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Synthesis and Selected Reactions of 4-(Diethoxyphosphorylmethyl)-3-furoic Acid

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Abstract—Reduction of 4-(ethoxycarbonyl)-3-furoyl chloride with sodium borohydride in dioxane–DMF mixture leads to an ethyl 4-hydroxymethylfuran-3-carboxylate. The treatment of the latter with thionyl chloride at boiling yields the corresponding chloromethyl derivative. The obtained chloride reacts with one equivalent of sodium iodide in acetone at room temperature to form iodomethylfuran. Halomethylfurans synthesized are phosphorylated with sodium diethyl phosphite and triethyl phosphite to give ethyl 4-(diethoxyphosphoryl-methyl)-3-carboxylate. The hydrolysis of this substance with one equivalent of potassium hydroxide in ethanol gives the corresponding furoic acid. Treating this substance in succession with ethyl chloroformate and sodium azide yields furoyl azide which while heating in toluene undergoes rearrangement to phosphorus-containing 3-furylisocyanate. Heating the latter with a mixture of acetic acid and acetic anhydride gives *N*-[4-(di-ethoxyphosphorylmethyl)furyl-3]acetamide. 4-(Diethoxyphosphorylmethyl)-3-furoic acid reacts with thionyl chloride to form the corresponding furoyl chloride. Its reduction with sodium borohydride in dioxane–DMF mixture leads to the phosphorylated 3-furylmethanol. Aminomethylation of its acetate with dimethyl-methyleneiminium chloride in acetonitrile does not proceed at the ring. Instead of that the unstable ester of 3-(di-methylamino)propionic acid and the phosphorylated 3-furylmethanol are formed. In slightly basic medium free Mannich base decomposed to give the starting acetate.

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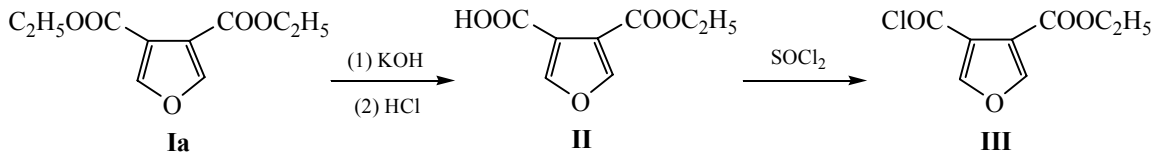
3,4-Bisfunctionalized derivatives of furan with unoccupied positions 2 and 5 of the ring still remain the most difficultly available compounds in the furan series. At the same time just the compounds with such type of substitution are structural fragments of natural bioregulators. For example, biosynthesis of cellulose and callose is regulated with the derivatives of 3-furylmethanol [1]. 3-Mono- and 3,4-disubstituted furyl fragments are present in quinolizidine alkaloids of nufaridine series [2] and in the terpenoids of sea organisms [3]. In connection with that the development of strategy for the synthesis of 3-substituted furans containing pharmacophore phosphoryl group in the position 4 of the ring seems actual and promising.

One of the versions to solve this problem may be the transformation of functions in the series of compounds synthesized from the relatively available dialkyl 3,4-furyldicarboxylates **I**.

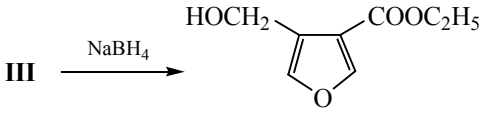
By selective hydrolysis of diethyl ester **Ia** according to the procedure [4] we have prepared monoester **II**. Treating the latter with thionyl chloride in benzene in the presence of DMF gave furoyl chloride **III**.



Ia **II** **III**

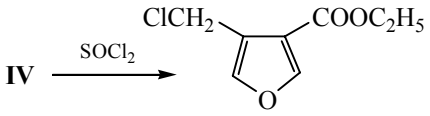
For the reduction of this substance to alcohol we used the recently developed procedure [5]. The reaction was carried out in dioxane–DMF mixture at 80–85°C. Sodium borohydride was used as the reducing agent. After decomposition of the reaction mixture with diluted acetic acid and extraction with

benzene the target alcohol **IV** was isolated by a vacuum distillation in 69% yield. Details of the procedure and spectral characteristics of the product are presented in Experimental.



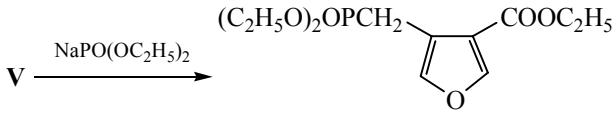
IV

Compound **IV** was boiled with thionyl chloride in benzene in the presence of DMF to form chloride **V**. The alternative procedure using thionyl chloride and pyridine common in the furan series did not provide a sufficient conversion of alcohol to chloride. Yield of compound **V** was 78%, bp 76°C (1 mm Hg).



V

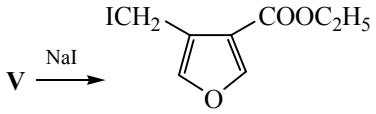
The phosphorylation of chloride **V** was carried out with sodium diethyl phosphite under the conditions of the Michaelis–Becker reaction in benzene at 80°C in the course of 18 h. It occurred that besides nucleophilic substitution sodium diethyl phosphite took part in some other unestablished transformations. Due to that at the complete consumption of the phosphorylating agent the conversion of chloride **V** was 60%, and the yield of phosphonate **VI** was 50% calculated on the consumed chloromethyl derivative. The reaction mixture was separated by vacuum distillation collecting the fractions with bp 75–78°C (1 mm Hg) and 156°C (1 mm Hg). The details of the experiment and spectral characteristics of phosphonate **VI** are presented in Experimental.



VI

Low reactivity of chloride **V** in phosphorylation compelled us to look for a more active alkylating agent. It was found that under the conditions of Finkelstein reaction compound **V** undergoes a quantitative exchange of chlorine for iodine in the course of one day under the action of sodium iodide dihydrate in acetone at room temperature in the absence of light.

Similarly to the other iodomethylfurans compound **VII** easily liberates iodine at elevated temperature. It is

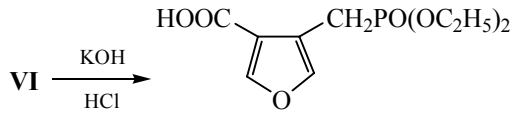


VII

a colorless oil which crystallizes at 6–7°C. In its ^{1}H NMR spectrum the singlet of iodomethyl group protons is observed at 4.50 ppm, while the signal of chloromethyl group protons in starting compound **V** is located at 4.68 ppm. Signals of the other protons in the compounds under consideration are practically identical.

The phosphorylation of iodide **VII** was carried out with small excess of triethyl phosphite (1.2 mol/mol). While mixing the reagents at room temperature the formation of crystals belonging probably to quasiphosphonium salt was observed. Its decomposition with the liberation of ethyl iodide began only at heating the reaction mixture above 110°C, and the reaction completed at 155°C. In the course of the vacuum distillation of reaction mixture a considerable amount of diethyl ethylphosphonate was collected, and the target product **VI** was obtained in 39% yield. The still contained significant amount of non-melting and insoluble polymer formed evidently in the course of thermal decomposition of the iodide.

The hydrolysis of the carboxylic ester group of phosphonate **VI** was carried out with 1 mol of potassium hydroxide in ethanol according to the procedure [6]. Yield of the acid **VIII** was 82%, white crystals with mp 101-102°C. Details of the procedure and spectral characteristics of the products are presented in Experimental.



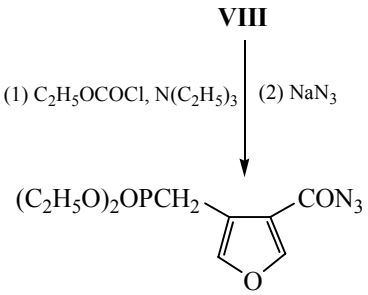
VIII

Hence, phosphorus-containing 3-furoic acid **VIII** occurred to be a relatively available substance which can be exposed to further transformations. First of all it should involve the carboxy group because it opens a pathway to a series of 3-functionalyzed 4-diethoxyphosphorylmethylfurans. As it was mentioned above, these compounds are promising from the point of view of the search for the biologically active structures.

First direction we studied was the conversion of acid **VIII** to acylazide **IX.**

The latter compound is interesting from two points of view. First of all, the azide-based synthesis of amides is considered the best for conserving the optical purity while acylation of chiral amines [7]. Thus the natural amino acids and peptides can be modified by introduction of pharmacophoric phosphorus-containing furyl fragment without the distortion of their structure. Another interesting pathway is the introduction of azide **IX** in Curtius rearrangement leading to the corresponding phosphorus-containing isocyanate [6], the starting substance for preparing 3-acylaminofurans.

The synthesis of acylazide **IX** was carried out according to the procedure [6] including the formation of mixed anhydride of the furoic and carbonic acids and treating it with sodium azide.

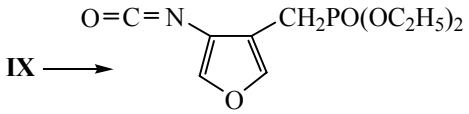


IX

Compound **IX** is a light brown oil stable at room temperature and soluble in common organic solvents. Its ^{i}H NMR spectrum contains the signals of diethoxyphosporylmethyl group and the furan ring protons. Their position is almost the same as in the ester **VI** and the acid **VIII**. A specific spectral feature of the azide **IX** is the high value of the remote coupling constant between the phosphorus nucleus and the H^5 proton of the furan ring ($^4J_{PH}$ 4 Hz) and also the revealing of coupling between H^2 and H^5 protons of the furan ring (J_{HH} ~ 1Hz). The chemical shift of phosphorus in this substance is 25.392 ppm which is characteristic of furylmethylphosphonates. Chemical shifts of carbon atoms in ^{13}C NMR spectrum of ester **VI**, acid **VIII**, and azide **IX** do not differ significantly, but the remote J_{PC} constants in the azide are larger and are resolved better. For example, in the ester **VI** $^2J_{PC^4}$ is 6.4 Hz, $^3J_{PC^3}$ 3.9 Hz, and $^3J_{PC^5}$ is not observed. In the azide **IX** the values of these constants are 7.5, 4.5, and 6.8 Hz respectively.

In the ^{1}H NMR spectrum of azide **IX** signals of impurities at 7.17–7.24 and 7.41–7.44 ppm are present. We failed to remove these admixtures using methods which do not cause the destruction of the target product. The detailed description of the process and spectral characteristics of the product are given in Experimental.

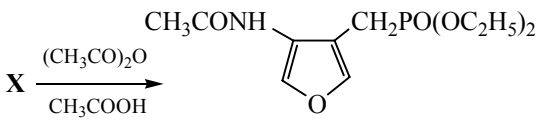
After refluxing the solution of azide **IX** in toluene for 3 h NMR spectra of the isolated preparation show striking changes. In the ^{1}H NMR spectrum the signal of PCH_2 protons undergoes upfield shift by 0.44 ppm, and the signals of the furan ring protons, by 0.20 ppm (H^5) and 0.66 ppm (H^2). The latter two signals overlap and form one broadened signal at 7.44 ppm. Hence, the character of spectral changes shows that electron-donating substituent appears in the position 3 of the furan ring. Analogous changes we observed recently while investigating Curtius rearrangement of the other (diethoxyphosphorylmethyl)furoyl azides [6]. In the ^{13}C NMR spectrum of compound under consideration the signals of carbon atoms of diethoxyphosphopyl-methyl group are located on their usual places, the signal of C^4 atom is shifted from 115.37 ppm ($^2J_{CP}$ 7.5 Hz) to 112.85 ppm ($^2J_{CP}$ 7.6 Hz), the signal of C^3 carbon atom practically does not shift (119.35 ppm in azide, 119.90 ppm in the product), but the coupling constant increases from 4.5 to 6.5 Hz. The signal of C^5 carbon atom shifts from 143.64 to 139.53 ppm, and $^2J_{CP}$ increases from 6.8 to 11.7 Hz. The signal of C^2 atom also shifts from 149.58 ppm to 141.22 ppm. The signal of the catbonyl carbon atom of the product is observed at 124.74 ppm characteristic of the isocyanate group [9]. Hence, the mentioned spectral alterations show that in the course of heating azide **IX** rearranges to isocyanate **X**.



X

The obtained isocyanate is a viscous light brown oil soluble in chloroform and aromatic hydrocarbons. The detailed description of compound **X** is given in Experimental.

Heating isocyanate **X** with a mixture of acetic acid and acetic anhydride in dioxane for 4 h leads to the formation of acetamide **XI**.



XI

In the ^{1}H NMR spectrum of this product signals of diethoxyphosphorylmethyl group protons are located on their usual place, a singlet of acetamide methyl group is observed at 2.17 ppm, and the furan ring protons give signals at 7.20 ppm (H^5, J_{PH} 4 Hz) and 7.29 ppm (H^2). The broad signal of the NH proton is observed at 8.10 ppm. Details of the experiment and spectral characteristics of the product **XI** are given in Experimental.

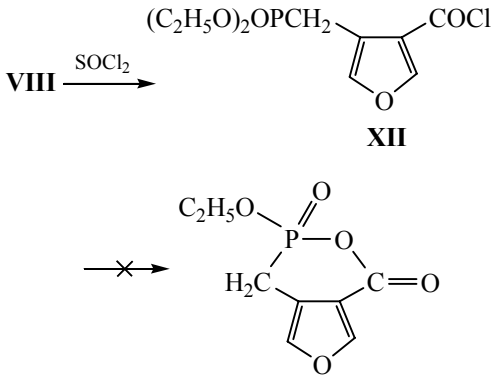
Amide **XI** is rather labile. In a free state it is a glass-like mass which does not change at room temperature for a week, but in ethyl acetate and ethanol solutions it decomposes with the formation of nonstudied products.

Another interesting direction of transformations of acid **VIII** includes the synthesis of acid chloride and its reduction to the corresponding 3-furylmethanol. This pathway is important because by this procedure it is possible to prepare the phosphorylated analog of aglycone, the regulator of biosynthesis of cellulose in higher plants [1].

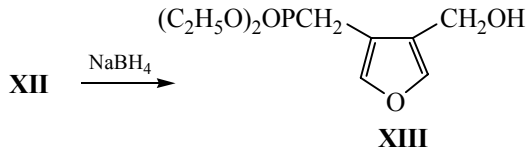
The synthesis of acid chloride **XII** was carried out by treating acid **VIII** with thionyl chloride in benzene in the presence of DMF according to the procedure [5] at 80°C for 4 h. The obtained substance is a light brown oil soluble in hydrocarbons and chlorinated hydrocarbons. In the ^{13}C NMR spectrum the carbon atoms of compound **XII** give signals at 115.247 ppm (C^4), 123.466 ppm (C^3), 144.292 ppm (C^5), 153.674 (C^2), and 165.285 ppm (COCl). Besides, one more set of signals with significantly weaker intensity including four singlets at 118.368 ppm (C^3), 142.826 ppm (C^5), 146.930 ppm (C^2), and 150.499 ppm (C=O) was observed. Considering the shift of the carbonyl carbon atom [8] these signals may be attributed to the anhydride of acid **VIII**. ^{1}H NMR spectrum contains only one set of signals of the corresponding protons. Evidently, the chemical shifts of protons in acid chloride and in the anhydride are the same.

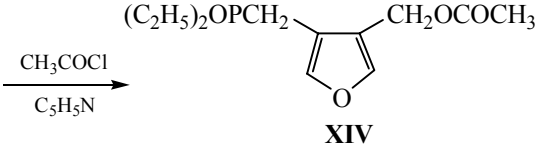
Acid chloride **XII** may be distilled in a vacuum [bp 145–146 (1 mm Hg)], but in the course of distillation a decomposition takes place, and the preparation obtained contains more admixtures than that isolated directly from the reaction mixture.

No traces of cyclization with the formation of oxaphosphorine heterocycle characteristic of 2,3-disubstituted (diethoxyphosphorylmethyl)furoyl chlorides [5] were found.



The reduction of acid chloride **XII** with sodium borohydride in DMF–dioxane mixture at 80°C according to the procedure [5] leads to phosphorylated 3-furylmethanol **XIII**. The admixture of carboxanhydride does not affect the reaction. Alcohol **XIII** is an oil stable at room temperature but decomposing in the course of vacuum distillation. Similarly to the previously studied cases [5] the phosphorus-containing fragment does not react with the reducing agent.





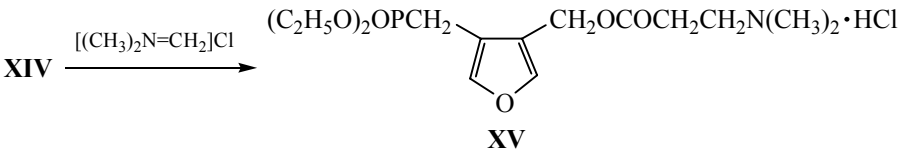
Compound **XIII** has two weak electron-acceptor substituents in the positions 3 and 4 of the furan ring while two highly reactive positions 2 and 5 are not occupied. In connection with that it was interesting from the theoretical and the practical point of view to establish in which position will enter the substituent in such compounds in the course of electrophilic substitution reactions. The signal of H^2 and H^5 protons are well distinguishable spectroscopically, and the first of them is a doublet with J_{PH} 4.4 Hz. Due to that it is easy to establish the reaction site.

As a model reaction we have chosen amino-methylation by dimethylmethyleneimmonium chloride which we previously studied rather thoroughly on the other phosphorus-containing derivatives of furan [9, 10]. In its course a tertiary amine salt is formed which can be easily separated from the non-polar starting substance and reliably identified by the signals of the methyl and methylene groups adjacent to the nitrogen atom.

Hydroxy-containing compounds cause alcoholysis of aminomethylating agent, and due to that the hydroxy group must be protected. To this purpose we have acetylated alcohol **XIII** by acetyl chloride in the presence of pyridine in ethyl acetate at room temperature. The reaction proceeded quantitatively, and no admixture of starting alcohol was found in acetate **XIV**. The product obtained occurred to be an oil stable at room temperature and containing only insignificant amount of spectroscopically distinguishable admixtures. The vacuum distillation of acetate **XIV** proceeds with decomposition [bp 152°C (1 mm Hg)], and the preparation obtained is more contaminated than the compound isolated directly from the reaction mixture.

The aminomethylation of acetate **XIV** was carried out in acetonitrile at 80°C for 10 h. After removing the solvent a syrup was obtained. It was well soluble in chloroform and water, but insoluble in diethyl ether which permitted the removal of the traces of non-reacted compound **XIV**. After removing the solvent a light yellow glass-like hydrochloride was obtained which we failed to crystallize.

Its ^{1}H NMR spectrum contained the signals of protons of phosphorus-containing residue and the furan protons H^2 and H^5. Their intensity ratio showed that the furan ring does not take part in the reaction. The signal of the methylene group $C(O)OCH_2$-furan was observed at 4.92 ppm characteristic of the ester fragment. The singlet of the methyl group protons of acetoxy residue was absent. The intense singlet at 2.59 ppm was attributed to the protons of $(CH_3)_2N$ fragment. In the spectral range 2.68–2.82 ppm where two triplets of $C(O)CH_2CH_2N$ group could be expected a complex multilet was observed instead. The monitoring of proton signals in this range showed that the shape of the multiplet changed in time, and in the other spectral ranges signals of admixtures began to appear. We suggest that the reaction of acetate **XIV** with dimethylmethyleneiminium chloride proceeds at the methyl group of acetoxy fragment to give the unstable β-aminoester **XV**.



XV

^{13}C NMR spectrum of the product formed contained the signals of phosphorus-containing fragment (16.103 ppm, CH_3-ethyl; 61.929 ppm, CH_2OP; 21.582 ppm, $^1J_{CP}$ 102.7 Hz, CH_2P), of the ester methylene group (56.204 ppm, $C(O)OCH_2$-furan), of the furan ring carbon atom (see Experimental), and of the carbonyl group (170.305 ppm). The signal at 29.096 ppm we attributed to the carbon atoms of $N(CH_3)_2$·HCl group [8, 11], and the signals at 34.552 ppm and 42.524 ppm, to the carbon atoms of the methylene groups $CH_2C(O)O$ and CH_2N respectively. The calculation of the chemical shift values for these carbon atoms by the additive scheme [8] gave δ_C values 37.0 and 42.5 ppm confirming the correctness of the attribution.

Hence, it follows from the spectral data that the aminomethylation of phosphonate **XIV** proceeds not at the furan ring, but at the protective group.

In order to prepare purer sample of amine **XV** we tried to isolate the free Mannich base. With this purpose water solution of hydrochloride synthesized was treated with sodium carbonate to pH 9 and the isolated oil was extracted with methylene chloride. After drying over sodium sulfate, removing the solvent, and keeping in a vacuum (1 mm Hg) at room temperature a brown oil was obtained. Its ^{1}H NMR spectrum showed that its main component was acetate **XIV**. The elimination of dimethylamine leading to the corresponding acrylate could be also expected, but no signals of olefin protons were observed. Hence, in basic medium Mannich base splits into the starting components. Another typical reaction pathway including elimination of dimethylamine and the formation of a double C=C bond does not take place.

Summarizing the results obtained it should be noted that the synthetic procedure for preparing 4-halomethyl derivatives of alkyl 3-furoates is developed and their phosphorylation under the conditions of the Arbuzov and the Michaelis–Becker reactions is studied. It is found that alkaline hydrolysis of obtained phosphonocarboxylic acid ester proceeds selectively at the carboxy group.

The acid obtained was used as the starting substance for preparing a large set of 3-functionalyzed 4-(diethoxyphosphorylmethyl)furans. It was found that in all cases the phosphorus-containing group was not affected.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker DPX-400 spectrometer (400.131 MHz), ^{13}C NMR spectra, on a Bruker DPX-400 (100.615 MHz) and Bruker DPX-300 (75.47 MHz) spectrometers, ^{31}P NMR spectra, on a Bruker AC-200 (81.014 MHz) instrument. All spectral studies were carried out in deuterochloroform.

Ethyl 4-hydroxymethyl-3-furoate (IV). To a suspension of 11.3 g of sodium borohydride in 120 ml of DMF a solution of 30.3 g of acid chloride **III** in 120 ml of dioxane was added dropwise with stirring at 45–50°C (reaction temperature was maintained by cooling with water). After the addition was complete the obtained mixture was stirred for 9 h at 80–85°C, cooled to room temperature, and decomposed with an excess of 20% acetic acid. Volatile substances were removed at a reduced pressure, and the syrup formed was dissolved in 60 ml of water and 3 times extracted with benzene. The obtained solution was dried over sodium sulfate and distilled in a vacuum to give 17.2 g (69%) of compound **IV**, bp 92°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.336 t (CH_3-ethyl, J_{HH} 7.6 Hz); 4.304 q (CH_2OOC, J_{HH} 7.6 Hz); 7.368 s (H^5-furan); 7.951 s (H^2-furan).

Ethyl 4-chloromethyl-3-furoate (V). To a solution of 17.2 g of alcohol **IV** in 50 ml of benzene 11 ml of thionyl chloride was added dropwise with stirring and cooling with water. After that 3 drops of DMF were added. After the completion of the intense gas evolution the obtained mixture was refluxed for 6 h. Then it was cooled, washed with water, with sodium bicarbonate solution, once more with water, and dried over sodium sulfate. The vacuum distillation gave 15.4 g (78%) of chloride **V**, bp 78°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.328 t (CH_3-ethyl, J_{HH} 7.2 Hz); 4.290 q (CH_2OCO, J_{HH} 7.2 Hz); 4.683 s (CH_2Cl); 7.424 s (H^5-furan); 7.975 s (H^2-furan).

Ethyl 4-iodomethyl-3-furoate (VII). Sodium iodide dehydrate, 6 g, was dissolved in 70 ml of acetone, and 5.1 g of chloride **V** was added to it dropwise. The obtained mixture was kept for a day protected from light and moisture, and then it was poured in a solution of 2 g of sodium sulfite in 100 ml of water. The target product was extracted with chloroform and dried over sodium sulfate. The solvent was distilled off at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Compound **VII**, 7.5 g (99%) was obtained, mp 6–7°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 t (CH_3-ethyl, J_{HH} 8 Hz); 4.34 q (CH_2O, J_{HH} 8 Hz); 4.50 s (CH_2J); 7.54 s (H^5-furan); 7.99 s (H^2-furan). While heating compound **VII** decomposes with the liberation of iodine, and while handling on light it becomes yellow.

Ethyl 4-(diethoxyphosphorylmethyl)-3-furoate (VI). *a. Michaelis-Becker reaction*. To a solution of sodium diethyl phosphite prepared from 1.9 g of sodium and 11.2 g of diethyl hydrogen phosphite in 60 ml of benzene 15.4 g of chloride **V** was added, and the mixture obtained was refluxed with stirring for 18 h. After that it was cooled, diluted with 50 ml of benzene, washed with water (2×30 ml), and dried over sodium sulfate. The solvent was removed at a reduced pressure, and the residue was distilled in a vacuum. Fractions of chloride **V** with bp 75–78°C (1 mm Hg), 6.1 g, and 7.2 g of phosphonate **VI** with bp 156°C (1 mm Hg) were obtained. The conversion of chloride **V** was 60%, and the yield of phosphonate **VI** with respect to the consumed chloride 50%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.236 t (CH_3-ethyl of phosphonate, J_{HH} 7.0 Hz); 1.304 t (CH_3-ethyl of carboxylate, J_{HH} 7.0 Hz); 3.401 d (CH_2P, J_{HP} 21.2 Hz); 4.038 m (CH_2OP, J_{HH} 7.0 Hz, J_{HP} 15.0 Hz); 4.354 q (CH_2OOC, J_{HH} 7.0 Hz); 7.467 br.s (H^5-furan); 7.927 s (H^2-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.082 (CH_3-carboxylate); 16.123 (CH_3-phosphonate); 20.839 d (CH_2P, $^1J_{CP}$ 142.0 Hz); 60.061 (CH_2OC); 61.790 (CH_2OP); 125.200 d (C^4-furan, $^2J_{CP}$ 6.7 Hz); 118.335 d (C^3-furan, $^3J_{CP}$ 3.9 Hz); 142.738 (C^5-furan); 148.206 (C^2-furan); 163.013 (C=O). ^{31}P NMR spectrum: δ_P 325.419 ppm.

b. Arbuzon reaction. A mixture of 7.5 g of iodomethylfuran **VII** and 5.5 ml of triethyl phosphite was heated with stirring. The liberation of ethyl iodide began at 110°C, and at 155°C the reaction completed. Total reaction time was 30 min. The distillation of the reaction mixture yielded 3.0 g (39%) of phosphonate **VI**, bp 146–150°C (0.9 mm Hg). Spectral characteristics of the compound obtained were identical to the above-presented data. In the course of distillation some amount of compound with bp 50–58°C (0.9 mm Hg) was isolated which was identified as diethyl ethylphosphonate.

4-(Diethoxyphosphorylmethyl)-3-furoic acid (VIII). To a solution of 1.2 g of potassium hydroxide in 40 ml of ethanol 5.7 g of ester **VI** was added in one portion, and the reaction mixture was refluxed with stirring until establishing pH 8. The mixture obtained was evaporated to dryness at a reduced pressure, the residue was dissolved in 15 ml of water, washed with 10 ml of diethyl ether, and acidified with hydrochloric acid to pH 3. The obtained mixture was saturated with sodium chloride and extracted with chloroform. The extract was dried over sodium sulfate, chloroform was distilled off at a reduced pressure, and the residue was triturated with hexane. The obtained crystals were filtered off and dried in air until the constant mass. Yield 4.2 g (82%), mp 101–102°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.271 t (CH_3-ethyl, J_{HH} 7.2 Hz); 3.382 d (CH_2P, J_{PH} 20.6 Hz); 4.042 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.6 Hz); 7.491 br.s (H^5-furan); 8.006 s (H^2-furan); 8.945 br.s (COOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.131 (CH_3-ethyl); 20.739 d (CH_2P, $^1J_{PC}$ 140.5 Hz); 62.342 (CH_2OP); 115.062 (C^4-furan); 118.321 (C^3-furan); 142.809 (H^5-furan); 149.161 (H^2-furan); 166.016 (C=O). ^{31}P NMR spectrum: δ_P 25.954 ppm.

4-(Diethoxyphosphorylmethyl)-3-furoyl azide (IX). To a solution of triethylammonium salt prepared from 2.6 g of acid **VIII** and 1.5 ml of triethylamine in 15 ml of acetone a solution of 1.1 ml of ethyl chloroformate in 5 ml of acetone was added dropwise with stirring at 0–2°C. The reaction mixture was stirred at this temperature for 1.5 h, and then the saturated solution of 1.3 g of sodium azide in water was added. The mixture obtained was stirred at 2–3°C for additional 4 h and then poured in 50 ml of benzene. Then it was saturated with sodium chloride, extracted with benzene, and the extract was dried over calcium chloride. The solvent was removed at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Azide **IX**, 1.5 g, was obtained as a light brown oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (CH_3-ethyl, J_{HH} 8 Hz); 3.33 d (CH_2P, J_{HP} 20 Hz); 4.08 m (CH_2OP, J_{HH} 8.0 Hz, J_{HP} 14 Hz); 7.54 d.d (H^5-furan, J_{PH} 4 Hz, J_{HH} ~ 1 Hz); 8.00 d (H^2-furan, J_{HH} ~ 1 Hz). Signals of admixtures are observed at 7.17– 7.20 and 7.41–7.44 ppm. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.105 s (CH_3-ethyl); 20.759 d (CH_2P, $^1J_{PC}$ 142.7 Hz); 61.960 (CH_2OP); 115.379 d (C^4-furan, $^2J_{PC}$ 7.5 Hz); 119.354 d (C^3-furan, $^3J_{PC}$ 4.5 Hz); 143.640 d (C^5-furan, $^3J_{PC}$ 6.8 Hz); 149.554 (C^2-furan); 167.723 (C=O). ^{31}P NMR spectrum: δ_P 25.392 ppm.

4-(Diethoxyphosphorylmethyl)furyl-3-isocyanate (X). A solution of 1.5 g of azide **IX** prepared in the previous stage in 20 ml of toluene was refluxed for 3 h. After that solvent was evaporated at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature to give 1.1 g of isocyanate **X** as a brown syrup. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (CH_3-ethyl, J_{HH} 8 Hz); 2.89 d (CH_2P, J_{HH} 20 Hz); 4.10 m (CH_2OP, J_{HH} 8 Hz, J_{HP} 14 Hz); 7.34 br.s ($H^{2,5}$-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.149 (CH_3-ethyl); 20.585 d (CH_2P, $^1J_{PC}$ 148.5 Hz); 62.226 d (CH_2OP, $^2J_{PC}$ 4.9 Hz); 112.654 d (C^4-furan, $^2J_{PC}$ 7.7 Hz); 119.905 d (C^3-furan, $^3J_{PC}$ 6.5 Hz); 124.943 (–N=C=O); 139.536 d (C^5-furan, $^3J_{PC}$ 11.7 Hz); 141.218 (C^2-furan). ^{31}P NMR spectrum: δ_P 23.927 ppm.

***N*-[4-(Diethoxyphosphorylmethyl)furyl-3]acetamide (XI)**. A solution of 1.1 g of isocyanate **X**, 4 ml of acetic acid, and 2 ml of acetic anhydride in 30 ml of dioxane was heated with stirring for 6 h at 106°C. Volatile products were removed at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Acetamide **XI** was obtained as a glass-like mass. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (CH_3-ethyl, J_{HH} 8 Hz); 2.17 s (CH_3CO); 2.98 d (CH_2P, J_{HH} 20 Hz); 4.10 m (CH_2OP, J_{HH} 8 Hz, J_{HP} 14 Hz); 7.20 d (H^5-furan, J_{HP} 4 Hz); 7.29 s (H^2-furan); 8.10 br.s (NH). ^{31}P NMR spectrum: δ_P 26.860 ppm.

4-(Diethoxyphosphorylmethyl)-3-furoyl chloride (XII). A mixture of 1.9 g of acid **VIII**, 0.7 ml of thionyl chloride, 2 drops of DMF, and 20 ml of benzene was boiled with stirring for 4 h, the solvent was removed under a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Acid chloride **XII,** 1.8 g, was obtained, brown oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.267 t (CH_3-ethyl, J_{HH} 7.0 Hz); 3.211 d (CH_2P, J_{HP} 20.4 Hz); 4.066 m (CH_2OP, J_{HH} 7.0 Hz, J_{HP} 14.8 Hz); 7.555 d (H^5-furan, J_{HP} 2.0 Hz); 8.196 s (H^2-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.159 (CH_3-ethyl); 20.882 d (CH_2P, $^1J_{PC}$ 143.5 Hz); 61.148 (CH_2OP); 115.247 (C^4-furan); 123.466 (C^3-furan); 144.292 (C^5-furan); 153.674 (C^2-furan); 165.286 (COCl). ^{31}P NMR spectrum: δ_P 24.947 ppm. Minor signals at 118.368 ppm (C^3-furan), 142.826 ppm (C^5-furan), 148.990 ppm (C^2-furan), and 159.448 (C=O) belong probably to anhydride. While storing the solution the intensity of these signals gradually increases.

Acid chloride **XII** can be distilled in a vacuum, bp 145–147°C (1 mm Hg), but the distillate is more contaminated than the non-distilled preparation.

Diethyl [4-(hydroxymethyl)furyl-3]methylphosphonate (XIII). A solution of 2.5 g of acid chloride **XII** in 5 ml of dioxane was added dropwise with stirring at 50°C to a suspension of 0.7 g of sodium borohydride in 10 ml of DMF. The mixture obtained was stirred for 7 h at 75°C, cooled, and decomposed with 10% acetic acid. Volatile products were evaporated at reduced pressure, and the syrup left was dissolved in 7 ml of water. The resulting mixture was saturated with sodium chloride, extracted with benzene, and dried over sodium sulfate. After removing the solvent at a reduced pressure and keeping of the residue in a vacuum (1 mm Hg) for 1 h at room temperature 1.6 g (~72%) of compound **XIII** was obtained, yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.215 t (CH_3-ethyl, J_{HH} 7.3 Hz); 2.982 d (CH_2P, J_{HP} 20.3 Hz); 3.999 m (CH_3OP, J_{HH} 7.3 Hz, J_{HP} 14.7 Hz); 4.437 (CH_2OH); 7.258 d (H^2-furan, J_{HP} 4.4 Hz); 7.376 s (H^5-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.025 (CH_3-ethyl); 21.577 d (CH_2P, $^1J_{PC}$ 143.6 Hz); 53.824 (CH_2OH); 62.478 d (CH_2OP, $^2J_{PC}$ 7.1 Hz); 114.189 d (C^3-furan, $^2J_{PC}$ 10.3 Hz); 125.323 (C^4-furan); 141.428 d (C^2-furan, $^3J_{PC}$ 9.3 Hz); 141.740 (C^5-furan). ^{31}P NMR spectrum: δ_P 26.389 ppm

Diethyl [4-(acetoxymethyl)furyl-3]methylphosphonate XIV. To a solution of 1.6 g of alcohol **XIII** and 0.6 ml of pyridine in 20 ml of ethyl acetate a solution of 0.5 ml of acetyl chloride in 3 ml of ethyl acetate was added dropwise at room temperature, and the reaction mixture was stirred for additional 3 h. On the next day it was washed with diluted hydrochloric acid, with sodium bicarbonate solution, then with water, and dried over sodium sulfate. The solvent was removed at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Acetate **XIV** was obtained as a light yellow oil, yield 0.9 g (48%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (CH_3-ethyl, J_{HH} 8 Hz); 2.06 s (CH_3CO); 2.99 d (CH_2P, J_{HP} 20 Hz); 4.08 m (CH_2OP, J_{HH} 8 Hz, J_{HP} 14 Hz); 5.03 s (CH_2OCO); 7.42 d (H^2-furan, J_{PH} 4 Hz); 7.45 s (H^5-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.184 (CH_3-ethyl); 19.923 (CH_3-acetyl); 21.727 d (CH_2P, $^1J_{PC}$ 107.6 Hz); 56.306 (CH_2O-acetyl); 62.015 (CH_2OP); 114.590 d (C^3-furan, J_{PC} 6.5 Hz); 120.608 s (C^4-furan); 141.116 (C^2–furan); 142.329 (C^5-furan); 170.419 (C=O). ^{31}P NMR spectrum: δ_P 25.657 ppm.

Acetate **XIV** distills in a vacuum with decomposition, bp 152°C (1 mm Hg).

Aminomethylation of acetate XIV with dimethylmethyleneiminium chloride. A solution of 1.7 g of acetate **XIV** and 0.7 g of dimethylmethyleneiminium chloride in 20 ml of acetonitrile was heated for 10 h at 70°C. After that the solvent was removed at a reduced pressure, the residue was triturated with 5 ml of ether, and the solvent was decanted. This operation was repeated once more, and the washed residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Compound **XV**, 1.2 g, was obtained as a light brown syrup. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 t (CH_3-ethyl, J_{HH} 7 Hz); 2.59 s (CH_3N); 2.68–2.82 m [$O(O)CCH_2$ + CH_2N + admixtures]; 2.89 d (CH_2P, J_{HP} 20 Hz); 3.97 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 14 Hz); 4.92 s (furan-CH_2OCO); 7.31 d (CH^5-furan, J_{PH} 4 Hz); 7.36 s (CH_2-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.103 (CH_3-ethyl); 21.582 d (CH_2P, $^1J_{CP}$ 102.7 Hz); 29.096 (CH_3N^+); 34.552 (CH_2CO); 42.524 (CH_2N^+); 56.204 (CH_2OCO); 61.959 (CH_2OP); 114.476 d (C^3-furan, $^3J_{CP}$ Hz); 120.520 (C^4-furan); 141.707 d (C^2-furan, $^3J_{CP}$ 5.8 Hz)); 142.245 (C^5-furan); 170.305 (C=O). ^{31}P NMR spectrum: δ_P 26.191 ppm. The solution of compound **XV** in chloroform is unstable. The largest changes in ^{1}H NMR spectra take place in the range 2.6–2.8 ppm. Due to that we failed to establish the exact location of signals of the $O(O)CCH_2CH_2N$ fragment.

The obtained sample of compound **XV** was dissolved in water and treated with the solution of sodium carbonate to pH 9. The resulting mixture was extracted with methylene chloride, the extract was dried over sodium sulfate, methylene chloride was evaporated, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. The obtained light brown oily substance consisted mainly of acetate **XIV**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.239 t (CH_3-ethyl, J_{HH} 7 Hz); 2.016 s (CH_3CO); 2.940 d (CH_2P, J_{PH} 21.2 Hz); 4.019 m (CH_2OP, J_{HH} 7.0 Hz, J_{HP} 14.4 Hz); 4.986 s (CH_2OCO); 7.374 d (H^2-furan, J_{PH} 4 Hz); 7.401 s (H^5-furan).

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