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N-Methyl-D-glucamine-Derived 4-Substituted 1,3-Oxazoles

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Abstract—Reaction of available derivatives of 1-acylamino-2,2-dichloroacrylic acids as well as diethyl esters of 1-acylamino-2,2,2-trichloroethylphosphonic acids with *N*-methyl-D-glucamine furnished previously unknown 1,3-oxazole derivatives containing nitrile, ester or phosphonyl groups in the position 4 and *N*-methyl-*D*-glucamine residue in the position 5.

Keywords: *N*-methyl-D-glucamine, 1-acylamino-2,2-dichloroacrylic acids, diethyl esters of 1-acylamino-2,2,2-trichloroethylphosphonic acids, heterocyclization, 4-substituted 1,3-oxazoles

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It was assumed previously that 1,3-oxazole derivatives are not promising for searching for bioactive agents because they are rarely found in natural objects [1]. However, in recent decades some studies [2–5] have shown that various bacteria and marine organisms are producers of many antibiotics of oxazole structure. Currently, there is a large number of synthetic bioregulators of oxazole series, which exhibit high antimicrobial, cytotoxic, immune-stimulating, neuroleptic, analgesic, and other biological activities [6, 7]. In addition, compounds having diverse biological activities were found among the 4-functionalized derivatives of 5-amino-1,3-oxazoles [8–13].

These facts induce the search for new synthetic approaches to introduction of pharmacophoric groups into 1,3-oxazole fragment. We believe that the modification of 1,3-oxazole ring with biologically active polyol molecules, which include available and widely used in the pharmaceutical practice *N*-methyl-D-glucamine, is promising.

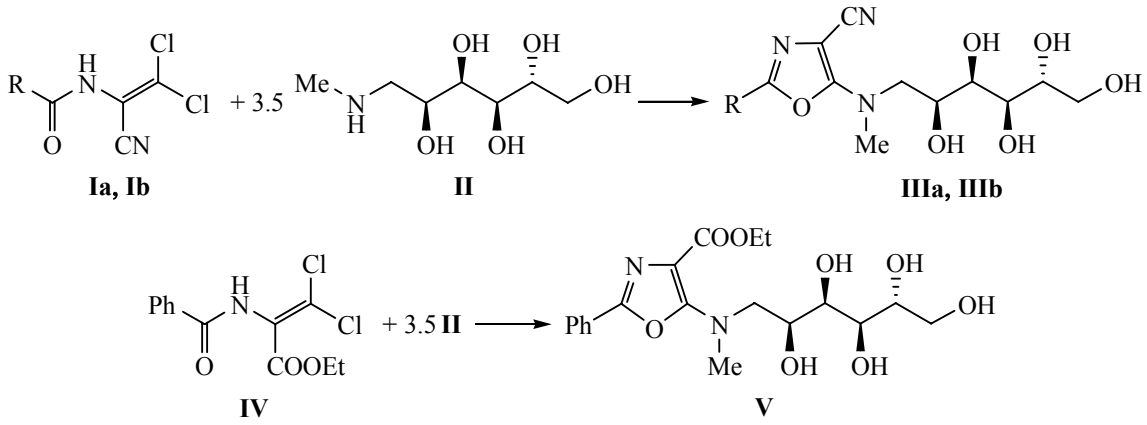
The incorporation of *N*-methyl-D-glucamine residues into the structure of known pharmaceutical preparations has a strong effect on their pharmacological properties. This is due to a decrease in the toxic effect on the body and a significant increase in water solubility of compounds [14]. *N*-Methyl-D-glucamine is not only salt-forming agent, but also has high pharmacological activity due to the presence of five hydroxy groups forming hydrogen bonds. This leads to the formation of stable complexes of aminoalcohol with cellular membranes proteins and to alteration of the charge and membrane hyperpolarization. Furthermore, *N*-methyl-D-glucamine reacts competitively with anions and therefore facilitates their selective transport through biological membranes [15]. High water solubility, buffering, solubilizing, and dose-dependent properties have enabled us to assume that use of *N*-methyl-D-glucamine is promising for the synthesis of new bioregulators with potentially a wide spectrum of activity.

The aim of this work is the synthesis of 4-functionalized 1,3-oxazole derivatives modified with *N*-methyl-D-glucamine in the position 5.

In the 70s of the last century Drach et al. [16] and Matsumura et al. [17] found that the interaction of available 1-acylamino-2,2-dichloroacrylonitriles **I** with primary or secondary amines afforded substituted 5-amino-1,3-oxazole-4-carbonitriles in high yields [16, 17]. Later the reaction was used for the preparation of 5-amino-1,3-oxazoles containing ester [18], phosphonyl [19], sulfonyl [20], and other group in the position 4. In [21] it was shown that dichloroacrylonitriles **I** also reacted with monoethanolamine and other amino alcohols to form the corresponding 1,3-oxazoles.

In the present work we found that the reaction of dichloroacrylonitriles **Ia** and **Ib** with an excess of *N*-

Scheme 1.



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

methyl-D-glucamine **II** produced 2-methyl(phenyl)-5-{methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]-amino}-1,3-oxazole-4-carbonitriles **IIIa** and **IIIb** in high yields. The reaction of **Ia** and **Ib** with an equimolar amount of *N*-methyl-D-glucamine in the presence of an excess of triethylamine resulted in the formation of compounds **IIIa** and **IIIb** with yield of ≤30%. The rection of compounds **I** and *N*-methyl-D-glucamine in various solvents (tetrahydrofuran, methanol, acetonitrile, dimethylformamide) in the temperature range of 5–100°C was thoroughly studied. The results showed that for reacting compounds **Ia** and **Ib** with an excess of *N*-methyl-D-glucamine the optimum temperature range 18–25°C. Methyl alcohol was chosen as the solvent because it dissolves well the reactants and the reaction products **IIIa** and **IIIb**. In addition, *N*-methyl-D-glucamine hydrochloride is poorly soluble in methanol and can be easily removed from the reaction medium by filtration (Scheme 1).

Under such conditions, ethyl 1-benzoylamino-2,2-dichloroacrylate **IV** reacted with *N*-methyl-D-glucamine to form ethyl 1,3-oxazole-4-carboxylate **V** in 60% yield. Oxazoles **IIIa**, **IIIb**, and **V** were colorless crystalline substances, well soluble in water, alcohol, and dichloromethane, sparingly soluble in hexane and benzene.

Composition and structure of the obtained compounds was in agreement with elemental analysis, ^{1}H and ^{13}C NMR, and IR spectra (Tables 1–3), and chromatography-mass spectrometry data. Thus, in the ^{1}H NMR spectra of compounds **IIIa** and **IIIb** the proton signals of the hydroxy groups of *N*-methyl-D-glucamine residue appeared as four doublets (*J* 6.5–4.5 Hz) and one multiplet in the range of 5.02–4.36 ppm. The singlet signals of NMe group were in the range of 3.26–3.10 ppm. The ^{1}H NMR spectrum of **IIIa** contained the signal of the methyl group at 2.24 ppm indicating the formation of 1,3-oxazole ring [16]. In the IR spectra of 1,3-oxazoles **IIIa** and **IIIb** the nitrile group absorption band was observed at 2214–2205 cm^{-1}. IR spectrum of compound **V** contained the absorption band of the ester group at 1678 cm^{-1}. Strong absorption in the ranges of 1643–1628 and 1606–1584 cm^{-1} corresponded to 5-amino-1,3-oxazole ring vibrations [22].

This reaction was used for obtaining diethyl 1,3-oxazol-4-ylphosphonates **VIIa**–**VIIe**. In this case, diethyl 1-acylamino-2,2,2-trichloroethylphosphonates **VIa**–**VIe** were involved into the reaction with *N*-methyl-D-glucamine. As a result, diethyl 2-R-5-{methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]-amino}-1,3-oxazol-4-ylphosphonates **VIIa**–**VIIc** were obtained in 89–92% yields. It should be noted that the yields of 2-phthalimidoalkyl-1,3-oxazoles **VIId** and **VIIe**, were lower (29–40%) due to formation of side products whose structure was not identified (Scheme 2).

Compounds **VIIa**–**VIId** were transparent viscous liquids, and compound **VIIe** was solid. Their structure was confirmed by ^{1}H, ^{31}P, and ^{13}C NMR spectra.

A particular attention should be paid to ^{13}C NMR spectral data of these compounds. Characteristic signals of the carbon atoms of 1,3-oxazole rings appeared as doublets due to the spin-spin coupling with the phosphorus nucleus. Thus, the carbon signals of C^{5} were in the range of 162.03–161.26 ppm with *J* 38.4–37.4 Hz; the signal of C^{2} atom appeared at

Table 1. Yields, melting points, and elemental analysis data of compounds **III**, **V**, **VII,** and **VIII**

Comp. no.	Yield, %	$[\alpha]_D$	mp, °C	Found, %		Formula	Calculated, %	
				N	P		N	P
IIIa	63	–4.20	124–126	13.85	–	$C_{12}H_{19}N_3O_6$	13.92	–
IIIb	56	–1.40	143–146	11.36	–	$C_{17}H_{21}N_3O_6$	11.53	–
V	60	–6.75	113–114	6.73	–	$C_{19}H_{26}N_2O_8$	6.85	–
VIIa	92	–3.85	Oil	6.89	7.68	$C_{14}H_{27}N_2O_9P$	7.09	7.76
VIIb	89	–11.50	Oil	6.59	7.51	$C_{15}H_{29}N_2O_9P$	6.75	7.45
VIIc	90	+23.30	Oil	5.80	6.43	$C_{20}H_{31}N_2O_9P$	5.95	6.60
VIId	40	–1.60	Oil	7.39	5.36	$C_{23}H_{32}N_3O_{11}P$	7.55	5.50
VIIe	29	+11.36	84–86	7.35	5.32	$C_{24}H_{34}N_3O_{11}P$	7.30	5.45
VIII	82	–	Oil	9.42	6.92	$C_{16}H_{32}N_3O_9P$	9.50	7.04

149.93–141.44 ppm with *J* 22.4–21.9 Hz; the carbon C^4 resonated in the area of 98.67–96.38 ppm with *J* 256.3–225.8 Hz. The signals of phosphorus nuclei in ^{31}P NMR spectra of phosphorylated oxazoles **VIIa**–**VIIe** were in the range of 13.49–14.61 ppm.

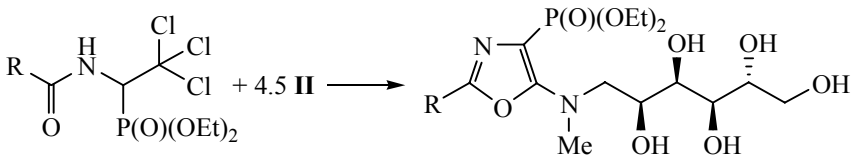
The IR spectra of compounds **VIIb**–**VIIe** contained strong absorption at 1646–1605 and 1601–1584 cm^{-1} typical of 5-amino-1,3-oxazole ring [22]. However, in the IR spectrum of oxazole **VIIa** there was only one broad strong absorption band at 1603 cm^{-1}. The medium absorption band in the IR spectra of **VIIa**–**VIIe** in the range of 1228–1202 cm^{-1} was assigned to the vibrations of P=O bond, and the strong absorption at 1017–1014 and 971–961 cm^{-1} corresponded to the vibrations of P–O–C bond.

Among the phosphorylated 1,3-oxazoles obtained, of particular interest are derivatives **VIId** and **VIIe** containing phthaloyl-protected aminoalkyl moieties in the position 2 of the oxazole ring. We found that treating diethyl 2-[2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)ethyl]-5-{methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-1,3-oxazol-4-ylphosphonate **VIIe** with an excess of hydrazine hydrate in 96% ethanol at 18–25°C resulted in removal of the phthaloyl protecting group with the formation of diethyl 2-(2-aminoethyl)-5-{methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-1,3-oxazol-4-ylphosphonate **VIII** in quantitative yield, which can be regarded as a promising synthon for further modification and as a substrate for phosphonopeptidomimetics synthesis [23, 24] (Scheme 3).

Oxazole **VIII** was a thick transparent oily substance, well soluble in most organic solvents and water. Its structure was supported by the spectral methods (Tables 2, 3).

In summary, the reaction of available 1-acylamino-2,2-dichloracrylic acids derivatives **Ia**, **Ib**, **IV** and diethyl 1-acylamino-2,2,2-trichloroethylphosphonates **VIa**–**VIe** with *N*-methyl-D-glucamine afforded in high yields the corresponding 1,3-oxazole-4-carbonitriles **IIIa** and **IIIb**, ethyl 1,3-oxazole-4-carboxylic acid **V**, and diethyl 1,3-oxazol-4-ylphosphonates **VIIa**–**VIIe**

Scheme 2.



VIa–VIe **VIIa–VIIe**

R = H (**a**), Me (**b**), Ph (**c**), PhtlCH$_2$ (**d**), Phtl(CH$_2$)$_2$ (**e**).

Table 2. Parameters of IR, ^{1}H NMR spectra and mass spectrometry data of compounds **III**, **V**, **VII** and **VIII**

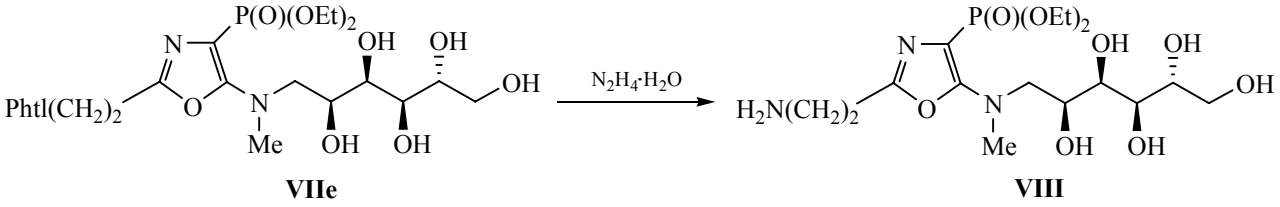
Comp. no.	ν, cm^{-1}	δ_H, ppm	Mass spectrum, *m*/*z*
IIIa	3436 (O–H), 2205(C≡N), 1643, 1606	4.91 d (1H, OH, $^3J_{HH}$ 4.5 Hz), 4.50 d (1H, OH, $^3J_{HH}$ 4.9 Hz), 4.45–4.37 m (2H, 2OH), 4.36–4.31 m (1H, OH), 3.89–3.82 m (1H, CH), 3.64–3.36 m (7H, 2CH$_2$, 3CH), 3.10 s (3H, NCH$_3$), 2.24 s (3H, CH$_3$)	302 $[M+1]^+$
IIIb	3323 (O–H), 2214(C≡N), 1635, 1591	7.84 d (2H, CH$_{arom}$, $^3J_{HH}$ 6.6 Hz), 7.54–7.45 m (3H, CH$_{arom}$), 5.02 d (1H, OH, $^3J_{HH}$ 5.0 Hz), 4.53 d (1H, OH, $^3J_{HH}$ 5.0 Hz), 4.47 d (1H, OH, $^3J_{HH}$ 6.5 Hz), 4.44 d (1H, OH, $^3J_{HH}$ 6.5 Hz), 4.36 t (1H, OH, $^3J_{HH}$ 6.0 Hz), 3.98–3.91 m (1H, CH), 3.65–3.38 m (7H, 2CH$_2$, 3CH), 3.23 s (3H, NCH$_3$)	364 $[M+1]^+$
V	3405 (O–H), 1678 (C=O), 1628, 1584	7.84 d (2H, CH$_{arom}$, $^3J_{HH}$ 7.4 Hz), 7.53–7.41 m (3H, CH$_{arom}$), 4.19 q (2H, O<u>CH$_2$</u>CH$_3$, $^3J_{HH}$ 6.9 Hz), 3.92–3.49 m (13H, 5OH, 4CH, 2CH$_2$), 3.26 s (3H, NCH$_3$), 1.25 t (3H, OCH$_2$<u>CH$_3$</u>, $^3J_{HH}$ 6.9 Hz)	411 $[M+1]^+$
VIIa	3344 (O–H), 1603, 1205 (P=O), 1014 (P–O–C), 963 (P–O–C–C)	7.76 s (1H, CH), 4.83 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.50 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.42 d (1H, OH, $^3J_{HH}$ 6.0 Hz), 4.38–4.31 m (2H, 2OH), 4.03–3.94 m (4H, 2O<u>CH$_2$</u>CH$_3$), 3.89–3.82 m (1H, CH), 3.60–3.35 m (7H, 2CH$_2$, 3CH), 3.13 s (3H, NCH$_3$), 1.22 t (6H, 2OCH$_2$<u>CH$_3$</u>, $^3J_{HH}$ 6.9 Hz)	399 $[M+1]^+$
VIIb	3344 (O–H), 1633, 1587, 1206 (P=O), 1014 (P–O–C), 961 (P–O–C–C)	4.82 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.52 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.45 d (1H, OH, $^3J_{HH}$ 6.0 Hz), 4.38–4.34 m (2H, 2OH), 4.01–3.92 m (4H, 2O<u>CH$_2$</u>CH$_3$), 3.89–3.83 m (1H, CH), 3.59–3.37 m (7H, 2CH$_2$, 3CH), 3.09 s (3H, NCH$_3$), 2.24 s (3H, CH$_3$), 1.22 t (6H, 2OCH$_2$<u>CH$_3$</u>, $^3J_{HH}$ 6.9 Hz)	413 $[M+1]^+$
VIIc	3346 (O–H), 1605, 1584, 1205 (P=O), 1016 (P–O–C), 961 (P–O–C–C)	7.83 d (2H, CH$_{arom}$, $^3J_{HH}$ 7.1 Hz), 7.49–7.43 m (3H, CH$_{arom}$), 4.93 br.s (1H, OH), 4.54 br.s (1H, OH), 4.45 br.s (2H, OH), 4.35 br.s (1H, OH), 4.10–4.00 m (4H, 2O<u>CH$_2$</u>CH$_3$), 3.98–3.93 m (1H, CH), 3.69–3.47 m (7H, 2CH$_2$, 3CH), 3.24 s (3H, NCH$_3$), 1.26 t (6H, 2OCH$_2$<u>CH$_3$</u>, $^3J_{HH}$ 7.1 Hz)	475 $[M+1]^+$
VIId	3357 (O–H), 1776, 1711 (C=O), 1646, 1601, 1228 (P=O), 1017 (P–O–C), 971 (P–O–C–C)	7.95–7.92 m (2H, CH$_{arom}$), 7.90–7.87 m (2H, CH$_{arom}$), 4.80 d (1H, OH, $^3J_{HH}$ 5.8 Hz), 4.77 s (2H, CH$_2$), 4.49 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.41 d (1H, OH, $^3J_{HH}$ 6.0 Hz), 4.34–4.30 m (2H, 2OH), 3.94–3.81 m (5H, 2O<u>CH$_2$</u>CH$_3$, CH), 3.55–3.39 m (7H, 2CH$_2$, 3CH), 3.08 s (3H, NCH$_3$), 1.13–1.09 m (6H, 2OCH$_2$<u>CH$_3$</u>)	558 $[M+1]^+$
VIIe	3346 (O–H), 1771, 1708 (C=O), 1626, 1585; 1202 (P=O), 1015 (P–O–C), 962 (P–O–C–C)	7.91–7.80 m (4H, CH$_{arom}$), 4.79 d (1H, OH, $^3J_{HH}$ 5.8 Hz), 4.50 d (1H, OH, $^3J_{HH}$ 5.5 Hz), 4.42 d (1H, OH, $^3J_{HH}$ 5.8 Hz), 4.37–4.29 m (2H, 2OH), 3.90–3.70 m (7H, 2O<u>CH$_2$</u>CH$_3$, CH$_2$,CH), 3.60–3.36 m (7H, 2CH$_2$, 3CH), 3.04 s (3H, NCH$_3$), 2.93 t (2H, CH$_2$, $^3J_{HH}$ 6.3 Hz), 1.09–1.05 m (6H, 2OCH$_2$<u>CH$_3$</u>)	572 $[M+1]^+$
VIII	3681, 3597 (N–H, O–H), 1606, 1233 (P=O), 1028 (P–O–C–C)	4.09–3.91 m (7H, NH$_2$, 5OH), 3.88–3.80 m (4H, 2O<u>CH$_2$</u>CH$_3$), 3.56–3.40 m (8H, 2CH$_2$, 4CH), 3.10 s (3H, NCH$_3$), 2.93–2.86 m (2H, CH$_2$), 2.74–2.67 m (2H, CH$_2$), 1.21 t (6H, 2OCH$_2$<u>CH$_3$</u>, $^3J_{HH}$ 6.9 Hz)	442 $[M+1]^+$

modified with pharmacophore *N*-methyl-D-glucamine residue in the position 5.

EXPERIMENTAL

NMR spectra of the solutions in DMSO-d_6 were obtained on a Bruker AVANCE DRX-500 spectrometer [500 (^{1}H), 202 (^{31}P), 125 MHz (^{13}C)], internal refernce TMS or external reference 85% phosphoric acid. IR spectra were recorded on a Vertex 70 spectrometer from a thin film or from KBr pellets. GC-MS spectra were registered on a liquid chromatography-mass spectrometry system HPLC Agilent 1100 Series equipped with a diode array detector Agilent

Scheme 3.



VIIe **VIII**

LC\MSD SL. Parameters of GC-MS analysis: Zorbax SB-C18 column (1.8 μm, 4.6 Ч 15 mm, PN 821975-932), solvent water–acetonitrile mixture (95 : 5), 0.1% of aqueous trifluoroacetic acid; eluent flow 3 mL min^{-1}; injection volume 1 μL; UV detecting at 215, 254, 265 nm; chemical ionization at atmospheric pressure (APCI), scan range *m*/*z* 80–1000. Elemental analysis was performed in the Institute of Bioorganic Chemistry and Petrochemistry of National Academy of Sciences of Ukraine. Melting points were measured on a Fisher-Johns apparatus. Optical rotation was determined on a MCP 300 polarimeter (Anton Paar GmbH). The reaction progress and purity of the synthesized compounds were monitored by TLC using Silufol UV-254 plates (dichloromethane–methanol, 98 : 2) detecting with UV irradiation.

1-Acylamino-2,2-dichloroacrylonitriles **Ia** and **Ib** were synthesized by the method described in [16]. Ethyl 1-benzoylamino-2,2-dichloroacrylate **IV** was

Table 3. Parameters of ^{13}C and ^{31}P NMR spectra of compounds **III**, **V**, **VII** and **VIII**

Comp. no.	δ_C, ppm	δ_P, ppm
IIIa	160.98 ($C^5_{oxazole}$), 149.78 d ($C^2_{oxazole}$), 117.12 (C≡N), 82.07 ($C^4_{oxazole}$), 71.83, 71.50, 70.26, 69.83, 63.38 (COH), 54.15 and 37.17 (NC), 13.21 (CH_3)	–
IIIb	160.81 ($C^5_{oxazole}$), 149.38 d ($C^2_{oxazole}$), 130.18, 129.17, 125.87, 125.22 (C_6H_5), 118.13 (C≡N), 84.09 ($C^4_{oxazole}$), 71.65, 71.55, 70.38, 70.08, 63.43 (COH), 54.49 and 37.44 (NC)	–
V	161.94 (C=O), 159.54 ($C^5_{oxazole}$), 148.41 ($C^2_{oxazole}$), 129.67, 129.05, 126.64, 125.11 (C_6H_5), 105.49 ($C^4_{oxazole}$), 71.95, 71.56, 70.66, 70.12, 63.45 (COH), 59.40 (O<u>C</u>H_2CH_3), 55.46 and 37.32 (NC), 14.56 ($OCH_2\underline{C}H_3$)	–
VIIa	161.52 d ($C^5_{oxazole}$, $^2J_{PC}$ 38.4 Hz), 141.44 d ($C^2_{oxazole}$, $^3J_{PC}$ 21.9 Hz), 96.38 d ($C^4_{oxazole}$, $^1J_{PC}$ 256.3 Hz), 71.98, 71.48, 70.76, 69.99, 63.44 (COH), 61.74 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.5 Hz), 55.17 and 38.70 (NC), 16.10 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.5 Hz)	14.53
VIIb	161.74 d ($C^5_{oxazole}$, $^2J_{PC}$ 37.4 Hz), 149.76 d ($C^2_{oxazole}$, $^3J_{PC}$ 22.4 Hz), 96.84 d ($C^4_{oxazole}$, $^1J_{PC}$ 225.8 Hz), 72.02, 71.51, 70.72, 70.01, 63.47 (COH), 61.59 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.5 Hz), 55.30 and 38.59 (NC), 16.18 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.0 Hz), 13.19 (CH_3)	14.61
VIIc	161.26 d ($C^5_{oxazole}$, $^2J_{PC}$ 38.4 Hz), 149.54 d ($C^2_{oxazole}$, $^3J_{PC}$ 22.4 Hz), 129.51, 129.07, 126.66, 124.91 (C_6H_5), 98.67 d ($C^4_{oxazole}$, $^1J_{PC}$ 254.6 Hz), 71.81, 71.56, 70.89, 70.24, 63.52 (COH), 61.89 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.0 Hz), 55.31 and 39.08 (NC), 16.22 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.5 Hz)	14.30
VIId	167.12 (C=O), 161.91 d ($C^5_{oxazole}$, $^2J_{PC}$ 37.4 Hz), 146.90 d ($C^2_{oxazole}$, $^3J_{PC}$ 21.9 Hz), 134.88, 131.53 and 123.49(C_{arom}), 97.01 d ($C^4_{oxazole}$, $^1J_{PC}$ 255.8 Hz), 72.09, 71.48, 70.68, 69.96, 63.47 (COH), 61.74 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.0 Hz), 55.21 and 38.73 (NC), 34.27 (CH_2), 15.96 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.5 Hz)	13.49
VIIe	167.55 (C=O), 162.03 d ($C^5_{oxazole}$, $^2J_{PC}$ 37.4 Hz), 149.93 d ($C^2_{oxazole}$, $^3J_{PC}$ 21.9 Hz), 134.59, 131.58 and 123.19(C_{arom}), 96.45 d ($C^4_{oxazole}$, $^1J_{PC}$ 253.3 Hz), 72.09, 71.50, 70.83, 69.99, 63.45 (COH), 61.51 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.0 Hz), 55.41 and 38.75 (NC), 35.15 and 26.15 ($2CH_2$), 16.02 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.5 Hz)	14.26
VIII	161.62 d ($C^5_{oxazole}$, $^2J_{PC}$ 37.4 Hz), 151.31 d ($C^2_{oxazole}$, $^3J_{PC}$ 22.4 Hz), 96.76 d ($C^4_{oxazole}$, $^1J_{PC}$ 256.8 Hz), 72.00, 71.50, 70.76, 69.99, 63.41 (COH), 61.63 d (PO<u>C</u>H_2CH_3, $^2J_{PC}$ 5.0 Hz), 55.27 (CH_2), 54.97 and 38.49 (NC), 29.89 (CH_2), 16.14 d ($POCH_2\underline{C}H_3$, $^3J_{PC}$ 6.5 Hz)	14.15

prepared as described in [18]. Diethyl 1-acylamino-2,2,2-trichloroethylphosphonates **VIa**–**VIe** were synthesized according to the procedures in [23, 25].

2-R-5-{Methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-1,3-oxazole-4-carbonitriles (IIIa, IIIb). To a solution of 0.01 mol of dichloroacrylonitrile **I** in 50 mL of methanol was added 0.035 mol of *N*-methyl-D-glucamine. The mixture was stirred for 12 h at a temperature of 22–25°C. The precipitated *N*-methyl-D-glucamine hydrochloride was filtered off. After removing the solvent, 20 mL of acetonitrile was added and the mixture was refluxed for 3–5 min. The resulting precipitate was filtered off, the solvent was removed in vacuum, and compound **III** was analyzed without further purification.

Ethyl 5-{methyl[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-2-phenyl-1,3-oxazole-4-carboxylic acid (V). To a solution of 0.01 mol of compound **IV** in 50 mL of methanol was added 0.035 mol of *N*-methyl-D-glucamine. The mixture was stirred for 78 h at 22–25°C. The precipitated *N*-methyl-D-glucamine hydrochloride was filtered off. After removing the solvent, 25 mL of dichloromethane, the insoluble *N*-methyl-D-glucamine hydrochloride was filtered off. The solvent was removed in a vacuum, and compound **V** was analyzed without further purification.

Diethyl 2-R-5-{methyl-[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-1,3-oxazol-4-phosphonates (VIIa–VIIe). To a solution of 0.01 mol of compound **VI** in 50 mL of methanol was added 0.045 mol of *N*-methyl-D-glucamine. The mixture was stirred for 6–12 h at a temperature of 18–25°C. The precipitated *N*-methyl-D-glucamine hydrochloride was filtered off. After the solvent removal, 20 mL of tetrahydrofuran was added to oily residue. The precipitate was filtered off, the solvent was removed in a vacuum, and the reaction products **VIIa**–**VIIc** were analyzed without further purification. Compounds **VIId** and **VIIe** were purified by column chromatography (dichloromethane–methanol, 95 : 5).

Diethyl 2-(2-aminoethyl)-5-{methyl-[(2*R*,3*S*,4*S*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]amino}-1,3-oxazol-4-ylphosphonate (VIII). A mixture of 0.01 mol of compound **VIIe**, 0.02 mol of hydrazine hydrate, and 20 mL of ethanol was stirred at 22–25°C for 12 h. The precipitated phthalazide was filtered off and the solvent was removed in a vacuum. Compound **VIII** was analyzed without further purification.

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