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Synthesis of 2-Functionalized 4-(Diethoxyphosphorylmethyl)-5-(1-bromoalkyl)furans and Their Reactions with Amines

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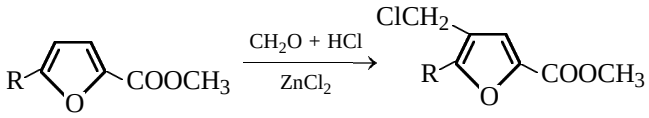
Abstract — Phosphorylation of esters and nitriles of 4-chloromethyl-5-alkylfuran-2-carboxylic acids with triethyl phosphite yields the corresponding phosphonates. These compounds are brominated with *N*-bromosuccinimide in carbon tetrachloride at the α-position of the alkyl radical. The resulting 2-(1-bromoethyl)-, 2-(1-bromopropyl)-, and 2-(1-bromoisobutyl)furans react with secondary amines following the scheme of nucleophilic substitution. The dehydrobromination product was isolated only in the reaction of ethyl 4-(diethoxyphosphorylmethyl)-5-(1-bromoisopropyl)furan-2-carboxylate with triethylamine, but its yield was low. The reactions of bromo phosphonates with lithium carbonate in DMF result in their decomposition.

Esters and nitriles of 5-(1-bromoalkyl)furan-2-carboxylic acids react with phosphorus nucleophiles along two pathways with the formation of alkenes and phosphorylation products [1]. In the presence of a strong acceptor in the furan ring, nucleophilic substitution is preferred, and accumulation of σ-donors such as methyl groups in the side chain facilitates the elimination of hydrogen bromide. This study was aimed to introduce an additional substituent with weak electron-acceptor properties, diethoxyphosphorylmethyl group, into the furan ring, to examine the direction of bromination of the resulting phosphorus-containing derivatives of 5-alkylfuran-2-carboxylic acids, and to carry out the reactions of the resulting bromo derivatives with secondary amines. Based on the previously established effect of substituents, it could be expected that the main direction of the process should be the alkylation of amines leading to phosphorus-containing derivatives of amino acids of the furan series.

Alkyl 5-alkylfuran-2-carboxylates **I**–**III** were chosen as the starting substances. They were chloromethylated with paraform in the presence of zinc chloride in dichloroethane. In all the three cases, the reaction proceeded with a considerable heat evolution, and the substituent entered 4-position of the furan ring.



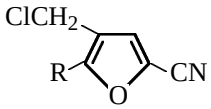
I–**III** **IV**–**VI**

R = C_2H_5 (**I**, **IV**), *n*-C_3H_7 (**II**, **V**), $(CH_3)_2CHCH_2$ (**III**, **VI**).

It was unexpectedly found that ethyl esters of the corresponding acids are extremely difficult to chloromethylate even at elevated temperatures (35–40°C).

Chloromethylated nitriles **VII**–**IX** were obtained by the following sequence of reactions.

The chlorine atom was substituted with acetoxy group by treatment with sodium acetate in a mixture of acetic acid and acetic anhydride boiling in the range 125–130°C. Hydrolysis of acetates **X**–**XIII** with aqueous sodium hydroxide yielded the corresponding



VII–**IX**

R = C_2H_5 (**VII**), *n*-C_3H_7 (**VIII**), $(CH_3)_2CHCH_2$ (**IX**).

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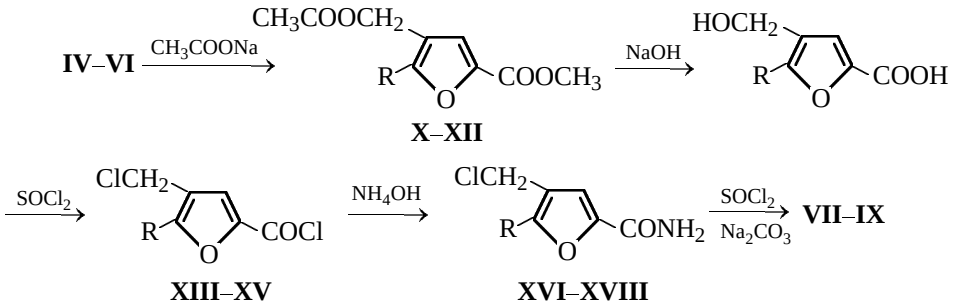
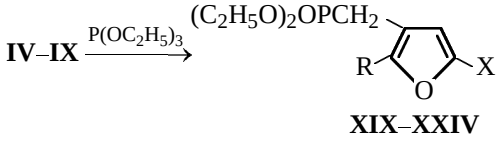


R = C_2H_5 (**X**, **XIII, XVI**), *n*-C_3H_7 (**XI, XIV, XVII**), $(CH_3)_2CHCH_2$ (**XII, XV, XVIII**).

hydroxy acids which were isolated as syrups. These compounds without special purification were brought into the reaction with 4 equiv of thionyl chloride in benzene. After refluxing for several hours and distillation in a vacuum, acid chlorides **XIII**–**XV** were obtained. These compounds were treated with ammonia at 0–10°C to obtain the corresponding amides **XVI**–**XVIII**. The chloromethyl group does not react under these conditions. The dehydration of amides to nitriles was carried out with thionyl chloride in toluene. Intermediate imidoyl chlorides under these conditions are dehydrochlorinated very slowly; therefore, after several hours of heating, the reaction mixture was treated with an excess of aqueous sodium carbonate. The previously developed procedure of dehydrochlorination of amides with phosphorus pentachloride [2] appeared to be inefficient.

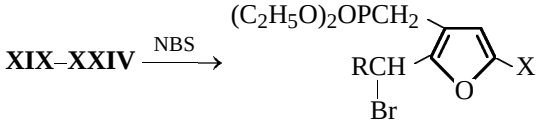
4-Chloromethylfurans **IV**–**IX** were phosphorylated by the Arbuzov reaction with triethyl phosphite at 150–190°C in the course of 2–2.5 h.



R = C_2H_5, X = $COOCH_3$ (**XIX**), CN (**XX**); R = *n*-C_3H_7, X = $COOCH_3$ (**XI**), CN (**XXII**); R = $(CH_3)_2CHCH_2$, X = $COOCH_3$ (**XXIII**), CN (**XXIV**).

The reaction yields the corresponding phosphonates. The products were isolated by vacuum distillation. In the case of ethyl- and propylfurans, the yields of phosphonates varied in the range 73–79%, but in the case of isobutyl derivatives they decreased to 59%. The decreased yield of phosphonates **XXIII**–**XXIV** may be due to mechanical losses associated with the high viscosity of these products.

Phosphonates **XIX**–**XXIV** were brominated with *N*-bromosuccinimide (NBS) in carbon tetrachloride at the equimolar reactant ratio in the presence of azodiisobutyronitrile as initiator. The reaction completion was judged from the absence of crystals of *N*-bromosuccinimide on the bottom of the reaction vessel. The reaction time was about 1.5 h.



R = CH_3, X = $COOC_2H_5$ (**XXV**), CN (**XXVI**); R = C_2H_5, X = $COOCH_3$ (**XXVII**), CN (**XXVIII**); R = $(CH_3)_2CH$, X = $COOCH_3$ (**XXIX**), CN (**XXX**).

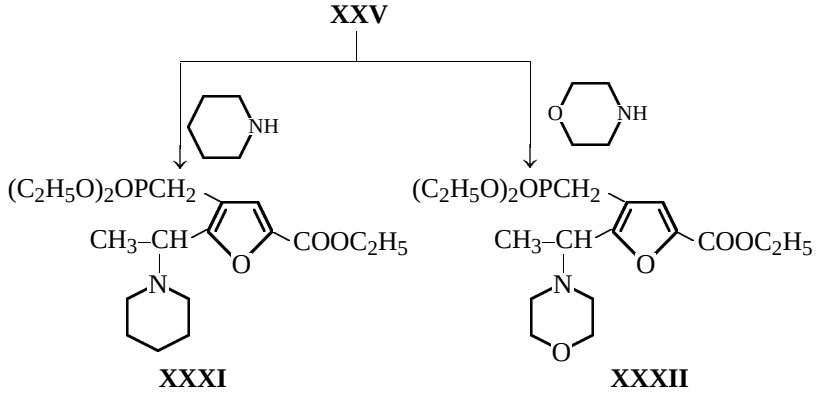
Bromo derivatives **XXV**–**XXX** are viscous oils with the color from yellow to orange. They cannot be distilled in a vacuum and gradually polymerize when stored as crude products, but solutions of these compounds in CCl_4 and aromatic hydrocarbons are stable. In this study, we tried to involve these bromides in further transformations immediately after isolation.

The ^1H NMR spectra of these compounds show that the bromination occurs at the α-position of the alkyl radical and does not involve the methylene group at phosphorus. The signal of the corresponding proton lies in the range δ 4.8–5.2 ppm, and in the series Et–Pr–*i*-Bu it regularly shifts upfield. No remote coupling between the phosphorus atom and the α-proton in the side chain was observed in any case.

Bromo phosphonates **XXV**–**XXX** were brought into the reaction with secondary amines (diethylamine, piperidine, morpholine). The reactions were carried out in benzene or toluene at 80–90°C for 5–6 h, and the amination products were extracted with dilute HCl. The aqueous extracts were alkalized, and amino phosphonates were extracted with ether. The solutions were dried, and the solvent was removed. The products are oils decomposing when heated in a vacuum below their boiling points. Unfortunately, we failed to obtain their crystalline salts, and therefore the

amino phosphonates were characterized only spectroscopically.

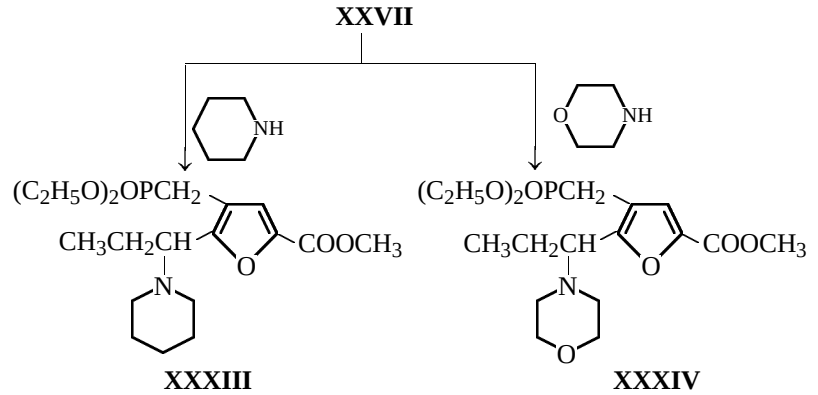
Bromide **XXV** was brought into the reactions with piperidine and morpholine.



Amino phosphonates **XXXI** and **XXXII** are yellow-brown oils. Their ^{1}H NMR spectra contained the signals of the CH–N fragment at the furan ring at δ 3.84 and 3.75 ppm, respectively. The methylene group at phosphorus in both cases gave two doublets with the constant J_{HP} 20 Hz (3.02 and 3.08 ppm for **XXXI**, and 2.88 and 2.91 ppm for **XXXII**).

The furan ring proton in both compounds also gave two signals at 7.01 and 7.16 ppm (phosphonate **XXXI**) and at 6.96 and 7.16 ppm (phosphonate **XXXII**). These data show that the compounds exist as mixtures of conformers.

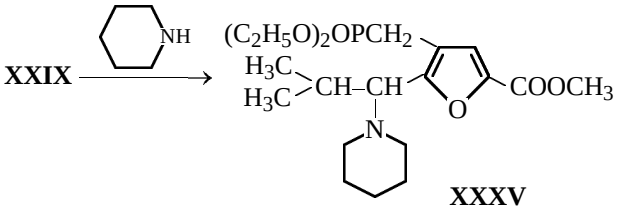
In the solution remaining after the extraction of amines, we detected no dehydrobromination products. Elimination of hydrogen bromide from the bromo phosphonates was not observed even upon refluxing with triethylamine in toluene. Bromide **XXVII** reacts with piperidine and morpholine to form the corresponding phosphonates **XXXIII** and **XXXIV**.



In these compounds, the methylene groups at phosphorus give signals at δ 2.89 and 2.93 ppm, and the signals of the CH–N fragment at the furan ring are located at 3.40 and 3.39 ppm, respectively. No spectroscopically distinguishable conformers of these compounds were revealed. The product of dehydrobromination of the side chain was not detected either.

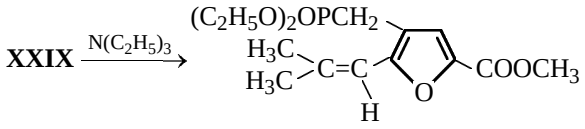
Isobutyl derivative **XXIX** was brought into the reactions with piperidine and triethylamine. In the first case, amino phosphonate **XXXV** was obtained. The signal of the CH_2P fragment in the ^{1}H NMR spectrum of this product is observed at 2.85 ppm, and that of the CH–N fragment, at 3.05 ppm. The proton of the furan ring gives two signals with chemical shifts of

7.17 and 7.24 ppm, which suggests the presence of two conformers.

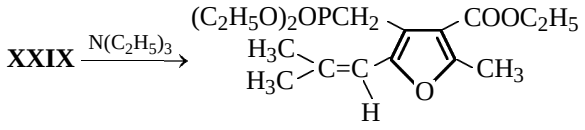


XXXV

Dehydrobromination of phosphonate **XXIX** was carried out by refluxing with an excess of triethylamine in toluene. As our goal was to detect the alkene, only the toluene solution remaining after the extraction of amines with hydrochloric acid was analyzed. Evaporation of this solution under reduced pressure and distillation of the residue in a vacuum gave a fraction with bp 178°C (2 mm Hg), identified as alkene **XXXVI** with a small impurity of unchanged phosphonate **XXIII** from the bromination step. The yield of alkene **XXXVI** was low. The signals of substituents at the double bond in the ^{1}H NMR spectrum well agree with the data for previously obtained alkene **XXXVII** {chemical shifts (δ, ppm) for **XXXVI**: 1.94 s, 2.04 s (CH_3 at the double bond); 5.91 s (H–C=); for **XXXVII** [3]: 1.92 s, 1.95 s, 2.02 s, 2.07 s (CH_3 at the double bond, two conformers); 5.85 s, 5.94 s (HC=, two conformers)}.



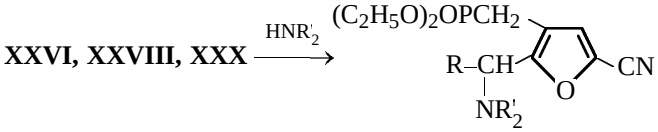
XXXVI



XXXVII

The reaction of bromo phosphonate **XXIX** with lithium carbonate leads to decomposition of the molecule.

The reactions of brominated nitriles **XXVI**, **XXVIII**, and **XXX** with morpholine, piperidine, and diethylamine were carried out similarly to those involving the above-mentioned esters.



XXXVIII–**XLI**

R = CH_3, R'_2 = $(CH_2)_2O(CH_2)_2$ (**XXXVIII**); R = CH_3, R' = C_2H_5 (**XXXIX**); R = C_2H_5, R'_2 = $(CH_2)_5$ (**XL**); R = $(CH_3)_2CH$, R'_2 = $(CH_2)_5$ (**XLI**).

Phosphorylated amino nitriles **XXXVIII**–**XLI** are viscous oils with the color varying from dark yellow to light brown. They cannot be distilled in a vacuum and do not form well crystallizing hydrochlorides.

In the ^{1}H NMR spectrum of phosphonate **XXXVIII**, the signal of the CH_2P group is observed at 2.96 ppm (d, J_{HP} 20 Hz), and the signal of the CH–N proton, at 3.60 ppm. Phosphonate **XXXIX** gives two signals of the CH_2P group at 2.98 and 3.14 ppm, and the signal of the CH–N fragment evidently overlaps with the multiplet of the CH_2OP group. Therefore, we failed to identify it.

Phosphonate **XL** is characterized by the signal of the CH_2P group at 2.94 ppm and the signal of the CH–N fragment at 3.44 ppm.

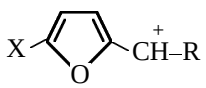
Phosphonate **XLI** exists as a mixture of two conformers. The isobutyl group in this compound gives two doublets with chemical shifts of 0.59 and 0.95 ppm, and the signals of the CH_2P group are observed at 2.87 and 2.89 ppm. The CH–N fragment gives a signal at 3.09 ppm.

Comparison of the spectral data for esters **XXXI**–**XXXV** and nitriles **XXXVIII**–**XLI** shows that the signal of the PCH_2 group in these compounds is located approximately in the same place irrespective of the structure of the alkyl substituent, whereas the signal of the CH–N fragment is regularly shifted upfield with an increase in the size of the alkyl substituent in the furan ring.

No products of dehydrobromination of nitriles **XXVI**, **XXVIII**, and **XXX** were detected.

Thus, introduction of an additional weakly electron-withdrawing substituent such as dialkoxyphosphorylmethyl group in the furan ring significantly complicates dehydrobromination under the action of bases. The alkene was detected only in trace amounts and only in the case of the compound with the most favorable structure. In all the other cases, alkylation of the amines took place exclusively.

Our results confirm the previously made assumption that elimination of hydrogen bromide in (1-bromoalkyl)furans proceeds through the intermediate carbenium ion **XLII**.



XLII

An increase in the electron density in the furan ring

and the accumulation of methyl groups with branching of the side-chain radical favor its stabilization [1].

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Tesla BS-497C spectrometer (100 MHz) in $CDCl_3$ against internal HMDS. The chemical shifts of phosphorus were calculated from the INDOR spectra.

Chloromethylation of 5-alkylfuran-2-carboxylates *(general procedure).* To a solution of 0.1 mol of ester **I**–**III** in 100 ml of dichloroethane, 0.15 mol of paraform and 0.025 mol of freshly ground zinc chloride were added. After that, a vigorous flow of hydrogen chloride was passed through the reaction mixture until the heat evolution ceased. The reaction temperature was maintained within the range 30–33°C. After the completion of heat evolution and homogenization of the mixture, it was kept for 30 min and then treated with water. The aqueous layer was extracted with 20 ml of dichloroethane, and the combined organic phases were washed with water and dried over $CaCl_2$. The solvent was removed at reduced pressure, and the residue was distilled in a vacuum.

Methyl 4-chloromethyl-5-ethylfuran-2-carboxylate IV. Yield 74%, bp 103°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.20 t (CH_3-ethyl, J_{HH} 7 Hz), 2.65 q (CH_2-ethyl, J_{HH} 7 Hz), 3.72 s (CH_3O), 4.32 s (CH_2Cl), 6.95 s (H^3-furan).

Methyl 4-chloromethyl-5-propylfuran-2-carboxylate V. Yield 67%, bp 114°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.92 t (CH_3-propyl, J_{HH} 7 Hz), 1.69 m (CH_2-propyl, J_{HH} 7 Hz), 2.62 s (CH_2-furan, J_{HH} 7 Hz), 3.73 s (CH_3O), 4.29 s (CH_2Cl), 6.94 s (H^3-furan).

Methyl 4-chloromethyl-5-isobutylfuran-2-carboxylate VI. Yield 78%, bp 127–128°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.88 d (CH_3-isobutyl, J_{HH} 7 Hz), 2.02 m (CH-isobutyl, J_{HH} 7 Hz); 2.48 d (CH_2-isobutyl, J_{HH} 7 Hz), 3.73 s (CH_3O), 4.25 s (CH_2Cl), 7.00 s (H^3-furan).

Reaction of chloromethylfurans IV–VI with sodium acetate *(general procedure).* The chloromethyl derivative, 0.1 mol, was dissolved in a mixture of acetic acid and acetic anhydride boiling in the range 125–132°C, and 0.2 mol of finely pulverized anhydrous sodium acetate was added. The mixture was refluxed with stirring for 15 h and then poured into water and extracted with methylene chloride. The extract was washed with water and dried over $CaCl_2$, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum.

Methyl 4-acetoxymethyl-5-ethylfuran-2-carboxylate X. Yield 82%, bp 125°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.20 t (CH_3-ethyl, J_{HH} 7 Hz), 1.90 s (CH_3COO), 2.67 q (CH_2-ethyl, J_{HH} 7 Hz), 3.72 s (CH_3O), 4.75 s (CH_2O-furan), 6.95 s (H^3-furan).

Methyl 4-acetoxymethyl-5-propylfuran-2-carboxylate XI. Yield 84%, bp 136°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.85 t (CH_3-propyl, J_{HH} 7 Hz), 1.65 m (CH_2-propyl, J_{HH} 7 Hz), 1.95 s (CH_3COO), 2.60 t (CH_2-furan, J_{HH} 7 Hz), 3.69 s (CH_3OOC), 4.75 s (CH_2O-furan), 6.98 s (H^3-furan).

Methyl 4-acetoxymethyl-5-isobutylfuran-2-carboxylate XII. Yield 83%, bp 135°C (0.7 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.86 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.91 m (CH_3-acetoxy + CH-isobutyl, overlapped), 2.46 d (CH_2-isobutyl, J_{HH} 7 Hz), 3.73 s (CH_3OOC), 4.76 s (CH_2O-furan), 6.93 s (H^3-furan).

4-Chloromethyl-5-ethyl-2-cyanofuran VII. *a*. To a solution of 12.5 g of sodium hydroxide in 60 ml of water, 17.6 g of acetate **X** was added, and the mixture was refluxed for 6 h. The resulting homogeneous mixture was cooled to 10°C and acidified with HCl to pH 1. The emulsion thus formed was extracted with ether, and the ether extract was dried over calcium chloride. After removing the solvent and keeping the residue for 1 h in a vacuum (1 mm) at room temperature, 16.3 g of crude 4-hydroxymethyl-5-ethylfuran-2-carboxylic acid was obtained as a brown syrup.

b. The product from the previous step was emulsified under stirring at elevated temperature in 150 ml of benzene, and 22 ml of thionyl chloride was added dropwise. The mixture was refluxed with stirring for 4 h, the solvent was distilled off at reduced pressure, and the residue was distilled in a vacuum to give 10.5 g of acid chloride **XIII**, bp 100–101°C (1 mm Hg).

c. Acid chloride **XIII**, 10.5 g, was added with vigorous stirring to 40 ml of 25% ammonia cooled to 0°C. The mixture was stirred for 1 h, and the precipitate of chloromethyl carboxamide **XVI** was filtered off. Yield 8.4 g, mp 132–133°C.

d. Amide **XVI**, 7.2 g, was suspended in 50 ml of toluene, and 4.2 ml of thionyl chloride was added in one portion. The mixture was refluxed with stirring for 8 h and cooled to room temperature, and a solution of 5 g of sodium carbonate in 50 ml of water was added dropwise. The resulting mixture was stirred for 90 min, washed with water, and dried over $CaCl_2$. The solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 2.9 g of nitrile **VII**, bp 92°C (1 mm Hg). ^{1}H NMR spectrum,

δ, ppm: 1.22 t (CH_3-ethyl, J_{HH} 7 Hz), 2.70 q (CH_2-ethyl, J_{HH} 7 Hz), 4.35 s ($ClCH_2$), 7.10 s (H^3-furan).

4-Chloromethyl-5-propyl-2-cyanofuran VIII. *a*. To a solution of 7 g of NaOH in 50 ml of water, 17.9 g of acetate **XI** was added in one portion, and the mixture was refluxed with stirring for 6 h. After that, the reaction mixture was cooled to room temperature and acidified with HCl to pH 1. The oil that separated out was extracted with ether; the extract was dried over $CaCl_2$, and the solvent was removed. The residue was kept in a vacuum (1 mm) for 1 h at 20–25°C to give 14.5 g of crude hydroxy acid as a syrup.

b. The syrup from the previous step was emulsified by stirring at elevated temperature in 150 ml of benzene, and 17 ml of thionyl chloride was added dropwise. The mixture was refluxed with stirring for 4 h, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 12.5 g of acid chloride **XIV**, bp 103–105°C (1 mm Hg). ^1H NMR spectrum, δ, ppm: 0.94 t (CH_3-propyl, J_{HH} 7 Hz), 1.73 m (CH_2-propyl, J_{HH} 7 Hz), 2.68 t (CH_2-furan, J_{HH} 7 Hz), 4.36 s ($ClCH_2$), 7.36 s (H^3-furan).

c. Ammonia, 50 ml of 25% solution, was cooled to 0°C, and 12.5 g of acid chloride **XIV** was added dropwise with vigorous stirring and cooling. A white precipitate formed almost immediately. The mixture was stirred for 15 min, and the crystals of amide **XVI** were filtered off, washed with a small amount of water, and dried. Yield 10.8 g, mp 123–124°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.88 t (CH_3-propyl, J_{HH} 7 Hz), 1.64 m (CH_2-propyl, J_{HH} 7 Hz), 2.66 t (CH_2-furan, J_{HH} 7 Hz), 4.64 s (CH_2Cl), 7.08 s (H^3-furan), 7.30 br.s and 7.67 br.s (NH_2).

d. Amide **XVII**, 3.5 g, was suspended in 15 ml of benzene, 2.5 ml of thionyl chloride were added in one portion, and the mixture was refluxed with stirring for 6 h. The resulting solution was distilled in a vacuum, and 2.6 g of the fraction with bp 110–140°C (1 mm Hg) was collected. This product was dissolved in benzene, and 4 ml of triethylamine was added. The mixture was stirred for 30 min, washed with two portions of water, dried over $CaCl_2$, and distilled to give 1.9 g of nitrile **VIII**, bp 96°C (1 mm Hg). ^1H NMR spectrum, δ, ppm: 0.92 t (CH_3-propyl, J_{HH} 7 Hz), 1.67 m (CH_2-propyl, J_{HH} 7 Hz), 2.65 t (CH_2-furan, J_{HH} 7 Hz), 4.35 s ($ClCH_2$), 7.00 s (H^3-furan).

4-Chloromethyl-5-isobutyl-2-cyanofuran IX. *a*. To a solution of 3 g of NaOH in 30 ml of water, 4.7 g of acetate **XII** was added, and the mixture was refluxed for 4 h. After cooling to room temperature, the mixture was acidified with HCl to pH 1, and the oil that separated out was extracted with ether. The extract was dried over $CaCl_2$, the solvent was distilled off, and the residue was dried in a vacuum (1 mm) for 1 h at 20–25°C. The crude hydroxy acid, 3.7 g, was obtained as a syrup.

b. The hydroxy acid from the previous step was suspended at elevated temperature in 50 ml of benzene, and 7 ml of thionyl chloride was added dropwise. The resulting mixture was refluxed for 4 h, the solvent was distilled off, and the residue was distilled in a vacuum to give 3.4 g of acid chloride **XV**, bp 119°C (1 mm Hg).

c. Ammonia, 25 ml of 25% solution, was cooled to 0°C, and 3.4 g of acid chloride **XV** was added dropwise with vigorous stirring. A colorless precipitate started to form within several minutes. The mixture was stirred for 2 h and diluted with water; the precipitate thus formed was filtered off and dried. Amide **XVIII**, 2.9 g, was obtained; mp 143–144°C.

d. A mixture of 2.9 g of amide **XVIII**, 2 ml of thionyl chloride, and 20 ml of toluene was refluxed with stirring for 5 h. The resulting solution was cooled to room temperature, and a solution of 5 g of sodium carbonate in 25 ml of water was added. The mixture was stirred for 1 h at 50°C, the aqueous layer was removed, and the toluene layer was washed with water, dried over $CaCl_2$, and distilled to give 0.6 g of nitrile **IX**, bp 109°C (1 mm Hg). ^1H NMR spectrum, δ, ppm: 0.89 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.97 m (CH-isobutyl), 2.52 d (CH_2-isobutyl, J_{HH} 7 Hz), 4.32 s ($ClCH_2$), 6.94 s (H^3-furan).

Phosphorylation of halomethylfurans IV–IX with triethyl phosphite *(general procedure).* A mixture of 0.05 mol of halomethylfuran **IV–IX** and 0.075 mol of triethyl phosphite was heated with stirring. At 150–155°C, it came to boil, and in the course of 2–2.5 h its boiling point gradually rose to 185–190°C. After the release of volatiles was complete, the mixture was cooled and distilled in a vacuum.

Methyl 4-(diethoxyphosphorylmethyl)-5-ethylfuran-2-carboxylate XIX. Yield 73%, bp 154–155°C (1 mm Hg). ^1H NMR spectrum, δ, ppm: 1.17 t (CH_3-ethyl, J_{HH} 7 Hz), 2.60 q (CH_2-furan from ethyl, J_{HH} 7 Hz), 2.71 d (CH_2P, J_{HP} 21 Hz), 3.70 s (CH_3COO), 3.92 s (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 6.95 s (H^3-furan). δ_P 22.7 ppm.

4-(Diethoxyphosphorylmethyl)-5-ethyl-2-cyanofuran XX. Yield 79%, bp 152°C (1 mm Hg). ^1H NMR spectrum δ, ppm: 1.22 t (CH_3-ethyl, J_{HH} 7 Hz), 2.64 q (CH_2-furan, J_{HH} 7 Hz), 2.74 d (CH_2P, J_{HP} 21 Hz), 3.95 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.00 s (H^3-furan). δ_P 22.1 ppm.

Methyl 4-(diethoxyphosphorylmethyl)-5-pro-

pylfuran-2-carboxylate XXI. Yield 70%, bp 168°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.88 t (CH_3-propyl, J_{HH} 7 Hz), 1.18 t (CH_3-ethyl, J_{HH} 7 Hz), 1.65 m (CH_2-propyl, J_{HH} 7 Hz), 2.53 t (CH_2-furan, J_{HH} 7 Hz), 2.67 d (CH_2P, J_{HP} 20 Hz), 3.69 s (CH_3OOC), 3.91 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 6.93 s (H^3-furan). δ_P 22.7 ppm.

4-(Diethoxyphosphorylmethyl)-5-propyl-2-cyanofuran XXII. Yield 74%, bp 167–168°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.84 t (CH_3-propyl, J_{HH} 7 Hz), 1.11 t (CH_3-ethyl, J_{HH} 7 Hz), 1.56 m (CH_2-propyl, J_{HH} 7 Hz), 2.53 t (CH_2-furan, J_{HH} 22 Hz), 3.90 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 6.94 s (H^3-furan). δ_P 20.7 ppm.

Methyl 4-(diethoxyphosphorylmetyl)-5-isobutylfuran-2-carboxylate XXIII. Yield 59%, bp 166–168°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.87 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.38 t (CH_3-ethyl, J_{HH} 7 Hz), 2.03 m (CH-isobutyl, J_{HH} 7 Hz), 2.45 d (CH_2-isobutyl, J_{HH} 7 Hz), 2.70 d (CH_2P, J_{HP} 21 Hz), 3.71 s (CH_3OOC), 3.92 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 6.96 s (H^3-furan). δ_P 22.3 ppm.

4-(Diethoxyphosphorylmethyl)-5-isobutyl-2-cyanofuran XXIV. Yield 59%, bp 169°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.83 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.27 t (CH_3-ethyl, J_{HH} 7 Hz), 1.92 m (CH-isobutyl, J_{HH} 7 Hz), 2.43 d (CH_2-isobutyl, J_{HH} 7 Hz), 2.69 d (CH_2P, J_{HP} 21 Hz), 3.95 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 6.99 s (H^3-furan). δ_P 22.0 ppm.

Bromination of phosphonates XIX–XXIV with *N*-bromosuccinimide *(general procedure).* To a solution of 0.03 mol of appropriate phosphonate in 50 ml of carbon tetrachloride, 0.031 mol of *N*-bromosuccinimide and 0.1 g of azodiisobutyronitrile were added. The mixture was refluxed with stirring until the precipitate of *N*-bromosuccinimide disappeared (1.5–2 h). The resulting mixture was left overnight at room temperature, succinimide was filtered off, the solvent was removed at reduced pressure, and the residue was kept in a vacuum (1 mm) for 1 h in at room temperature. The products were not subjected to any additional purification.

Ethyl 4-(diethoxyphosphorylmethyl)-5-(1-bromoethyl)furan-2-carboxylate XXV. Orange oil. ^{1}H NMR spectrum, δ, ppm: 1.14 m (CH_3-ethyl), 1.80 d (CH_3–CHBr, J_{HH} 7 Hz), 2.71 d (CH_2P, J_{HP} 21 Hz), 3.84 m (CH_2OP, J_{HH} 7, J_{HP} 13 Hz), 4.12 q (CH_2OOC, J_{HH} 7 Hz), 5.22 q (CHBr, J_{HH} 7 Hz), 6.81 s (H^3-furan). δ_P 21.4 ppm.

4-(Diethoxyphosphorylmethyl)-5-(1-bromoethyl)-2-cyanofuran XXVI. Orange oil. ^{1}H NMR spectrum, δ, ppm: 1.20 q (CH_3-ethyl, J_{HH} 7 Hz), 1.95 d (CH_3–CHBr, J_{HH} 8 Hz), 2.80 d (CH_2P, J_{HP} 1 Hz), 3.94 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 5.26 q (CHBr, J_{HH} 8 Hz), 6.95 s (H^3-furan). δ_P 21.0 ppm.

Methyl 4-(diethoxyphosphorylmethyl)-5-(1-bromopropyl)furan-2-carboxylate XXVII. Dark orange oil. ^{1}H NMR spectrum, δ, ppm: 0.94 t (CH_3-propyl, J_{HH} 7 Hz), 1.17 t (CH_3-ethyl, J_{HH} 7 Hz), 2.40 m (CH_2-propyl, J_{HH} 7 Hz), 2.77 d (CH_2P, J_{HP} 20 Hz), 3.73 s (CH_3OOC), 3.80 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 5.00 t (CHBr, J_{HH} 7 Hz), 6.91 d (H^3-furan, J_{HP} 2 Hz). δ_P 21.5 ppm.

4-(Diethoxyphosphorylmethyl)-5-(1-bromopropyl)-2-cyanofuran XXVIII. Orange oil. ^{1}H NMR spectrum, δ, ppm: 0.93 t (CH_3-propyl, J_{HH} 7 Hz), 1.16 m (CH_3-ethyl, J_{HH} 7 Hz), 2.16 m (CH_2-propyl, J_{HH} 7 Hz), 2.80 d (CH_2P, J_{HP} 20 Hz), 3.93 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 4.94 t (CHBr, J_{HH} 7 Hz), 6.93 s (H^3-furan). δ_P 20.7 ppm.

Methyl 4-(diethoxyphosphorylmethyl)-5-(1-bromoisobutyl)furan-2-carboxylate XXIX. Yellow oil. ^{1}H NMR spectrum, δ, ppm: 0.87 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.40 m (CH_3-ethyl), 2.50 m (CH-isobutyl), 2.67 d (CH_2P, J_{HP} 21 Hz), 2.79 d (CH_2P, J_{HP} 21 Hz), 3.75 s (CH_3OOC), 3.94 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 4.84 d (CHBr, J_{HH} 7 Hz), 6.95 s (H^3-furan). δ_P 21.1 ppm.

4-(Diethoxyphosphorylmethyl)-5-(1-bromoisobutyl)-2-cyanofuran XXX. Yellow oil. ^{1}H NMR spectrum, δ, ppm: 0.88 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.20 t (CH_3-ethyl, J_{HH} 7 Hz), 2.50 m (CH-isobutyl), 2.78 d (CH_2P, J_{HP} 22 Hz), 3.95 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 4.78 d (CHBr, J_{HH} 9 Hz), 6.98 s (H^3-furan). δ_P 20.7 ppm.

Reaction of bromophosphonates with secondary amines *(general procedure).* A mixture of 0.01 mol of bromo phosphonate, 0.25 mol of secondary amine, and 30 ml of toluene were heated with stirring at 80–90°C for 5–6 h and left overnight. On the next day, the mixture was washed witih three or four portions of dilute HCl, and the combined aqueous extracts were alkalized with stirring to pH 9–9.5 and immediately extracted with ether. The ether extracts were kept until the emulsified aqueous layer settled and were then carefully decanted. The resulting solutions were dried over $CaCl_2$, the solvent was removed, and the residue was kept in a vacuum (1 mm) at room temperature for 1 h. The product yields can be estimated at 60–80%. More accurate estimation is not convincing because the purity of the starting bromides is unknown.

Ethyl 4-(diethoxyphosphorylmethyl)-5-[1-(*N*-piperidyl)ethyl]furan-2-carboxylate XXXI. Yellow-

brown oil. ^{1}H NMR spectrum, δ, ppm: 1.10–1.35 m (CH_3 + CH_2 of the ring), 2.37 m (CH_2N-piperidyl), 3.02 d + 3.08 d (CH_2P, J_{HP} 20 Hz), 3.84 q (CH_2N, J_{HH} 7 Hz), 4.00 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 4.17 q (CH_2OOC, J_{HH} 7 Hz), 7.01 s + 7.16 s (H^3-furan). δ_P 23.0 ppm.

Ethyl 4-(diethoxyphosphorylmethyl)-5-[1-(*N*-morpholyl)ethyl]furan-2-carboxylate XXXII. Yellow-brown oil. ^{1}H NMR spectrum, δ, ppm: 1.10–1.38 m (CH_3), 2.35 m (CH_2-morpholine), 2.88 d + 2.91 d (CH_2P, J_{HP} 20 Hz), 3.50 m (CH_2O-morpholine), 3.75 q (CHN, J_{HH} 7 Hz), 3.93 m + 3.96 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 4.16 q (CH_2OOC, J_{HH} 7 Hz), 6.96 s + 7.17 s (H^3-furan). δ_P 22.7 ppm.

Methyl 4-(diethoxyphosphorylmethyl)-5-(1-*N*-piperidyl)propyl]furan-2-carboxylate XXXIII. Brown syrup. ^{1}H NMR spectrum, δ, ppm: 0.75 t (CH_3-propyl, J_{HH} 7 Hz), 1.18 t (CH_3-ethyl, J_{HH} 7 Hz), 1.21 m (CH_2 of the ring), 1.84 m (CH_2-propyl, J_{HH} 7 Hz), 2.33 m (CH_2N-piperidyl), 2.89 d (CH_2P, J_{HP} 21 Hz), 3.40 t (NCH-furan, J_{HH} 7 Hz), 3.73 s (CH_3OOC), 4.02 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.17 s (H^3-furan). δ_P 23.2 ppm.

Methyl 4-(diethoxyphosphorylmethyl)-5-[1-(*N*-morpholyl)propyl]furan-2-carboxylate XXXIV. Brown syrup. ^{1}H NMR spectrum, δ, ppm: 0.86 t (CH_3-propyl, J_{HH} 7 Hz), 1.20 t (CH_3-ethyl, J_{HH} 7 Hz), 1.86 m (CH_2-propyl, J_{HH} 7 Hz), 2.35 m (CH_2N-morpholyl), 2.93 d (CH_2P, J_{HP} 20 Hz), 3.39 t (NCH-furan, J_{HH} 7 Hz), 3.50 m (CH_2O-morpholine), 3.75 s (CH_2OOC), 4.02 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.16 s (H^3-furan).

Methyl 4-(diethoxyphosphorylmethyl)-5-[1-(*N*-piperidyl)isobutyl]furan-2-carboxylate XXXV. Light brown oil. ^{1}H NMR spectrum, δ, ppm: 0.95 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.19 t (CH_3-ethyl, J_{HH} 7 Hz), 1.46 m (CH_2-piperidyl), 2.30 m (CH_2N + CH-isobutyl), 2.85 d (CH_2P, J_{HP} 20 Hz), 3.05 d (CHN, J_{HH} 8 Hz), 3.76 s (CH_3OOC), 4.00 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.17 s + 7.24 s (H^3-furan). δ_P 22.6 ppm.

4-(Diethoxyphosphorylmethyl)-5-[1-(*N*-morpholyl)ethyl]-2-cyanofuran XXXVIII. Yellow oil. ^{1}H NMR spectrum, δ, ppm: 1.25 m (CH_3-ethyl, J_{HH} 7 Hz), 2.39 m (CH_2N-morpholyl), 2.96 d (CH_2P, J_{HH} 21 Hz), 3.60 m (CH_2O-morpholine + N–CH), 4.00 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.04 s (H^3-furan). δ_P 22.1 ppm.

4-(Diethoxyphosphorylmethyl)-5-[1-(*N*-diethylamino)ethyl]-2-cyanofuran XXXIX. Brown oil. ^{1}H NMR spectrum, δ, ppm: 0.75 m (CH_3-ethyl, J_{HH} 7 Hz), 1.24 m (CH_2-ethyl, J_{HH} 7 Hz), 2.43 m (CH_2N, J_{HH} 7 Hz), 2.98 d (CH_2P, J_{HP} 20 Hz), 3.14 d (CH_2P, J_{HP} 20 Hz), 4.00 m (CH–N, CH_2OP, J_{HH} 7, J_{HP} 11 Hz); 7.05 s (H^3-furan). δ_P 22.9 ppm.

4-(Diethoxyphosphorylmethyl)-5-[1-(*N*-piperidyl)propyl]-2-cyanofuran XL. Light brown oil. ^{1}H NMR spectrum, δ, ppm: 0.72 t (CH_3-propyl, J_{HH} 7 Hz), 1.19 t (CH_3-ethyl, J_{HH} 7 Hz), 1.42 m (CH_2-piperidyl), 1.77 m (CH_2-propyl, J_{HH} 7 Hz), 2.30 m (N–CH_2-piperidyl), 2.94 d (CH_2P, J_{HP} 20 Hz), 3.44 t (CHN, J_{HH} 7 Hz), 4.02 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.15 s (H^3-furan). δ_P 22.4 ppm.

4-(Diethoxyphosphorylmethyl)-5-[1-(*N*-piperidyl)isobutyl]-2-cyanofuran XLI. Light brown oil. ^{1}H NMR spectrum, δ, ppm: 0.59 d (CH_3-isobutyl, J_{HH} 7 Hz), 0.95 d (CH_3-isobutyl, J_{HH} 7 Hz), 1.23 t (CH_3-ethyl, J_{HH} 7 Hz), 1.49 m (CH_2-piperidyl), 2.31 m (CH_2N-piperidyl + CH-isobutyl), 2.87 d + 2.89 d (CH_2P, J_{HP} 22 Hz), 3.09 d (CHN, J_{HH} 7 Hz), 4.02 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 7.14 s (H-furan). δ_P 21.0 ppm.

Dehydrobromination of phosphonate XXIX with triethylamine. A solution of 2.6 g of phosphonate **XXIX** and 3 ml of triethylamine in 25 ml of toluene was refluxed for 8 h. The resulting mixture was washed with dilute HCl and water, dried over calcium chloride, and distilled in a vacuum to give the product with bp 178°C (2 mm Hg) as a very viscous dark yellow oil. Yield 0.5 g. ^{1}H NMR spectrum, δ, ppm: 1.16 t (CH_3-ethyl, J_{HH} 7 Hz), 1.94 s (CH_3-*trans*), 2.04 (CH_3-*cis*), 2.65 d (CH_2P, J_{HP} 21 Hz), 3.70 s (CH_3OOC), 3.90 m (CH_2OP, J_{HH} 7, J_{HP} 11 Hz), 5.91 br.s (CH=), 6.94 s (H^3-furan).

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