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Dedicated to Full Member of the Russian Academy of Sciences I. P. Beletskaya on occasion of her jubilee

Synthesis and Biological Activity of 4-Chloromethyl-substituted 1,3,2-Dioxaphosphorinanes Phosphates and Amidophosphates

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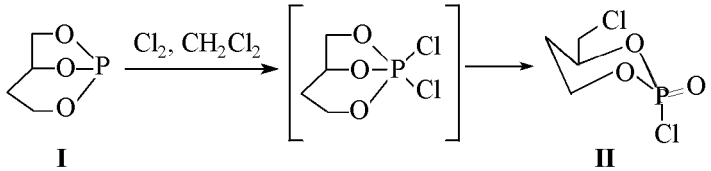
Abstract—A series of 2-N and 2-O-substituted 2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinanes were prepared by reaction of amines and alcohols with 2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphosphorinane. The structure of compounds obtained was proved by means of ^{1}H and ^{13}C NMR spectroscopy. Some cyclic amidocyclophosphates possessed biological activity as inhibitors of mitotic fission and of Na^{+}/H^{+} exchange.

Unsymmetrical bicyclophosphite, 2,7,8-trioxa-1-phosphabicyclo[3.2.1]octane (**I**) is known to undergo halogenation readily and selectively with rupture of phospholane and retention of phosphorinane ring [1]. According to published data the latter exists in the *chair* conformation with an equatorial orientation of the chloromethyl group [2]. Proceeding from 2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphosphorinane (**II**) the corresponding piperidino- and methoxyphosphates were prepared [3]. Further chemical reactions of compound **II** were not investigated, apparently because the attention of researchers turned to structurally more complicated cyclic chlorophosphates [4, 5]. These structures alongside the phosphorinane fragment contained in the molecules rests of carbohydrates, polyhydric alcohols, or nucleotides. Their structure was studied in detail applying NMR spectroscopy and X-ray diffraction analysis [6, 7]. It was shown that some cycloamidophosphates prepared from natural polyols possess antiproliferative [8. 9] and immunotropic activity [10].

Taking the above into account it is reasonable to expect appearance of biological activity also in 2-N- and 2-O-substituted 2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinanes. These expectations are based on the one hand on the similar structure of the principal fragment (phosphorinane ring) in phosphorinane **II** and in more complex cyclophosphates, on the other hand, as a template for their synthesis serves a natural triol, 1,2,4-trihydroxybutane that is found in phospholipids composition.

The main attention in the synthesis of new phosphates we paid to increasing the yield of individual geometric isomers of arising phosphorinanes. To this end it was necessary to obtain the individual 2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphosphorinane (**II**), the key compound for further transformations. This task was not solved previously, and the researchers worked with a mixture of *cis*- and *trans*-chlorophosphates of compound **II**.*

Under conditions we developed (–30 to –60°C, CH_2Cl_2) the chlorination started with formation of an intermediate compound containing pentacoordinated phosphorus atom. This compound is unstable, but it can be detected by ^{31}P NMR spectroscopy. Its singlet resonance signal is observed in the region of –27.0 ppm. On raising the temperature of the reaction



I **II**

* According to the common classification the phosphorane with the similar relative position of 4-chloromethyl group and the phosphoryl oxygen in the ring is described as *cis*-isomer, and the compound with different positions of these substituents is regarded as *trans*-isomer.

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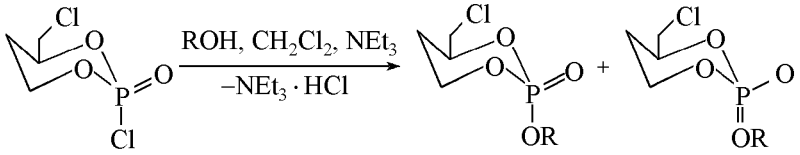
mixture to –20°C the intermediate gradually transforms into chlorophosphate with a signal at –3.0 ppm. Phosphorinane **II** was prepared as individual substance and did not require additional purification.

Thus when this reaction is carried out under mild conditions it is not only regioselective with respect to the site of the nucleophilic attack [3] but also is specific concerning the isomer composition of the target product. Apparently *cis*-chlorophosphate **II** was obtained in the process. The reaction performed under less mild conditions (0 to –5°C) gave rise to two isomeric chlorophosphates appearing as signals in the ^{31}P NMR spectrum at δ –3.0 and 7.7 ppm in 2 : 1 ratio.

To replace the chlorine at phosphorus atom cyclophosphate **II** was treated with alcohols or amines. The nucleophilic attack afforded products with different configuration at the phosphorus atom depending on the reagent character.

As a rule the reaction of cyclic chlorophosphites with alcohols occurs with retention of the configuration. In this case a "hard" nucleophile predominantly attacks from the side opposite to the phosphorinane oxygen. The subsequent pseudorotation of substituents in the intermediate necessary for departure of halogen from the favorable apical position brings about the same location of the entering group as that of the leaving one in the reconstructed system of the four-coordinated phosphorus [11, 12].

All cycloalkylphosphate syntheses were carried out in dichloromethane. Triethylamine served as an acceptor of the liberated hydrogen chloride. It is advisable to perform the process without heating for 3–40 h depending on the nucleophilicity and structure of the alcohol. The branched alcohols reacted slower (10–40 h) than those with a normal chain due to lesser accessibility of the hydroxy group (steric factor). It was established that excess alcohol should not be used for it increased the amount of side products. Under conditions applied notwithstanding the alcohol character formed in a nearly quantitative yield the more stable *cis*-isomers of phosphates **III–XI**. Only with tetrahydrofurfuryl alcohol were obtained both isomers **VIIa, b** in 10 : 1 *cis/trans* ratio.



II *cis*-(**III–XI**) *trans*-(**VIIb**)

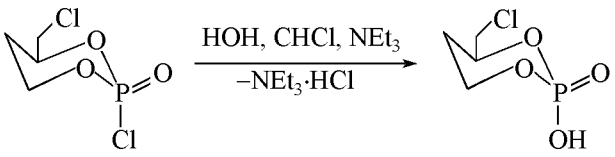
R = Et (**III**), Bu (**IV**), C_6H_{13} (**V**), (**VI**), (**VIIa, b**),

(**VIII**), *i*-Pr (**IX**), C_6H_{11} (**X**), (**XI**).

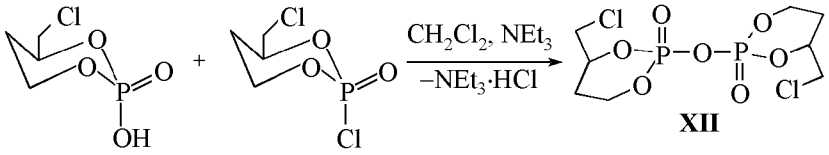
Regretfully, compounds **III–XI** are thick uncrystallizable and undistillable colorless syrupy substances difficult for purification. Therefore on completion of the reaction (^{31}P NMR monitoring) the reaction mixture was filtered or washed with water, concentrated, and submitted to chromatography on silica gel. This workup procedure furnished individual compounds only in 20–85% yield, and compound **XI** completely decomposed during the workup. Therewith the yield measured by the integral intensity of signals in the ^{31}P NMR spectrum of the reaction mixture is as a rule by 10–15% higher that estimated by the amount of the compound obtained after chromatography.

During chromatographic purification of isopropylideneglycerol ester **VI** we isolated one of side products that appeared in the ^{31}P NMR spectrum of the reaction mixture as a signal at δ –20.0 ppm. Similar signal appeared in the spectra of the other reaction mixtures, for instance, in the synthesis of phosphates **III** and **IX**. We were interested in exact identification of the compound. Some data on forma-

tion in analogous reactions of substances with similar signals in phosphorus NMR spectra were published (δ_P −25 ppm) [13]. These signals were assigned to intermediate adducts of five- or four-coordinate phosphorus with pyridine or other amines. No reliable proofs of the structure of these compounds were presented. In our case it might be expected that such adduct could arise from 2-oxo-2-chloro-4-chloromethyl-1,3,2-dioxaphosphorinane and triethylamine. However the ^{13}C NMR spectroscopy did not reveal the formation of such adduct. In the ^{13}C NMR spectrum of the isolated substance appeared the signals from the carbon atoms of cyclophosphate and no peaks from ethyl groups of triethylamine. Probably pyrophosphate **XII** formed from acid chloride and water.



II



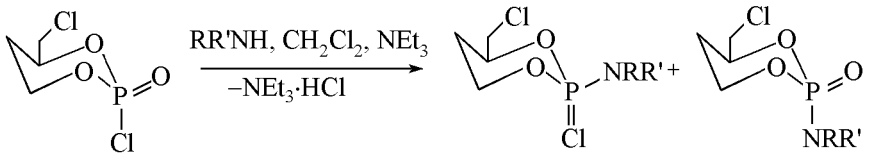
XII

This assumption was proved by preparation of pyrophosphate **XII** by an appropriate reaction of chlorophosphate **II** with water in dioxane and by comparison of spectra recorded from various samples of compound **XII**.

The existence of compound **XII** was also proved by mass spectrometry. In the electron impact spectrum a molecular ion *m/z* 354 was observed in agreement with the calculated molecular weight (M 355). Thus compound appearing as a peak at δ_P −20 ppm is symmetrical and cannot be an intermediate in the reaction. Under more stringent condition pyrophosphate **XII** has an ample possibility to undergo alcoholysis affording phosphates **III, VI, IX**. In this respect it may be regarded as an intermediate reaction product.

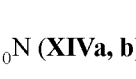
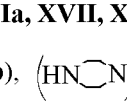
The chemical shifts of carbon signals from phosphorinane moiety of the molecule almost do not change at replacement of chlorine in compound **II** by alkoxy group. The signals of carbon atoms in the respective alcohols directly bonded to the hydroxy group shift downfield on formation of the phosphoester by 5–9 ppm depending on the structure of the alcohol rest. As a rule the signals of carbons close to phosphorus atoms are split into doublets. The ^{13}C NMR spectrum of 1α,2;3,4-O-diisopropylidene-6-D-galactopyranosyl ester **VIII** has more complex multiplicity of the phosphorinane fragment of the molecule. This spectral pattern apparently originates from diastereomeric anisochronism effected by chirality of the carbohydrate substituent.

Next stage of our research consisted in preparation of a series of cycloamidophosphates. Usually chlorophosphate reaction with amides occurs with prevailing configuration reversal. This result corresponds to the nucleophile attack from the side opposite to the



II

trans-(**XIII, XIVa, XV, XVIa, XVII, XVIIIa**) *cis*-(**XIVb, XIVa, b, XVIIIb**)

NRR' = BuNH (**XIII**), $C_5H_{10}N$ (**XIVa, b**),  (**XV**),  (**XVIa, b**).

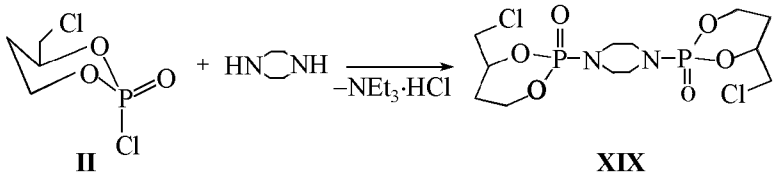
departing halogen (along the mechanism of bimolecular nucleophilic substitution or through formation of a trigonal-bipyramidal intermediate) [11, 12].

Preparation conditions for cycloamidophosphates **XIII–XVIII** are similar to those reported above for the synthesis of phosphates **III–IX**. Since the nucleophilicity of amines under study varied in wider range than that of the alcohol series the reaction time also varied very significantly (from 30 min to 72 h). The aniline derivative **XVII** was obtained only applying sodium anilide.

The reactions occurred with overall yield 38–64% affording prevailingly one of isomers. In a number of syntheses the ratio of *trans*- and *cis*-isomers of amidoester in the reaction mixture amounted approximately to 2 : 1 according to ^{31}P NMR data. The reactions of chlorocyclophosphate **II** with dibutylamine, dodecylamine, and piperidine provided considerable amounts of both isomers, therefore the repeated chromatographic purification on silica gel furnished individual *cis*- and *trans*-isomers. The *trans*-amidophosphates were obtained with higher selectivity at the use of less nucleophilic aromatic amines. Nonetheless we did not observe complete reversal of configuration at phosphorus in any of the syntheses performed. Thus the selectivity of chlorine replacement in mixed anhydride **II** by amide group under similar conditions is lower than substitution by an ester group.

The isolation of individual compounds **XIII–XVIII** was performed by column chromatography on silica gel, as also that of obtained esters. The phosphamides synthesized are colorless syrupy or crystalline substances. It should be mentioned that no formation of pyrophosphate **XII** was observed in the syntheses of amidophosphates **XIII–XVIII**.

At the use of diamine (piperazine) we were able to perform phosphorylation at one or both nitrogen atoms depending on the reagents ratio.



II **XIX**

The homogeneity of amidophosphates was confirmed by TLC and ^{31}P NMR spectra. The structure of compounds obtained was proved by ^{13}C NMR spectroscopy. The phosphorus NMR signals were located in the region –(1–15) ppm (–11 ppm for compound **XVI**). The resonance signals of isomers **XIVa, b** and **XVIIIa, b** differed in the ^{31}P NMR spectrum by 8–10 ppm.

In the carbon spectra of amidophosphates appear signals both from phosphocyclic and amidophosphate parts of the molecules (see table). The spectrum of symmetrical 1,4-piperazinodiphosphate **XIX** contains one signal less than piperazinophosphate **XV**, because four methylene groups in the former compound are magnetically equivalent. Therefore they appear in the spectrum of **XIX** as a single peak, and in the spectrum of **XV** as two resonances.

The comparison of carbon spectra of *trans*- and *cis*-isomers **XIVa** and **XIVb** revealed more significant differences. These differences are due to essentially dissimilar structure of the isomers.

The synthesized series of 2-amino(alkoxy)-2-oxo-4-chloromethyl-1,3,2-phosphorinanes were tested* in the Institute of Biophysics of the Russian Academy of Sciences (Pushchino) for their effect on growth and fission of cells, on the processes of transmission of receptor signal into the cell through a membrane occurring with participation of ions Ca^{2+}, Na^{+}, H^{+}, and also on the respiratory chain of cells and mitochondria.

Compounds **XIV, XVI, XVIII** suppressed the activity of Na^{+}/H^{+} exchange in the cell membrane preventing the increase in pH of the cytoplasm under treatment with agents activating the proliferation of cells. They turned out to be regulators of mitotic fission: at high concentration (10^{-4} M) initiated blocking of activated cells fission, and at low concentrations (10^{-5} M) retarded the fission for 1.5–2 cycles. Besides, compound **XVIII** affected

* The authors are grateful to Professor V. P. Zinchenko for performing the biophysical studies.

the membrane potential of mitochondria and thus inhibited the respiratory chain. Therewith as should be expected the individual geometric isomers of 2-amino-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinanes exhibit different biological activity. In the pair **XIVa, b** the *cis*-isomer was more active. In contrast to the *trans*-isomer it efficiently suppressed the fast phase of Ca^{2+} entrance into reticulum and efficiently depolarized the cell membrane. Among the isomers **XVIIIa, b** the *trans*-isomer was more active. It not only inhibited the entrance of Ca^{2+} into a cell but also stimulated the exit of the ion from the internal cell structures (reticulum) and therefore this phosphorinane possessed pronounced ability to inhibit respiratory function of mitochondria. Thus the said compounds inhibit cell fission as do also more complex amidocyclophosphates of carbohydrates [3].

EXPERIMENTAL

All syntheses were carried out in anhydrous solvents. The derivatives of trivalent phosphorus were prepared in dry argon atmosphere. ^{31}P NMR spectra were registered on spectrometer Bruker V80SY at operating frequency 32.4 MHz, external reference 85% phosphoric acid. ^{13}C NMR spectra were recorded on Bruker AC-200 instrument at operating frequency 50.32 MHz, internal reference TMS. Parameters of spectra of compounds **III–XIX** are listed in the table. Column chromatography was carried out on silica gel L 100/250 or L 40/100 m. Thin-layer chromatography was performed on Silufol UV-254 plates, eluents benzene–dioxane, 3:1 (A), benzene–dioxane, 5:1 (B), hexane–dioxane, 1:1 (C), and benzene–dioxane, 1:1 (D).

2,7,8-Trioxa-1-phosphabicyclo[3.2.1]octane (**I**) was prepared by a known procedure [14].

2-Oxo-2-chloro-4-chloromethyl-1.3.2-dioxaphosphorinane (II). Through a solution of 2.5 g of compound **I** in 50 ml of dichloromethane at –20°C was passed a flow of dry chlorine till the solution turned yellow-green (20–30 min). Then the reaction mixture was allowed to warm to 5–10°C, and the dichloromethane was removed in a vacuum. Yield 3.78 g (98%), ^{31}P NMR spectrum, δ_P –2.7 ppm.

General procedure of synthesis of phosphorinanes (III–XIX). To a mixture of equimolar amounts of an appropriate alcohol (or amine) and triethylamine dissolved in a 5-10-fold excess of CH_2CI_2 was added dropwise 10–15% solution of an equimolar amount of chlorophosphate **II** in CH_2CI_2. The reaction progress was monitored by TLC or ^{31}P NMR spectroscopy. The synthesis of compounds took the following time: 45 min (**XIV**), 1 h (**XV**), 25 h (**XVII**), 5 h (**XVII**), 72 h (**XVIII**), 1 h (**XIX**). The separated precipitate was filtered off, the filtrate was concentrated in a vacuum, 1 ml of solvent system A was added thereto, and the solution was submitted to column chromatography on silica gel. Using sytem A as eluent we collected fractions with the indicated R_f values. Compounds **VIII, XII, XIV, XVI, XVIII** were subjected to chromatography for the second time applying elution system B or C, the solvents were removed in a vacuum, the reaction products were dried in a vacuum at 40–50°C till constant weight.

2-Oxo-4-chloromethyl-2-ethyloxy-1,3,2-dioxaphosphorinane (III). From 0.3 g (1.5 mmol) of chlorophosphate **II** and 0.07 g (1.7 mmol) of ethanol in the presence of 0.17 g (1.7 mmol) of NEt_3 we obtained 0.25 g (78%) of phosphate **III**, syrupy substance, R_f 0.53 (A), 0.28 (B). ^1H NMR spectrum (200 MHz, C_6D_6), δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, 3J 7.2), 1.62 m (1H, H^{5e}, $^2J_{5a,5e}$ 14.2 , $^3J_{5e,6a}$ 7.2, $^4J_{5e}$, P 2.7), 1.84 d.d.d.d (1H, H^5a, $^3J_{4,5a}$ 11.0, $^3J_{5a,6a}$ 11.1, $^3J_{5a,6e}$ 4.5, $^4J_{5a,P}$ 0), 3.47 m (2H, CH_2Cl, ^2J 5.8), 3.97 m (2H, CH_2CH_3, $^3J_{(CH_2CH_3,P)}$ 8.8), 4.07 m (1H, H6e, $^3J_{5a,6e}$ 4.5, $J_{6e,P}$ 17.0), 4.24 d.d.d.d (1H, H^{6a}, $^2J_{6a,6e}$ 11.0, $^3J_{6a,P}$ 3.3), 4.58 m (1H, H^4, $J_{4,5e}$ 5.1, $^3J_{4,P}$ 0). Found, %: C 33.43; H 5.63; P 14.42. $C_6H_{12}ClO_4P$. Calculated, %: C 33.58; H 5.64; P 14.43.

2-Butyloxy-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (IV). From 2 g (1.1 mmol) of chlorophosphate **II** and 0.1 g (1.4 mmol) of 1-butanol in the presence of 0.15 g (1.6 mmol) of NEt_3 we obtained 0.21 g (85%) of phosphate **IV**, syrupy compound, R_f 0.65 (A), 0.42 (B). ^1H NMR spectrum (200 MHz, C_6D_6), δ, ppm (*J*, Hz): 0.77 t (3H, CH_3), 1.26 m (2H, CH_2CH_3), 1.46 m (2H, $CH_2CH_2CH_3$), 1.62 m (1H, H^{5e}), 1.67 d.d.d.d (1H, H^{5a}), 3.15 m (2H, CH_2Cl), 3.82 m (2H, $OCH_2CH_2CH_2CH_2CH_3$), 4.0 m (1H, H^{6e}), 4.15 m (1H, H^{6a}), 4.48 m (1H, H^4). Found, %: C 39.53; H 6.62; P 12.71. $C_8H_{16}ClO_4P$. Calculated, %: C 39.60; H 6.65; P 12.77.

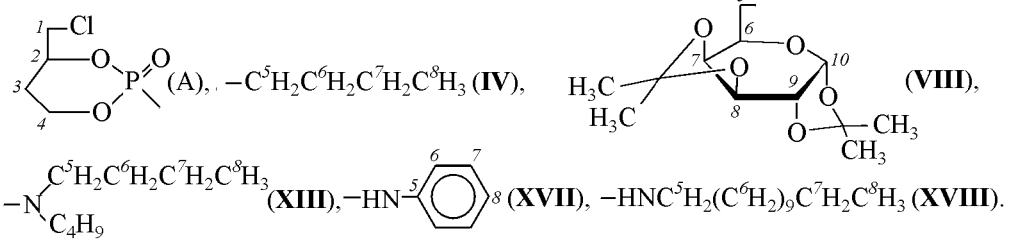
2-Hexyloxy-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (V). From 0.32 g (1.6 mmol) of chlorophosphate (**II**) and 0.16 g (1.6 mmol) of 1-hexanol in the presence of 0.17 g (1.8 mmol) of NEt_3 we obtained 0.21 g (49%) of phosphate **V**, syropy substance, R_f 0.38 (A). ^1H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.80 t (3H, ^3J 7.3), 1.1 m [6H, $CH_2(CH_2)_3CH_3$], 1.5 m (2H,

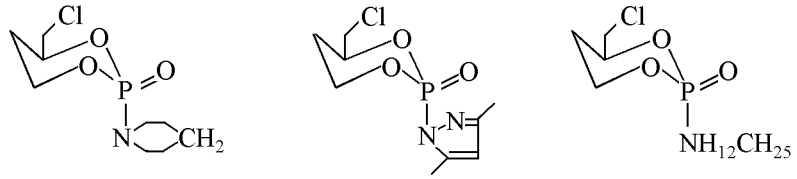
^{13}C and ^{31}P NMR chemical shifts (δ, ppm) and couplimg constants $^{13}C–^{31}P$ Hz (given in parentheses)[a]

Compd no.	^{13}C NMR spectrum										^{31}P NMR spectrum
	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	P
III	46.9(7.4)	78.2(5.6)	28.7(6.8)	66.7(5.9)	65.2(6.6)	6.5(6.0)					–6.1
IV	46.7(8.5)	77.5(4.9)	28.8(6.4)	66.3(5.6)	68.9(6.4)	32.9(6.3)	19.3	14.0			–5.6
V	46.8(8.3)	77.8(5.3)	28.8(6.2)	66.4(5.6)	69.3(6.2)	30.9(6.5)	25.7	31.9	23.2	14.6	–5.6
VI	45.9(6.9)	77.9(5.9)	27.8(6.5)	66.2(5.9)	68.3(6.3)	74.3(7.5)	65.9	109.7	26.8	25.3	–6.2
VIIa	46.7(6.4)	78.7(5.7)	28.5(7.2)	66.8(5.7)	70.4 6.7)	77.6 (7.2)	28.0	26.2			–6.4
VIII	45.5(6.2, 4.7)	78.3(6.6, 6.1)	27.6(8.7, 9.7)	66.1(5.8, 6.0)	67.2(6.5) (4.3)	70.7 (7.9)	67.5	70.8	70.9	96.5	–6.8
IX	45.24 (8.46)	76.77 (5.56)	27.77 (6.48)	65.43 (5.65)	73.69 (6.67)	22.97 (5.4)					–6.2
X	46.8(8.4)	78.8(6.1)	28.8(6.3)	66.3(5.6)	77.8(5.3)	33.8	23.9	25.7			–6.2
XII	45.3	80.1	28.5	68.9		(4.7					–20
XIII	45.76 (10.28)	74.23 (4.80)	27.14 (4.04)	63.74 (5.61)	43.63 (4.91)	28.27	18.53	12.53			7.3
XIVa	47.19	71.46 (4.36)	36.80 (6.20)	40.47	45.44 (<1)	26.14 (5.06)	25.54				14.4
XIVb	46.59 (10.76)	75.58 (5.54)	28.57 (4.48)	65.16 (5.56)	45.03 (3.23)	25.77	24.15				4.9
XV	46.63 (10.69)	75.83 (5.21)	28.75 (4.44)	65.44 (5.66)	45.93 (3.69)	44.95					4.75
XVIb	46.93 (11.85)	73.16 (4.6)	36.76 (4.3)	41.28 (6.22)	11.12 (3.23)	104.6	143.71				–10.7
XVII	47.07(0)	73.47 (4.88)	36.00 (4.48)	41.07 (<1)	140.20 (5.56)	118.78 (3.23)	129.59	122.45 (6.34)	(7.24)		0.98
XVIIIb	47.42 (9.75)	75.54 (4.83)	28.28 (4.70)	64.58 (5.42)	40.71	25.9–31.4	22.10	13.93			5.8
XIX	47.34 (10.45)	75.81 (5.24)	26.70 (4.21)	65.39 (5.58)	45.91 (3.62)						5.0

[a] The spectra of compounds **III, X, XIII, XVI, XVII** were recorded in C_6D_6, the other spectra in $CDCl_3$.

[b] Examples of numeration of carbons in the core of the molecule (A) and in substituents of compounds are given below.





XIV **XVI** **XVIII**

OCH_2CH_2, $^3J_{(OCH_2CH_2,OCH_2CH_2)}$ 6.4), 1.5 m (2H, $H^{5a,5e}$, $^3J^{5e,6e}$ 3.4, $^3J_{5a,6e}$ 4.5, $^3J_{5e,6a}$ 5.5, $^3J_{5a,6a}$ 10.8), 2.9 d.d (2H, CH_2Cl, ^2J 5.1, ^3J(4, CH HCl) 1.7, $^3J_{(4,}$ CH'HCl) 2.6, $^3J_{(CH_2Cl,}$ P) 0.9), 3.6 m (1H, H^{6e}, $^2J_{6e,6a}$ 8.5, $^3J_{6e,5e}$ 3.4, $^3J_{6a,5e}$ 4.5, $^3J_{6e,P}$ 19.2), 3.9 m (1H, H^{6a}, $^2J_{6a,6e}$ 8.5, $^3J_{6a,5e}$ 5.5, $^3J_{6a,5a}$ 10.8, $^3J_{6a,P}$ 8.5), 4.0 d.t (2H, OCH_2CH_2, $^3J_{(OCH_2CH_2,OCH_2CH_2)}$ 6.4, $^3J_{(OCH_2CH_2,P)}$ 7.3), 4.2 m (1H, H*4*, ^3J(4, CH'HCl) 1.7, ^3J(4, CH HCl) 2.6, $^3J_{4,5a}$ 11.5, $^3J_{4,5e}$ 13.1). Found, %: C 44.28; H 7.43; P 11.36. $C_{10}H_{20}ClO_4P$. Calculated, %: C 44.37; H 7.45; P 11.44.

2-(2-*O*,3-*O*-Isopropylideneglycer-1-oxy)-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (VI). From 0.30 g (1.5 mmol) of chlorophosphate **II** and 0.19 g (1.5 mmol) of 2-*O*,3-*O*-isopropylideneglycerol in the presence of 0.15 g (1.5 mmol) of NEt_3 we obtained 0.23 g (68%) of phosphate **VI**, syrupy fluid, R_f 0.56 (A). Found, %: C 45.99; H 7.01; P11.72. $C_{10}H_{18}ClO_4P$. Calculated, %: C 46.07; H 6.96; P 11.88.

2-Oxo-2-tetrahydrofurfuryloxy-4-chloromethyl-1,3,2-dioxaphosphorinanes (VIIa, b). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.14 g (1.6 mmol) of tetrahydrofurfuryl alcohol in the presence of 0.15 g (1.5 mmol) of NEt_3 we obtained 0.142 g (38%) of *cis*-isomer **VIIa** and 0.015 g 4% of *trans*-isomer **VIIb**, syrupy fluids, R_f 0.36 (**VIIa**) (A), 0.15 (**VIIb**) (A). ^{31}P NMR spectrum, P –6.4 (**VIIa**), –7.6 (**VIIb**) ppm. Found for isomer **VIIa**, %: C 39.82; H 5.94; P 11.42. $C_9H_{16}ClO_5P$. Calculated, %: C 39.94; H 5.96; P 11.44.

2-(1α-*O*,2-*O*;3-*O*,4-*O*-Diisopropylidene-6-D-galactopyranosyloxy)-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (VIII). From 0.32 g (1.6 mmol) of chlorophosphate **II** and 0.42 g (1.6 mmol) of 1,2;3,4-*O*-diisopropylidene-α-D-galactopyranose in the presence of 0.17 g (1.7 mmol) of NEt_3 we obtained 0.21 g (30%) of phosphate **VIII**; syrupy fluid, R_f 0.38 (B). Found, %: C 44.77; H 6.08; P 7.16. $C_{16}H_{26}ClO_9P$. Calculated, %: C 44.82; H 6.11; P 7.22.

2-Isopropyloxy-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (IX). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.08 g (1.4 mmol) of 2-propanol in the presence 0.15 g (1.5 mmol) of NEt_3 we obtained 0.21 g (65%) of phosphate **IX**, suropy fluid, R_f 0.34 (B). ^{1}H NMR spectrum (200 MHz, CD_3Cl), δ, ppm (*J*, Hz): 1.4 d (6H, $(CH_3)_2CHO$, $^3J(CH_3,$ $OCH(CH_3)_2$) 6.4), 2.0 m (1H, H^{5e}, $^2J_{5e,5a}$ 11.1, $^3J_{5e,6a}$ 2.1, $^3J_{5e,6e}$ 3.4), 2.2 m (1H, H^{5a}, $^2J_{5a,5e}$ 11.1, $^3J_{5a,6a}$ 2.1), 3.62 t (1H, CH'HCl, ^2J 11.0, $^3J_{(CH'HCl,}$ 4) 4.5), 3.7 t (1H, CH'HCl, ^2J 11.0, $^3J_{(CH'HCl,}$ 4) 5.1), 4.4 m (1H, H^{6e}, $^2J_{6e,6a}$ 11.1, $^3J_{6e,5e}$ 3.4, $^3J_{6e,P}$ 11.6), 4.5 m (1H, H^{6a}, $^2J_{6a,6e}$ 11.1, $^3J_{6a,5e}$ 2.1, $^3J_{6a,5a}$ 2.1, $^3J_{6a,P}$ 7.2), 4.7 m (1H, $OCH(CH_2)_3$, $^3J_{(OCH(CH_3)_2,\ OCH(CH_3)_2)}$ 6.4, $^3J_{(OCH(CH_3)_2,}$ P) 7.3), 4.8 m (1H, $^3J_{(4,}$ CH'HCl) 4.5, $^3J_{(4,}$ CH'HCl) 5.1). Found, %: C 36.69; H 6.14; P 13.52. $C_7H_{14}ClO_4P$. Calculated, %: C 36.78; H 6.17; P 13.55.

2-Oxo-2-cyclohexyloxy-4-chloromethyl-1,3,2-dioxaphosphorinane (X). From 0.32 g (1.6 mmol) of chlorophosphate **II** and 16 g (1.6 mmol) of cyclohexanol in the presence of 0.17 g (1.7 mmol) of NEt_3 we obtained 0.28 g (65%) of phosphate **X**, syrupy fluid, R_f 0.39 (A). Found, %: C 44.59; H 6.71; P 11.49. $C_{10}H_{18}ClO_4P$. Calculated, %: C 44.70; H 6.75; P 11.53.

Bis-*O*-(2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane) (XII). From 0.32 g (1.6 mmol) chlorocyclophosphate **II** and 0.014 g (0.8 mmol) of water in the presence of 0.15 g (1.5 mmol) of triethylamine we obtained 0.21 g (75%) of pyrophosphate **XII**, syrupy fluid, R_f 0.87 (C). ^{31}P NMR spectrum, *p*, ppm: –21.4. Found, %: C 26.99; H 3.94; P 17.42. C8H14Cl2O7P2. Calculated, %: C 27.06; H 3.97; P 17.45.

2-Butylamino-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (XIII). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.17 g (1.4 mmol) of butylamine in the presence of 0.15 g (1.5 mmol) of NEt_3 we obtained 0.23 g (55%) of amidophosphate **XIII**, syrupy fluid, R_f 0.32 (C), 0.83 (D). Found, %: C 48.29; H 8.44; P 10.38. $C_{12}H_{25}ClNO_3P$. Calculated, %: C 48.39; H 8.38; P 10.41.

2-Oxo-2-piperidino-4-chloromethyl-1,3,2-dioxaphosphorinanes (XIVa, b). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.12 g (1.4 mmol) of piperidine in the presence of 0.15 g (1.5 mmol) of NEt_3 we obtained 0.10 g (27%) of *trans*-isomer **XIVa**, syrupy fluid, R_f 0.50 (A), 0.84 (D), and 0.07 g (20%) of *cis*-isomer **XIVb**, mp 52–54°C, R_f 0.28 (A), 0.61 (D). Found for isomer **XIVb**, %: C 42.59; H 6.72; P 12.18. $C_9H_{17}ClNO_3P$. Calculated, %: C 42.61; H 6.75; P 12.21.

2-Oxo-2-piperazino-4-chloromethyl-1,3,2-dioxaphosphorinane (XV). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.12 g (1.4 mmol) of piperazine in the presence of 0.15 g (1.5 mmol) of

NEt_3 we obtained 0.13 (37%) amidophosphate **XV**, syrupy fluid, R_f 0.36 (C), 0 (A). Found, %: C 37.39; H 6.92; P 12.14. $C_8H_{18}ClN_2O_3P$. Calculated, %: C 37.41; H 7.01; P 12.08.

2-(2,4-Dimethylpyrazol-1-yl)-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinanes (XVIa, b). From 0.28 g (1.4 mmol) of chlorophosphate **II** and 0.13 g (1.4 mmol) of 2,4-dimethylpyrazole in the presence of 0.15 g (1.6 mmol) of NEt_3 we obtained 0.056 g (15%) of cis-isomer of amidophosphate **XVIa** and 0.043 g (12%) of *trans*-isomer **XVIb**, syrupy fluids, R_f 0.71 (**XVIa**) (A), 0.45 (**XVIb**) (A). ^{31}P NMR spectrum, δ, ppm: –10.7 (**XVIa**), –15.5 (**XVIb**). Found for isomer (**XVIa**), %: C 40.83; H 5.30; P 11.68. $C_9H_{14}ClN_2O_3P$. Calculated, %: C 40.85; H 5.33; P 11.70.

2-Anilino-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinane (XVII). From 0.32 g (1.6 mmol) of chlorophosphate **II** and.18 g (1.6 mmol) of sodium anilide we obtained 0.126 g (30%) amidophosphate **XVII**; syrupy fluid, R_f 0.45 (A), 0.79 (D). Found, %: C 45.88; H 4.99; P 11.81. C10H^{13}ClNO3P. Calculated, %: C 45.91; H 5.01; P 11.84.

2-Dodecylamino-2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinanes (XVIIIa, b). From 0.32 g (1.6 mmol) of chlorophosphate **II** and 0.30 g (1.6 mmol) of dodecylamine in the presence of 0.17 g (1.7 mmol) of NEt_3 we obtained 0.12 g (22%) of *trans*-isomer of amidophosphate **XVIIIa**, syrupy fluid, R_f 0.23 (C), 0.45 (D), and 0.16 g (29%) of *cis*-isomer **XVIIIb**, mp 63–64°C, R_f 0.5 (A), 0.9 (Cß). ^{31}P NMR spectrum, δ, ppm: 5.8 (**XVIIIa**), 15.4 (**XVIIIb**). Found for isomer (**XVIIIb**), %: C 54.30; H 9.40; P 8.69. $C_{16}H_{33}ClNO_3P$. Calculated, %: C 54.31; H 9.40; P 8.75.

***N,N'*-Bis(2-oxo-4-chloromethyl-1,3,2-dioxaphosphorinan-2-yl)piperazine (XIX).** From 0.56 g (2.8 mmol) of chlorophosphate **II** and 0.12 g (1.4 mmol) of piperazine in the presence of 0.28 g (2.8 mmol) of NEt_3 we obtained 0.31 g (53%) of diamidophosphate **XIX**, R_f 0.35 (C), mp 81–83×C. Found, %: C 34.04; H 5.23; P 14.63. $C_{12}H_{22}Cl_2N_2O_6P_2$. Calculated, %: C 34.06; H 5.24; P 14.64.

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