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3- and 4-Dialkoxyphosphorylmethyl Derivatives of 5-*tert*-Butylfuran with Electron-Withdrawing Substituents in Position 2

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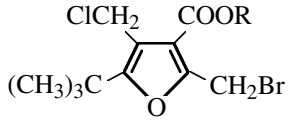
Abstract — A procedure for preparing 3- and 4-halomethyl derivatives of 5-*tert*-butylfuran containing electron-withdrawing substituents in position 2 was developed, and phosphorylation of the resulting products under the conditions of the Arbuzov and Michaelis–Becker reactions was studied. 3-Bromomethyl derivatives are phosphorylated with trimethyl phosphite considerably faster than their 4-chloromethyl analogs. At the same time, 3- and 4- chloromethyl derivatives of *N,N*-diethyl-5-*tert*-butylfuran-2-carboxamide under the conditions of the Michaelis–Becker reaction only slightly differ in chemical properties.

Recently we have studied in detail phosphorus-containing derivatives of 3-functionalized 5-*tert*-butylfurans [1, 2]. We found that 2-halomethyl derivatives of this series enter the Arbuzov reaction considerably more easily than their 4-halomethyl analogs. This allowed us to perform selective phosphorylation of 2-bromomethyl-4-chloromethylfuran **I** and involve the resulting chloro phosphonate into the reaction with secondary amines and sodium butylthiolate [3].

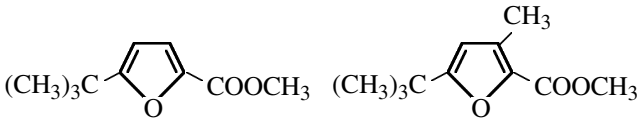


I

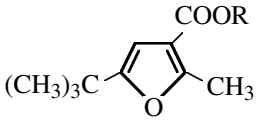
At the same time, phosphorus-containing 2-functionalized 5-*tert*-butylfurans were unknown, and no synthetic routes to them were developed. Study of phosphorylation of 3- and 4-halomethyl derivatives of these compounds is important, because this reaction allows selective introduction of a phosphorus-containing group into the β-position of the ring and subsequent modification of the second β-position.

The procedure developed by Cologne and Girantet [4] for *tert*-butylation of furancarboxylic acids by the Friedel–Crafts reaction allows easy preparation of the starting 5-*tert*-butyl derivatives **II** and **III**.

The synthesis of a series of 4-halomethyl derivatives of 2-functionalized 5-*tert*-bytulfuran was started from chloromethylation of ester **II**. The reaction

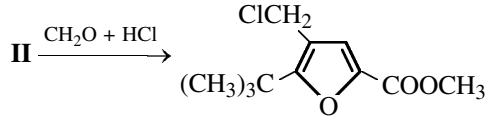


II **III**



IV

proceeds only at elevated temperatures (55–60°C) and largely resembles chloromethylation of **IV** [2].



V

Thus, the steric hindrance to electrophilic substitution in the ring of *tert*-butylfurans makes the reaction conditions considerably more severe but does not affect the substitution direction: the position being substituted is determined by the location of the ester group.

4-Chloromethyl-5-*tert*-butylfurancarboxamides were prepared the commonly used sequence of reactions.

Ester **V** reacts with sodium acetate in acetic acid to give ester **VI**. Its saponification with potassium hydroxide gave hydroxymetylfurancarboxylic acid **VII**. The latter was treated with excess thionyl chlo-

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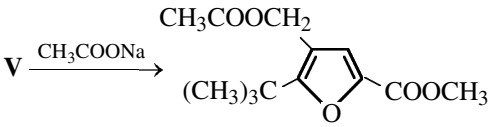
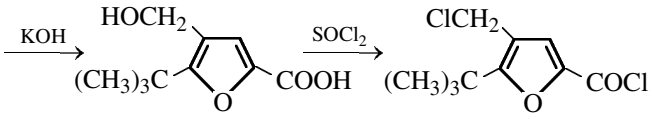
ride in benzene at 80°C to give chloromethylated acyl chloride **VIII**.

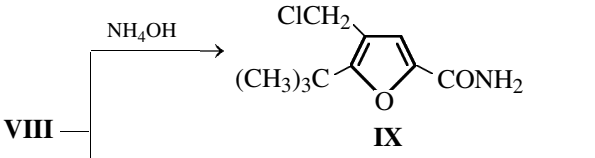


VI

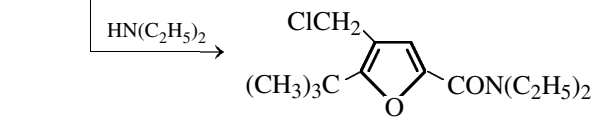


VII **VIII**

Below 20°C, product **VIII** reacts with aqueous ammonia and diethylamine only at the acyl chloride group to give chloromethyl amides **IX** and **X**.

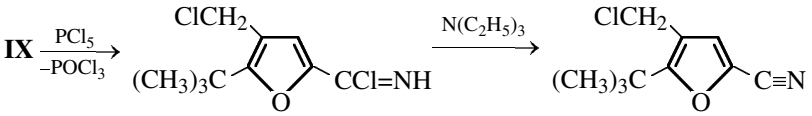


IX



X

Amide **IX** was dehydrated with phosphorus pentachloride to form nitrile **XI**. Contrary to compounds that do not contain the *tert*-butyl substituent, the reaction proceeds difficultly. Thermal dehydrochlorination of the intermediate imidoyl chloride does not take place to a noticeable extent, but in the presence of triethylamine dehydrochlorination of the freshly distilled imidoyl chloride containing a small impurity of nitrile **XI** is fairly efficient.

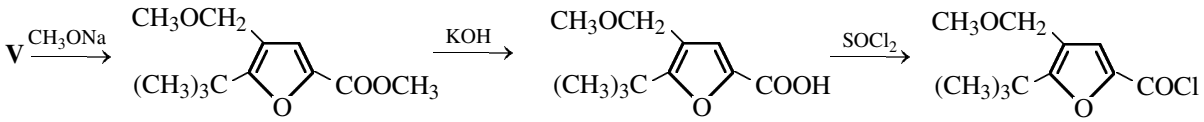


XI

Preliminary distillation of the reaction mixture is necessary, because, when the mixture obtained after removing phosphorus oxychloride is dissolved in benzene and treated with triethylamine, it undergoes tarring.

The acetyl group was introduced into position 2 of 5-*tert*-butylfuran by the standard procedure involving formation of the methoxy derivative and then acyl chloride, reaction with the ethoxymagnesium derivative of diethyl malonate, and acid hydrolysis [1, 2].

Chlorine in ester **V** was substituted with methoxy group by treatment with sodium methylate in methanol–benzene at 55–60°C. Hydrolysis of the resulting product **XII** yielded acid **XIII**, and its treatment with a twofold excess of thionyl chloride gave acyl chloride **XIV**.

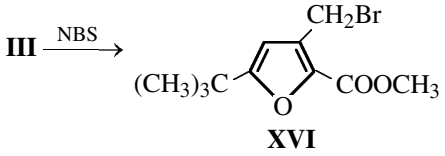


XII **XIII** **XIV**

Acylation of ethoxymagnesium derivative of diethyl malonate gave diethyl acylmalonate, which was hydrolyzed without isolation with a mixture of hydrochloric and acetic acids. Decarboxylation of the keto acid was accompanied by cleavage of the ether bond in the side chain with the formation of chloromethyl ketone **XV**.

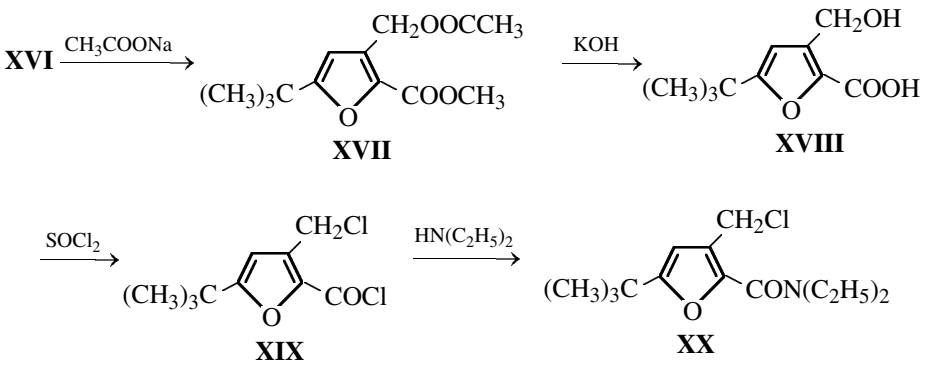
XV

Synthesis of a series of 3-halomethyl compounds was started from the bromination of ester **III** with *N*-bromosuccinimide (NBS). The reaction was performed in carbon tetrachloride, with azobis(isobutyronitrile) as the initiator. Bromination proceeded selectively at the methyl group in position 3 of the ring.



XVI

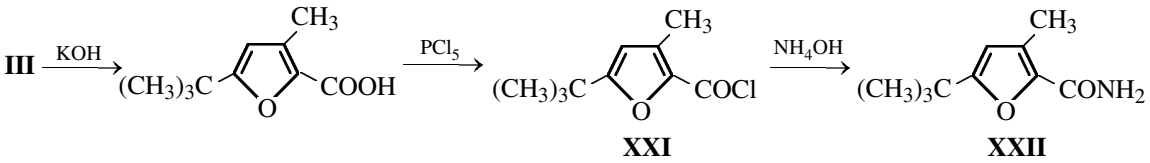
To prepare halomethyl amides, we attempted to use the above-mentioned procedure based on the selectivity of the reaction of chloromethylfurancarboxylic acid chlorides with amines at decreased temperatures. The reaction was carried out according to the following scheme:



XVII **XVIII** **XIX** **XX**

Formation of acetate **XVII**, its hydrolysis, and synthesis of the acid chloride proceed similarly to the corresponding reactions of the 4-substituted products, but the reactions with amines are different. Acyl chloride **XIX** smoothly reacts with diethylamine in benzene, but treatment of a dioxane solution of **XIX** with ammonia even at ~12–15°C causes strong tarring of the reaction mixture, and no unsubstituted amide was isolated.

In this connection, we made an attempt first to introduce the nitrile group into position 2 of the furan ring and then to perform the bromination. Acyl chloride **XXI** prepared by hydrolysis of ester **III** and treatment of the resulting acid with phosphorus pentachloride smoothly reacts with ammonium hydroxide in aqueous acetonitrile to form amide **XXII**.

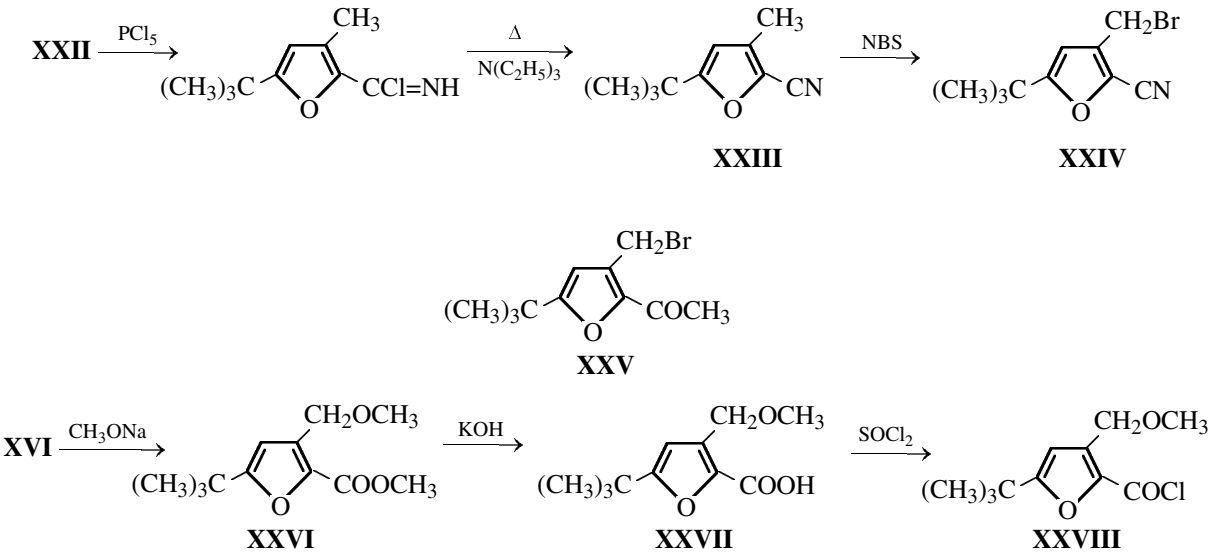


XXI **XXII**

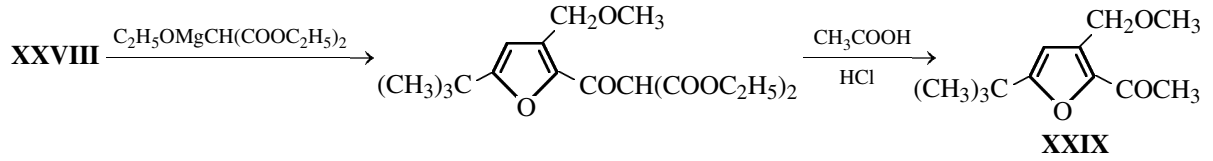
Compound **XXII** reacts with phosphorus pentachloride to form a mixture of imidoyl chloride and nitrile **XXIII**; this mixture is finally dehydrochlorinated after distillation by treatment with triethylamine.

Product **XXIII** is smoothly brominated with *N*-bromosuccinimide at the methyl group in position 3 of the ring to form the desired nitrile **XXIV**.

Acetyl derivative **XXV** was prepared by a scheme similar to that described for **XV**. Treatment of bromide **XVI** with sodium methylate in methanol–benzene gives **XXVI**, and saponification of the ester group followed by treatment with thionyl chloride yields acyl chloride **XXVIII**.



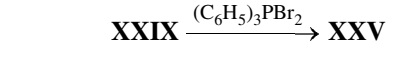
Compound **XXVIII** was involved in the reaction with the ethoxymagnesium derivative of diethyl malonate, and the resulting acyl derivative was hydrolyzed with a mixture of acetic and hydrochloric acids to obtain the methoxymethyl acetylfuran derivative **XXIX**.



In the process, the ether bond was preserved. Apparently, the lability of this group toward acidic agents is a specific feature of alkoxymethyl derivatives of 2-*tert*-butylfuran in which the substituent is located in the range of the effect of the *tert*-butyl group, i.e., in positions 3 and 5 of the ring. Otherwise, *tert*-butylfuran acts as a compound containing no *tert*-butyl substituent; in such compounds, the alkoxymethyl group is stable to the action of a mixture of acetic and hydrochloric acids.

Ether **XXIX** was converted to bromide **XXV** by treatment with triphenyldibromophosphorane in anhydrous acetonitrile at 80°C. The resulting bromo ketone is relatively labile, and therefore the yield of the target compound is as low as 46% at 80% conversion of the starting compound.

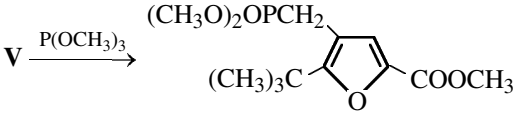
According to the ^{1}H NMR spectrum, the mixture obtained by bromination contained 75% bromide **XXV** and 25% starting ether **XXIX**; it could not be separated by of vacuum distillation. This mixture was involved in the Arbuzov reaction without further purification.



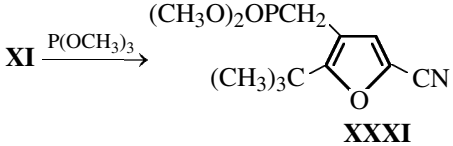
Thus, we have prepared two series of 3- and 4-halomethyl derivatives of 5-*tert*-butylfuran-containing ester, amido, cyano, and acetyl groups in position 2. These products were involved under the similar conditions in the reaction with phosphorus nucleophiles, and their relative reactivities were qualitatively evaluated if possible.

4-Chloromethyl derivatives **V**, **XI**, and **XV** and 3-bromomethyl compounds **XVI**, **XXIV**, and **XXV** were involved in the Arbuzov reaction with trimethyl phosphite, following the commonly used procedure [1, 2]. The resulting phosphorylation products were isolated by vacuum distillation. We found that the compounds containing chloromethyl group in position 4 react with the phosphite relatively slowly. Ester **V**

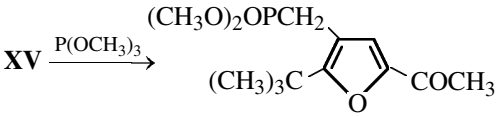
was completely consumed at 118–120°C in 12 h; nitrile **XI**, in 8 h; and the conversion of ketone **XV** was 72% in 10 h. The yields of phosphonates **XXX**–**XXXII** were 78, 60, and 50%, respectively.



XXX

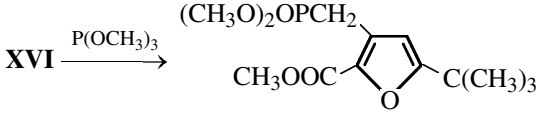


XXXI

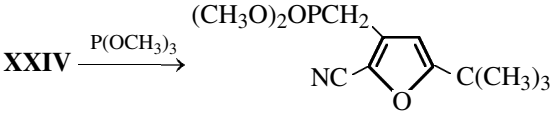


XXXII

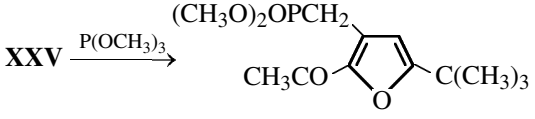
At the same time, 3-bromomethylfurans were completely converted in 60–105 min, and the yields of phosphonates **XXXIII**–**XXXV** were 73, 59, and 89%, respectively.



XXXIII



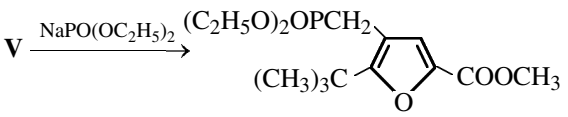
XXXIV



XXXV

Due to the low reactivity of 3-chloromethyl compounds in the Arbuzov reaction, we attempted to use the Michaelis–Becker reaction for their phosphorylation. The reaction was performed in benzene at 80°C, following the standard procedure [1].

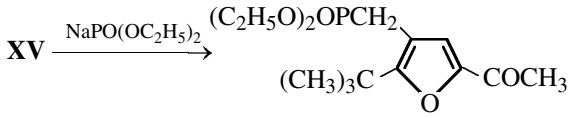
Ester **V** was refluxed with a sodium diethyl phosphite solution for 9 h. A large amount of a white tarry precipitate was formed. Vacuum distillation of the reaction mixture showed that the conversion of the target product was as low as 48%, and the yield of phosphonate **XXXVI** based on the converted product was 32%.



XXXVI

The ^{1}H NMR spectrum of the obtained sample of **XXXVI** showed that it contained a small (<10%) impurity of phosphonate **XXX**. Evidently, the cause of so inefficient phosphorylation is the concurent ester interchange of sodium diethyl phosphite with compound **V** to form sodium dimethyl phosphite, which tends to form polymeric ester salts inactive in nucleophilic substitution. Our results also suggest that it initiates the polymerization of sodium diethyl phosphite, because the latter appeared to be completely consumed, but no appreciable amount of the product containing the ethoxycarbonyl group was detected. The latter fact shows that the extent of the ester interchange is low.

Acetylfuran **XV** was phosphorylated under the conditions of the Michaelis–Becker reaction for 9 h. The conversion of the starting compound was 83%, and the desired phosphonate **XXXVII** was isolated in 50% yield.

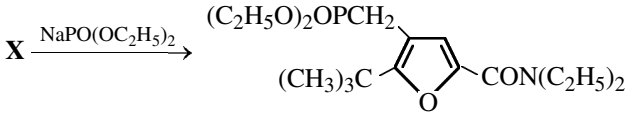


XXXVII

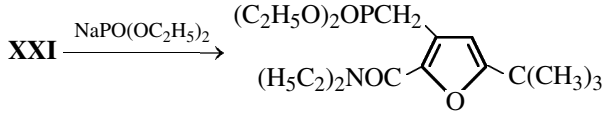
Thus, sodium diethyl phosphite in the case of 4-chloromethyl-5-*tert*-butylfurans functionalized in position 2 is not a more effective phosphorylating agent than trimethyl phosphite; the reaction times, conversions of the starting compounds, and yields of the target products are comparable.

Dialkyl carboxamides containing a chloromethyl group in the β-position of the furan ring do not enter the Arbuzov reaction to a noticeable extent [5]. Therefore, chlorides **X** and **XXI** were phosphorylated under the conditions of the Michaelis–Becker reaction. Diethylamide **X** is consumed more slowly. After refluxing for 14 h in benzene, its conversion was 75%, while the conversion of 3-isomer was complete in 13 h. At the same time, the yield of phosphonate **XXXVIII** was 62%, and compound **XXXIX** was obtained in 43% yield.

Thus, 3-bromomethyl derivatives of 2-functionalized 5-*tert*-butylfurans enter the Arbuzov reaction much more readily than the 4-chloromethyl compounds. This allows us to expect selective 3-phosphorylation of molecules containing both groups.



XXXVIII



XXXIX

At the same time, in the presence of weaker electron-withdrawing substituents like diethylamido group the difference in the reactivity of 3- and 4-chloromethyl groups is insignificant.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Tesla BS-487C (80 MHz) and Tesla BS-497C (100 MHz) spectrometers in carbon tetrachloride. The chemical shifts of phosphorus were calculated from the INDOR spectra.

Methyl 4-chloromethyl-5-*tert*-butylfuran-2-carboxylate V. A fast flow of hydrogen chloride was passed for 2 h through a vigorously stirred mixture of 9.8 g of methyl 5-*tert*-butylfuran-2-carboxylate **II**, 2.4 g of paraform, 1.8 g of zinc chloride, and 50 ml of carbon tetrachloride at 55–60°C. After that, the reaction mixture was cooled and treated with 25 ml of water; the organic layer was separated, washed with water, dried over calcium chloride, and distilled in a vacuum. The starting compound, 1.3 g, bp 67–68°C (1 mm), and 8.2 g of chloride **V**, bp 103–105°C (1 mm), were obtained. Conversion of the starting compound 87%; yield 76%. ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.36 s [$(CH_3)_3C$], 3.71 s, (CH_3OOC), 4.63 s (CH_2Cl), 7.10 s (H^3-furan).

Methyl 4-acetoxymethyl-5-*tert*-butylfuran-2-carboxylate VI. A mixture of 15.9 g of chloride **V**, 10 g of sodium acetate, and 40 ml of acetic acid was refluxed with stirring at 130°C for 13 h. The resulting mixture was diluted with chloroform, the mixture of sodium chloride and acetate was filtered off, the solvent was removed at reduced pressure, and the residue was treated with 50 ml of water. The product was extracted with chloroform, washed with a dilute sodium carbonate solution and with water, dried over calcium chloride, and distilled in a vacuum to give 14.8 g (84%) of the target product **VI**, bp 140–142°C (2 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.32 s [$(CH_3)_3C$], 1.92 s (CH_3COO), 3.67 s (CH_3OOC), 4.90 s (OCH_2), 6.90 s (H^3-furan).

4-Hydroxymethyl-5-*tert*-butylfuran-2-carboxylic acid VII. Acetate **VI**, 7.3 g, was refluxed for 6 h with stirring with a solution of 5.6 g of potassium hydroxide in 30 ml of water. The resulting mixture was acidified with hydrochloric acid and extracted with ether. The ether extract was dried over calcium chloride, the ether was distilled off, and the residue was kept in a vacuum for 1 h. Acid **VII**, 5.2 g, was obtained as a light brown viscous liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.43 s [$(CH_3)_3C$], 4.51 s (CH_2O), 7.16 s (H^3-furan).

4-Chloromethyl-5-*tert*-butylfuran-2-carboxylic acid chloride VIII. A mixture of 11.5 g of acid **VII**, 25 ml of thionyl chloride, and 30 ml of benzene was refluxed with stirring for 6 h. The volatile products were removed at reduced pressure, and the residue was distilled in a vacuum to give 10.5 g of acyl chloride **VIII**, bp 111°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.37 s [$(CH_3)_3C$], 4.45 s (CH_2Cl), 7.25 s (H^3-furan).

4-Chloromethyl-5-*tert*-butylfuran-2-carboxamide IX. A solution of 5.3 g of acyl chloride **IX** in 5 ml of dioxane was added with vigorous stirring to a mixture of 20 ml of aqueous ammonia, 15 ml of dioxane, and 25 g of crushed ice. After melting of the ice, the mixture was diluted with water until a well-formed precipitate was obtained and stirred for 15 min; the precipitate was filtered off and dried in air. Amide **IX**, 4 g, was obtained, mp 122–123°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.41 s [$(CH_3)_3C$], 4.65 s (CH_2Cl), 6.90 s (H^3-furan), 7.05 and 7.23 br.s (NH_2).

4-Chloromethyl-5-*tert*-butylfuran-2-diethylcarboxamide X. A 5-ml portion of diethylamine was added to a vigorously stirred solution of 5.2 g of acyl chloride **VIII** in 50 ml of benzene at room temperature. The resulting mixture was stirred for 1 h and left overnight. After that, diethylamine hydrochloride was filtered off, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 4.4 g of amide **X**, bp 160–161°C (2 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.34 m [$(CH_3)_3C$ + CH_3-ethyl]; 3.41 q (CH_2N, J_{HH} 7 Hz), 4.46 s (CH_2Cl), 6.76 s (H^3-furan).

4-Chloromethyl-5-*tert*-bytul-2-cyanofuran XI. To a suspension of 3.4 g of amide **X** in 15 ml of toluene, 3.4 g of phosphorus pentachloride was added with vigorous stirring at room temperature. The mixture was refluxed for 7 h and distilled in a vacuum. A fraction with bp 97–170°C (1 mm) was collected.

It was dissolved in toluene, and 3 ml of triethylamine was added. The resulting mixture was stirred for 20 min, triethylamine hydrochloride was filtered off, and the filtrate was distilled in a vacuum to give 1.1 g of nitrile **XI**, bp 91°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.36 s [$(CH_3)_3C$], 4.41 s (CH_2Cl), 6.86 s (H^3-furan).

Methyl 4-methoxymethyl-5-*tert*-butylfuran-2-carboxylate XII. Sodium, 1.9 g, was dissolved in 15 ml of anhydrous methanol, and 30 ml of benzene was added. After that, 18.2 g of chloride **V** was added in one portion with stirring. The resulting mixture was heated for 12 h at 55–60°C with vigorous stirring, after which it was poured into 40 ml of water. After shaking in a separating funnel, the organic layer was removed, and the aqueous layer was saturated with sodium chloride and extracted with benzene. The combined benzene solutions were dried over calcium chloride and distilled in a vacuum to give 10.2 g of **XII**, bp 116°C (2 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.31 s [$(CH_3)_3C$], 3.21 s (CH_3O), 3.71 s (CH_3OOC), 4.21 s (CH_2O-furan), 6.89 s (H^3-furan).

4-Methoxymethyl-5-*tert*-butylfuran-2-carboxylic acid chloride XIV. Ether **XII**, 10.2 g, was refluxed with stirring for 5 h with a solution of 5 g of potassium hydroxide in 40 ml of 50% aqueous ethanol. After that, the ethanol was distilled off at reduced pressure, and the residue was acidified with hydrochloric acid to pH 1. The resulting oil was separated, the aqueous layer was extracted with ether, and the combined organic phases were dried over calcium chloride. The ether was removed, and the remaining oil was dissolved in 30 ml of benzene and refluxed with stirring with 10 ml of thionyl chloride and 0.8 ml of DMF for 5 h. The solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 8.0 g of acyl chloride **XIV**, bp 105–107°C (1 mm).

4-Chloromethyl-5-*tert*-butyl-2-acetylfuran XV. Absolute ethanol, 3 ml, and a small crystal of iodine were added to 0.85 g of magnesium turnings. After the hydrogen evolution started, a solution of 6.0 ml of diethyl malonate in 10 ml of absolute ethanol was added at a rate providing the boiling of the reaction mixture. After the addition was complete, the reaction mixture was stirred at 60–70°C for 1 h and cooled; 100 ml of anhydrous ether was added. After the complete dissolution of the ethoxymagnesium derivative, the reaction mixture was cooled to 10°C, and 8.0 g of acyl chloride **XIV** was added dropwise with stirring at 10–15°C. The resulting mixture was stirred at room temperature for 4 h and left overnight. After that, the reaction mixture was treated with dilute hydrochloric acid. The ether layer was separated, and the aqueous layer was extracted with ether. The combined extracts were dried over calcium chloride, and the solvent was removed. The residue was dissolved in 20 ml of glacial acetic acid, 3 ml of hydrochloric acid was added, and mixture was refluxed for 6 h. The resulting mixture was poured into 100 ml of water, and the product was extracted with ether. The combined organic layers were washed with a solution of sodium carbonate and water and then dried over calcium chloride. Vacuum distillation gave 4.6 g of acetylfuran **XV**, bp 110–111°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.42 s [$(CH_3)_3C$], 2.30 s (CH_3CO), 4.50 s (CH_2Cl), 6.42 s (H^3-furan).

Methyl 3-bromomethyl-5-*tert*-butylfuran-2-carboxylate XVI. A vigorously stirred mixture of 25.3 g of ester **III**, 24 g of *N*-bromosuccinimide, 0.2 g of azobis(isobutyronitrile), and 200 ml of carbon tetrachloride was heated to initiate an exothermic reaction. After the end of spontaneous boiling, the reaction mixture was refluxed with stirring for 3 h and left overnight. After that, succinimide was filtered off, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 23.7 g of bromide **XVI**, bp 121°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.37 s [$(CH_3)_3C$], 3.74 s (CH_3OOC), 4.51 s (CH_2Br), 6.05 s (H^4-furan).

Methyl 3-(acetoxymethyl)-5-*tert*-butylfuran-2-carboxylate XVII. A mixture of 11.5 g of bromide **XVI**, 8 g of sodium acetate, and 50 ml of acetic acid was refluxed with stirring for 12 h. After that, the reaction mixture was poured into 200 ml of water and extracted with chloroform. The extract was dried over calcium chloride and distilled in a vacuum to give 6.6 g of acetate **XVII**, bp 132–134°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.34 s [$(CH_3)_3C$], 2.06 s (CH_3COO), 3.82 s ($COOCH_3$), 5.19 s (CH_2O-furan), 6.12 s (H^4-furan).

3-Hydroxymethyl-5-*tert*-butylfuran-2-carboxylic acid XVIII. Acetate **XVII**, 6.6 g, was refluxed for 4 h with a solution of 6 g of sodium hydroxide in 50 ml of water. The resulting mixture was cooled and acidified to pH 1. After storage for 3 h, the product crystallized. The crystals were filtered off, washed with water, and dried in air. Yield of acid **XVIII** 4.9 g, mp 119–120°C (with decomposition).

3-Chloromethyl-5-*tert*-butylfuran-2-carboxylic acid chloride XIX. A mixture of 4.9 g of acid **XVIII**, 7 ml of thionyl chloride, and 15 ml of benzene was refluxed with stirring for 4 h and distilled in a vacuum to give 3.8 g of acid chloride **XIX**, bp 109°C (1 mm).

***N,N*-Diethyl-3-chloromethyl-5-*tert*-butylfuran-2-carboxamide XX.** A solution of 2.9 ml of diethyl-

amine in 3 ml of benzene was added dropwise with stirring at 15–20°C to a solution of 3 g of acyl chloride **XIX** in 15 ml of benzene. The mixture was stirred for 2 h and left overnight. After that, diethylamine hydrochloride was filtered off, and the benzene filtrate was washed with dilute hydrochloric acid and then with water, dried over calcium chloride, and distilled in a vacuum to give 1.1 g of amide **XX**, bp 125–126°C (1 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 m [CH_3-ethyl + $(CH_3)_3C$], 3.29–3.49 br.s (CH_2N), 4.72 s (CH_2Cl), 6.12 s (H^4-furan).

3-Methyl-5-*tert*-butylfuran-2-carboxylic acid chloride XXI. 3-Methyl-5-*tert*-butylfuran-2-carboxylic acid, 9 g, was suspended in 50 ml of benzene, and 10.3 g of finely ground phosphorus pentachloride was added in small portions with stirring. After the addition was complete, the reaction mixture was refluxed for 4 h and distilled in a vacuum to give 9.1 g of acyl chloride **XXI**, bp 86°C (1 mm).

3-Methyl-5-*tert*-butylfuran-2-carboxamide XXII. Acyl chloride **XXI**, 5.1 g, was dissolved in 5 ml of acetonitrile, and this solution was added in one portion with vigorous stirring to 25 ml of 25% aqueous ammonia. The resulting mixture was stirred for 30 min; the precipitate that formed was filtered off and dried in air. Yield 4.3 g, mp 149–150°C.

3-Methyl-5-*tert*-butyl-2-cyanofuran XXIII. Amide **XXII**, 3.6 g, was suspended in 10 ml of benzene, and 4.2 g of finely ground phosphorus pentachloride was added in several portions. The reaction mixture was refluxed for 4 h and distilled in a vacuum. The fraction with bp 70–121°C (1 mm) was collected. It was dissolved in 10 ml of benzene, 2 ml of triethylamine was added, and the mixture was stirred for 2 h. Triethylamine hydrochloride was filtered off, and the filtrate was distilled in a vacuum to give 1.6 g of cyanofuran **XXIII**, bp 84–86°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.12 s [$(CH_3)_3C$], 2.07 s (CH_3-furan), 5.82 m (H^4-furan).

3-Bromomethyl-5-*tert*-butyl-2-cyanofuran XXIV. Nitrile **XXIII**, 1.6 g, was dissolved in 15 ml of carbon tetrachloride, 1.7 g of *N*-bromosuccinimide and 0.2 g of azobis(isobutyronitrile) were added in one portion, and the resulting mixture was refluxed for 2 h. After the disappearance of traces of *N*-bromosuccinimide, the reaction mixture was left overnight. After that, succinimide was filtered off, and the filtrate was distilled in a vacuum to give 1.3 g of bromide **XXIV**, bp 105°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.32 s [$(CH_3)_3C$], 4.24 s (CH_2Br), 6.09 s (H^4-furan).

Methyl 3-methoxymethyl-5-*tert*-butylfuran-2-carboxylate XXVI. Sodium, 0.8 g, was dissolved in 15 ml of ethanol, and a solution of 8.2 g of bromide **XVI** in 20 ml of benzene was added with stirring. The reaction mixture was stirred for 16 h at 45–50°C, the precipitate that formed was filtered off, the solvents were removed at reduced pressure, and the residue was treated with 20 ml of water. The resulting mixture was extracted with ether, the extract was dried over calcium chloride, the ether was distilled off, and the residue was distilled in a vacuum to give 4.4 g of ester **XXVI**, bp 104–105°C (1 mm). ^{1}H NMR spectrum, δ, ppm: 1.27 s [$(CH_3)_3C$], 3.27 s (CH_3O), 3.75 s (CH_3OOC), 4.47 s (CH_2O-furan), 6.05 s (H^4-furan).

3-Methoxymethyl-5-*tert*-butylfuran-2-carboxylic acid chloride XXVIII. Compound **XXVI**, 4.4 g, was refluxed for 4 h with a solution of 2.2 g of potassium hydroxide in 20 ml of water. The resulting homogeneous solution was acidified, and compound **XXVII** was extracted with ether. The combined extracts were dried over calcium chloride, the ether was distilled off, and the residue was kept in a vacuum. Acid **XXVII**, 3.5 g, was obtained as a viscous liquid. The product was dissolved in 26 ml of benzene, 0.5 ml of DMF and 4 ml of thionyl chloride were added, and the resulting mixture was refluxed with stirring for 4 h. Vacuum distillation of the reaction mixture gave 2.8 g of acyl chloride **XXVIII**, bp 100°C (1 mm).

3-Methoxymethyl-5-*tert*-butyl-2-acetylfuran XXIX. Magnesium turnings, 0.7 g, were treated with 3 ml of absolute ethanol, a small crystal of iodine was added, and after the start of the reaction a solution of 5 ml of diethyl malonate in 10 ml of anhydrous ethanol was added. After the completion of the vigorous reaction, the mixture was stirred for 15 min at 60–70°C and cooled; 20 ml of ether were added. After that, a solution of 6.2 g of acyl chloride **XXVIII** in 10 ml of anhydrous ether was added dropwise with stirring. The reaction mixture was stirred for 2 g at room temperature and left overnight. Then the mixture was treated with dilute hydrochloric acid, the ether layer was separated, and the aqueous layer was extracted with ether. The combined extracts were dried over calcium chloride, the ether was distilled off, and the residue was dissolved in 20 ml of acetic acid. The solution was treated with 6 ml of hydrochloric acid, and the resulting mixture was refluxed with stirring for 6 h. After that, the reaction mixture was treated with water, extracted with ether, dried over calcium chloride, and distilled in a vacuum to give 3.6 g of ketone **XXIX**, bp 84–86°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.21 s [$(CH_3)_3C$], 2.24 s (CH_3CO), 3.24 s (CH_3OC), 4.44 s (CH_2O-furan), 6.15 s (H^4-furan).

Cleavage of the ether bond with triphenyldibromophosphorane. Triphenylphosphine, 4.5 g, was dissolved at elevated temperature in 50 ml of anhydrous acetonitrile, the solution was cooled to 5°C, and 0.9 ml of bromine was added dropwise with stirring. To the resulting suspension of triphenyldibromophosphorane, a solution of 3.6 g of ketone **XXIX** in 5 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 6 h at 80°C. After that, the major fraction of acetonitrile was distilled off at reduced pressure, and the residue was poured into 25 ml of water. The resulting mixture was extracted with ether, the crystals of triphenylphosphine oxide were filtered off, and the filtrate was dried over calcium chloride. The ether solution was filtered once more and distilled in a vacuum to give 2.3 g of the fraction with bp 100°C (1 mm). According to ^{1}H NMR spectrum, it consisted of bromide **XXV** and unchanged ether **XXIX** in 3 : 1 molar ratio. Yield of bromide 46%, conversion of methoxy derivative 83%. ^{1}H NMR spectrum of bromide **XXV** (CCl_4), δ, ppm: 1.29 s [$(CH_3)_3C$], 2.34 s (CH_3CO), 4.57 s (CH_2Br), 6.12 s (H^4-furan).

Methyl 4-(dimethoxyphosphorylmethyl)-5-*tert*-butylfuran-5-carboxylate XXX. A mixture of 3.1 g of chloride **V** and 7 ml of trimethyl phosphite was heated with stirring. At 70°C, the mixture got turbid, and at 109°C ethyl chloride started to evolve. The mixture was refluxed for 12 h; the temperature was maintained at 118–120°C and in the last 30 min gradually raised to 145°C. Vacuum distillation gave a product with bp 168–170°C (1 mm). Yield of phosphonate **XXX** 3.2 g (78%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 s [$(CH_3)_3C$], 3.00 d (CH_2P, J_{HP} 21 Hz), 3.68 d (CH_3OP, J_{HP} 11 Hz), 6.90 s (H^3-furan). δ_P 23.6 ppm.

4-Dimethoxyphosphorylmethyl-5-*tert*-butyl-2-cyanofuran XXXI. A mixture of 1.8 g of nitrile **XI** and 6 ml of trimethyl phosphite was heated with stirring. At 109°C, methyl chloride started to evolve. After that, the temperature of the reaction mixture rose to 122°C and remained at this level for 8 h. In the last 30 min, the temperature of the reaction mixture started to rise further and reached 130°C. Vacuum distillation gave nitrile **XXXI**, bp 158°C (1 mm). Yield 1.5 g (60%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 s [$(CH_3)_3C$], 2.90 d (CH_2P, J_{HP} 20 Hz), 3.60 d (CH_3OP, J_{HP} 10 Hz), 6.92 s (H^3-furan).

4-(Dimethoxyphosphorylmethyl)-5-*tert*-butyl-2-acetylfuran XXXII. A mixture of 2.5 g of chloro ketone **XV** and 6 ml of trimethyl phosphite was heated with stirring for 10 h. During the first hour, the temperature of the reaction mixture gradually rose from 101 to 122°C and remained at this level for 8.5 h. In the last 30 min, it reached 136°C. Vacuum distillation of the reaction mixture gave 0.7 g of the starting chloride **XV** with bp 115–125°C (1 mm) and 1.2 g of keto phosphonate **XXXII**, bp 169–170°C (1 mm). Conversion of the starting compound 72%, yield of the target product 50%. ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.36 s [$(CH_3)_3C$], 2.24 d (CH_3CO), 2.91 d (CH_2P, J_{HP} 21 Hz), 3.68 d (CH_3OP, J_{HH} 11 Hz), 6.90 s (H^3-furan), δ_P 25.2 ppm.

Methyl 3-(dimethoxyphosphorylmethyl)-5-*tert*-butylfuran-2-carboxylate XXXIII. A mixture of 2.1 g of bromide **XVI** and 6 ml of trimethyl phosphite was heated with stirring. At 95°C, methyl bromide started to evolve. The mixture came to boil, and its temperature gradually rose from 101 to 130°C in the course of 100 min. Vacuum distillation of the reaction mixture gave 1.7 g (73%) of phosphonate **XXXIII**, bp 159–160°C (1 mm). ^{1}H NMR spectrum, δ, ppm: 1.40 s [$(CH_3)_3C$], 3.35 d (CH_2P, J_{HP} 22 Hz), 3.70 d (CH_3OP, J_{HP} 11 Hz), 3.86 s (CH_3OOC), 6.10 s (H^4-furan). δ_P 23.3 ppm.

3-(Dimethoxyphosphorylmethyl)-5-*tert*-butyl-2-cyanofuran XXXIV. A mixture of 1.3 g of bromide **XXIV** and 4 ml of trimethyl phosphite was heated with stirring. At 95°C, methyl bromide started to evolve, and at 101°C the reaction mixture came to boil. It was refluxed for 105 min, with the temperature gradually rising to 130°C. Vacuum distillation of the reaction mixture gave 1.0 g (59%) of the desired phosphonate **XXXIV**, bp 159°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.20 s [$(CH_3)_3C$], 2.91 d (CH_2P, J_{HP} 21 Hz), 3.62 d (CH_3OP, J_{HP} 12 Hz), 6.14 s (H^4-furan). δ_P 22.4 ppm.

3-(Dimethoxyphosphorylmethyl)-5-*tert*-butyl-2-acetylfuran XXXV. A mixture of 2.3 g of crude bromide **XXV** (1.73 g of the main substance) and 5 ml of trimethyl phosphite was heated with stirring. At 106°C, methyl bromide started to evolve, and the reaction mixture came to boil. It was refluxed for 1 h, and the temperature rose to 132°C. Vacuum distillation of the reaction mixture gave 1.7 g (89%) of phosphonate **XXXV**, bp 157–158°C (1 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.24 s [$(CH_3)_3C$], 2.27 s (CH_3CO), 3.29 d (CH_2P, J_{HP} 23 Hz), 3.56 d (CH_3OP, J_{HP} 10 Hz), 6.18 s (H^4-furan), δ_P 24.0 ppm.

4-(Diethoxyphosphorylmethyl)-5-*tert*-butyl-2-acetylfuran XXXVII. A solution of 1.8 g of chloride **XV** in 3 ml of benzene was added to a solution of sodium diethyl phosphite (prepared from 0.2 g of sodium and 1.5 ml of diethyl hydrogen phosphite in 15 ml of benzene) at 80°C. After some time, sodium chloride started to precipitate, but no heat evolution

was observed. The mixture was refluxed with stirring for 9 h, sodium chloride was removed on a centrifuge, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 0.3 g of the starting chloride, bp 120–125°C (1 mm), and 1.1 g of phosphonate **XXXVI**, bp 168–168°C (1 mm). Conversion of the starting product 83%, yield of the desired phosphonate 50%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (CH_3-ethyl, J_{HH} 7 Hz), 1.45 s [$(CH_3)_3C$], 2.34 s (CH_3CO), 2.96 d (CH_2P, J_{HP} 21 Hz), 3.99 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 10 Hz), 6.98 s (H^3-furan).

Reaction of chloride V with sodium diethyl phosphite. A solution of chloride **V** in 3 ml of benzene was added with stirring to a solution of sodium diethyl phosphite (prepared from 0.27 g of sodium and 2 ml of diethyl hydrogen phosphite) at 80°C. Sodium chloride started to precipitate almost immediately, but no heat evolution was observed at the instant of mixing the reactants. The reaction mixture was refluxed for 9 h, sodium chloride was removed on a centrifuge, and the resulting solution was distilled in a vacuum to give 1.4 g of the starting compound **V**, bp 109–110°C (1 mm), and 0.6 g of phosphonate **XXXVI**, bp 158–160°C. Conversion of the starting compound 48%, yield of phosphonate **XXXVI** 32%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 t (CH_3-ethyl, J_{HH} 7 Hz), 1.41 s [$(CH_3)_3C$], 2.97 d (CH_2P, J_{HP} 22 Hz), 3.70 s (CH_3OOC), 3.93 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 6.90 s (H^3-furan). δ_P 23.6 ppm; impurity signal 3.67 d (CH_3OP, J_{HP} 10 Hz).

***N,N*-Diethyl-4-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-2-carboxamide XXXVIII.** A solution of 4.4 g of amide **X** in 5 ml of benzene was added to a solution of sodium diethyl phosphite (prepared from 0.4 g of sodium and 2.6 ml of diethyl hydrogen phosphite in 30 ml of benzene) at 80°C. The resulting mixture was refluxed for 14 h, the sodium chloride precipitate was removed on a centrifuge, the benzene was distilled off at reduced pressure, and the residue was distilled in a vacuum to give 1.1 g of the starting chloride **X**, bp 159–165°C (1 mm), and 2.8 g of phosphonate **XXXVIII**, bp 196–198°C (1 mm). Conversion of the starting product 75%, yield of the phosphonate 62%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (CH_3-ethyl), 1.40 s [$(CH_3)_3C$], 2.93 d (CH_2P, J_{HP} 22 Hz), 3.49 q (CH_2N-ethyl, J_{HH} 7 Hz), 3.98 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 6.78 s (H^3-furan). δ_P 22.9 ppm.

***N,N*-Diethyl-3-(diethoxyphosphorylmethyl)-5-*tert*-butylfuran-2-carboxamide XXXIX.** A solution of 1.1 g of chloride **XXI** in 2 ml of benzene was added with stirring 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) at 80°C. The resulting mixture was refluxed for 13 h, the sodium chloride precipitate was removed on a centrifuge, the solvent was removed at reduced pressure, and the residue was distilled in a vacuum to give 0.7 g (43%) of phosphonate **XXXIX**, bp 169–172°C (1 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.00–1.15 m [CH_3-ethyl + $(CH_3)_3C$], 3.10 d (CH_2P, J_{HP} 21 Hz), 3.35 br.q (CH_2N, J_{HH} 7 Hz), 3.90 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz), 6.12 s (H^4-furan). δ_P 23.0 ppm.

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