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Synthesis of Isomeric Bromo(diethoxyphosphorylmethyl)furans

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Abstract—Series of the previously unknown bromo(diethoxyphosphorylmethyl)furans including four of six possible regioisomers is synthesized. The target products were obtained by bromination of the corresponding (diethoxyphosphorylmethyl)furans or by a four-step synthesis including bromination of isomeric methyl-furancarboxylates, reduction of the products formed to the corresponding alcohols, substitution of hydroxy group with halogen and phosphorylation by the Michaelis–Becker reaction. It was established for the first fime that in the course of bromination of alkyl carboxylates and phosphonates of the furan series under the typical conditions of electrophilic reaction (Br_2 + 10% molar of $AlCl_3$, chloroform) the substituent enters not only into the heteroring, but also into the side chain. In the case of 5-methyl-2-(diethoxyphosphorylmethyl)furan only the last reaction pathway is observed. It is shown that bromo(chloromethyl)furans react with sodium diethyl phosphite not only according to the Michaelis–Becker scheme leading to phosphonates, but also by the pathway of debromination of the furan ring. The last unexpected reaction may acquire a practical use for removing a substituent protecting the α-position of the furan ring under mild conditions.

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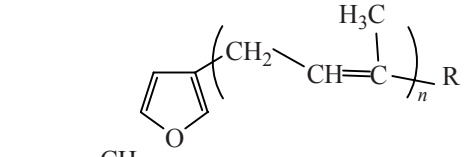
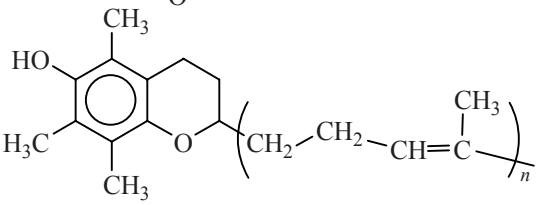
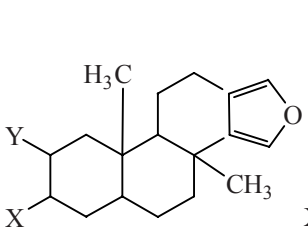
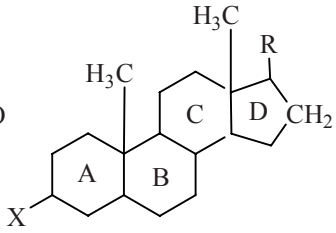
Subaqueous fauna and flora are the abundant sources of biologically active compounds with the structure resembling that of the substances found on the dry land, but distinguished by the presence of the furan rings instead of the carbocyclic or heterocyclic fragments present in the overland analogs. For example, furanosesquiterpenoids of sponges have the unsaturated side chain analogous to that of tocotrienes found in the wheat bran, rice, and the Hevea latex, but instead of the chroman ring these marine products contain 3-furyl radical [1, 2].





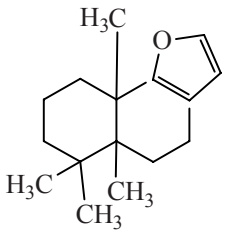
The carbon skeleton of a series of polycyclic triterpenoids isolated from sponges [3, 4] resembles the steroid one, but the place of cyclopentane fragment D is occupied by the furan ring.



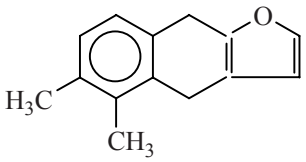


This trend probably reflects the general tendency in the structure of the bioregulators of marine organisms.

Formation of furoterpene structures was developed in the course of total synthesis of pallescensines A and E [5, 6]. Its key stage is the condensation of (diethoxyphosphorylmethyl)furan or the phosphonium salt of similar structure with the derivatives of formylcyclohexane under the conditions of the Wittig–Horner reaction.



Pallescensine A



Pallescensine E

From the point of view of the search for new biologically active compounds introduction of substituents in the furan ring of such substances presents a great interest. One of the very attractive substituents is bromine because it is found that the bromine-containing terpenoids of marine organisms exhibit an expressed antitumor activity [1].

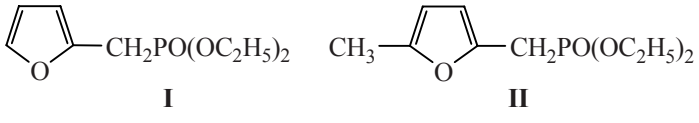
At the same time the simplest (dialkoxyphosphorylmethyl)furans containing the bromine atom in the ring are not studied at all and no synthetic approaches to them are developed.

The aim of this work is the investigation of pathways to the synthesis of such structures.

Two most evident routes can be principally suggested. One of them is bromination of phosphonomethylated furans under the electrophilic substitution conditions, while another one includes phosphorylation of the corresponding bromo(halomethyl)furans according to the Michaelis–Becker reaction. In the course of our work both approaches were tested.

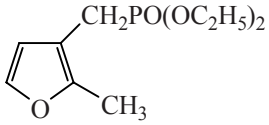
The electrophilic bromination of furans was studied incompletely mainly by the example of 2-substituted compounds. Furan and its homologs were brominated with bromine in the presence of such hydrogen bromide acceptors as pyridine and DMF [5], or with dioxane dibromide [6]. 2-Furoic acid was brominated with bromine in the presence of red phosphorus [7], and its esters, with bromine without a catalyst [5]. The monobromination of furfural in the position 5 was carried out with bromine in the presence of sulfur and hydroquinone in boiling dichloroethane [8]. A selective 4,5-dibromination of furfural, alkyl 2-furoates, and acetylfuran was attained in the reaction with bromine in $AlCl_3$ medium [9,10]. Studies of bromination of furans were in general completed to the end of nineteen seventies and afterwards this problem was not specially tackled.

The data mentioned show that the range of brominating systems is not wide. While deciding upon the conditions of bromination of (dialkoxyphosphorylmethyl)furans it should be considered that the substituent present is a weak acceptor and somewhat deactivated the furan ring for the electrophilic substitution reactions. Besides, under the action of hydrogen bromide dealkylation can proceed leading to the formation of alkyl bromide and the hydroxy group on phosphorus. That is why it seems the most reasonable to carry out the bromination with the elementary bromine in chloroform in the presence of pyridine. Phosphonates **I–IV** were chosen as substrates.

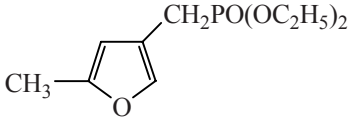


I

II



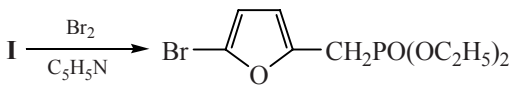
III



IV

Each of these compounds has only one position most active in the electrophilic substitution reactions. At the same time the effect of α- and β-phosphonomethyl group on the course of bromination in different positions of the ring might be traced.

The bromination of phosphonate **II** was carried out in chloroform in the presence of 1 mol of pyridine at 25°C. Reaction proceeded with the heat evolution, and the bromine was consumed practically in the moment of addition. The workup of the reaction mixture gave crude bromophosphonate **V** as a mobile dark oil. The substance obtained contained no starting compound. Its ^{31}P NMR spectrum contained a signal of phosphonate at δ_P 21.5 ppm and a minor signal of diethyl hydrogen phosphate at δ_P 10.9 ppm showing that the oxidative cleavage of P–C bond took place. Yield of bromophosphonate **V** was evaluated at 69%.



V

The substance isolated from the reaction mixture was distilled in a vacuum with partial decomposition, but the distillate with bp 128°C (1 mm Pп) was a spectroscopically pure phosphonate **V**.

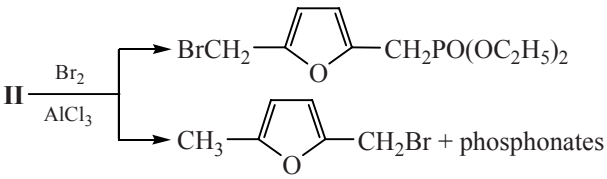
The reaction of phosphonate **II** with bromine was carried out analogously. The coloration with bromine quickly disappeared in the course of the process, but analysis of the reaction products showed that no substitution in the furan ring took place. ^{31}P NMR spectrum contained the signal of diethyl hydrogen phosphate at δ_P 10.975, and a signal with δ_P –79.910 ppm attributed by us to bromophosphate. The treatment of the reaction mixture permitted recovering 23% of the starting phosphonate **II**, and to obtain a mixture of the products of oxidative dephosphorylation of the initial substance which we failed to separate and identify.

With the purpose to turn the reaction of phosphonate **II** with bromine to the pathway of electrophilic substitution we used aluminum chloride as catalyst in an amount of 6 mol %. The consumption of bromine in the course of the reaction started at 10°C and occurred just after the addition of each new portion of the reagent. ^{1}H NMR spectrum of reaction mixture permitted the identification of the starting phosphonate **II**, bromomethylphosphonate **VI** [^{1}H NMR spectrum, δ, ppm: 3.213 d (CH_2P, J_{HP} 21.6 Hz), 4.393 s (CH_2Br), 6.150 s (H_3-furan), 6.256 s (H^4-furan), δ_P 19.888 ppm], and 5-methyl-2-bromomethylfuran **VII** [^{1}H NMR spectrum, δ, ppm: 2.307 s (CH_3-furan), 4.468 s (CH_2Br), 5.917 s (H^4-furan), 6.250 s (H^3-furan)]. Bromomethyl derivatives were removed by treating the reaction mixture with triethylamine, and 37% of starting phosphonate **II** was recovered from the residue. Crystals of the salt obtained in the course of the workup of the reaction mixture were identified spectroscopically as the triethylammonium salt with an inorganic anion. It had no clear melting point, and most probably it was a mixture. The elimination of triethylammonium salts from the quarternary ammonium ones is characteristic of furans [11] and may be considered an indirect evidence of their formation, and hence of the presence of bromomethyl compounds in the mixture under investigation.

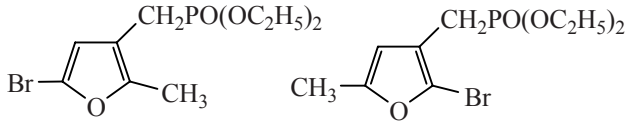
^{31}P NMR spectrum of the reaction mixture besides the above-mentioned signals contains also the signals of phosphates with δ_P 12.020, 10.849, and 0.457 ppm.

Hence, it was established that the reaction of phosphonate **II** with bromine under typical conditions of the aromatic electrophilic substitution proceeds according to two pathways exclusively in the side chain.

At the same time no substitution in the furan ring was established.



Reaction of phosphonate **II** with bromine was carried out in chloroform at room temperature in the presence of pyridine. Under these conditions bromine was completely consumed, but a large amount of the starting compound remained in the reaction mixture. ^{1}H NMR spectrum of the isolated mixture of substances contained intense signals in the range 2.5–4.0 ppm related to the aliphatic compounds. In ^{31}P NMR spectrum of this preparation the signals with δ_P 27.903, 24.675, 23.556, and 21.471 ppm characteristic of the aliphatic phosphonates were observed. The signals of phosphates at δ_P 0.868 and 0.471 ppm and of bromophosphate at δ_P –72.881 ppm were also identified. Minor signals with δ 6.282 ppm in ^{1}H NMR spectrum and with δ_P 25.161 ppm in ^{31}P NMR spectrum were attributed to the bromination product **VIII** (for pure compound **VIII** signal of the ring proton H^4 appeared at δ 6.157 ppm and the signal of phosphorus was observed at δ_P 25.418, see below). Hence, in the case of phosphonate **III** the main pathway of the reaction with bromine is the opening of the furan ring without the cleavage of P–C bond. Oxidative dephosphorylation and bromination of the furan ring become the side pathways.



VIII **IX**

Reaction of phosphonate **IV** with bromine was carried out analogously to the previous case. In ^{1}H NMR spectrum of the obtained mixture of products the were identified starting phosphonate **IV**, bromide **IX** [^{1}H NMR spectrum δ 6.033 ppm (H^4-furan), ^{31}P NMR spectrum, δ_P 24.664 ppm. Bromide **IX** obtained according to the Michaelis–Becker reaction, ^{1}H NMR spectrum δ 6.040 ppm (H^4-furan), ^{31}P NMR spectrum δ_P 24.671 ppm (see below)]. In the range 2.5–4.0 ppm numerous signals of aliphatic protons belonging to nonidentified compounds were observed. ^{31}P NMR spectrum contained also the signals of phosphates with δ_P 6.758 and 0.14 ppm.

Hence, reaction of phosphonate with bromine proceeds also according to several pathways including

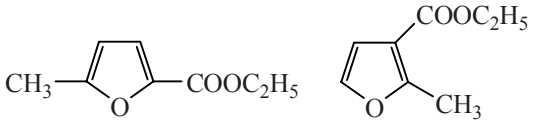
bromination of the furan ring, its cleavage, and rupture of the P–C bond.

The data presented shows that only bromophosphonate **V** may be prepared by direct bromination of phosphonate **I**.

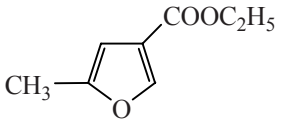
Second approach to the synthesis of bromophosphonates includes the preparation of halomethylfurans brominated in the ring and their subsequent phosphorylation under the conditions of the Michaelis–Becker reaction.

2-Chloromethyl-4-bromofuran, the only known compound series, was obtained by the four-step synthesis from 4,5-dibromo-2-furaldehyde [12].

Synthesis of isomeric bromo(chloromethyl)furans was planned to include bromination of the corresponding alkyl furoates, the reduction of the compounds obtained to alcohols, and substitution of hydroxy groups with chlorine.



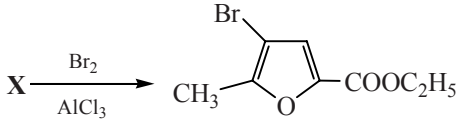
X **XI**



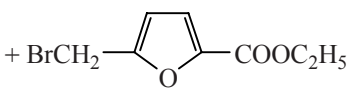
XII

Bromination of the esters **X–XII** with bromine in chloroform according to the procedure used for alkyl 2-furoates [6] showed that conversion of the esters **XI, XII** was not high, and compound **X** did not react at all. In connection with that we tried to use the $AlCl_3$ catalyst in the amount up to 10% mol.

It proved that the reaction of compound **X** with bromine under these conditions began at 40°C and led to the formation of two products **XIII, XIV**.



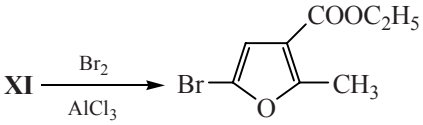
XII



XIV

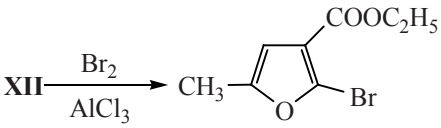
Ratio of the reaction products depended on temperature, and at 40–42°C it was 0.8:1 (conversion 79%, overall yield 54%), at 51–52°C it is 1.7:1 (conversion 78%, overall yield 55%) at 55–56°C it was 2.1:1 (conversion 78%, overall yield 58%), and at 64-65°C it decreased to 0.7:1 (conversion 72%, overall yield 37%). Bromomethyl compound **XIV** was removed by treating the reaction mixture with triethylamine.

Bromination of the ester **XI** in the presence of small amount of the aluminum chloride in chloroform proceeded at room temperature to form single product **XV** in 71% yield.

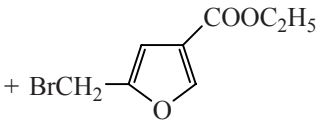


XV

Bromination of compound **XII** proceeded under the analogous conditions to form the products of substitution in the ring and in the side chain, the product ratio being 1.00:0.22. The overall yield reached 89%. Bromomethyl derivative **XVII** was removed by treating the mixture obtained with triethylamine.



XVI



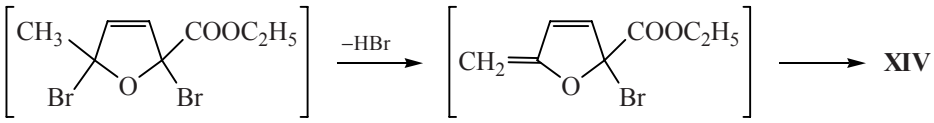
XVII

Hence, it was shown that the reaction of alkyl furoates with bromine under the typical conditions of electrophilic substitution was directed in the ring as well as in the side chain. The extent of the last pathway increases with the decrease in the activity of the participating position of the ring in the electrophilic substitution reactions.

The formation of bromomethyl derivatives is understandable within the framework of existing knowledge on the reactions of furans with electrophiles. As known, compounds of the furan series react according to two mechanisms [13]. The first one

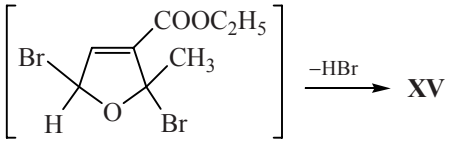
resembles electrophilic substitution in the aromatic ring, while the second one includes formation and subsequent decomposition of the adduct by the positions 2 and 5 of the ring. In the case of monosubstituted furans the same products are formed, while in the case of polysubstituted substances it is necessary to analyse the preferred direction of decomposition of the intermediate adduct of alkyl methylfuroates with bromine.

In the case of ester **X** adduct **XVIII** was formed. The elimination of bromide ion in this case must proceed from the position 5 because the electronic density on the Br^5 atom is higher than on the Br^2 one exposed to the effect of the ethoxycarbonyl group. The intermediate **XIX** formed is stabilized by the system of conjugated bonds and is capable of further stabilization by the transfer of bromine in the side chain with the restoration of heteroaromatic structure.

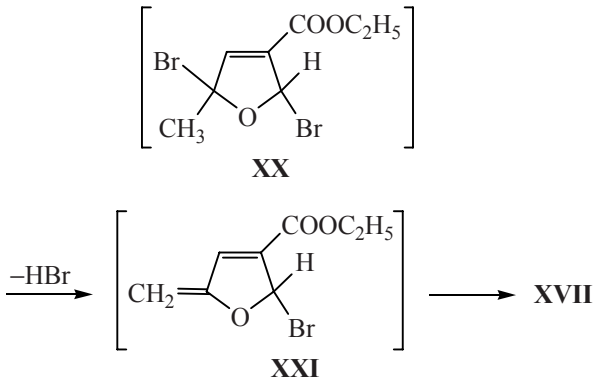


XVIII **XIX**

Considering this scheme in the case of the ester **XI** it may be suggested that the elimination of bromide ion takes place from the position 2 with the subsequent deprotonation of the position 5, though most probably the reaction proceeds according to the usual scheme of electrophilic substitution including the formation of σ-complex. At least the energetic advantages of the reaction proceeding according to the addition-elimination pathway are not evident.



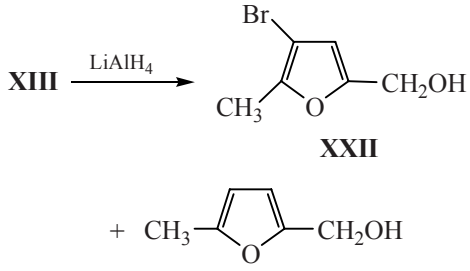
In the case of ester **XII** adduct **XX** should eliminate the bromide ion from the position 5 having the highest electronic density, and in the intermediate **XXII** two C=C bonds will be conjugated with the carbonyl group of the ester fragment. Moderate yield of compound **XVII** in this case is connected evidently with the high activity of the position 2 in the electrophilic substitution.



XX **XXI**

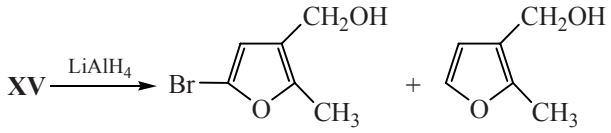
Reduction of the brominated esters **XIII, XV, XVI** to alcohols was carried out with lithium aluminum hydride in ether.

Bromide **XIII** was reduced to form two alcohols **XXII, XXIII**. At 10°C their ratio was 1:0.2.



XXII **XXIII**

Analogously the reduction of bromide **XV** led to products **XXIV, XXV**. At 36°C their ratio is 1:0.65, and at 10°C it decreases to 1:0.1.

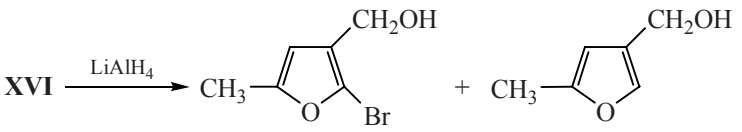


XXIV **XXV**

Bromide **XVI** reacts with lithium aluminum hydride to give the mixture of alcohols **XXVI, XXVII**. At 36°C their ratio is 1.00:1.45, and at 10°C it is equal to 1.00:1.12.

The brominated alcohols are stable at 0°C for several days, but heating in a vacuum (1 mm Hg) causes their polymerization at the temperatures below their boiling points.

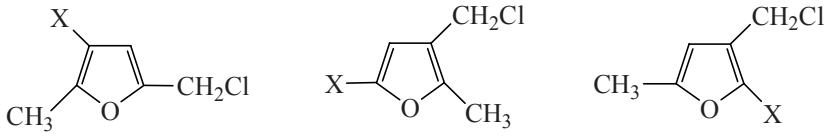
Comparison of ratio of the brominated and debrominated products shows that stronger electron-



XXVI **XXVII**

acceptor effect of the ester group and the furan ring oxygen on bromine corresponds to the higher yield of debrominated alcohol. That is why it can be stated that just the ester undergoes the debromination, and the ratio of the rates of the debromination and reduction of the ester group mainly determines the ratio of the reaction products. This conclusion agrees also with the existing concepts on the debromination of aromatic systems under the action of lithium aluminum hydride in a nucleophilic substitution reaction [14, 15].

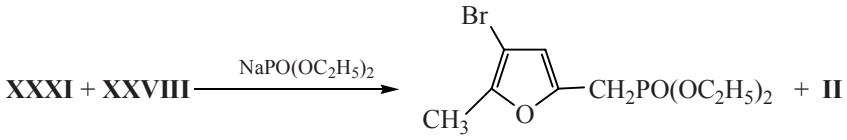
Substutition of hydroxy group with halogen in the alcohols synthesized was carried out with thionyl chloride in the presence of pyridine at 10–20°C according to the typical procedure [12]. Due to the high lability of the obtained mixtures of brominated and debrominated hydroxymethylfurans it was impossible to obtain pure substances, so firther transformations were carried out using the products isolated directly from the reaction mixtures. It turned out, that bromo(chloromethyl)furans **XXXI–XXXIII** are significantly more stable than the corresponding alcohols. They can be purified by vacuum distillation what permitted to prepare spectroscopically pure bromide **XXXII** and the mixtures consisting of compounds **XXXI, XXVIII** in the 1:0.3 ratio and of products **XXXIII, XXX** in the 1:0.12 ratio. Details of the process are given in the Experimental.



X = H (**XXVIII**) X = H (**XXIX**) X = H (**XXX**)
X = Br (**XXXI**) X = Br (**XXXII**) X = Br (**XXXIII**)

Phosphorylation of bromo(halomethyl)furans synthesized was carried out under the conditions of the Michaelis–Becker reaction in benzene at 80°C according to the typical procedure [16]. The starting substrates were the mixtures of chlorides obtained, therefore in all cases the material balance of the reactions was checked considering the data on phosphorylation of the individual chloromethylfurans **XXVIII–XXX.**

Phosphorylation of the mixture of compounds **XXXI, XXVIII** led to the formation of a mixture of phosphonates **XXXIV, II** in 1:0.13 ratio.

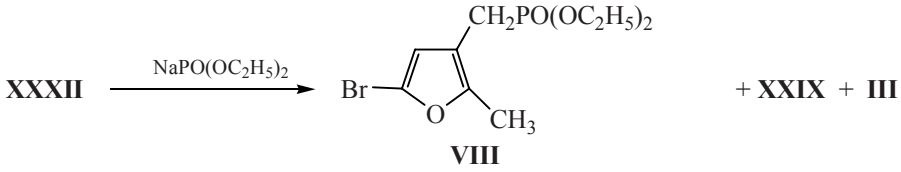


XXXIV

Yield of bromophosphonate **XXXIV** was 84%, and the product **II** was formed in 39% yield. At the same time phosphorylation of pure chloride **XXVIII** under the analogous conditions permitted to obtain phosphonate **II** in 72% yield [16]. Such decrease in the yield arises probably from the higher rate of the reaction of bromo(chloromethyl)furan **XXXI** with sodium diethyl phosphite as compared to the compound **XXVIII**. Due to that the concentration of phosphorylating agent quickly decreases, and the solution obtained has low content of chloromethylfuran **XXVIII** as well as of sodium diethyl phosphite. Under these conditions the latter substrate reacts slowly.

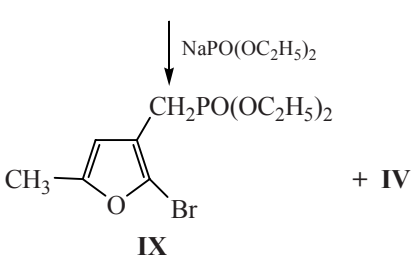
Reaction of bromo(chloromethyl)furan **XXXII** with sodium diethyl phosphite was carried out analogously. Distillation of the reaction mixture in a vacuum

yielded chloride **XXIX** with bp 32–34°C (1 mm Hg) and a fraction with bp 136–138°C (1 mm Hg) consisting of bromophosphonate **VIII** with a small admixture of phosphonate **III**.



Yield of chloromethylfuran **XXIX** was 16%, of phosphonate **VIII,** 49%, and the yield of phosphonate **III** was evaluated at 2–3%. Composition of the reaction products shows that besides phosphorylation according to the Michaelis–Becker scheme the halogenophilic attack of phosphite anion on the bromine atom in the furan ring leading to reduction of compound **XXXII** to chloromethylfuran **XXIX** takes place. The latter in its turn is phosphorylated with sodium diethyl phosphite, but this reaction proceeds slower than the phosphorylation of bromide. Formation of phosphonate **III** by debromination of phosphonate **VIII** seems hardly probable.

The reaction of a mixture of chloromethylfurans **XXXIII** with sodium diethyl phosphite was carried out analogously. ^{1}H NMR spectrum of the reaction mixture taken after removing the solvent permitted establishing that it is a mixture of phosphonates **IX, IV** in 1:0.5 ratio. After distillation in a vacuum the mixture obtained consisted of the same products in 1:0.7 molar ratio due to the stronger decomposition of phosphonate **IX**. Evaluation of the material balance of this process showed that the greater part of phosphonate **IV** was formed not from the starting chloride **XXXI**, but through debromination of bromofurans **XXXIII, IX**. The data obtained do not permit to conclude which of these compounds is the main precursor of phosphonate **IV**.



Hence, it was established that bromo(chloromethyl)furans react with sodium diethyl phosphite according to two pathways. The main one is the formation of phosphonates according to the classical scheme of the Michaelis–Becker reaction. The side process is the halogenophilic attack of bromine atom in α-position of the furan ring leading to its substitution with hydrogen. The halogenophilic attack of phosphate anion takes place when the bromine atom carries the effective positive charge. In the case under consideration substituents present in the furan ring are weak acceptors, and the main contribution to the polarization of bromine is provided by oxygen of the furan ring. It is particularly valuable because under the conditions excluding the other reaction pathways mild reduction of 2-bromofurans can be carried out. Protecting of position 2 in the furan ring by means of bromination and subsequent debromination is used in the synthesis of 3-substituted furans, but the existing debromination procedures by zinc in the acetic acid at boiling [10, 17], or with butyllithium [18] are applicable only to a narrow range of compounds.

Cases of the halogenophilic attack in the furan series were observed recently and sufficiently thoroughly studied [19, 20]. All of them concerned the compounds with a bromine atom in the α-position of the side chain. Depending on the substrate structure either formation of the P–C bond or reduction of the bromine-containing group was observed. Our new data show that these reactions may proceed independently with the participation of different reaction centers. The halogenophilic attack is directed on the bromine atom bound with the heteroaromatic ring whose influence is creating the effective positive charge.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker DPX-400 spectrometer (400.131 MHz), and ^{31}P NMR spectra on a Bruker AC-200 device (80.014 MHz ^{31}P) in deuterochloroform.

Bromination of phosphonates I–IV *(general procedure).* To a solution of 0.01 mol of phosphonate **I–IV** and 0.01 mol of pyridine in 30 ml of chloroform a solution of 0.01 mol of bromine in 5 ml of chloro-

form was added dropwise with stirring at room temperature. After the complete addition of bromine the reaction mixture was kept at room temperature for 1 h, shaken with a mixture of 5 g of ice and 10 ml of water, washed with 5% HCl cooled to 0°C, with the cooled water solution of sodium bicarbonate, and then dried over calcium chloride. The oil-like residue obtained after removing the solvent was analyzed by spectral methods.

5-Bromo-2-(diethoxyphosphorylmethyl)furan (V). Yield of undistilled phosphonate **V** 69%. Distillation of 1.94 g of the crude product in a vacuum gave 0.64 g of light brown oil with bp 128°C (1 mm Hg). ^{1}H and ^{31}P NMR spectra of both products were identical. ^{1}H NMR spectrum, δ, ppm: 1.226 t (CH_3-ethyl, J_{HH} 7.6 Hz), 3.129 d (CH_2P, J_{HP} 21.2 Hz), 4.017 m (CH_2OP, J_{HH} 7.5 Hz, J_{HP} 15.2 Hz), 6.151 s (H^3+H^4-furan, overlapping), δ_P 21.527 ppm.

Bromination of phosphonate (II). ^{31}P NMR spectrum of the obtained product, δ_P, ppm: 23.740 (phosphonate **II**), 10.975 (diethyl hydrogen phosphate), –79.910 (probably bromophosphate). Recovery of phosphonate **II** 23%, ^{1}H NMR spectrum, δ, ppm: 1.223 t (CH_3-ethyl), 2.159 s (CH_3-furan), 3.150 d (CH_2P, J_{HP} 20.4 Hz), 4.007 m (CH_2OP), 5.824 s (H^4-furan), 6.025 (H^3-furan).

Bromination of phosphonate (II) in the presence of aluminum chloride. Bromination of a mixture of 2.9 g of phosphonate **II**, 100 mg of $AlCl_3$ and 35 ml of chloroform with a solution of 0.7 ml of bromine in 5 ml of chloroform at 15–20°C followed by decomposition of reaction mixture with a mixture of water with ice, washing with water, with sodium bicarbonate solution, drying over calcium chloride, and removing the solvent in a vacuum gave 2.49 g of brown viscous oil. ^{1}H NMR spectrum, δ, ppm: phosphonate **II**: 2.159 s (CH_3-furan), 3.150 d (CH_2P, J_{HP} 20.4 Hz), 5.801 s (H^4-furan), 6.023 s (H^3-furan), δ_P 23.118 ppm; bromomethylphosphonate **VI**: 3.213 d (CH_2P, J_{HP} 21.6 Hz), 4.393 s (CH_2Br), 6.150 s (H^3-furan), 6.256 s (H^4-furan), δ_P 19.888; 5-methyl-2-bromomethylfuran **VII**: 2.307 s (CH_3-furan, 4.468 s (CH_2Br), 5.917 s (H^4-furan), 6.250 s (H^3-furan); common signals of ester groups: 1.223 m (CH_3-ethyl), 4.000 m (CH_2OP). ^{31}P NMR spectrum of phosphates, δ_P, ppm: 12.020, 10.889, –0.457.

The substance obtained was dissolved in 30 ml of benzene, 3 ml of triethylamine was added, and the resulting mixture was left overnight. The crystals formed were filtered off, and the filtrate was distilled in a vacuum to give 1.07 g (30%) of phosphonate **II**, bp 102°C (1 mm Hg). The crystals were ground with acetone, treated with ethyl acetate, filtered, and dried. Yield 1.03 g, mp 230–250°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.170 t (CH_3), 3.100 q (CH_2N^+), 8.260 br.s (NH^+).

Bromination of esters (X-XII) *(general procedure).* To a solution of ester in chloroform aluminum chloride was added and the mixture was stirred for 10–15 min until homogenization. After that a solution of bromine in chloroform was added dropwise with stirring at the desired temperature, and the reaction mixture was maintained for the given time. Then in was poured on a mixture of water with ice. Organic layer was separated, washed with water, dried over $CaCl_2$, solvent was removed, and the residue was distilled in a vacuum.

Ethyl 4-bromo-5-methylfuran-2-carboxylate (XIII). A solution of 14.5 g of the ester **XII** in 150 ml of chloroform containing 1.3 g of $AlCl_3$ was brominated with a solution of 5 ml of bromine in 10 ml of chloroform. The mixture obtained was maintained for 2 h. Distillation of the reaction mixture gave 3.2 g of the starting ester and 9.9 g of a fraction with bp 95-112°C (1 mm Hg) consisting of a mixture of bromides **XIII, XIV** in 2.58:1 ratio. The substance obtained was dissolved in 100 ml of benzene, treated with 2.5 ml of triethylamine, and left overnight. On the next day the liquid phase was decanted from crystals, washed with diluted HCl, dried over $CaCl_2$, and distilled in a vacuum to give 4.0 g of bromide **XIII**, bp 80°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.293 t (CH_3-ethyl), 2.303 s (CH_3-furan), 4.286 q (CH_2OOC), 7.036 (H^4-furan).

Ethyl 5-bromomethylfuran-2-carboxylate (XIV). ^{1}H NMR spectrum, δ, ppm: 1.293 t (CH_3-ethyl), 4.286 q (CH_2OOC), 4.456 s (CH_2Br), 6.463 d (H^4-furan, J_{HH} 3.6 Hz), 7.066 d (H^3-furan, J_{HH} 3.6 Hz).

Ethyl 2-methyl-5-bromofuran-3-carboxylate (XV). A solution of 12.2 g of the ester **XI** in 100 ml of chloroform containing 1.2 g of $AlCl_3$ was brominated with a solution of 4.4 ml of bromine in 10 ml of chloroform at 20–23°C with the subsequent keeping for 15 min. Vacuum distillation gave 13.2 g (71%) of bromide **XV** with bp 70–71°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.289 t (CH_3-ethyl), 2.511 s (CH_3-furan), 4.237 q (CH_2OOC), 6.511 s (H^4-furan).

Ethyl 2-bromo-5-methylfuran-3-carboxylate (XVI). A solution of 41 g of the ester **XII** in 150 ml of chloroform containing 3.2 g of $AlCl_3$ was brominated with a solution of 14.4 ml of bromine in 30 ml of chloroform at 20°C. The distillation of the reaction mixture in a vacuum gave 55.3 g of the fraction with bp 92°C (1 mm Hg) consisting of bromide **XVI** and bromomethylfuran **XVII** in 1.0:0.22 molar ratio. The mixture obtained was dissolved in 150 ml of benzene, 6.5 ml of triethylamine was added, and the resulting mixture was stirred for 1 h and left overnight. On the next day benzene solution was decanted from the crystals, washed with diluted hydrochloric acid, with water, dried over $CaCl_2$, and distilled in a vacuum to give 33.5 g of bromide **XVI** with bp 85°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.229 t (CH_3-ethyl), 2.241 s (CH_3-furan), 4.254 t (CH_2OOC), 6.035 s (H^4-furan).

Reduction of alkyl bromofurancarboxylates *(general procedure).* To a suspension of lithium aluminum hydride in the anhydrous ether a solution of alkyl bromofurancarboxylate in the anhydrous ether was added dropwise with stirring at 10°C. The mixture obtained was stirred for 2 h at 10°C and left overnight. On the next day the reaction mixture was treated with an excess ethyl acetate, and then with the saturated NH_4Cl solution until the separation of phases. Organic phase was decanted, dried over $CaCl_2$, and evaporated in a vacuum.

Reduction of bromide (XIII). To a suspension of 0.7 g of lithium aluminum hydride in 50 ml of ether a solution of 4 g of bromide **XIII** in 15 ml of ether was added. A mixture of alcohols **XXII, XXIII,** 2.5 g, in the 5:1 ratio was obtained. ^{1}H NMR spectrum, δ, ppm: 2-hydroxymethyl-4-bromo-5-methylfuran **XXII**: 2.240 s (CH_3-furan), 4.458 (CH_2O), 6.207 s (H^3-furan); 2-hydroxymethyl-5-methylfuran **XXIII**: 2.240 s (CH_3-furan), 4.458 s (CH_2OH), 5.685 s (H^4-furan), 6.133 s (H^3-furan).

Reduction of bromide (XV). To a suspension of 0.9 g of lithium aluminum hydride in 70 ml of ether a solution of 5 g of bromide **XV** in 15 ml of anhydrous ether was added. 2-Methyl-5-bromo-3-hydroxymethylfuran **XXIV**, 4.0 g, with a small admixture of 2-methyl-3-hydroxymethylfuran **XXV** was obtained. ^{1}H NMR spectrum, δ, ppm: 2-methyl-5-bromo-3-hydroxymethylfuran **XXIV**: 2.228 s (CH_3-furan), 2.608 br.s (OH), 4.347 br.s (CH_2O), 6.241 s (H^4-furan); 2-methyl-3-hydroxymethylfuran **XXV**: 2.239 s (CH_3-furan), 4.403 s (CH_2O), 6.323 s (H^4-furan), 7.211 s (H^3-furan).

Reduction of bromide (XVI). To a suspension of 1.1 g of lithium aluminum hydride in 70 ml of anhydrous ether a solution of 7.1 g of bromide **XVI** in 20 ml of anhydrous ether was added. A mixture of 2-bromo-5-methyl-3-hydroxymethylfuran **XXVI** and 5-methyl-3-hydroxymethylfuran **XXVII** in the 1:1.12 ratio, 3.6 g, was obtained. ^{1}H NMR spectrum, δ, ppm: 2-bromo-5-methyl-3-hydroxymethylfuran **XXVI**: 2.238 s (CH_3-furan), 4.343 s (CH_2O). 6.071 s (H^4-furan); 5-methyl-3-hydroxymethylfuran **XXVII**: 2.238 s (CH_3-furan), 4.427 s (CH_2O), 5.898 s (H^4-furan), 7.211 s (H^2-furan).

Reaction of hydroxymethylfurans with thionyl chloride *(general procedure).* To a mixture of alcohol and pyridine in anhydrous ether a solution of thionyl chloride in ether was added dropwise with stirring at 5–10°C. The mixture obtained was stirred for 4 h at 10-15°C, pyridinium chloride was filtered off, ether was removed, and the residue was distilled in a vacuum.

Reaction of a mixture of alcohols (XXII,XXIII) with thionyl chlorode. Treating a solution of 2.5 g of a mixture of alcohols **XXII, XXIII** (1:0.2) and 1.2 ml of pyridine in 100 ml of anhydrous ether with a solution of 1.1 ml of thionyl chloride in 10 ml of ether yielded 1.6 g of a mixture of chlorides **XXXI**, **XXVII** in 1:0.3 molar ratio, bp 51°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 4-bromo-5-methyl-2-chloromethylfuran **XXXI**: 2.286 s (CH_3-furan), 4.482 s (CH_2Cl), 6.309 s (H^3-furan); 5-methyl-2-chloromethylfuran **XXVII**: 2.286 s (CH_3-furan), 4.538 s (CH_3Cl), 5.911 d (H^4-furan, J_{HH} 2.0 Hz), 6.921 d (H^3-furan, J_{HH} 2.0 Hz).

Reaction of a mixture of alcohols (XXIV,XXV) with thionyl chloride. Treating a solution of 4.0 g of a mixture of alcohols **XXIV, XXV** (1:0.1) and 1.8 ml of pyridine in 50 ml of anhydrous ether with a solution of 1.5 ml of thionyl chloride in 5 ml of ether yielded 2.9 g of 2-methyl-5-bromo-3-(chloromethyl)furan **XXXI**, bp 49–51°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 2.261 s (CH_3-furan), 4.349 s (CH_2Cl), 6.250 s (H^4-furan).

Reaction of a mixture of alcohols (XXVI, XXVII) with thionyl chloride. Treating a solution of 5.8 g of a mixture of alcohols **XXVI, XXVII** (1:1.12) and 4.6 ml of pyridine in 100 ml of ether with a solution of 3.9 ml of thionyl chloride in 10 ml of ether yielded 1.4 g of a mixture of chlorides **XXXIII,XXX** in 1:0.12 molar ratio, bp 53°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 2-bromo-5-methyl-3-(chloromethyl)furan **XXXIII**:

2.240 s (CH_3-furan), 4.315 s (CH_2Cl), 6.023 s (H^4-furan); 5-methyl-3-(chloromethyl)furan **XXX**: 2.249 s (CH_3-furan), 4.425 s (CH_2Cl), 6.423 s (H^4-furan), 7.420 s (H^2-furan).

General procedure of phosphorylation with sodium diethyl phosphite. To a solution of sodium diethyl phosphite in benzene an appropriate substrate was added in one portion at 80°C, and the mixture obtained was refluxed with stirring for the desired time. Precipitate of the inorganic salt was removed on a centrifuge, benzene was distilled off, and the residue was distilled in a vacuum.

Phosphorylation of a mixture of chlorides (XXXI, XXVIII). Reaction of 0.2 g of sodium, 1.6 ml of diethyl hydrogen phosphite, and 1.5 g of a mixture of chlorides **XXXI**, **XXVIII** (1:0.3) gave 1.9 g of a mixture of phosphonates **XXXIV, II** in 1:0.13 molar ratio, bp 134°C (1mm Hg), reaction time 6 h. ^{1}H NMR spectrum, δ, ppm: 5-methyl-4-bromo-2-(diethoxyphosphorylmethyl)furan **XXXIV**: 1.237 m (CH_3-ethyl), 2.165 s (CH_3-furan), 3.083 d (CH_3P, J_{HP} 20.6 Hz), 4.027 m (CH_2OP), 6.118 s (H^3-furan), δ_P 21.846 ppm; 5-methyl-2-(diethoxyphosphorylmethyl)furan **II**: 1.237 m (CH_3-ethyl), 2.127 s (CH_3-furan), 3.083 d (CH_2P, J_{HP} 20.6 Hz), 4.027 m (CH_2OP), 5.927 s (H^4-furan), 6.018 s (H^3-furan), δ_P 22.735 ppm.

Phosphorylation of chloride (XXXII). Reaction of 0.32 g of sodium, 2.2 ml of diethyl hydrogen phosphite, and 2.0 g of chloromethylfuran **XXXII** in 45 ml of benzene gave 0.3 g (16%) of 2-methyl-3-(chloromethyl)furan **XXIX** with bp 32–34°C (1 mm Hg), and 2.1 g (~49%) of phosphonate **VIII** containing small admixture of phosphonate **III**, bp 136–138°C (1 mm Hg). Reaction time 16 h. ^{1}H NMR spectrum, δ, ppm: 2-methyl-3-(chloromethyl)furan **XXIX**: 2.200 s (CH_3-furan), 4.231 s (CH_2Cl), 6.240 s (H^4-furan), 7.148 s (H^5-furan); 2-methyl-5-bromo-3-(diethoxyphosphorylmethyl)furan **VIII**: 1.271 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.159 d (CH_3-furan, J_{HH} 3.2 Hz), 2.731 d (CH_2P, J_{HP} 19.6 Hz), 3.818 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 6.157 s (H^4-furan), δ_P 24.458 ppm; 2-methyl-3-(diethoxyphosphorylmethyl)furan **III**: 1.217 t (CH_3-ethyl, J_{HH} 7 Hz), 2.191 br.s (CH_3-furan), 2.828 d (CH_2P, J_{HP} 20 Hz), 3.818 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 6.284 s (H^4-furan), 7.182 s (H^5-furan), δ_P 26.248 ppm.

Phosphorylation of a mixture of chlorides (XXXIII, XXX). Reaction of 0.17 g of sodium, 1.2 ml of diethyl hydrogen phosphite, and 1.4 g of a mixture of chlorides **XXXIII, XXX** (1:0.12 molar ratio) gave a mixture of phosphonates **IX, IV** in 1:0.5 molar ratio. Reaction time 14 h. Distillation in a vacuum gave 0.6 g of a mixture of these compounds with bp 117-120°C/1 mm, ratio of phosphonates **IX, IV** 1:0.7. ^{1}H NMR spectrum, δ, ppm: 2-bromo-5-methyl-3-(diethoxyphosphorylmethyl)furan **IX**: 1.247 m (CH_3-ethyl), 2.177 s (CH_3-furan), 2.763 d (CH_2P, J_{HP} 21.2 Hz), 4.022 m (CH_2OP), 6.040 s (H^4-furan), δ_P 24.671 ppm; 5-methyl-3-(diethoxyphosphorylmethyl)furan **IV**: 1.247 m (CH_3-ethyl), 2.126 s (CH_3-furan), 2.816 d (CH_2P, J_{HP} 21.2 Hz), 4.022 m (CH_2OP), 5.928 s (H^4-furan), 7.124 (H^2-furan), δ_P 26.048 ppm.

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