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2-(1-Chloroalkyl)furans in the Reaction with Sodium Diethyl Phosphite

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Abstract—2-(1-Chloroethyl) and 2-(1-chloro-2-methylpropyl)furans react with sodium diethyl phosphite to give two products, 2-(1-diethoxyphosphorylmethyl)furan and 2-alkyl-5- (diethoxyphosphoryloxy)furan. The fraction of the latter product increases with increasing size of the alkyl radical. 2-Methyl substitution in the substrate completely suppresses phosphate formation. 2-(1-Chloroethyl)-5-(2-methylpropyl)furan under the action of sodium diethyl phosphite eliminates hydrogen chloride to give the corresponding alkene.

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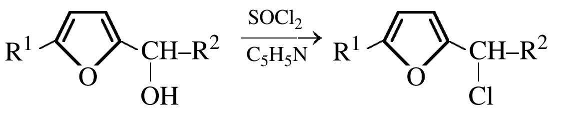
2-Hydroxyalkylfurans easily prepared from 2-furaldehyde and its homologs are traditionally considered to be extremely acidophobic compounds [1]. Evidently, for this reason no attempts to convert these alcohols to the corresponding chlorides have been reported. At the same time, such secondary chlorides present great interest as substrates for phosphorylation, because in this case phosphorus is attached to an asymmetric carbon atom, and further transformations of the phosphorus-containing function may lead to optically active phosphines. In this connection we prepared 2-(1-chloroalkyl)furans and made an attempt to react them with sodium diethyl phosphite.

We chose as substrates a series of furans of general formula **I**.



Ia–Ie **IIa–IIe**

R^1 = H, R^2 = CH$_3$ (**a**); R^1 = R^2 = CH$_3$ (**b**); R^1 = H, R^2 = CH(CH$_3$)$_2$ (**c**); R^1 = CH$_3$, R^2 = CH(CH$_3$)$_2$ (**d**); R^1 = CH$_2$CH(CH$_3$)$_2$, R^2 = CH$_3$ (**e**).

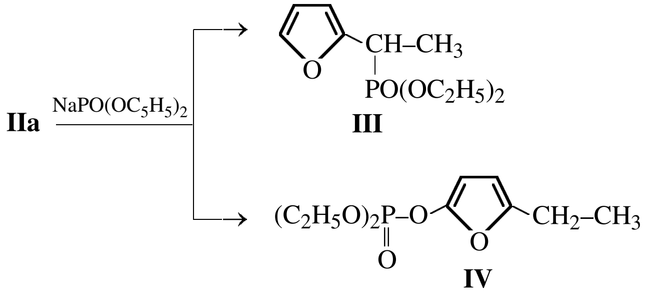
Substitution of the hydroxy group by chlorine in compounds **Ia**–**Ie** was carried out by means of thionyl chloride in the presence of pyridine at 20–25°C. The resulting products were isolated by vacuum distillation.

2-(1-Chloroethyl)furan (**IIa**) occurred to be sufficiently stable. It can be distilled in a vacuum without noticeable decomposition, bp 23–24°C (1 mm Hg), but it quickly becomes dark brown in air. We failed the ^{1}H NMR spectrum of compound **IIa** of reasonable quality, because its solutions in CDCl$_3$ quickly gelatinized.

Compound **IIa** was phosphorylated with sodium diethyl phosphite in benzene at 80°C for 4 h. The resulting products were isolated by vacuum distillation. A mixture of compounds boiling in the range 96–98°C (1 mm Hg) was obtained. Its ^{1}H NMR spectrum contained two well-resolved sets of signals.

The main product gave a doublet of doublets at 1.26 ppm (J_{HH} 7 Hz, J_{HP} 16 Hz) assignable to the side-chain methyl group, a doublet of distorted quartets at 3.16 ppm (J_{HH} ~7 Hz, J_{HP} 21 Hz) belonging to the CH group on phosphorus, two broadened singlets at 6.25 ppm and 7.29 ppm, and a broadened doublet at 6.18 ppm (J_{HP} ~2 Hz). The δ_P of this product was 23.8 ppm. The presented spectral data well describe phosphonate **III**.

The other set of signals comprised a quartet at 2.66 ppm characteristic of the methylene group of ethyl at the furan ring and two broadened singlets at 6.03 and 6.96 ppm belonging to furan ring protons. The δ_P of this product was 1.4 ppm. The absence of the third ring proton signal below δ 7 ppm provide evidence to show that the product is a 2,5-disubstituted furan with a strong electron-acceptor substituent

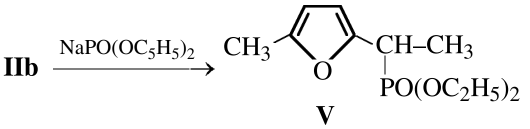


III

IV

in the 2 position, which follows from the different chemical shifts of protons in the 3 and 4 positions of the ring. The absence of noticeable splitting of the furan proton signal from phosphorus and the δ_P of this product suggest that it is diethyl heteryl phosphate. Its structure can be described by formula **IV**.

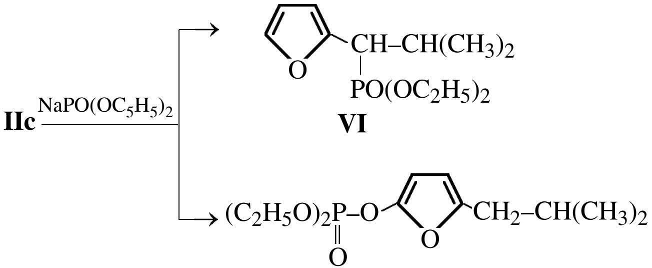
From the integral intensity ratio of the ring proton signals the molar ratio of compounds **III** and **IV** was estimated at 4 : 1.



V

Chloride **IIb** is much more labile than its analog **IIa**. In the course of vacuum distillation [bp 32–33°C (1 mm Hg)] it gets strongly colored, and a brown film deposits on walls of the distillation system. Immediately after distillation product **IIb** was dissolved in benzene and involved in reaction with sodium diethyl phosphite.

Phosphorylation of chloride **IIb** was carried out in benzene at 80°C for 6.5 h. The only phosphorus-containing product was phosphonate **V**. The ^{1}H NMR spectrum of this compound showed two doublets of distorted quartets at 2.79 and 3.06 ppm (J_{HH} ~7 Hz, J_{HP} 21 Hz) related to the CH–P fragment. The intensity ratio of the upfield and downfield signals was 1 : 3. The presented data show that phosphonate **V** exists as a mixture of two conformers. The yield of the product was 45%.



VI

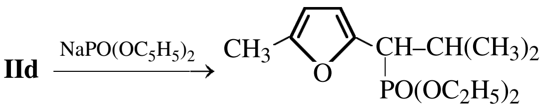
VII

Chloride **IIc** occurred to be so stable that we managed not only to distill it in a vacuum [bp 39–40°C (1 mm Hg)], but also to obtain its well-resolved ^{1}H NMR spectrum. Methyl groups of the isobutyl fragment in this compound give two doublets at 0.91 and 1.04 ppm (J_{HH} 7 Hz) in a 1 : 1 ratio. Most probably, this observable points to nonequivalence of these groups, rather than to the fact that chloride **IIc** exists as a mixture of two conformers.

Phosphorylation of compound **IIc** with sodium diethyl phosphite was carried out in benzene at 80°C for 6 h. Vacuum distillation gave a fraction [bp 30–40°C (1 mm Hg)] that comprised diethyl hydrogen phosphite and chloride **IIc**, and a fraction boiling at 110°C (1 mm Hg).

The ^{1}H NMR spectrum of the high-boiling fraction contained two well-resolved sets of signals. The first included a doublet of doublets at 3.00 ppm (CH-P, J_{HH} 7 Hz, J_{HP} 23 Hz), a broadened signal at 6.26 ppm (furan H^3 and H^4), and a signal at 7.29 ppm (furan H^5). The δ_P of this product was 22.7 ppm. This set of signals characterizes phosphonate **VI**.

The second set of signals included a distorted doublet at 2.50 ppm characteristic of the methylene fragment of the isobutyl group at the furan ring and two doublets at 6.02 ppm and 6.93 ppm characteristic of ring protons (furan H^3 and H^4, J_{HH} 2 Hz). The δ_P of this product is 1.28 ppm. The presented spectral data characterize phosphate **VII**. The **VI**: **VII** ratio in the obtained material was estimated at 1 : 1.4.

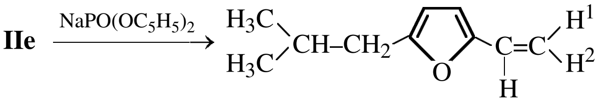


VIII

Chloride **IId** occurred to be less stable than its analog **IIc**. It can also be distilled in a vacuum [bp 38°C (0.8 mm Hg)] but immediately darkens in air, and a suspension of polymeric products quickly forms in it. We failed to obtain a well-resolved spectrum of this compound.

Chloride **IId** was phosphorylated with sodium diethyl phosphite in benzene at 80°C for 9.5 h. Phosphonate **VIII** was isolated by vacuum distillation in 48% yield. The ^{1}H NMR spectrum of this product contained two doublets of doublets at 2.60 (J_{HH} 7 Hz, J_{HP} 21 Hz) and 2.88 ppm (J_{HH} 7 Hz, J_{HP} 21 Hz), related to the CHP fragment. The intensity ratio of these signals was 1 : 2. This fact provides evidence to show that phosphonate **VIII**, like **V**, exists as a mixture of two conformers. In both cases, the conformer giving the downfield signal is preferred.

The isobutyl fragment of phosphonate **VIII** has nonequivalent methyl groups. In the ^{1}H NMR spectrum, they give doublets of equal intensity at 0.91 (J_{HH} 7 Hz) and 1.05 ppm (J_{HH} 7 Hz).

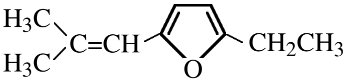


IX

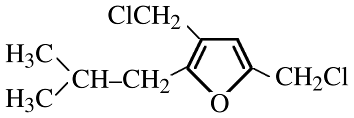
Chloride **IIe** is thermally unstable. Even during vacuum distillation (bp 40°C) a black polymeric film deposits on the internal surface of the distillation system. For this reason, we failed to obtain a well-resolved ^{1}H NMR spectrum of this compound. Immediately after distillation chloride **IIe** was involved in reaction with sodium diethyl phosphite. The process was carried out at 80°C in benzene for 5 h. Vacuum distillation of the reaction mixture gave a mixture of alkene **IX** and diethyl hydrogen phosphite. No formation of phosphorus-containing furans was observed in this case.

Hence, whether the reaction of 2-(1-chloroalkyl)-furans with sodium diethyl phosphite takes one or another pathway depends significantly on the structure of the chloroalkyl radical and on the substituent in the 5 position of the ring.

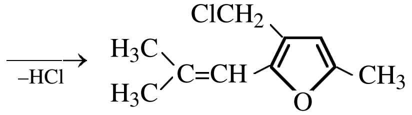
The formation of phosphonates most probably proceeds by a usual Michaelis–Becker scheme and only slightly depends on the structure of the chloroalkyl radical (the yields of phosphonates **V** and **VIII** are 45 and 48%, respectively). It should be emphasized that the reaction proceeds in a nonpolar solvent with an unionized substrate. The formation of alkene **IX** on dehydrohalogenation of chloride **IIe** may well occur thermally, which is indirectly evidenced by the facility of its polymerization on vacuum distillation. Performing the reaction in a dilute solution and binding hydrogen chloride with sodium diethyl phosphite favors stabilization of the final product. Note that dehydrohalogenation involves no isomerization to form compound **X**, whereas with bis(chloromethyl)furan **XI** this isomerization is the main reaction pathway [2].



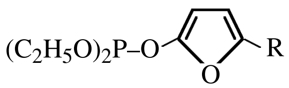
X



XI



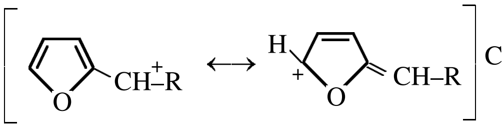
The formation of unusual products **IV** and **VII** can be explained as follows. While studying the reactions of 2-(1-chloroalkyl)furans with sodium diethyl phosphite we never observed products formed by halogenophilic attack. Therefore, the formation of phosphates should be explained by oxidation of the corresponding phosphites with air oxygen at elevated temperatures. Hence, phosphites **XII** and **XIII** should appear on a certain stage of the process.



XII, XIII

R = C_2H_5 (**XII**), $CH_2CH(CH_3)_2$ (**XIII**).

It is known [3] that sodium diethyl phosphite is alkylated by its oxygen atom in polar solvents only. Therefore, in the process under study, certain conditions arise that favor increased polarity of the medium. As already noted, compounds **II** lose chloride ion fairly easily. If this process is accompanied by fast deprotonation, alkene formation takes place. Otherwise, formation of an ion pair would be expected. It is this case that conditions for local increase of the dielectric permittivity of the medium are created. This increase is very significant, because the charges of ion centers rather than effective charges arise on the dipole poles. The structure of such an ion pair can conventionally be presented by formula **XIV**.



XIV

Sodium diethyl phosphite that appears in the sphere of its influence behaves as if it is placed in a polar medium, i.e. it reacts by the oxygen atom. Therewith, the phosphite formed by the α-attack on the side chain occurs to be affected by the same factors that favor elimination of chloride ion. As a consequence, no O-alkylation products by this site are found. Contrary to that, phosphites **XII** and **XIII** are stable and undergo oxidation of the phosphorus-containing group only. The increase of the fraction of the phosphite as compared to phosphonate (5.6-fold) is consistent with the concept that the stability of the carbocation in ion pair **XIV** increases due to the stronger electron-donor effect of the isopropyl group compared to methyl and due to the enhanced shielding of the carbocationic center. 5-Methyl substitution in the furan suppresses completely phosphite formation in spite of the expected enhanced stability of the carbocation. This result provides further evidence for facile elimination of the anion from the α position of the side chain.

The above reasoning allows us to conclude that the main factor determining the pathway of the reaction is ionization of haloalkylfuran. If it creates conditions for O-alkylation of the phosphite salt, trialkyl phosphites are formed. Therewith, the phosphite ion can be attacked both by the furan ring and by the side chain, but in the last case no stable products are formed. In principle, anion exchange with the ion pair can only take place without P–O–C bond formation. Deprotonation of the cation in such ion pair leads to alkene formation. Unionized haloalkylfuran enters the Michaelis–Becker reaction with sodium diethyl phosphite to form phosphonate.

EXPERIMENTAL

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

Substitution of hydroxyl with chlorine in 2-(1-hydroxyalkyl)furans (I) *(general procedure).* To a solution of 0.1 mol of 2-(1-hydroxyalkyl)furan and 0.105 mol of pyridine in 100 ml of ether, a solution of 0.1 mol of thionyl chloride in 50 ml of ether was added dropwise with vigorous stirring at 10–15°C. The reaction mixture was stirred at this temperature for 4-5 h, pyridine hydrochloride was filtered off, ether was distilled off at reduced pressure, and the residue was distilled in a vacuum. The resulting compounds were involved in further transformations as soon as possible.

2-(1-Chloroethyl)furan (IIa). Yield 47%, bp 23–24°C (1 mm Hg).

2-(1-Chloroethyl)-5-methylfuran (IIb). Yield 42%, bp 32–33°C (1 mm Hg).

2-(1-Chloro-2-methylpropyl)furan (IIc). Yield 59%, bp 39–40°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.91 d (isobutyl CH_3, J_{HH} 7 Hz); 1.04 d (isobutyl CH_3, J_{HH} 7 Hz); 2.30 m (isobutyl CH); 4.56 d (CHCl, J_{HH} 7 Hz); 6.19 br.s (furan H^3 + H^4); 7.25 s (furan H^5).

2-(1-Chloro-2-methylpropyl)-5-methylfuran (IId). Yield 49%, bp 38°C (0.8 mm Hg).

2-(1-Chloroethyl)-5-(2-methylpropyl)furan (IIe). Yield 23%, bp 40°C (1 mm Hg).

Reaction of chloride (IIa) with sodium diethyl phosphite. To a solution of sodium diethyl phosphite prepared from 0.6 g of sodium and 4 ml of diethyl hydrogen phosphite in 30 ml of benzene, a solution of 3.5 g of chloride **IIa** in 4 ml of benzene was added in one portion at 70°C. The reaction mixture was refluxed with stirring for 4 h, sodium chloride was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum to give 3.0 g of a fraction with bp 96–98°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: phosphonate **III**: 1.21 m (ethyl CH_3), 1.26 d.d (CH_3–CHP, J_{HH} 7 Hz, J_{HP} 16 Hz); 3.16 d.q (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz); 4.00 m (CH_2OP); 6.18 br.d (furan H^3, J_{HP} 2 Hz); 6.25 br.s (furan H^4); 7.29 br.s (furan H^5); δ_P 23.8 ppm; phosphate **IV**: 1.21 m (ethyl CH_3); 2.66 q (CH_2–furan, J_{HH} 7 Hz); 4.00 m (CH_2OP); 6.03 br.s (furan H^3); 6.96 br.s (furan H^4), δ_P 1.4 ppm.

Phosphonate **III**/phosphate **IV** ratio 4 : 1.

2-(1-Diethoxyphosphorylethyl)-5-methylfuran (V). To a solution of sodium diethyl phosphite prepared from 0.6 g of sodium and 4.2 ml of diethyl hydrogen phosphite in 35 ml of benzene, a solution of 3.4 g of cloride **IIb** in 5 ml of benzene was added in one portion with stirring at 70°C. The reaction mixture was refluxed with stirring for 6.5 h, sodium chloride was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum to give 2.6 g (45%) of phosphonate **V**, bp 116–118°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.26 t (ethyl CH_3, J_{HH} 7 Hz); 1.40 d.d (CH_3–CHP, J_{HH} 7 Hz, J_{HP} 16 Hz); 2.18 s (CH_3-furan), 2.79 d.q (CH–P, J_{HH} 7 Hz, J_{HP} 21 Hz); 3.06 d.q (CH-P, J_{HH} 7 Hz, J_{HP} 21 Hz); 3.96 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz); 5.81 br.d (furan H^4, J_{HH} 3 Hz); 6.98 d.d (furan H^3), J_{HH} 3 Hz, J_{HP} 2 Hz); δ_P 26.8 ppm. The ratio of the conformers (form the intensities of the signals at 3.06 and 2.79 ppm) is 3 : 1.

Reaction of chloride IIc with sodium diethyl phosphite. To a solution of sodium diethyl phosphite prepared from 0.6 g of sodium and 4 ml of diethyl hydrogen phosphite in 30 ml of benzene, a solution of 4.5 g of chloride **IIc** in 10 ml of benzene was added with stirring in one portion at 70°C. The reaction mixture was refluxed with stirring for 6 h, sodium chloride was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum to give a fraction (1.2 g) with bp 30–40°C (1 mm Hg) consisting of diethyl hydrogen phosphite with a small admixture of chloride **IIc** and a fraction (3.6 g) with bp 110°C (1 mm Hg). ^{1}H NMR spectrum, δ_P, ppm: phosphonate **VI**: 0.90 m [$(CH_3)_2C$]; 1.20 m (ethyl CH_3, J_{HH} 7 Hz); 2.10 m (isobutyl CH, J_{HH} 7 Hz); 3.00 d.d (CHP, J_{HH} 7 Hz, J_{HP} 23 Hz), 3.95 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz); 6.26 br.s (furan H^3 + H^4); 7.29 br.s (furan H^5); δ_P 22.7 ppm; phosphate **VII**: 0.90 m [$(CH_3)_2C$]; 1.20 m (ethyl CH_3); 1.90 m (isobutyl CH J_{HH} 7 Hz); 2.50 d (isobutyl CH_2), J_{HH} 7 Hz, J_{HP} 11 Hz); 6.02 d (furan H^4, J_{HH} 2 Hz); 6.93 d (furan H^3, J_{HH} 2 Hz), δ_P 1.28 ppm. Phosphonate **VI** : phosphate **VII** ratio 1 : 1.4.

2-(1-Diethoxyphosphoryl-2-methylpropyl)-5-methylfuran (VIII). To a solution of sodium diethyl phosphite prepared from 0.9 g of sodium and 6 ml of phosphite in 40 ml of benzene, a solution of 6.3 g of chloride **IId** in 10 ml of benzene was added in one portion with stirring at 70°C. The reaction mixture was refluxed with stirring for 9.5 h, sodium chloride was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum to give 4.9 g (48%) of phosphonate **VIII**, bp 103°C (0.8 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.91 d (isobutyl CH_3, J_{HH} 7 Hz); 1.05 d (isobutyl CH_3, J_{HH} 7 Hz); 1.30 t (ethyl CH_3, J_{HH} 7 Hz); 1.80–2.20 m (isobutyl CH); 2.22 s (CH_3–furan); 2.60 d.d (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz); 2.88 d.d (CHP, J_{HH} 7 Hz, J_{HP} 21 Hz); 4.00 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 11 Hz); 5.83 br.d (furan H^4, J_{HH} 2 Hz); 6.11 br.d (furan H^3, J_{HH} 2 Hz); δ_P 22.9 ppm. The ratio of the conformers (from the intensities of the signals at 2.60 and 2.88 ppm) is 1:2.

Reaction of chloride IIe with sodium diethyl phosphite. To a solution of sodium diethyl phosphite prepared from 0.2 g of sodium and 2 ml of diethyl hydrogen phosphite in 12 ml of benzene, a solution of 1.2 g of chloride **IId** in 5 ml of benzene was added in one portion with stirring at 70°C. The reaction mixture was refluxed with stirring for 5 h, sodium chloride was removed by centrifugation, the solvent was evaporated at reduced pressure, and the residue was distilled in a vacuum to give 0.9 g of a fraction with bp 42–46°C (1 mm Hg), consisting of alkene **IX** and diethyl hydrogen phosphite. ^{1}H NMR spectrum, δ, ppm: alkene **IX**: 0.82 d (isobutyl CH_3, J_{HH} 7 Hz); 1.95 m (isobutyl CH, J_{HH} 7 Hz); 2.42 d (isobutyl CH_2, J_{HH} 7 Hz); 4.99 d (*trans*-CH^1=, J_{HH} 12 Hz); 5.50 d (*cis*-CH^2=, J_{HH} 17 Hz); 5.91 d (furan H^3, J_{HH} 2 Hz); 6.07 d (furan H^4, J_{HH} 2 Hz); 6.36 d.d (CH=, J_{H^1H} 17 Hz, J_{H^2H} 12 Hz). The yield of the alkene was estimated at ~70%.

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