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To the 80th Anniversary of B.I. Ionin

Synthesis of 2-Substituted 3,4-Bis(diethoxyphosphorylmethyl)furans

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Abstract—Bromination of ethyl 4-(diethoxyphosphorylmethyl)-5-methylfuran-2-carboxylate and 4-(diethoxyphosphorylmethyl)-5-methylfuran-2-carbonitrile with *N*-bromosuccinimide followed by phosphorylation via the Arbuzov reaction have yielded the corresponding 2-substituted 4,5-bis(diethoxyphosphorylmethyl)furans. Synthesis and transformations of bisphosphorylated 2-furoic acid and its derivatives are described.

Keywords: diphosphonate, synthesis, 2,4,5-substituted furan, furancarboxylic acid derivative

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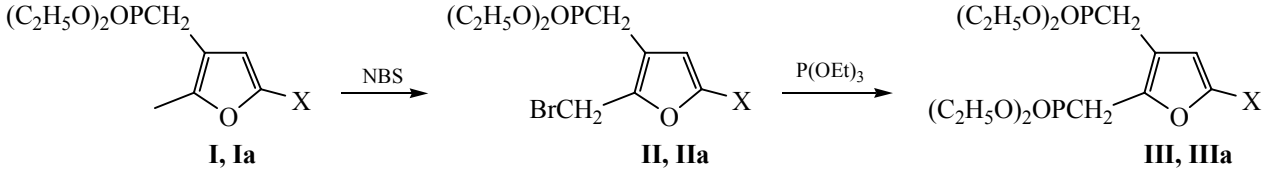
Aromatic and heteroaromatic compounds containing two fragments of phosphonic acid have been widely studied as inhibitors of various enzymes; affecting the exchange processes during osteoporosis treatment is among the major fields of interest [1]. Diphosphonates are known to inhibit pyrophosphatase-induced ion transfer as well [2]. Diphosphonates bearing imidazole, pyridine, or benzofuran rings or diphenyl moieties bound to these nitrogen-containing heterocycles inhibit enzymes involved in isoprenoids synthesis [3]. In view of the above, bisphosphonic acid derivatives of furans are promising as inhibitors and ion carriers. These with adjacent methanephosphonic substituents in the furan ring are of special interest due to the possible chelating effect.

In this work we present and discuss methods of synthesis and chemical transformations of 2-substituted 4,5-bis(diethoxyphosphorylmethyl)furans. Preparation of non-substituted tetraalkyl bisphosphonate was reported earlier [4], but its chemical properties were not studied.

Dialkyl (2-methyl-5-ethoxycarbonylfur-3-yl)- and (2-methyl-5-cyanofur-3-yl)methanephosphonates **I** and **Ia** were used as starting compounds. Their bromination with *N*-bromosuccinimide led to 2-bromomethyl derivatives **II** and **IIa**; the products were phosphorylated with triethyl phosphite under the conditions of Arbuzov reaction to give diphosphonates **III** and **IIIa** in the 94% and 92% yield, respectively. The prepared diphosphonates were viscous syrup-like liquids not crystallizing within several months and decomposing upon heating in vacuum below their boiling points (≈200°C) (Scheme 1).

^{31}P NMR spectra of compounds **III** and **IIIa** each contained a pair of signals of interacting phosphorus

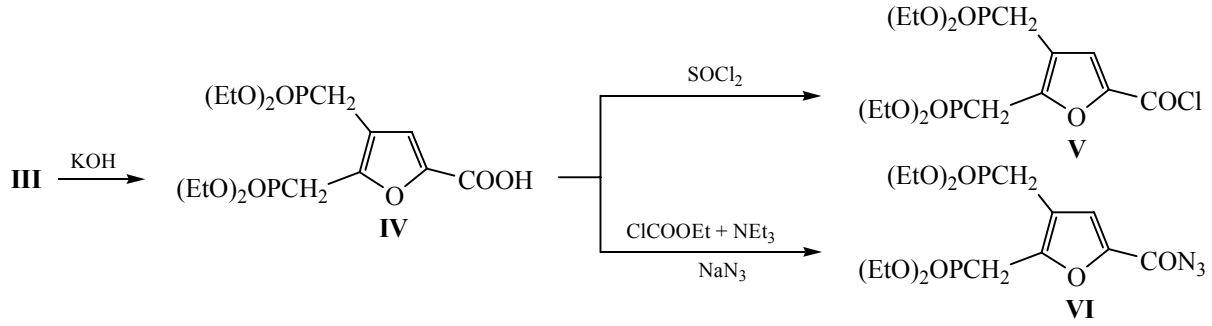
Scheme 1.



I, Ia **II, IIa** **III, IIIa**

X = COOEt (**I, II, III**); CN (**Ia, IIa, IIIa**).

Scheme 2.



atoms [**III**: δ_P, ppm: 21.74 (P^4), 25.78 (P^5), J_{PP} 13.9 Hz; **IIIa**: δ_P, ppm: 21.06 (P^4), 25.04 (P^5), J_{PP} 13.4 Hz]. Signals of carbon atoms in positions 4 and 5 of the furan ring were also split due to the interactions with the both phosphorus atoms. In both cases $^2J_{PC} = {}^3J_{PC}$ but the splitting constants were different for the carbon atoms [**III**: δ_C, ppm: 114.90 (C^4, $^2J_{PC} = {}^3J_{PC}$ = 8.7 Hz), 147.93 (C^5, $^2J_{PC} = {}^3J_{PC}$ = 11.0 Hz); **IIIa**: δ_C, ppm: 111.76 (C^4, $^2J_{PC} = {}^3J_{PC}$ = 8.6 Hz), 149.51 (C^5, $^2J_{PC} = {}^3J_{PC}$ = 11.2 Hz].

The reaction of compound **III** with the ethanol solution of potassium hydroxide proceeded as saponification of the ester group while the phosphonate groups remained intact. The reaction was complete at the KOH : the ester molar ratio of no less than 1.5 yielding 98% of the acid **IV**. Coupling constant between the phosphorus atoms J_{PP} of 13.8 Hz was observed in ^{31}P NMR spectra of the product. Similarly to compound **III,** the coupling constants for C^4 and C^5 carbon atoms in ^{13}C NMR spectra of the acid **IV** were different (C^4, $^2J_{PC} = {}^3J_{PC}$ = 8.6 Hz; C^5, $^2J_{PC} = {}^3J_{PC}$ = 11.1 Hz) (Scheme 2).

Acid **IV** was converted to acid chloride **V** in 86% yield via refluxing with thionyl chloride in benzene in the presence of DMF during 7 h. Compound **V** was a syrup-like liquid not crystallizing on storage. The reaction proceeded selectively involving the carboxyl group whereas the phosphonate fragments were stable under the reaction conditions. Coupling between the phosphorus atoms with J_{PP} 13.2 Hz was observed in ^{31}P NMR spectra of the acid chloride **V**. ^{13}C NMR spectrum revealed different coupling constants for C^4 and C^5 carbon atoms (C^4, $^2J_{PC} = {}^3J_{PC}$ = 8.3 Hz; C^5, $^2J_{PC} = {}^3J_{PC}$ = 10.8 Hz).

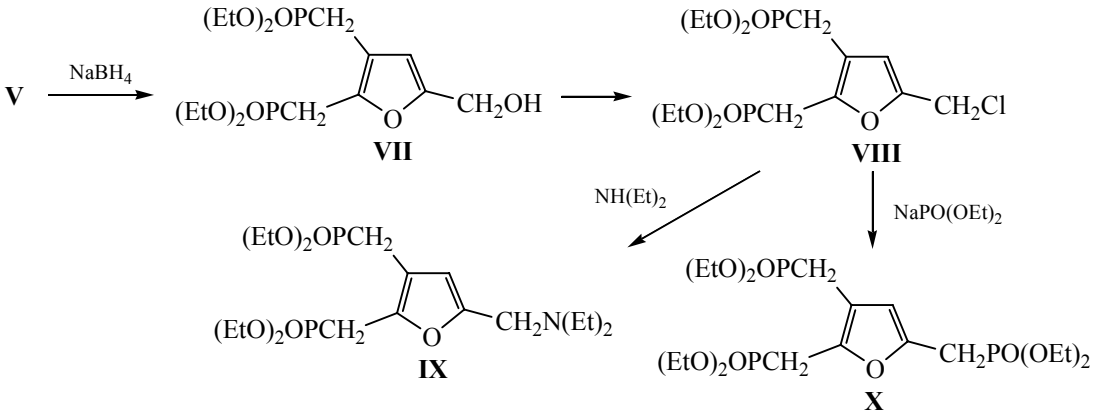
The acid **IV** was converted to acyl azide **VI** as described elsewhere [5]. Treating of acetone solution of compound **IV** with ethyl chloroformate in the presence of triethylamine upon ice bath cooling led to mixed anhydride of monocarbonate and furoic acid which was further involved in the reaction with saturated aqueous solution of sodium azide without isolation. After decomposition of the reaction mixture with icy water a yellow syrup-like liquid was isolated via extraction with ethyl acetate. IR spectrum of the product contained a band at 2147 cm^{-1} characteristic of azide group was observed. The product structure was further confirmed with the ^{1}H, ^{13}C, and ^{31}P NMR data.

Azide **VI** was stable within several days at room temperature, but decomposed upon heating to give a complex mixture of products. IR spectrum of the mixture showed an absorption band at 2226 cm^{-1} assigned to isocyanate, but its concentration was too low to detect a signal of H^3 proton of the isocyanate furan ring (about 6.0 ppm [5]). ^{13}C NMR spectrum of the major decomposition products contained several signals of the carbonyl carbon bound to the furan ring at 159–163 ppm. Hence, the Curtius rearrangement was not the major pathway of the acyl azide **VI** transformation.

Reduction of acid chloride **V** with sodium borohydride gives corresponding alcohol **VII** in 58% yield. Reaction was carried out according to the description in [6] in DMF–dioxane mixture. Similarly to the case of monophosphonates, diethoxyphosphorylmethyl group was not involved in the reaction.

The prepared alcohol **VII** was light-yellow syrup-like liquid not crystallizing upon storage and decomposing below its boiling point in the course of vacuum distillation. ^{1}H NMR spectrum of compound **VII** contained a signal of hydroxymethyl group at 4.45 ppm. Signal of the corresponding carbon atom was registered in the ^{13}C NMR spectrum at 56.97 ppm. Coupling constant between the phosphorus atoms J_{PP} was up to 15.5 Hz. The $^2J_{PC}$ and $^3J_{PC}$ coupling

Scheme 3.



constants were equal in the cases of both C^4 (9.0 Hz) and C^5 (12.1 Hz) carbon atoms retained.

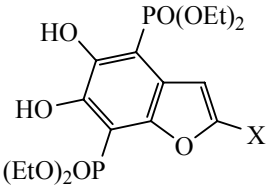
Treatment with thionyl chloride and pyridine in methylene chloride at room temperature led to conversion of phosphorylated alcohol **VII** into the chloride **VIII** in 76% yield. The latter was much more stable in the presence of acidic agents as compared with furfuryl chloride and diethyl (5-chloromethylfur-2-yl)methanephosphonate [7]. The presence of chloromethyl group in compound **VIII** was confirmed by a signal at 4.50 ppm in the ^{1}H NMR spectrum. Signal of the corresponding carbon atom was observed at 29.65 ppm in the ^{13}C NMR spectrum. The coupling constant corresponding to the phosphorus atoms interaction was of J_{PP} 14.9 Hz. Signals of C^4 and C^5 carbon atoms appeared as triplets with the coupling constants of 9.1 and 11.6 Hz, respectively. Hence, equality of $^2J_{PC}$ and $^3J_{PC}$ coupling constants was preserved.

The chloride **VIII** was introduced in reactions with selected N- and P-nucleophiles. In particular, diethylamine was used as N-nucleophile. Alkylation was carried out in benzene at the chloride : amine molar ratio 1 : 4.6 during 9 h at 70°C. Yield of aminodiphosphonate **IX** was of 52%. The product was viscous oil readily soluble in ethyl acetate, chloroform, and benzene. We failed to obtain its crystalline hydrochloride or picrate. The product structure was confirmed by NMR spectroscopy data. In the ^{1}H NMR spectrum, signals of diethylaminomethyl group were observed at 1.05 ppm (CH_3, J_{HH} 6.8 Hz), 2.50 ppm (CH_2N, J_{HH} 6.8 Hz), and 3.59 ppm (furan–CH_2N). In the ^{13}C NMR spectrum, that group gave rise to the signals at 11.88 ppm (CH_3), 46.70 ppm (CH_2–ethyl), and 48.68 ppm (furan–CH_2N). Signals of C^4 and C^5 carbon atoms were triplets with the coupling constants of 9.2 Hz and 11.9 Hz, respectively. Doublets of phosphorus nuclei in the ^{31}P NMR spectrum were observed at 23–27 ppm, the coupling constant J_{PP} being of 15.5 Hz.

The Michaelis–Becker reaction between the chloride **VIII** and sodium diethyl phosphite (benzene, 80°C, 8.5 h) led to formation of the triphosphonate **X** in 45% yield. The product was viscous syrup-like liquid readily soluble in common organic solvents and poorly soluble in water. To the best of our knowledge, that compound was the first example of a furan derivative containing three phosphorus atoms in a molecule. Its ^{31}P NMR spectrum contained three signals: at 22.82 ppm (d, P^5, $J_{P^2P^5}$ 9.0 Hz), 23.54 ppm (d.d, P^2, $J_{P^2P^5}$ 9.0 Hz, $J_{P^2P^3}$ 15.6 Hz), and 26.62 ppm (d, P^3, $J_{P^2P^3}$ 15.6 Hz). Hence, the coupling between phosphorus nuclei could be observed through five as well as six bonds when phosphorus-containing groups were located in positions 2 and 5 of furan ring. The ^{13}C NMR signal of the C^2 carbon atom of compound **X** at 142.41 ppm was broadened, and we failed to evaluate the coupling constants J_{PC}. Other carbon atom signals were as follows: C^3 at 113.37 ppm, triplet of doublets with $^2J_{P^3C} = {}^3J_{P^2C}$ = 9.1 Hz, and $^4J_{P^5C}$ = 2.6 Hz; C^4 at 111.60 ppm, triplet with $^3J_{P^3C} = {}^3J_{P^5C}$ = 3.1 Hz; and C^5 at 144.55 ppm, doublet of doublets with $^2J_{P^5C}$ = 8.1 Hz and $^4J_{P^2C}$ = 3.0 Hz. The presented example demonstrated that the presence of two coupling phosphorus atoms (P–CH_2–C=C–CH_2–P) significantly increased the $^2J_{PC}$ and $^3J_{PC}$ values (Scheme 3).

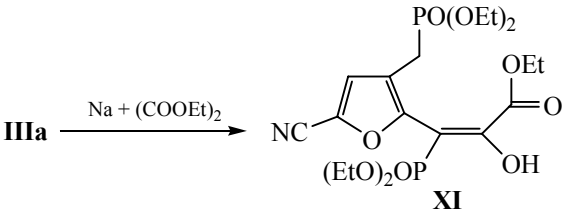
Diethoxyphosphorylmethyl group at the furan ring bearing an electron-accepting substituent exhibits significant CH-acidity and may participate in the Claisen condensation with ethyl formate and diethyl

oxalate in the presence of sodium foil [8]. In view of that, we introduced diphosphonates **III** and **IIIa** in that reaction. It was expected that the both methylene groups would take part in condensation to form phosphorylated derivatives of dihydroxybenzofuran.



The reaction was carried out in toluene according to the protocol [8] at varied ratio of diethyl oxalate to sodium foil and the process temperature. The conversion of diphosphonate **III** was as low as about 10% yielding a complex mixture of phosphonates and phosphates, and we failed to isolate the individual products.

On the contrary, the reaction of bisphosphorylated nitrile **IIIa** with diethyl oxalate was noticeably exothermal. The conversion of compound **IIIa** reached 88% at the phosphonate : sodium : oxalate molar ratio of 1 : 1.1 : 1.2. The diethoxyphosphorylmethyl group at position 5 of the furan ring was exclusively involved in the reaction. The condensation product was partially hydrolyzed during extraction of the reaction mixture with water (about 50% of the final product was converted back into diphosphonate **IIIa**). ^{1}H NMR spectrum of the condensation product contained a broad exchange signal at 9.18 ppm evidencing of the enol form of the compound present in the solution. The ^{13}C NMR spectrum contained the signals assigned to P–C= fragment of the side chain (90.26 ppm, $^{1}J_{PC}$ 181.9 Hz), =C–OH fragment (160.81 ppm, $^{2}J_{PC}$ 22.3 Hz), and carbonyl group (163.93 ppm, $^{3}J_{PC}$ 8.8 Hz). The spectral parameters coincided with the data from [8]; the condensation product was identified as enol **XI** with *trans*-location of carboxyl and phosphoryl groups with respect to the double bond.



XI

The signal of P^{5} atom was observed at 20.03 ppm and that of P^{4} was found at 25.17 ppm in ^{31}P NMR spectrum of compound **XI**, the J_{P4P5} value being of 6.5 Hz, two times lower than in the cases of other prepared diphosphonates. Similarly to the other diphosphonates, the $^{2}J_{PC}$ and $^{3}J_{PC}$ values of C^{4} as well as C^{5} carbon atoms of the furan ring were equal (6.5 Hz and 11.0 Hz, respectively).

To conclude, introduction of second diethoxyphosphorylmethyl group at the furan ring significantly altered the properties of the studied furan compounds. Thermal stability of 2-hydroxymethyl- and 2-chloromethyl derivatives increased, whereas thermal stability of the acylazide significantly decreased; the latter derivative practically did not participate in the Curtius rearrangement. 2,3-Bis(diethoxyphosphorylmethyl)furans were much weaker CH-acids than the monophosphonates. Methylene group in β-position of the furan ring was not involved in the Claisen condensation even if the molecule was activated with cyanide electron-accepting group.

Phosphorus atoms of the studied compounds could magnetically interact via 5 or 6 bonds. The coupling constants $^{5}J_{PP}$ were of 13–16 Hz for diethoxyphosphorylmethyl groups in the positions 2 and 3. If methylene group in the position 2 was substituted with a double bond conjugated with the furan ring, $^{5}J_{PP}$ value decreased to 6.5 Hz. $^{2}J_{PC}$ and $^{3}J_{PC}$ of carbon atoms in α- and β-positions of the furan ring were pairwise equal; therefore, the corresponding signals appeared as triplets in the ^{13}C NMR spectra. The mentioned constants of C^{2} carbon atom were significantly higher than for the C^{3} atom. Hence, polarization of π-electronic system of the furan ring caused by the presence of oxygen led to anisotropy of the magnetic interaction.

EXPERIMENTAL

^{1}H, ^{31}P, and ^{13}C NMR spectra were registered with a Bruker DPX-400 spectrometer (400.13, 161.97, and 100.16 MHz, respectively) (solution in $CDCl_3$). IR spectra were registered with a Shimadzu 8400S spectrometer (KBr pellets).

Diethyl (2-bromomethyl-5-ethoxycarbonylfur-3-yl)methanephosphonate (II). 3.0 g of *N*-bromosuccinimide and 0.15 g of azobisisobutyronitrile were added upon stirring to a solution of 4.6 g of diethyl (2-methyl-5-ethoxycarbonylfur-3-yl)methanephosphonate in 70 mL of carbon tetrachloride. The mixture was heated until the exothermic reaction started at 78–80°C. After the completion of heat evolution, the reaction

mixture was refluxed upon stirring during 3 h until disappearance of *N*-bromosuccinimide crystals. The reaction mixture was cooled to room temperature, and succinimide was filtered off. After removal of the solvent, the residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of the target product 5.6 g (97%), light-brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.25 t (6H, CH_3-phosphonate, J_{HH} 7.0 Hz), 1.31 t (3H, CH_3-ester, J_{HH} 7.0 Hz), 2.93 d (2H, CH_2P, J_{PH} 20.8 Hz), 4.04 m (4H, CH_2OP, J_{PH} 14.0 Hz, J_{HH} 7.0 Hz), 4.30 q (2H, $\underline{CH_2}OC$, J_{HH} 7.0 Hz), 4.51 s (2H, CH_2Br), 7.09 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 14.24 (CH_3-ester), 16.34 d (CH_3-phosphonate, $^3J_{PC}$ 5.5 Hz), 20.56 (CH_2Br), 23.29 d (CH_2P, $^1J_{PC}$ 142.9 Hz), 61.15 (CH_2O), 62.44 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 116.35 d (C^3-furan, $^3J_{PC}$ 9.4 Hz), 120.33 d (C^4-furan, $^3J_{PC}$ 2.7 Hz), 144.09 (C^5-furan), 151.34 d (C^2-furan, $^3J_{PC}$ 10.3 Hz), 158.21 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 24.29.

Diethyl (2-bromomethyl-5-cyanofur-3-yl)methanephosphonate (IIa) was prepared similarly from 2.8 g of diethyl (2-methyl-5-cyanofur-3-yl)methanephosphonate, 50 mL of carbon tetrachloride, 2.2 g of *N*-bromosuccinimide, and 0.11 g of azobisisobutyronitrile. Yield 3.5 g (96%), light-brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.24 t (6H, CH_3-phosphonate, J_{HH} 7.2 Hz), 2.92 d (2H, CH_2P, J_{PH} 20.8 Hz), 4.04 m (4H, CH_2OP, J_{PH} 14.4 Hz, J_{HH} 7.2 Hz), 4.45 s (2H, CH_2Br), 7.05 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.36 d (CH_3-phosphonate, $^3J_{PC}$ 5.6 Hz), 19.57 (CH_2Br), 23.04 d (CH_2P, $^1J_{PC}$ 143.1 Hz), 62.58 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 110.90 (CN), 116.02 d (C^3-furan, $^3J_{PC}$ 9.4 Hz), 124.65 d (C^4-furan, $^3J_{PC}$ 3.0 Hz), 125.57 (C^5-furan), 152.65 d (C^2-furan, $^3J_{PC}$ 10.4 Hz). ^{31}P NMR spectrum, δ_P, ppm: 24.60.

Ethyl 4,5-bis(diethoxyphosphorylmethyl)furan-2-carboxylate (III). A mixture of 16.9 g of bromide **II** and 8.2 mL of triethyl phosphite was heated upon vigorous stirring. Distillation of ethyl bromide started at 110°C. The reaction mixture was gradually heated up to 155°C (evolution of ethyl bromide was complete) and then incubated during 2–3 min at 155–160°C. Total reaction time was of 7–8 min. After removal of excess of triethyl phosphite and diethyl ethanephosphonate [bp 25–43°C (1 mmHg)], the residue was incubated in vacuum (1 mmHg) during 30 min at 45–50°C. Yield 18.0 g (94%), light-brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.17–1.28 m (15H, CH_3-ethyl), 2.95 d (2H, CH_2P^4, J_{PH} 20.0 Hz), 3.30 d (2H, CH_2P^5, J_{PH} 21.2 Hz), 3.94–4.03 m (8H, CH_2OP), 4.22 q (2H, $\underline{CH_2}OC$, J_{HH} 7.2 Hz), 7.05 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 14.18 (CH_3-ester), 16.15d (CH_3-phosphonate, $^3J_{PC}$ 5.6 Hz), 16.20 d (CH_3-phosphonate, $^3J_{PC}$ 6.0 Hz), 22.73 d (CH_2P^4, $^1J_{PC}$ 142.4 Hz), 25.57 d (CH_2P^5, $^1J_{PC}$ 141.0 Hz), 60.72 ($\underline{CH_2}OC$), 62.15 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 62.48 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 114.90 t (C^4-furan, $^2J_{P4C}$ 9.4 Hz, $^3J_{P5C}$ 9.4 Hz), 120.60 (C^3-furan), 147.93 t (C^5-furan, $^3J_{P4C}$ 11.0 Hz, $^2J_{P5C}$ 11.0 Hz), 149.30 d (C^2-furan, $^4J_{P(5)}$ 2.8 Hz), 158.21 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 21.74 d (P^5), 25.78 d (P^4), $^5J_{PP}$ 13.9 Hz.

4,5-Bis(diethoxyphosphorylmethyl)-2-cyanofuran (IIIa) was prepared similarly from 3.8 g of bromide **IIa** and 4.0 mL of triethyl phosphite. Yield 3.6 g (92%), yellowish brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.18–1.23 m (12H , CH_3-ethyl), 2.94 d.d (2H, CH_2P^4, J_{P4H} 20.4 Hz, J_{P5H} 2.2 Hz), 3.28 d.d (2H, CH_2P^5, J_{P4H} 21.2 Hz, J_{P5H} 1.6 Hz), 3.95–4.04 m (8H, CH_2OP), 7.02 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.25 d (CH_3-phosphonate, $^3J_{PC}$ 6.6 Hz), 16.31 d (CH_3-phosphonate, $^3J_{PC}$ 6.6 Hz), 22.52 d (CH_2P^4, $^1J_{PC}$ 142.7 Hz), 25.65 d (CH_2P^5, $^1J_{PC}$ 141.5 Hz), 62.29 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 62.61 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 111.17 (CN), 114.76 t (C^4-furan, $^2J_{P4C}$ 8.6 Hz, $^3J_{P5C}$ 8.6 Hz), 124.79, 124.83 (C^3-furan, C^2-furan), 149.51 t (C^5-furan, $^3J_{P4C}$ 11.2 Hz, $^2J_{P5C}$ 11.2 Hz). ^{31}P NMR spectrum, δ_P, ppm: 21.06 d (P^5), 25.04 d (P^4), $^5J_{PP}$ 14.0 Hz.

4,5-Bis(diethoxyphosphorylmethyl)-2-furoic acid (IV). A solution of 4.7 g of diphosphonate **III** in 15 mL of ethanol was added upon stirring to a solution of 0.9 g of potassium hydroxide in 5 mL of ethanol. The reaction mixture was refluxed during 5 h and then evaporated to dryness. The residue was dissolved in 25 mL of water; the solution was washed with 8 mL of diethyl ether, saturated with sodium chloride, and acidified with concentrated sulfuric acid to pH 2–3. The oil-like substance was extracted with chloroform (3 × 10 mL) and dried over sodium sulfate. After removal of the solvent the residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of compound **IV** 4.3 g (98%), brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.15–1.24 m (12H, CH_3-ethyl), 2.96 d (2H, CH_2P^4, J_{PH} 20.4 Hz), 3.30 d (2H, CH_2P^5, J_{PH} 20.8 Hz), 3.96–4.12 m (8H, CH_2OP), 7.01 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.14 d (CH_3-phosphonate, $^3J_{PC}$ 6.1 Hz), 16.23 d (CH_3-phosphonate, $^3J_{PC}$ 6.2 Hz), 22.60 d (CH_2P^4, $^1J_{PC}$ 142.3 Hz), 25.45 d (CH_2P^5, $^1J_{PC}$ 141.1 Hz), 62.43 d (CH_2OP, $^2J_{PC}$ 5.9 Hz), 62.73 d (CH_2OP, $^2J_{PC}$ 6.3 Hz),

114.64 t (C^4-furan, $^2J_{P4C}$ 8.6 Hz, $^3J_{P5C}$ 8.6 Hz), 120.51 (C^3-furan), 143.34 (C^2-furan), 147.74 t (C^5-furan, $^3J_{P4C}$ 11.4 Hz, $^2J_{P5C}$ 11.4 Hz), 158.21 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 22.18 d (P^5), 26.11 d (P^4), $^5J_{PP}$ 14.1 Hz.

4,5-Bis(diethoxyphosphorylmethyl)-2-furoic acid chloride (V). 3 mL of thionyl chloride and 4 drops of DMF were added upon stirring to a solution of 4.2 g of the acid **IV** in 40 mL of benzene. The reaction mixture was refluxed during 7 h, volatile substances were distilled off, and the residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield 3.8 g (86%), brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.26 t (12H, CH_3-ethyl, J_{HH} 7.2 Hz), 3.04 d.d (2H, CH_2P^4, J_{P4H} 20.8 Hz, J_{P5H} 1.2 Hz), 3.33 d (2H, CH_2P^5, J_{PH} 20.8 Hz), 4.01–4.19 m (8H, CH_2OP), 7.42 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.25 d (CH_3-phosphonate, $^3J_{PC}$ 6.0 Hz), 16.36 d (CH_3-phosphonate, $^3J_{PC}$ 5.8 Hz), 22.74 d (CH_2P^4, $^1J_{PC}$ 142.6 Hz), 26.09 d (CH_2P^5, $^1J_{PC}$ 140.0 Hz), 62.48 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 62.85 d (CH_2OP, $^2J_{PC}$ 6.4 Hz), 116.93 t (C^4-furan, $^2J_{P4C}$ 8.3 Hz, $^3J_{P5C}$ 8.3 Hz), 127.34 (C^3-furan), 144.35 d (C^2-furan, $^4J_{P5C}$ 2.7 Hz), 152.98 t (C^5-furan, $^3J_{P4C}$ 10.8 Hz, $^2J_{P5C}$ 10.8 Hz), 154.77 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 20.72 d (P^5), 25.10 d (P^4), $^5J_{PP}$ 13.3 Hz.

4,5-Bis(diethoxyphosphorylmethyl)-2-furoyl-azide (VI). 1.3 mL of triethylamine was added to a solution of 3.5 g of the acid **IV** in 30 mL of acetone, and then a solution of 0.8 g of ethyl chloroformate in 5 mL of acetone was added dropwise upon vigorous stirring at 2–3°C. The mixture was stirred at that temperature during 1.5 h; then saturated solution of 1.2 g of sodium azide in water was added at 2–3°C, and the resulting mixture was incubated at that temperature during 5 h, poured in 100 mL of water, and extracted with ethyl acetate (3 × 30 mL). The extract was dried over sodium sulfate, and the solvent was removed. The residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of compound **VI** 3.4 g (91%), light-brown oil. IR spectrum, ν, cm^{-1}: 2148 (C–N_3). ^{1}H NMR spectrum, δ, ppm: 1.23–1.27 m (12H, CH_3-ethyl), 3.02 d.d (2H, CH_2P^4, J_{P4H} 20.4 Hz, J_{P5H} 2.0 Hz), 3.37 d (2H, CH_2P^5, J_{P4H} 1.0 Hz, J_{P5H} 21.4 Hz), 3.99–4.07 m (8H, CH_2OP), 7.18 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.26 d (CH_3-phosphonate, $^3J_{PC}$ 6.0 Hz), 16.36 d (CH_3-phosphonate, $^3J_{PC}$ 5.8 Hz), 22.77 d (CH_2P^4, $^1J_{PC}$ 142.2 Hz), 25.90 d (CH_2P^5, $^1J_{PC}$ 140.6 Hz), 62.24 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 62.63 d (CH_2OP, $^2J_{PC}$ 6.5 Hz), 116.02 t (C^4-furan, $^2J_{P4C}$ 8.5 Hz, $^3J_{P5C}$ 8.5 Hz), 122.97 (C^3-furan), 143.98 (C^2-furan), 150.61 t (C^5-furan, $^3J_{P4C}$ 10.8 Hz, $^2J_{P5C}$ 10.8 Hz), 161.87 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 21.25 d (P^5), 25.40 d (P^4), $^5J_{PP}$ 13.6 Hz.

4,5-Bis(diethoxyphosphorylmethyl)fur-2-ylmethanol (VII). A solution of 3.7 g of acid chloride **V** in 15 mL of dioxane was added dropwise upon stirring at 30–40°C to a solution of 0.5 g of sodium borohydride in 20 mL of DMF; the reaction mixture was stirred during 7 h at 90°C, left overnight, and then acidified with 10% acetic acid to pH 4–5. Volatile compounds were distilled off on a rotary evaporator. The residue was treated with 15 mL of water; the mixture was saturated with sodium chloride and extracted with benzene (4 × 15 mL). The extract was dried over sodium sulfate, and the solvent was removed. The residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of compound **VII** 2.0 g (58%), brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.22–1.27 m (12H, CH_3-ethyl), 2.92 d.d (2H, CH_2P^4, J_{P4H} 20.4 Hz, J_{P5H} 2.4 Hz), 3.33 d.d (2H, CH_2P^5, J_{P4H} 2.0 Hz, J_{P5H} 20.4 Hz), 3.99–4.08 m (8H, CH_2OP), 4.45 s (2H, CH_2OH), 6.23 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.29 d (CH_3-phosphonate, $^3J_{PC}$ 5.2 Hz), 16.75 d (CH_3-phosphonate, $^3J_{PC}$ 5.6 Hz), 22.30 d (CH_2P^4, $^1J_{PC}$ 142.9 Hz), 25.09 d (CH_2P^5, $^1J_{PC}$ 142.3 Hz), 56.97 (CH_2OH), 62.16 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 62.43 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 110.66 (C^3-furan), 112.75 t (C^4-furan, $^2J_{P4C}$ 9.0 Hz, $^3J_{P5C}$ 9.0 Hz), 142.48 t (C^5-furan, $^3J_{P4C}$ 12.1 Hz, $^2J_{P5C}$ 12.1 Hz), 153.65 (C^2-furan). ^{31}P NMR spectrum, δ_P, ppm: 23.43 d (P^5), 26.73 d (P^4), $^5J_{PP}$ 15.5 Hz.

2-Chloromethyl-4,5-bis(diethoxyphosphorylmethyl)furan (VIII). 0.25 mL of pyridine and 0.2 mL of thionyl chloride were sequentially added to a solution of 1.0 g of alcohol **VII** in 20 mL of methylene chloride. The reaction mixture was incubated at 20°C during 24 h, sequentially washed with water, saturated aqueous sodium hydrocarbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. After removal of the solvent, the residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of chloride **VIII** 0.8 g (76%), light-brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.23–1.31 m (12H, CH_3-ethyl), 2.96 d.d (2H, CH_2P^4, J_{P4H} 20.4 Hz, J_{P5H} 2.0 Hz), 3.28 d (2H, CH_2P^5, J_{P5H} 20.8 Hz), 4.0–-4.09 m (8H, CH_2OP), 4.50 s (2H, CH_2Cl), 6.36 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 16.36 br.s (CH_3-phosphonate), 22.85 d (CH_2P^4, $^1J_{PC}$ 142.5 Hz), 25.31 d (CH_2P^5, $^1J_{PC}$ 141.8 Hz), 29.65 (CH_2Cl), 62.10 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 62.40 d (CH_2OP, $^2J_{PC}$ 6.6 Hz), 113.09 (C^3-furan), 113.52 t (C^4-

furan, $^{2}J_{P^4C}$ 9.1 Hz, $^{3}J_{P^5C}$ 9.1 Hz), 144.27 t (C^5-furan, $^{3}J_{P^4C}$ 11.6 Hz, $^{2}J_{P^5C}$ 11.6 Hz), 148.89 d (C^2-furan, $^{4}J_{P^5C}$ 3.2 Hz). ^{31}P NMR spectrum, δ_P, ppm: 22.74 d (P^5), 26.39 d (P^4), $^{5}J_{PP}$ 14.9 Hz.

2-(*N,N*-Diethylaminomethyl)-4,5-bis(diethoxyphosphorylmethyl)furan (IX). A mixture of 0.7 g of chloride **VIII**, 0.8 mL of diethylamine, and 10 mL of benzene was heated upon stirring at 70°C during 9 h, cooled to room temperature, and washed with a solution of 2 mL of concentrated hydrochloric acid in 15 mL of water. The water extract was treated with sodium carbonate to pH 10 and saturated with sodium chloride; the isolated oil was extracted with chloroform (3 × 15 mL). The extract was dried over sodium sulfate, and the solvent was evaporated. The residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of amine **IX** 0.4 g (52%), light-brown oil. ^{1}H NMR spectrum, δ, ppm: 1.05 t (6H, CH_3-amine, J_{HH} 6.8 Hz), 1.24–1.30 m (12H, CH_3-ethyl), 2.50 q (4H, CH_2N-ethyl, J_{HH} 6.8 Hz), 2.97 d.d (2H, CH_2P^4, J_{P^4H} 20.4 Hz, J_{P^5H} 2.6 Hz), 3.27 d.d (2H, CH_2P^5, J_{P^4H} 2.0 Hz, J_{P^5H} 20.8 Hz), 3.59 s (2H, furan-CH_2N), 4.00–4.09 m (8H, CH_2OP), 6.18 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: 11.86 (CH_3-amine), 16.35 d (CH_3, $^{3}J_{PC}$ 5.2 Hz), 16.41 d (CH_3, $^{3}J_{PC}$ 5.2 Hz), 22.94 d (CH_2P^4, $^{1}J_{PC}$ 142.9 Hz), 25.21 d (CH_2P^5, $^{1}J_{PC}$ 142.4 Hz), 46.70 (CH_2N-ethyl), 48.68 (furan-CH_2N), 62.01 d (CH_2OP, $^{2}J_{PC}$ 6.4 Hz), 62.19 d (CH_2OP, $^{2}J_{PC}$ 6.4 Hz), 111.98 (C^3-furan), 112.54 t (C^4-furan, $^{2}J_{P^4C}$ 9.2 Hz, $^{3}J_{P^5C}$ 9.2 Hz), 142.23 t (C^5-furan, $^{3}J_{P^4C}$ 11.9 Hz, $^{2}J_{P^5C}$ 11.9 Hz), 151.17 (C^2-furan). ^{31}P NMR spectrum, δ_P, ppm: 23.41 d (P^5), 26.83 d (P^4), $^{5}J_{PP}$ 15.5 Hz.

2,3,5-Tris(diethoxyphosphorylmethyl)furan (X). A solution of 1.0 g of chloride **VIII** in 5 mL of benzene was added to a solution of sodium diethyl phosphite (prepared from 0.1 g of sodium and 0.8 mL of diethyl hydrogen phosphite in 10 mL of benzene). The mixture was refluxed upon stirring at 80°C during 8.5 h, then diluted with 20 mL of benzene, and washed consequently with 10 mL of water and 10 mL of saturated aqueous solution of sodium chloride. The organic layer was dried over sodium sulfate, and the solvent was evaporated. The residue was incubated in vacuum (1 mmHg) at room temperature during 1 h. Yield of trisphosphonate 0.6 g (45%), light-brown syrup. ^{1}H NMR spectrum, δ, ppm: 1.23–1.30 m (16H, CH_3-ethyl), 2.96 d.d (2H, CH_2P^3, J_{P^3H} 20.4 Hz, J_{P^2H} 2.6 Hz), 3.15 br.d (2H, CH_2P^2, J_{P^2H} 20.0 Hz), 3.25 d (2H, CH_2P^5, J_{P^5H} 20.4Hz), 4.00–4.11 m (12H, CH_2OP), 6.24 d (1H, H^4-furan, J_{P^5H} 2.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.35 d (CH_3, $^{3}J_{PC}$ 4.6 Hz), 16.40 d (CH_3, $^{3}J_{PC}$ 4.7 Hz), 22.95 d (CH_2P^3, $^{1}J_{PC}$ 142.7 Hz), 25.16 d (CH_2P^2, $^{1}J_{PC}$ 145.2 Hz), 26.61 d (CH_2P^5, $^{1}J_{PC}$ 145.1 Hz), 62.02 d (CH_2OP, $^{2}J_{PC}$ 6.6 Hz), 62.16 d (CH_2OP, $^{2}J_{PC}$ 8.0 Hz), 62.23 d (CH_2OP, $^{2}J_{PC}$ 4.8 Hz), 62.28 d (CH_2OP, $^{2}J_{PC}$ 5.7 Hz), 111.60 d (C^4-furan, $^{3}J_{P^5C}$ 3.1 Hz), 113.37 d.t (C^3-furan, $^{3}J_{P^2C}$ 9.1 Hz, $^{2}J_{P^3C}$ 9.1 Hz, $^{4}J_{P^5C}$ 2.6 Hz), 142.41 br.s (C^2-furan), 144.55 d.d (C^5-furan, $^{2}J_{P^5C}$ 9.1 Hz, $^{4}J_{P^2C}$ 3.0 Hz). ^{31}P NMR spectrum, δ_P, ppm: 22.82 d (P^5, $^{6}J_{P^2P^5}$ 9.0 Hz), 23.15 d.d (P^2, $^{5}J_{P^2P^3}$ 15.6 Hz, $^{6}J_{P^2P^5}$ 9.0 Hz), 26.62 d (P^3, $^{5}J_{P^2P^3}$ 15.6 Hz).

Reaction of 4.5-bis(diethoxyphosphorylmethyl)-2-cyanofuran (IIIa) with diethyl oxalate. 0.2 g of freshly prepared sodium foil was added upon vigorous stirring to a solution of 2.6 g of diphosphonate **IIIa** and 1.0 mL of diethyl oxalate in 30 mL of toluene. The reaction mixture was gradually heated from 19 to 38°C and then cooled back. The reaction mixture was stirred during 4 h until complete dissolution of sodium and left overnight. Then the mixture was extracted with water (4 × 20 mL); the extract was washed with 10 mL of diethyl ether, saturated with sodium chloride, and acidified with concentrated hydrochloric acid to pH 3–4. The obtained oil was extracted with ethyl acetate (2 × 15 mL), the extract was dried over sodium sulfate, and the solvent was removed. The residue was incubated in vacuum (1 mmHg) at room temperature during 1 h to give 1.4 g of a mixture of diphosphonates **IIIa** and **XI** in the 1 : 1.2 molar ratio according to NMR data. ^{1}H NMR spectrum, δ, ppm: common signals**:** 1.27–1.39 m (CH_3-ethyl), 4.06–4.20 m (CH_2OP); **IIIa:** 3.05 d.d (2H, CH_2P^4, J_{P^4H} 20.4 Hz, J_{P^5H} 2.2 Hz), 3.38 d.d (2H, CH_2P^5, J_{P^4H} 21.2 Hz, J_{P^5H} 1.6 Hz), 7.09 br.s (1H, H^4-furan); **XI:** 2.90 d.d (2H, CH_2P^4, J_{P^4H} 21.2 Hz, J_{P^5H} 2.2 Hz), 4.34 q (2H, CH_2OC, J_{HH} 7.0 Hz), 7.26 br.s (1H, H^4-furan). ^{13}C NMR spectrum, δ_C, ppm: common signals**:**, 16.07 d (CH_3, $^{3}J_{PC}$ 6.9 Hz), 16.27 d (CH_3, $^{3}J_{PC}$ 5.9 Hz), 16.33 d (CH_3, $^{3}J_{PC}$ 5.8 Hz), 62.76 d (CH_2OP, $^{2}J_{PC}$ 7.2 Hz), 63.11 d (CH_2OP, $^{2}J_{PC}$ 6.8 Hz), 63.63 d (CH_2OP, $^{2}J_{PC}$ 5.5 Hz), 63.86 d (CH_2OP, $^{2}J_{PC}$ 5.6 Hz), 64.11 d (CH_2OP, $^{2}J_{PC}$ 5.9 Hz), 64.33 d (CH_2OP, $^{2}J_{PC}$ 6.9 Hz); **IIIa:** 22.48 d (CH_2P^4, $^{1}J_{PC}$ 143.7 Hz), 25.60 d (CH_2P^5, $^{1}J_{PC}$ 142.4 Hz), 111.11 (CN), 114.65 t (C^4-furan, $^{2}J_{P^4C}$ 9.3 Hz, $^{3}J_{P^5C}$ 9.3 Hz), 125.09, 125.38 (C^3-furan, C^2-furan), 149.28 t (C^5-furan, $^{3}J_{P^4C}$ 11.0 Hz, $^{2}J_{P^5C}$ 11.0 Hz); **XI:** 13.61 (CH_3), 22.82 d (CH_2P^4, $^{1}J_{PC}$ 144.8 Hz), 62.86 (CH_2O), 90.26 d (P^5–C=, $^{1}J_{PC}$ 181.9 Hz), 111.28 (CN), 116.55 t (C^4-furan, $^{2}J_{P^4C}$ 6.5 Hz, $^{3}J_{P^5C}$ 6.5 Hz),

124.27, 124.76 (C^3-furan, C^2-furan), 149.28 t (C^5-furan, $^3J_{P^4C}$ 11.0 Hz, $^2J_{P^5C}$ 11.0 Hz), 160.81 d (=C–O, $^2J_{PC}$ 22.3 Hz), 163.93 d (C=O, $^3J_{PC}$ 8.8 Hz). ^{31}P NMR spectrum, δ_P, ppm: **IIIa:** 21.29 d (P^5), 25.27 d (P^4), $^5J_{PP}$ 13.8 Hz; **XI:** 20.03 d (P^5), 25.17 d (P^4), $^5J_{PP}$ 6.5 Hz.

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