H 7.00; N 4.06.

Synthesis of biscarbamets IV. To a stirred mixture of hydrophosphoryl compound (4.5 mmol) and benzyl carbamate (4.5 mmol) in acetic anhydride (3–4 ml) at room temperature was added the corresponding catalyst and then added dropwise the freshly distilled aldehyde (5.0 mmol). The reaction mixture was stirred for 15–40 min, diluted with excess toluene, evaporated in a vacuum at the bath temperature below 40°C. The semicrystalline residue was dissolved in 20 ml of chloroform, washed with water (2×5 ml). The organic layer was dried over magnesium sulfate, concentrated in a vacuum, and chromatographed on silica gel [eluents benzene, chloroform–benzene (1:1), chloroform, chloroform–isopropanol (5%)]. Biscarbamates **IVa–IVe** [R_f 0.7–0.8, chloroform–acetone, (4–5):1] were readily separated from *N*-benzyloxycarbonyl-α-aminophosphinic acids **VIIb–VIIh, VIIl** and **VIIm** [R_f 0.1–0.2, chloroform–acetone, (4–5):1].

In the case of α-aminophosphonate **VIIa** [R_f 0.6, chloroform–acetone, 4:1] and α-aminophosphine oxide **VIIn** [R_f 0.4, chloroform–acetone, 4:1] the separation of target compounds **VII** and **IVe** was done as follows. After the reaction mixture concentrating, the residue was refluxed in CCl_4, cooled, and filtered off. Crystalline biscarbamate **IVb** was recrystallized from hexane–ethanol mixture (~10:1). The filtrate was concentrated and crystallized from diethyl ether–ethanol mixture (~10:1) to obtain compound **VIIn.**

The separation procedure was monitored with TLC and ^{1}H, ^{31}P NMR spectroscopy. The physicochemical constants and spectral data of α-aminoalkylphosphoryl compounds **VII** correspond to those of compounds obtained by the three-component synthesis. Data of biscarbamates **IV** correspond to those of compounds synthesized in acetic anhydride (see below).

Synthesis of biscarbamates IV in acetic anhydride medium. To a solution of benzyl carbamate (5.0 mmol) in acetic anhydride (5 ml) at room temperature was added TFA (0.05 mmol) and then slowly aldehyde (2.5 mmol) or the corresponding acetal (2.5 mmol) under stirring. The stirring was continued for 3–10 h. The reaction progress was monitored by TLC. The reaction mixture was concentrated in a vacuum. The residue was dissolved in chloroform (20 ml) and diluted with water (20 ml). The aqueous layer (20 ml) was neutralized to pH 6–7. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was crystallized from diethyl ether or hexane and recrystallized from diethyl ether–ethanol mixture.

***N*,*N*'-Ethylidenebis(benzyl carbamate) (IVa).** Yield 64%, mp 203–204°C. ^{1}H NMR spectrum

(DMSO-d_6:CCl_4 = 1:3), δ, ppm: 1.23 d (3H, CH_3, $^3J_{HH}$ 6.6 Hz), 5.00 br.s (4H, $2CH_2O$), 5.14 m (1H, CHN), 7.34 m (10H, 2Ph), 7.61 d (2H, 2NH, $^3J_{HH}$ 5.0 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2 (CH_3), 56.1 (CHN), 65.2 ($2CH_2O$), (127.6, 127.7, 127.8, 128.4, 137.1) (12C, Ar), 154.6 (C=O). Found, %: C 65.57, 65.71; H 6.21, 6.27; N 8.61, 8.66. $C_{18}H_{20}N_2O_4$. Calculated, %: C 65.84; H 6.14; N 8.53.

***N*,*N*'-Propylidene bis(benzyl carbamate) (IVb).** Yield 67%, mp 153–155°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 t (3H, CH_3), 1.85 m (2H, CH_2), 4.91 m (1H, CHN), 5.08 br.s (4H, $2CH_2O$), 5.50 m (2H, 2NH), 7.33 m (10H, 2Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.1 (CH_3), 27.5 (CH_2), 61.9 (CHN), 66.8 ($2CH_2O$), (128.0, 128.0, 128.4, 136.2) (12C, Ar), 155.4 (C=O). Found, %: C 66.57, 66.51; H 6.54, 6.57; N 8.11, 8.20. $C_{19}H_{22}N_2O_4$. Calculated, %: C 66.65; H 6.48; N 8.18.

***N*,*N*'-Isobutylidene bis(benzyl carbamate) (IVc).** Yield 77%, mp 152–154°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 d (6H, $2CH_3$, $^3J_{HH}$ 6.6 Hz), 2.05 m (1H, C*H*CH_3), 4.64 m (1H, CHN), 5.01 br.s (4H, $2CH_2O$), 5.45 m (2H, 2NH), 7.26 m (10H, 2Ph). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (6H, $2CH_3$, $^3J_{HH}$ 6.8 Hz), 1.81 m (1H, C*H*CHN), 4.82 m (1H, CHN), 5.01 br.s (4H, $2CH_2O$), 7.33 m (10H, 2Ph), 7.47 m (2H, 2NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.4 ($2CH_3$), 32.0 (*C*HCHN), 64.8 (CHN), 65.2 ($2CH_2O$), (127.7, 128.3, 137.1) (12C, Ar), 155.3 (C=O). Found, %: C 67.37, 67.31; H 6.94, 6.87; N 7.76, 7.63. $C_{20}H_{24}N_2O_4$. Calculated, %: C 67.40; H 6.79; N 7.86.

***N*,*N*'-Isoamylidene bis(benzyl carbamate) (IVd).** Yield 63%, mp 97–98°C. ^1H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 0.83 d (6H, $2CH_3$, $^3J_{HH}$ 5.3 Hz), 1.35–1.62 m (3H, CH + CH_2), 5.00 br.s (4H, $2CH_2O$), 5.10 m (1H, CHN), 7.33 m (10H, 2Ph), 7.52 d (2H, 2NH, $^3J_{HH}$ 5.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 22.2 (CH_3), 24.2 (*C*HCH_3), 43.4 (*C*H_2CHN), 58.2 (CHN), 65.2 ($2CH_2O$), (127.8, 128.3, 137.1) (12C, Ar), 155.0 (C=O). Found, %: C 68.01, 67.95; H 7.21, 7.27; N 7.39, 7.47. $C_{21}H_{26}N_2O_4$. Calculated, %: C 68.09; H 7.07; N 7.56.

***N*,*N*'-Benzylidene bis(benzyl carbamate) (IVe).** Yield 76%, mp 156–157°C. ^1H NMR spectrum (DMSO-d_6:CCl_4 = 1:3), δ, ppm: 5.05 br.s (4H, $2CH_2O$), 6.23 t (1H, CH, $^3J_{HH}$ 7.5 Hz), 7.20–7.55 m (15H, 3Ph), 8.08 d (2H, 2NH, $^3J_{HH}$ 7.5 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 61.8 (CHN), 65.5 ($2CH_2O$), 126.4, 127.8, 128.3, 128.4, 136.9, 140.0 (18C, Ar), 155.2 (C=O). Found, %: C 70.57, 70.54; H 5.81, 5.71; N 7.23, 7.11. $C_{23}H_{22}N_2O_4$. Calculated, %: C 70.75; H 5.68; N 7.17.

Reaction of biscarbamates IV with hydrophosphoryl compounds VI. To a solution of *N*,*N*'-alkylidenebis(carbamate) **IV** (5 mmol) in 4 ml of acetic anhydride under stirring was added dropwise PH-component **VI** (5 mmol). The reaction progress was monitored by the ^{31}P NMR spectroscopy. As the reaction completed, the mixture was concentrated in a vacuum, diluted with 30 ml of chloroform and 10 ml of water. The organic layer was dried over sodium sulfate, concentrated, and crystallized twice from diethyl ether or hexane. The physicochemical and spectral constants of the obtained compounds **VII** were in accordance with those for compounds obtained by the three-component synthesis.

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