

Heterocyclic Analogs of Prostaglandins: III.* Synthesis of 10-Oxa-13-aza, 11-Oxa-13-aza, and 9-Oxa-7-aza Prostanoids from 3-Acyl- and 3-(3-Arylprop-2-enoyl)furan-2,4-diones

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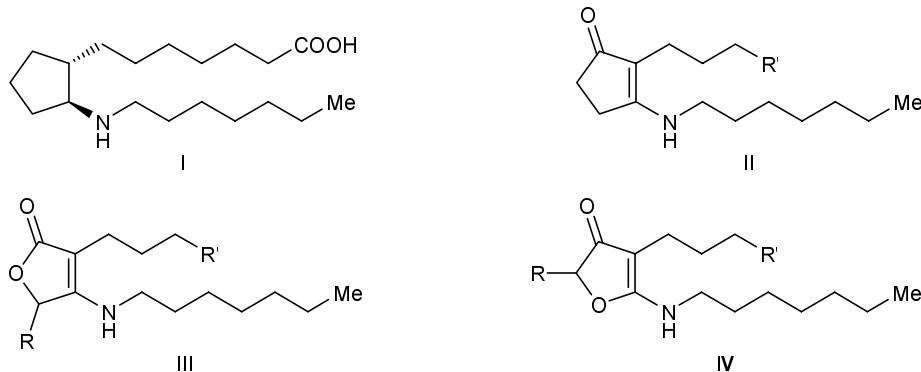
Abstract—A number of new 10-oxa-13-aza, 11-oxa-13-aza, and 9-oxa-7-aza prostanoids belonging to the B series were synthesized on the basis of 3-acyl- and 3-(3-arylprop-2-enoyl)furan-2,4(3*H*,5*H*)-diones. The scheme of synthesis includes selective hydrogenation of the exocyclic carbonyl group and reduction of the conjugated double bond in the acyl fragment of 3-acyl- and 3-(3-arylprop-2-enoyl)furan-2,4(3*H*,5*H*)-diones to obtain 3-alkyl- and 3-(3-arylpropyl)furan-2,4(3*H*,5*H*)-diones, transformation of the latter into the corresponding regioisomeric enol ethers via regioselective O-alkylation, and treatment of the enol ethers with primary aliphatic amines.

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One of the most promising ways of structural modification of prostaglandins implies replacement of one or several carbon atoms in the prostane skeleton by heteroelements [2]. In this connection, derivatives of 13-azaprostanic acid (**I**), which is a potent and specific antiaggregatory agent [3], attract strong scientific and practical interest.

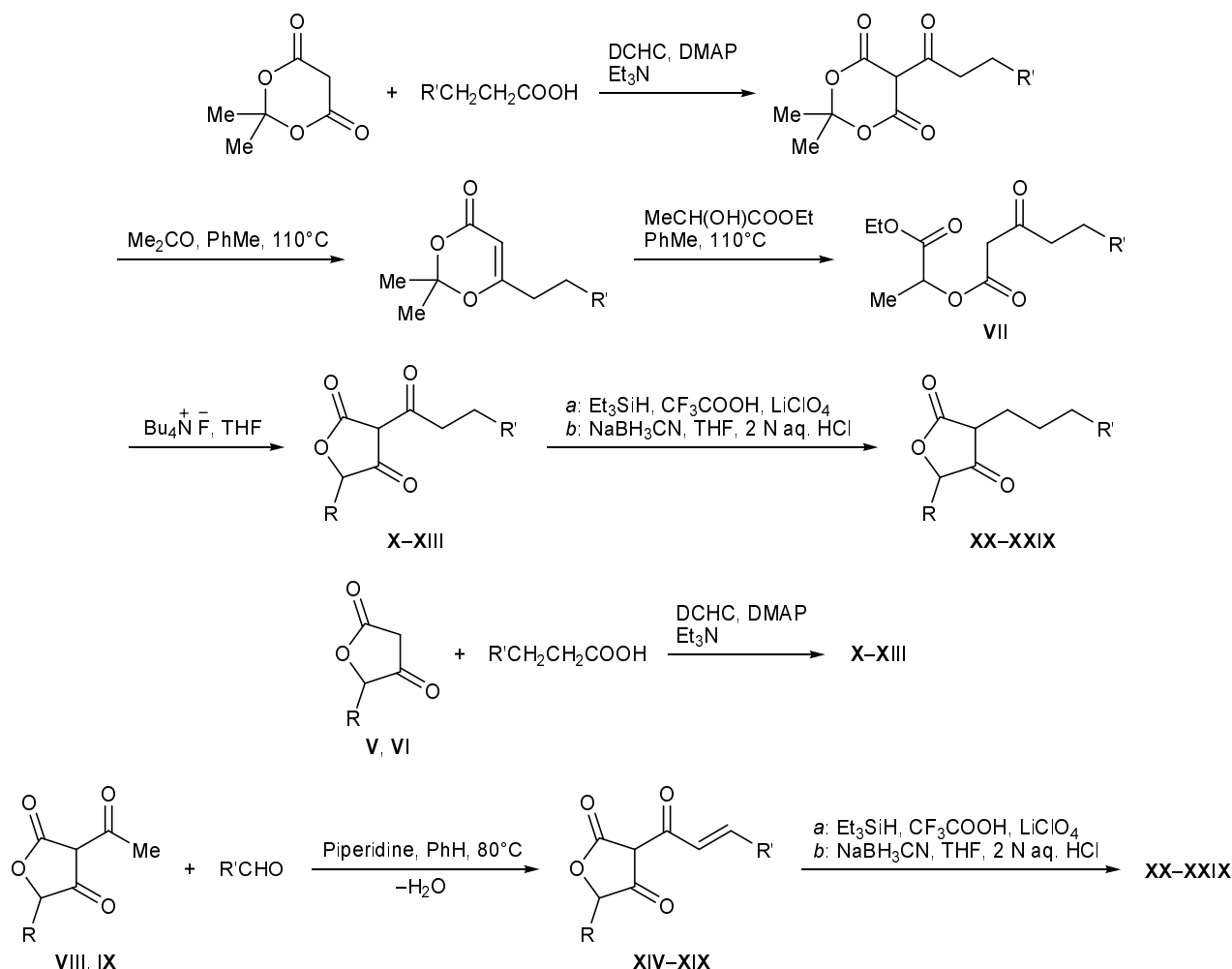
We previously synthesized 13-aza, 10-oxa-13-aza, and 11-oxa-13-aza prostanoids **II–IV** of the B series which possess a tetrahydrofuran fragment [4] or 1,5-inter-*p*-phenylene moiety [5] in the α -chain. If modification of the prostanoid α -chain is not taken

into account, compounds **II–IV** radically differ from 13-azaprostanic acid (**I**) by the geometric structure of the five-membered ring near the pharmacophoric NH group [sp^2 hybridization of the carbon atoms in positions 8, 9, and 12 (hereinafter, prostaglandin atom numbering is used) and the presence of a heteroatom in position 10 (**III**) or 11 (**IV**)]; in addition, the lone electron pair on the nitrogen atom is involved in conjugation with the ring. Despite the above differences, some compounds **II–IV** showed a pronounced antiaggregatory effect [6]. Like natural prostaglandins, these compounds exhibited a strong antiulcer activity (toward



* For communication II, see [1].

Scheme 1.



V, VIII, R = H; VI, IX, R = Me; VII, R' = C₅H₁₁; X, XX, R = H, R' = Me(CH₂)₄; XI, XXI, R = Me, R' = Me(CH₂)₄; XII, XXII, R = H, R' = EtOC(O)(CH₂)₃; XIII, XXIII, R = H, R' = MeOC(O)(CH₂)₃; XIV, XXIV, R = H, R' = 2-furyl; XV, XXV, R = Me, R' = 2-furyl; XVI, XXVI, R = H, R' = 2-thienyl; XVII, XXVII, R = Me, R' = 2-thienyl; XVIII, XXVIII, R = H, R' = *m*-MeOC₆H₄; XIX, XXIX, R = H, R' = *m*-MeOC₆H₄.

ethanol-induced ulcers) [7, 8]. Some heteroelement-containing prostaglandin analogs were shown to possess radioprotective [8], antiinflammatory [4], anti-exudative, immunotropic, and antitumor properties [7].

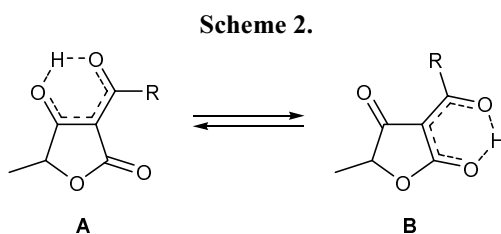
In continuation of our studies on the synthesis of prostaglandin heteroanalogs with a view to obtain new effective compounds possessing important biological properties, the present article reports on the preparation of new 10-oxa-13-aza, 11-oxa-13-aza, and 9-oxa-7-aza prostanoids which are characterized by considerably greater structural diversity of the α - and ω -chains. The target products were synthesized from 3-acylfuran-2,4(3*H*,5*H*)-diones X–XIII and 3-(3-arylprop-2-enoyl)furan-2,4(3*H*,5*H*)-diones XIV–XIX. Compounds X–XIX were prepared in three ways: (1) C-Acylation

of tetrone acids V and VI with octanoic acid or heptanedioic acid monoesters (compounds X–XIII); (2) Dieckmann cyclization of 1-ethoxycarbonyl ethyl 3-oxodecanoate (VII) (compound XI); and (3) condensation of 3-acetyltetrone acids VIII and IX with aromatic and heteroaromatic aldehydes (compounds XIV–XIX) (Scheme 1). The corresponding procedures were described in detail in the first communication of the present series [9], as well as in [10, 11].

According to the ¹H NMR spectra, cyclic β -tricarboxyl compounds X–XIX in solution exist as mixtures of two enol tautomers. The spectra of X, XII, and XIII contain two singlets from the C⁵H₂ methylene protons in the region δ 4.57–4.70 ppm, the difference between their positions being 0.10–0.12 ppm. The 3-H signal in

the ^1H NMR spectrum of **XI** appears as a multiplet. In addition, the spectra of compounds **X** and **XIII** are characterized by some doubling of the triplet signal at δ 2.92–2.96 ppm ($\Delta\delta = 0.02$ – 0.03 ppm), which belongs to the methylene protons neighboring to the carbonyl group of the 3-acyl substituent. Tautomeric forms of 3-acryloyl derivatives **XIV**, **XV**, **XVIII**, and **XIX** considerably differ in the chemical shifts of the methylene protons on C^5 (δ 4.59–4.67 ppm, s; $\Delta\delta = 0.06$ ppm) and 3-H (δ 4.74–4.83 ppm, q; $\Delta\delta = 0.06$ – 0.08 ppm), as well as in the positions of two doublets from protons at the *trans*-configured conjugated double bond (δ 7.55–8.04 ppm, $J = 15.5$ – 16.0 Hz; $\Delta\delta_1 = 0.05$ – 0.08 , $\Delta\delta_2 = 0.02$ ppm). Unlike compounds **XIV** and **XVIII**, thienylacryloyl derivative **XVI** showed in the ^1H NMR spectrum no doubling of the C^5 -methylene proton signal (δ 4.62 ppm). The 5-H signal in the spectrum of 5-methyl derivative **XVII** appeared as a multiplet at δ 4.78 ppm. The olefinic protons in the side chain of compounds **XVI** and **XVII** gave rise to a downfield doublet signal at δ 8.16–8.18 ppm ($J = 15.5$ Hz) and a multiplet at δ 7.50–7.51 ppm, the latter being overlapped by a doublet signal from one proton in the thienyl residue.

The data on the structure of tautomers of some 3-acyltetronic acids in solution, which were obtained by studying their IR [12] and ^1H NMR spectra [13], are contradictory. Jacobsen et al. [14] performed a systematic study on the ^{13}C NMR spectra of 3-acyltetronic acids and concluded that these compounds in solution exist as equilibrium mixtures of two tautomers **A** and **B** differing by the mode of intramolecular hydrogen bonding (Scheme 2); as a result, two sets of signals are present in their NMR spectra.



The transformation of 3-acyl- and 3-(3-arylprop-2-enoyl)furan-2,4(3*H*,5*H*)-diones **X**–**XIX** into the corresponding 3-alkyl and 3-(3-arylpropyl) derivatives **XX**–**XXIX** was effected using two reducing systems: triethylsilane in trifluoroacetic acid (ionic hydrogenation, method *a*) [15] and sodium cyanotrihydridoborate–tetrahydrofuran–2 N hydrochloric acid (method *b*) [16] (Scheme 1). Both procedures turned out to be equally

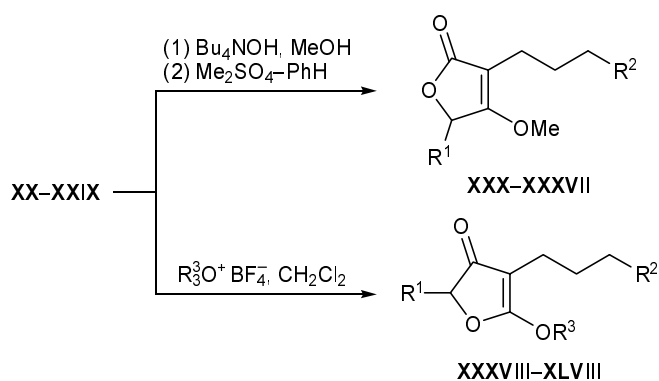
effective in the reduction of 3-acyltetronic acids **X**, **XI**, **XVIII**, and **XIX**, and the corresponding β -dicarbonyl compounds **XX**, **XXI**, **XXVIII**, and **XXIX** were obtained in high yields [9, 11]. In the synthesis of furandiones **XXII** and **XXIII**, the system triethylsilane–trifluoroacetic acid is preferred, for in this case the reduction is not accompanied by hydrolysis of the ester group [9].

We previously showed [10] that ionic hydrogenation of 3-(2-furyl)acryloyl derivatives of cyclic β -dicarbonyl compounds leads to formation of the corresponding products having a tetrahydrofuran fragment in the side chain. It is also known that ionic hydrogenation of alkyl thienyl ketones and α -alkylthiophenes smoothly affords α -alkyltetrahydrothiophenes as the only product [17]. With a view to obtain tetronic acids with a side-chain tetrahydrothiophen-2-ylalkyl fragment we performed ionic hydrogenation of 3-[3-(2-thienyl)prop-2-enoyl]furan-2,4-dione (**XVI**). However, unlike 3-[3-(2-furyl)prop-2-enoyl]furan-2,4(3*H*,5*H*)-diones, the reaction led to formation of a complex mixture of products which we failed to identify; presumably, tetronic acids having a 3-(tetrahydrothiophen-2-yl)propyl fragment on C^3 are unstable under these conditions. Therefore, ionic hydrogenation cannot be applied to the synthesis of 3-[3-(tetrahydrothiophen-2-yl)propyl]furan-2,4-diones from the corresponding 3-(2-thienyl)propyl precursors.

According to our previous data [16], 3-(2-furyl)acryloyl derivatives of cyclopentane-1,3-dione and 2*H*-pyran-2-one are reduced with the system sodium cyanotrihydridoborate–THF–2 N hydrochloric acid with conservation of the furan ring in the alkyl chain. Thus the use of different reducing systems makes it possible to obtain products having either furyl or tetrahydrofuryl fragment in the side chain.

The synthesis of prostaglandins E and F with furan and thiophene fragments in the prostanoid α - and ω -chains was reported in [18]. In order to obtain precursors of new prostanoids having heteroaromatic fragments in the side chains, furyl and thienyl derivatives **XIV**–**XVII** were reduced with the system NaBH_3CN –THF–2 N HCl. As might be expected, β -dicarbonyl compounds **XXIV**–**XXVII** were formed. The presence in molecules **XXIV** and **XXV** of an enolized β -dicarbonyl fragment (vinylogous acid) and an acidophobic unconjugated furan ring makes these compounds unstable. Unlike solid reaction products [16], oily compounds **XXIV** and **XXV** readily underwent decomposition; therefore, they were converted into stable

Scheme 3.



XXX, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}(\text{CH}_2)_4$; **XXXI**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}(\text{CH}_2)_4$; **XXXII**, $\text{R}^1 = \text{H}$, $\text{R}^2 = 2\text{-furyl}$; **XXXIII**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = 2\text{-furyl}$; **XXXIV**, $\text{R}^1 = \text{H}$, $\text{R}^2 = 2\text{-thienyl}$; **XXXV**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = 2\text{-thienyl}$; **XXXVI**, $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-MeOC}_6\text{H}_4$; **XXXVII**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = m\text{-MeOC}_6\text{H}_4$; **XXXVIII**, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}(\text{CH}_2)_4$, $\text{R}^3 = \text{Et}$; **XXXIX**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}(\text{CH}_2)_4$, $\text{R}^3 = \text{Et}$; **XL**, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{EtOC}(\text{O})(\text{CH}_2)_3$, $\text{R}^3 = \text{Me}$; **XLI**, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{EtOC}(\text{O})(\text{CH}_2)_3$, $\text{R}^3 = \text{Et}$; **XLII**, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{MeOC}(\text{O})(\text{CH}_2)_3$, $\text{R}^3 = \text{Et}$; **XLIII**, $\text{R}^1 = \text{H}$, $\text{R}^2 = 2\text{-furyl}$, $\text{R}^3 = \text{Et}$; **XLIV**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = 2\text{-furyl}$, $\text{R}^3 = \text{Et}$; **XLV**, $\text{R}^1 = \text{H}$, $\text{R}^2 = 2\text{-thienyl}$, $\text{R}^3 = \text{Et}$; **XLVI**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = 2\text{-thienyl}$, $\text{R}^3 = \text{Et}$; **XLVII**, $\text{R}^1 = \text{H}$, $\text{R}^2 = m\text{-MeOC}_6\text{H}_4$, $\text{R}^3 = \text{Et}$; **XLVIII**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = m\text{-MeOC}_6\text{H}_4$, $\text{R}^3 = \text{Et}$.

4-methoxy derivatives **XXXII** and **XXXIII** (Scheme 3) immediately after isolation from the reaction mixture (without additional purification). By contrast, thiophene-containing compounds **XXVI** and **XXVII** turned out to be quite stable.

10-Oxa-13-aza and 11-oxa-13-aza prostanoids may be regarded as enamino derivatives (vinylogous amides) of tetrone acids. One method for the preparation of enamino derivatives of cyclic β -dicarbonyl compounds is based on the direct reaction of the latter with amines. However, this procedure is readily applicable only to secondary cyclic amines [19]. Primary amines react with most cyclic β -dicarbonyl compounds only in the presence of Lewis acids, and the yield of the target enamino derivatives is usually poor [19, 20]. Moreover, the presence in molecules **XXIV** and **XXV** of an acidophobic furan ring prevents application of this procedure for the preparation of the corresponding enamino derivatives.

Another approach is based on reaction of amines with enol derivatives of β -dicarbonyl compounds, such as ketovinyl chlorides or enol ethers [21]. Although an additional step is necessary for the synthesis of appropriate enol derivatives, the overall yield of the target enamino compounds is fairly high. As applied to tetrone acids, one more advantage of the second

procedure is that, unlike carbocyclic β -dicarbonyl compounds, the carbonyl groups in furan-2,4-diones are chemically nonequivalent; therefore, two different enol derivatives may be obtained therefrom, at the ketone and lactone carbonyl groups. The direct amination ensures preparation of only one type of enamino derivatives.

As previously [4, 5], regioisomeric enol ethers were synthesized using regioselective O-alkylation procedures [22]. The alkylation of tetrabutylammonium salts of 3-alkyltetrone acids **XX-XXIX** with dimethyl sulfate gave 59–96% of 4-methoxy derivatives **XXX-XXXVII** (Scheme 3). As we already noted, 4-methoxyfuran-2(5*H*)-ones **XXXII** and **XXXIII** turned out to be fairly stable compounds, contrary to their dicarbonyl precursors **XXIV** and **XXV** having a furan ring in the side alkyl chain.

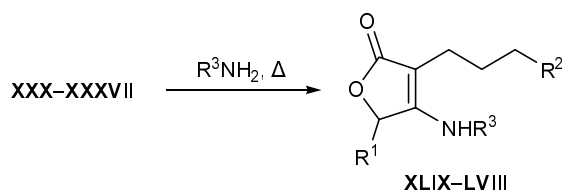
Treatment of compounds **XX-XXIII** and **XXVI-XXIX** with Meerwein salts (trimethyl- and triethyl-oxonium tetrafluoroborates) in methylene chloride afforded exclusively (yield 80–98%) the corresponding enol ethers **XXXVIII-XLII** and **XLV-XLVIII** at the lactone carbonyl group. This reaction is accompanied by liberation of strong tetrafluoroboric acid which promotes decomposition of furan-containing enol ethers **XLIII** and **XLIV** during the process; therefore, compounds **XLIII** and **XLIV** were brought into the next synthetic step immediately after quick treatment of the reaction mixture (without purification). It should be emphasized that the alkylation of tetrone acids with Meerwein salts is not generally regioselective, i.e., it could give rise to both 4-alkoxy derivatives and mixtures of isomeric enol ethers [22]. The presence of an alkyl group on C^3 forces the alkylation to occur exclusively at the lactone carbonyl group, though the origin of the observed orienting effect of the 3-alkyl substituent remains unclear.

Regioisomeric tetrone acid enol ethers are clearly distinguished by the IR spectra. 4-Methoxy derivatives **XXX-XXXVII** characteristically show in the spectra absorption bands due to stretching vibrations of the conjugated lactone carbonyl group at $1750\text{--}1765\text{ cm}^{-1}$ and the double bond at $1670\text{--}1675\text{ cm}^{-1}$. The IR spectra of isomeric enol ethers **XXXVIII-XLII** and **XLV-XLVIII** resemble those typical of enol ethers derived from cyclopentane-1,3-diones [23]. In particular, stretching vibrations of the conjugated carbonyl group in ethers **XXXVIII-XLII** and **XLV-XLVIII** appear at $1688\text{--}1700\text{ cm}^{-1}$, while the endocyclic double bond gives rise to absorption in the region $1610\text{--}1628\text{ cm}^{-1}$.

The ^1H NMR spectra of regioisomeric enol ethers differ in the positions of signals from the methylene (or methine) protons in the five-membered ring and protons nearest to the heteroring, i.e., in the methyl group on C^5 (C^2) and methylene group in the side chain. For example, signals from the C^5H_2 (δ 4.65–4.66 ppm, s) or C^5H protons (δ 4.68–4.70 ppm, q) in 4-methoxy derivatives **XXX–XXXVII** are located in a weaker field than the corresponding signals of isomeric ethers **XXXVIII–XLII** and **XLV–XLVIII** (δ 4.53–4.56 and 4.60–4.61 ppm, respectively). Analogous relations are observed for the triplet signals from the exocyclic methylene protons: δ 2.24–2.44 ppm in the spectra of 4-methoxy derivatives **XXX–XXXVII** and δ 2.06–2.19 ppm in the spectra of enols **XXXVIII–XLII** and **XLV–XLVIII** derived from the lactone carbonyl group. By contrast, the doublet signals from the 5- CH_3 group in 4-methoxy derivatives **XXXI**, **XXXIII**, **XXXV**, and **XXXVII** are displaced upfield (δ 1.41–1.42 ppm) relative to the 2- CH_3 signals in the spectra of isomeric enol ethers **XXXIX**, **XLVI**, and **XLVIII** (δ 1.48 ppm).

Regioisomeric enol ethers **XXX–XXXVII** and **XXXVIII–XLVIII** were brought into reaction with primary aliphatic amines. 4-Methoxy derivatives **XXX–XXXVII** turned out to be considerably less reactive than 5-methoxy isomers **XXXVIII–XLVIII**, and the former reacted with amines only on heating to give the corresponding 10-oxa-13-aza prostanoids **XLIX–LVIII** in 36–76% yield (Scheme 4). As we showed previously [5], this procedure is inappropriate

Scheme 4.

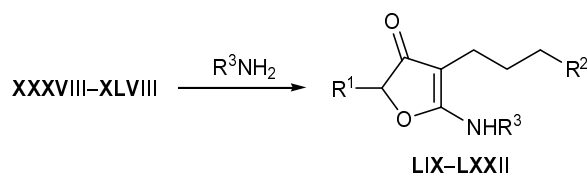


Compound no.	R ¹	R ²	R ³
XLIX	H	Me(CH ₂) ₄	<i>cyclo</i> -C ₆ H ₁₁
L	Me	Me(CH ₂) ₄	C ₇ H ₁₅
LI	Me	Me(CH ₂) ₄	C ₈ H ₁₇
LII	Me	Me(CH ₂) ₄	PhCH ₂
LIII	H	2-Furyl	C ₇ H ₁₅
LIV	Me	2-Furyl	C ₇ H ₁₅
LV	H	2-Thienyl	C ₈ H ₁₇
LVI	Me	2-Thienyl	C ₇ H ₁₅
LVII	H	<i>m</i> -MeOC ₆ H ₄	C ₇ H ₁₅
LVIII	Me	<i>m</i> -MeOC ₆ H ₄	C ₇ H ₁₅

for the preparation of 10-oxa-13-aza prostanoids having an ester moiety in the side chain, for severe reaction conditions promote aminolysis of the ester group and the resulting amides become the major products.

By contrast, enol ethers **XXXVIII–XLII** and **XLV–XLVIII** reacted with amines even at room or slightly elevated temperature (to accelerate the process), leading to the corresponding 11-oxa-13-aza prostanoids **LIX–LXV** and **LXVIII–LXXII** in 60–81% yield (Scheme 5). The lower overall yield of 11-oxa-13-aza prostanoids **LXVI** and **LXVII** (36 and 40%, respectively) having a furan ring in the α -chain may be attributed to instability of enol ethers **XLIII** and **XLIV** under the conditions of their synthesis (see above).

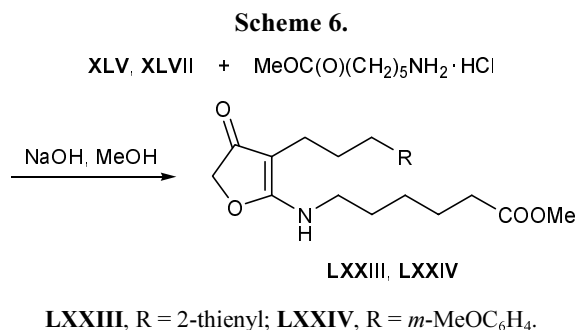
Scheme 5.



Compound no.	R ¹	R ²	R ³
LIX	H	Me(CH ₂) ₄ CH ₃	<i>cyclo</i> -C ₆ H ₁₁
LX	Me	Me(CH ₂) ₄ CH ₃	C ₇ H ₁₅
LXI	Me	Me(CH ₂) ₄ CH ₃	CH ₂ Ph
LXII	H	EtOC(O)(CH ₂) ₃	C ₇ H ₁₅
LXIII	H	MeOC(O)(CH ₂) ₃	C ₇ H ₁₅
LXIV	H	MeOC(O)(CH ₂) ₃	C ₈ H ₁₇
LXV	H	MeOC(O)(CH ₂) ₃	PhCH ₂
LXVI	H	2-Furyl	C ₇ H ₁₅
LXVII	Me	2-Furyl	C ₇ H ₁₅
LXVIII	H	2-Thienyl	C ₈ H ₁₇
LXIX	Me	2-Thienyl	C ₇ H ₁₅
LXX	H	<i>m</i> -MeOC ₆ H ₄	C ₇ H ₁₅
LXXI	H	<i>m</i> -MeOC ₆ H ₄	<i>cyclo</i> -C ₆ H ₁₁
LXXII	Me	<i>m</i> -MeOC ₆ H ₄	C ₇ H ₁₅

The use of amino acid esters as amine component allowed us to obtain 9-oxa-7-aza prostanoids in which the 3-alkyl or 3-arylalkyl substituent constitutes the ω -chain. In particular, the reaction of enol ether **XLV** with methyl 6-aminohexanoate gave 9-oxa-7-aza prostanoid **LXXIII** containing a thiophene ring in the ω -chain, while from enol ether **XLVII** we obtained 9,19-dioxa-7-aza-16,17,18-trinor-15,19-inter-*m*-phenylene derivative **LXXIV** (Scheme 6).

Like the initial enol ethers, the resulting regioisomeric enamincarbonyl derivatives are clearly distinguished by the IR spectra. 10-Oxa-13-aza prostanoids **XLIX–LVIII** showed in the IR spectra absorption



bands belonging to the lactone carbonyl group (1720–1730 cm⁻¹) and conjugated double bond (1630–1640 cm⁻¹), as well as stretching vibration bands of the NH group at 3100–3110 and 3310 cm⁻¹. The enaminoketone fragment in 11-oxa-13-aza and 9-oxa-7-aza prostanoids **LIX–LXXIV** is characterized by a broad absorption band with its maximum at 1570–1575 cm⁻¹; analogous absorption band is typical of enamino derivatives of cyclopentane-1,3-dione [19]. The NH group in **LIX–LXXIV** also gives rise to a broad absorption band centered at 3210–3220 cm⁻¹. The low-frequency shift of the IR absorption band corresponding to the unsaturated bond in the enaminoketone fragment in heteroprostanoids **LIX–LXXIV**, as compared to compounds **XLIX–LVIII**, suggests stronger conjugation in the molecules of the former.

The ¹H NMR spectra of 10-oxa-13-aza and 11-oxa-13-aza prostanoids revealed analogous relations in the chemical shifts of indicator protons, as in the spectra of their precursors. Signals from the methylene (δ 4.62–4.65 ppm, s) or methine protons in the heteroring (δ 4.76–4.81 ppm, q), as well as from the methylene protons neighboring to the heteroring (δ 2.10–2.24 ppm, t), in the spectra of 10-oxa-13-aza prostanoids **L–LVIII** appeared in a weaker field than the corresponding signals of 11-oxa-13-aza prostanoids **LX–LXX** and **LXXII** (δ 4.48–4.60, 4.54–4.65, and 2.06–2.18 ppm, respectively). Exceptions were regioisomeric heteroprostanoids **XLIX**, **LIX**, and **LXXI** containing a cyclohexane fragment in the ω-chain; these compounds showed no difference in the chemical shifts of the side-chain methylene protons nearest to the heteroring. By contrast, “floating” signals from the NH proton (δ 4.07–4.60 ppm) and quartet signals from the side-chain methylene protons at the nitrogen atom (δ 3.06–3.25 ppm) in the spectra of 10-oxa-13-aza prostanoids are displaced upfield relative to the corresponding signals of 11-oxa-13-aza derivatives (δ 4.73–5.96 and 3.31–3.37 ppm, respectively). Spatial proximity of the 11-methyl group to the ω-chain methylene

group at the nitrogen atom in 11-methyl-10-oxa-13-aza prostanoids **L**, **LI**, **LIV**, **LVI**, and **LVIII** is responsible for broadening of the quartet signal from that group or its splitting to a quartet of doublets (*J* = 6.7, 2.0–2.5 Hz), though there is no appreciable difference in the chemical shifts of the 11-Me protons in both regioisomers (δ 1.45–1.48 ppm). Likewise, the doublet signal from the NCH₂Ph protons (δ 4.47 ppm) in 10-oxa-13-aza prostanoid **LII** and the multiplet signal from the NCH proton in the cyclohexane fragment (δ 2.90–3.12 ppm) of 10-oxa-13-aza prostanoid **XLIX** are located in a stronger field than analogous signals of isomeric 11-oxa-13-aza prostanoids **LXV** (δ 4.58 ppm), **LIX** (δ 3.56–3.78), and **LXXI** (δ 3.51–3.72 ppm). The NH signal in the spectrum of 10-oxa-13-aza prostanoid **XLIX** having a cyclohexane fragment in the ω-chain appears as a broadened doublet at δ 4.48 ppm with a coupling constant *J* of 9.0 Hz, indicating *trans* orientation of that proton with respect to the axial CH proton in the cyclohexane ring.

Thus various methods for building up the 3-acyl chain in combination with various methods for hydrogenation of the carbonyl group in the 3-acyl substituent (differing in their selectivity), as well as the possibility of using various primary amines, including amino acid esters, give rise to a huge structural diversity of the α- and ω-chains in the resulting heteroprostanoids. In addition, ambident reactivity of tetric acids makes it possible to obtain two types of isomeric enol derivatives which are capable of reacting with amines to give two types of enaminocarbonyl derivatives, enaminolactones and enaminoketones. As applied to the synthesis of heteroprostanoids, 10-oxa-13-aza and 11-oxa-13-aza prostanoids of the B series, **XLIX–LVIII** and **LIX–LXXII**, respectively, can be synthesized.

EXPERIMENTAL

The melting points were determined on a Boetius melting point apparatus. The ¹H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 MHz using CDCl₃ as solvent and TMS as internal reference. The IR spectra were measured on a UR-20 spectrometer from samples prepared as thin films or KBr pellets. The mass spectra (electron impact, 70 eV) were run on a Varian MAT-311 instrument. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates. Silica gel (100/160 μm, Czechia) and aluminum oxide were used for column chromatography.

3-Acylfuran-2,4(3*H*,5*H*)-diones **X–XIII** were synthesized by C-acylation of tetronic acids **V** and **VI** with carboxylic acids. Compound **XI** was also prepared by the Dieckmann cyclization of 1-ethoxycarbonyl ethyl 3-oxodecanoate (**VII**) [9]. The spectral parameters and physical constants of compounds **X**, **XI**, and **XIII** were reported in [9].

Ethyl 7-(2,4-dioxotetrahydrofuran-3-yl)-7-oxoheptanoate (XII). Yield 83%, mp 54–55°C (from diethyl ether–hexane). IR spectrum, ν , cm^{-1} : 1230, 1270, 1310, 1345, 1370, 1390, 1440, 1465, 1620, 1665, 1735, 1750, 1775, 3225 br. ^1H NMR spectrum, δ , ppm: 1.26 t (3H, OCH_2CH_3 , $J = 7.0$ Hz), 1.44 m [2H, $\text{C}(\text{O})(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{Et}$], 1.60–1.82 m [4H, $\text{C}(\text{O})\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$], 2.31 t (2H, $\text{CH}_2\text{CO}_2\text{Et}$, $J = 7.5$ Hz), 2.93 t [2H, $\text{C}(\text{O})\text{CH}_2$, $J = 7.5$ Hz], 4.13 q (2H, OCH_2CH_3 , $J = 7.0$ Hz), 4.57 s and 4.69 s (2H, furan), 8.10 br (1H, OH, enol). Mass spectrum: m/z 270 [M]⁺. Found, %: C 57.26; H 6.92. $\text{C}_{13}\text{H}_{18}\text{O}_6$. Calculated, %: C 57.77; H 6.71.

Condensation of 3-acetylfuran-2,4(3*H*,5*H*)-diones VIII and IX with aromatic aldehydes. Compound **VIII** or **IX**, 20 mmol, was dissolved in 40 ml of anhydrous benzene, and 2.96 ml (30 mmol) of piperidine and 18 mmol of the corresponding aromatic aldehyde were added. The mixture was heated for 5 h under reflux in a flask equipped with a Dean–Stark trap and was left overnight at room temperature. The solvent was distilled off under reduced pressure, and the residue was acidified with 1 N hydrochloric acid to pH 2. The precipitate was filtered off, washed with 1 N hydrochloric acid and water, dried in air, and recrystallized from appropriate solvent.

(*E*)-3-[3-(2-Furyl)prop-2-enoyl]furan-2,4(3*H*,5*H*)-dione (XIV). Yield 74%, mp 149–151°C (from acetone). IR spectrum, ν , cm^{-1} : 1275 sh, 1290, 1300, 1370 sh, 1390, 1410 sh, 1465, 1540, 1620 br (max.), 1675 sh, 1750. ^1H NMR spectrum, δ , ppm: 4.59 s and 4.65 s (2H, CH_2), 6.60 d.d (1H, CH, furyl, $J = 3.5$, 1.5 Hz), 6.94 t (1H, CH, furyl, $J = 3.5$ Hz), 7.55 d (0.5H, =CH, $J_{\text{trans}} = 15.5$ Hz), 7.63 d (0.5H, =CH, $J_{\text{trans}} = 15.5$ Hz), 7.67 m (1H, CH, furyl), 7.79 d (0.5H, CH=, $J_{\text{trans}} = 15.5$ Hz), 7.81 d (0.5H, CH=, $J_{\text{trans}} = 15.5$ Hz). Mass spectrum: m/z 220 [M]⁺. Found, %: C 59.83; H 3.82. $\text{C}_{11}\text{H}_8\text{O}_5$. Calculated, %: C 60.01; H 3.66.

(*E*)-3-[3-(2-Furyl)prop-2-enoyl]-5-methylfuran-2,4(3*H*,5*H*)-dione (XV). Yield 50%, mp 142–143°C (from acetone). IR spectrum, ν , cm^{-1} : 1275, 1290, 1320, 1345, 1370, 1395, 1460, 1540, 1595 (max.),

1620 (max.), 1690. ^1H NMR spectrum, δ , ppm: 1.53 d (3H, CH_3 , $J = 7.0$ Hz), 4.74 q and 4.80 q (1H, CH_3CH , $J = 7.0$ Hz), 6.59 m (1H, CH, furyl), 6.92 t (1H, CH, furyl, $J = 3.5$ Hz), 7.56 d and 7.61 d (1H, CH=, $J_{\text{trans}} = 15.5$ Hz), 7.66 m (1H, CH, furyl), 7.77 d and 7.79 d (1H, =CH, $J_{\text{trans}} = 15.5$ Hz). Mass spectrum: m/z 234 [M]⁺. Found, %: C 61.12; H 4.26. $\text{C}_{12}\text{H}_{10}\text{O}_5$. Calculated, %: C 61.54; H 4.30.

(*E*)-3-[3-(2-Thienyl)prop-2-enoyl]furan-2,4(3*H*,5*H*)-dione (XVI). Yield 63%, mp 147–150°C (from acetone). IR spectrum, ν , cm^{-1} : 1370, 1420, 1450, 1510, 1565, 1625 (max.), 1665 sh, 1690, 1735, 1760. ^1H NMR spectrum, δ , ppm: 4.62 s (2H, CH_2), 7.17 d.d (1H, CH, thienyl, $^3J = 5.0$, 3.5 Hz), 7.51 br.d and m (2H, CH, thienyl, CH=, $^3J = 3.5$ Hz), 7.64 br.d (1H, CH, thienyl, $^3J = 5.0$ Hz), 8.18 d (1H, =CH, $J_{\text{trans}} = 15.5$ Hz), 9.42 br (1H, OH, enol). Mass spectrum: m/z 236 [M]⁺. Found, %: C 56.15; H 3.38. $\text{C}_{11}\text{H}_8\text{O}_4\text{S}$. Calculated, %: C 55.92; H 3.41.

(*E*)-5-Methyl-3-[3-(2-thienyl)prop-2-enoyl]furan-2,4(3*H*,5*H*)-dione (XVII). Yield 61%, mp 103–105°C (from acetone). IR spectrum, ν , cm^{-1} : 1295, 1325, 1390, 1420, 1450, 1515, 1590, 1630 br (max.), 1700, 1760. ^1H NMR spectrum, δ , ppm: 1.55 d (3H, CH_3CH , $J = 7.0$ Hz), 4.78 m (1H, CH_3CH), 7.17 d.d (1H, CH, thienyl, $^3J = 5.0$, 3.5 Hz), 7.50 br.d and m (2H, CH, thienyl, CH=, $^3J = 3.5$ Hz), 7.62 br.d (1H, CH, thienyl, $^3J = 5.0$ Hz), 8.16 d (1H, =CH, $J_{\text{trans}} = 15.5$ Hz), 9.24–11.00 br (1H, OH, enol). Mass spectrum: m/z 250 [M]⁺. Found, %: C 57.76; H 4.10. $\text{C}_{12}\text{H}_{10}\text{O}_4\text{S}$. Calculated, %: C 57.59; H 4.03.

The spectral parameters and physical constants of compounds **XVIII** and **XIX** were reported in [11].

3-Alkylfuran-2,4(3*H*,5*H*)-diones XX–XXIX were synthesized by reduction of β -tricarbonyl compounds **X–XIX** with triethylsilane in trifluoroacetic acid (method *a*) or with sodium cyanotrihydridoborate in the system THF–2 N hydrochloric acid (method *b*) according to the procedures described in [9].

The spectral parameters and physical constants of compounds **XX**, **XXI**, and **XXIII** were reported in [9], and of **XXVIII** and **XXIX**, in [11].

Ethyl 7-(2,4-dioxotetrahydrofuran-3-yl)heptanoate (XXII). Yield 86%, mp 45–46°C (from diethyl ether–hexane). IR spectrum, ν , cm^{-1} : 1235, 1270, 1285, 1300, 1320, 1350, 1410, 1455, 1465 sh, 1650 br (max.), 1740 (max.), 2720 br. ^1H NMR spectrum, δ , ppm: 1.27 t (3H, OCH_2CH_3 , $J = 7.0$ Hz), 1.32 m [4H, $(\text{CH}_2)_2(\text{CH}_2)_2(\text{CH}_2)_2\text{CO}_2\text{Et}$], 1.49 quint [2H, CH_2CH_2 -

(CH₂)₄CO₂Et, $J = 7.5$ Hz], 1.60 quint (2H, CH₂CH₂-CO₂Et, $J = 7.2$ Hz), 2.20 t [2H, CH₂(CH₂)₅CO₂Et, $J = 7.5$ Hz], 2.31 t (2H, CH₂CO₂Et, $J = 7.2$ Hz), 4.12 q (2H, OCH₂CH₃, $J = 7.0$ Hz), 4.64 s (2H, 5-H). Mass spectrum: m/z 256 [M]⁺. Found, %: C 60.85; H 7.79. C₁₃H₂₀O₅. Calculated, %: C 60.92; H 7.87.

Unstable compounds **XXIV** and **XXV** were characterized as the corresponding enol ethers **XXXII** and **XXXIII**.

3-[3-(2-Thienyl)propyl]furan-2,4(3H,5H)-dione (XXVI). Yield 80%, mp 106–108°C, 119–120°C (from ethyl acetate). IR spectrum, ν , cm⁻¹: 1360, 1400, 1470, 1590–1670 br, 1730, 2380–2840. ¹H NMR spectrum, δ , ppm: 1.86 quint (2H, CH₂CH₂CH₂, $J = 7.5$ Hz), 2.28 t (2H, 3-CH₂, $J = 7.5$ Hz), 2.81 t (2H, CH₂CS, $J = 7.5$ Hz), 4.62 s (2H, 5-H), 6.76 br.d (1H, CH, thienyl, ³ $J = 3.0$ Hz), 6.88 d.d (1H, CH, thienyl, ³ $J = 5.0$, 3.0 Hz), 7.07 br.d (1H, CH, thienyl, ³ $J = 5.0$ Hz), 8.50 br (1H, OH, enol). Mass spectrum: m/z 224 [M]⁺. Found, %: C 59.12; H 5.40. C₁₁H₁₂O₃S. Calculated, %: C 58.91; H 5.39.

5-Methyl-3-[3-(2-thienyl)propyl]furan-2,4(3H,5H)-dione (XXVII). Yield 84%, oily substance. IR spectrum, ν , cm⁻¹: 1295, 1355, 1390, 1415, 1470, 1660 br (max.), 1740, 2380–2800 br. ¹H NMR spectrum, δ , ppm: 1.46 d (3H, 5-CH₃, $J = 6.5$ Hz), 1.86 quint (2H, CH₂CH₂CH₂, $J = 7.5$ Hz), 2.28 t (2H, 3-CH₂, $J = 7.5$ Hz), 2.81 t (2H, CH₂CS, $J = 7.5$ Hz), 4.78 q (1H, CH₃CH, $J = 6.5$ Hz), 6.76 br.d (1H, CH, thienyl, ³ $J = 3.0$ Hz), 6.87 d.d (1H, CH, thienyl, ³ $J = 5.0$, 3.0 Hz), 7.07 br.d (1H, CH, thienyl, ³ $J = 5.0$ Hz), 7.89 br (1H, OH, enol). Mass spectrum: m/z 238 [M]⁺. Found, %: C 60.81; H 5.98. C₁₂H₁₄O₃S. Calculated, %: C 60.48; H 5.92.

O-Alkylation of 3-alkylfuran-2,4(3H,5H)-dione XX–XXIX tetrabutylammonium salts with dimethyl sulfate. 3-Alkylfuran-2,4(3H,5H)-dione **XX–XXIX**, 0.001 mol, was dissolved in 10 ml of methanol, 1.25 ml (0.001 mol) of a 0.8 M solution of tetrabutylammonium hydroxide in methanol was added under stirring, and the mixture was stirred for 1 h at room temperature. The solvent was distilled off under reduced pressure, and residual water was removed from the red oily salt by azeotropic distillation with benzene. The salt was dissolved in benzene, 0.14 ml (0.0015 mol) of dimethyl sulfate was added, and the mixture was stirred for 24 h at room temperature. The product was isolated by column chromatography on silica gel using diethyl ether–petroleum ether as eluent.

4-Methoxy-3-octylfuran-2(5H)-one (XXX). Yield 96%, mp 45–48°C (from diethyl ether). IR spectrum, ν , cm⁻¹: 1265, 1280, 1300, 1335, 1353, 1390, 1450 sh, 1480, 1680 (max.), 1750. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, $J = 6.5$ Hz), 1.10–1.40 m (10H, CH₂), 1.49 quint (2H, CH₂, $J = 7.0$ Hz), 2.24 t (2H, 3-CH₂, $J = 7.5$ Hz), 3.95 s (3H, OCH₃), 4.66 s (2H, 5-H). Mass spectrum: m/z 226 [M]⁺. Found, %: C 68.83; H 9.94. C₁₃H₂₂O₃. Calculated, %: C 68.99; H 9.80.

4-Methoxy-5-methyl-3-octylfuran-2(5H)-one (XXXI). Yield 95%, oily substance. IR spectrum, ν , cm⁻¹: 1260, 1280, 1305, 1365, 1385, 1465, 1670 (max.), 1765. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, $J = 6.5$ Hz), 1.10–1.38 m (10H, CH₂), 1.42 d (3H, 5-CH₃, $J = 6.5$ Hz), 1.52 m (2H, CH₂), 2.36 t (2H, 3-CH₂, $J = 7.5$ Hz), 3.98 s (3H, OCH₃), 4.70 q (1H, 5-H, $J = 6.5$ Hz). Mass spectrum: m/z 240 [M]⁺. Found, %: C 69.47; H 10.25. C₁₄H₂₄O₃. Calculated, %: C 69.96; H 10.07.

3-[3-(2-Furyl)propyl]-4-methoxyfuran-2(5H)-one (XXXII). Yield 62%, oily substance. IR spectrum, ν , cm⁻¹: 1270, 1300, 1310, 1350, 1390, 1450 sh, 1475, 1520, 1610, 1680 (max.), 1760. ¹H NMR spectrum, δ , ppm: 1.87 quint (2H, CH₂CH₂CH₂, $J = 7.5$ Hz), 2.31 t (2H, 3-CH₂, $J = 7.5$ Hz), 2.66 t (2H, CH₂CO, $J = 7.5$ Hz), 3.92 s (3H, OCH₃), 4.66 s (2H, 5-H), 6.01 d.d (1H, CH, furyl, ³ $J = 3.0$, ⁴ $J = 1.0$ Hz), 6.28 d.d (1H, CH, furyl, ³ $J = 3.0$, 2.0 Hz), 7.29 br.d (1H, CH, furyl, ³ $J = 2.0$ Hz). Mass spectrum: m/z 222 [M]⁺. Found, %: C 65.04; H 6.40. C₁₂H₁₄O₄. Calculated, %: C 64.85; H 6.35.

3-[3-(2-Furyl)propyl]-4-methoxy-5-methylfuran-2(5H)-one (XXXIII). Yield 59%, mp 31–33.5°C (from diethyl ether). IR spectrum, ν , cm⁻¹: 1295, 1310, 1335, 1365, 1370, 1465, 1520, 1610, 1680 (max.), 1765. ¹H NMR spectrum, δ , ppm: 1.42 d (3H, 5-CH₃, $J = 6.7$ Hz), 1.89 quint (2H, CH₂CH₂CH₂, $J = 7.5$ Hz), 2.42 t (2H, 3-CH₂, $J = 7.5$ Hz), 2.69 t (2H, CH₂CO, $J = 7.5$ Hz), 3.98 s (3H, OCH₃), 4.69 q (1H, 5-H, $J = 6.7$ Hz), 6.03 br.d (1H, CH, furyl, ³ $J = 3.0$ Hz), 6.28 d.d (1H, CH, furyl, ³ $J = 3.0$, 2.0 Hz), 7.30 br.d (1H, CH, furyl, ³ $J = 2.0$ Hz). Mass spectrum: m/z 236 [M]⁺. Found, %: C 65.98; H 6.78. C₁₃H₁₆O₄. Calculated, %: C 66.08; H 6.83.

4-Methoxy-3-[3-(2-thienyl)propyl]furan-2(5H)-one (XXXIV). Yield 68%, oily substance. IR spectrum, ν , cm⁻¹: 1295, 1305, 1350, 1390, 1450, 1470, 1680 (max.), 1760. ¹H NMR spectrum, δ , ppm: 1.90 quint (2H, CH₂CH₂CH₂, $J = 7.5$ Hz), 2.32 t (2H, 3-CH₂, $J = 7.5$ Hz), 2.85 t (2H, CH₂CS, $J = 7.5$ Hz),

3.90 s (3H, OCH₃), 4.66 s (2H, 5-H), 6.81 br.d (1H, CH, thienyl, ³J = 3.5 Hz), 6.91 d.d (1H, CH, thienyl, ³J = 5.0, 3.5 Hz), 7.11 d.d (1H, CH, thienyl, ³J = 5.0, ⁴J = 1.0 Hz). Mass spectrum: *m/z* 238 [M]⁺. Found, %: C 60.66; H 5.91. C₁₂H₁₄O₃S. Calculated, %: C 60.48; H 5.92.

4-Methoxy-5-methyl-3-[3-(2-thienyl)propyl]-furan-2(5H)-one (XXXV). Yield 70%, oily substance. IR spectrum, ν , cm⁻¹: 1300, 1315, 1340, 1365 sh, 1380, 1390 sh, 1460, 1475, 1685 (max.), 1775. ¹H NMR spectrum, δ , ppm: 1.42 d (3H, 5-CH₃, *J* = 6.7 Hz), 1.93 quint (2H, CH₂CH₂CH₂, *J* = 7.5 Hz), 2.44 t (2H, 3-CH₂, *J* = 7.5 Hz), 2.89 t (2H, CH₂CS, *J* = 7.5 Hz), 3.96 s (3H, OCH₃), 4.70 q (1H, 5-H, *J* = 6.7 Hz), 6.81 d.d (1H, CH, thienyl, ³J = 3.5, ⁴J = 1.0 Hz), 6.92 d.d (1H, CH, thienyl, ³J = 5.0, 3.5 Hz), 7.12 d.d (1H, CH, thienyl, ³J = 5.0, ⁴J = 1.0 Hz). Mass spectrum: *m/z* 252 [M]⁺. Found, %: C 62.05; H 6.42. C₁₃H₁₆O₃S. Calculated, %: C 61.88; H 6.39.

The spectral parameters and physical constants of compounds XXXVI and XXXVII were reported previously [11].

O-Alkylation of 3-alkylfuran-2,4(3H,5H)-diones XX–XXIX with trialkyloxonium tetrafluoroborates. Compound XX–XXIX, 2.5 mmol, was dissolved in 30 ml of methylene chloride, and 1.42 g (7.5 mmol) of triethyloxonium tetrafluoroborate or 1.11 g (7.5 mmol) of trimethyloxonium tetrafluoroborate was added under stirring. When the reaction was complete (TLC), the mixture was passed through a layer of silica gel using chloroform as eluent. The eluate was evaporated under reduced pressure, and the residue was subjected to chromatography on a short column charged with aluminum oxide using diethyl ether and hexane as eluents; the corresponding enol ethers were isolated as mobile oily substances.

The spectral parameters and physical constants of compounds XXXIX and XLII were reported in [9]. Unstable enol ethers XLIII and XLIV were not characterized.

5-Ethoxy-4-octylfuran-3(2H)-one (XXXVIII). Yield 98%. IR spectrum, ν , cm⁻¹: 1265, 1285, 1310, 1360, 1390, 1430, 1450, 1490, 1615 (max.), 1710. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, *J* = 6.5 Hz), 1.14–1.40 m (12H, CH₂), 1.44 t (3H, OCH₂CH₃, *J* = 7.0 Hz), 2.08 t (2H, 4-CH₂, *J* = 7.0 Hz), 4.44 q (2H, OCH₂CH₃, *J* = 7.0 Hz), 4.54 s (2H, 2-H). Mass spectrum: *m/z* 240 [M]⁺.

Ethyl 7-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (XL). Yield 88%. IR spectrum, ν , cm⁻¹:

1255 br.w, 1285 w, 1300 w, 1345 br.w, 1390, 1480, 1610 (max.), 1700, 1735. ¹H NMR spectrum, δ , ppm: 1.25 t (3H, OCH₂CH₃, *J* = 7.5 Hz), 1.31 m [4H, (CH₂)₂(CH₂)₂(CH₂)₂CO₂Et], 1.42 quint [2H, CH₂CH₂-(CH₂)₄CO₂Et, *J* = 7.0 Hz], 1.60 quint (2H, CH₂CH₂-CO₂Et, *J* = 7.5 Hz), 2.07 t (2H, 3-CH₂, *J* = 7.0 Hz), 2.28 t (2H, CH₂CO₂Et, *J* = 7.5 Hz), 4.05 s (3H, OCH₃), 4.12 q (2H, OCH₂CH₃, *J* = 7.5 Hz), 4.54 s (2H, 5-H). Mass spectrum: *m/z* 270 [M]⁺.

Ethyl 7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (XLI). Yield 91%. IR spectrum, ν , cm⁻¹: 1260, 1310, 1360, 1395, 1430, 1450, 1490, 1620 (max.), 1710, 1745. ¹H NMR spectrum, δ , ppm: 1.18–1.51 m (6H, CH₂), 1.26 t (3H, CH₃, *J* = 7.0 Hz), 1.44 t (3H, OCH₂CH₃, *J* = 7.0 Hz), 1.63 m (2H, CH₂CH₂CO₂Et), 2.08 t (2H, 3-CH₂, *J* = 7.0 Hz), 2.30 t (2H, CH₂CO₂Et, *J* = 7.5 Hz), 4.13 q (2H, COOCH₂CH₃, *J* = 7.0 Hz), 4.45 q (2H, OCH₂CH₃, *J* = 7.0 Hz), 4.55 s (2H, 5-H). Mass spectrum: *m/z* 284 [M]⁺.

5-Ethoxy-4-[3-(2-thienyl)propyl]furan-3(2H)-one (XLV). Yield 84%. IR spectrum, ν , cm⁻¹: 1295, 1310, 1360, 1395, 1430 sh, 1450, 1495, 1590 sh, 1610 (max.), 1700. ¹H NMR spectrum, δ , ppm: 1.44 t (3H, OCH₂-CH₃, *J* = 7.0 Hz), 1.84 quint (2H, CH₂CH₂CH₂, *J* = 7.5 Hz), 2.19 t (2H, 4-CH₂, *J* = 7.5 Hz), 2.83 t (2H, CH₂CS, *J* = 7.5 Hz), 4.44 q (2H, OCH₂CH₃, *J* = 7.0 Hz), 4.56 s (2H, 2-H), 6.81 d.d (1H, CH, thienyl, ³J = 3.5, ⁴J = 1.0 Hz), 6.92 d.d (1H, CH, thienyl, ³J = 5.0, 3.5 Hz), 7.11 d.d (1H, CH, thienyl, ³J = 5.0, ⁴J = 1.0 Hz). Mass spectrum: *m/z* 252 [M]⁺.

5-Ethoxy-2-methyl-4-[3-(2-thienyl)propyl]furan-3(2H)-one (XLVI). Yield 82%. IR spectrum, ν , cm⁻¹: 1295, 1310, 1360, 1395, 1435, 1450, 1495, 1615 (max.), 1705. ¹H NMR spectrum, δ , ppm: 1.43 t (3H, OCH₂CH₃, *J* = 7.0 Hz), 1.48 d (3H, 2-CH₃, *J* = 7.0 Hz), 1.84 quint (2H, CH₂CH₂CH₂, *J* = 7.5 Hz), 2.17 t (2H, 4-CH₂, *J* = 7.5 Hz), 2.82 t (2H, CH₂CS, *J* = 7.5 Hz), 4.42 q (2H, OCH₂CH₃, *J* = 7.0 Hz), 4.61 q (1H, 2-H, *J* = 7.0 Hz), 6.80 d.d (1H, CH, thienyl, ³J = 3.5, ⁴J = 1.0 Hz), 6.91 d.d (1H, CH, thienyl, ³J = 5.0, 3.5 Hz), 7.10 d.d (1H, CH, thienyl, ³J = 5.0, ⁴J = 1.0 Hz). Mass spectrum: *m/z* 266 [M]⁺.

5-Ethoxy-4-[3-(3-methoxyphenyl)propyl]furan-3(2H)-one (XLVII). Yield 87%. IR spectrum, ν , cm⁻¹: 1270, 1285, 1310, 1360, 1395, 1430 sh, 1450, 1495, 1595 sh, 1610 (max.), 1705. ¹H NMR spectrum, δ , ppm: 1.43 t (3H, OCH₂CH₃, *J* = 7.0 Hz), 1.78 quint (2H, CH₂CH₂CH₂, *J* = 7.5 Hz), 2.16 t (2H, 4-CH₂, *J* = 7.5 Hz), 2.60 t (2H, CH₂C₆H₄, *J* = 7.5 Hz), 3.80 s (3H, OCH₃), 4.43 q (2H, OCH₂CH₃, *J* = 7.0 Hz), 4.54 s

(2H, 2-H), 6.68–6.82 m (3H, H_{arom}), 7.19 t (1H, H_{arom}, $J = 7.5$ Hz). Mass spectrum: m/z 276 [M]⁺.

5-Ethoxy-4-[3-(3-methoxyphenyl)propyl]-2-methylfuran-3(2H)-one (XLVIII). Yield 80%. IR spectrum, ν , cm⁻¹: 1270, 1285 sh, 1310, 1365, 1395, 1440, 1450, 1495, 1615 (max.), 1705. ¹H NMR spectrum, δ , ppm: 1.42 t (3H, OCH₂CH₃, $J = 7.0$ Hz), 1.48 d (3H, 2-CH₃, $J = 7.0$ Hz), 1.77 quint (2H, CH₂-CH₂CH₂, $J = 7.5$ Hz), 2.15 t (2H, 4-CH₂, $J = 7.5$ Hz), 2.58 t (2H, CH₂C₆H₄, $J = 7.5$ Hz), 3.80 s (3H, OCH₃), 4.41 q (2H, OCH₂CH₃, $J = 7.0$ Hz), 4.60 q (1H, 2-H, $J = 7.0$ Hz), 6.68–6.82 m (3H, H_{arom}), 7.19 br.t (1H, H_{arom}, $J = 7.5$ Hz). Mass spectrum: m/z 290 [M]⁺.

Reactions of methyl enol ethers XXX–XXXVII with amines. A mixture of 0.001 mol of enol ether XXX–XXXVII and 0.004 mol of the corresponding amine was heated at the boiling point until the reaction was complete (TLC). The mixture was cooled and treated with 2 N hydrochloric acid until strongly acidic reaction (indicator paper). The aqueous phase was extracted with diethyl ether, the extract was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel using chloroform as eluent.

4-Cyclohexylamino-3-octylfuran-2(5H)-one (XLIX). Yield 65%, oily substance. IR spectrum, ν , cm⁻¹: 1255, 1270, 1350, 1385, 1435 sh, 1460, 1565 sh, 1575, 1640 br (max.), 1730, 3100, 3305. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, $J = 6.5$ Hz), 1.05–1.54 m (16H, CH₂), 1.54–1.72 m (2H, CH₂), 1.72–1.87 m (2H, CH₂), 1.87–2.00 m (2H, CH₂), 2.10 t (2H, 3-CH₂, $J = 7.0$ Hz), 2.90–3.12 m (1H, NHCH), 4.48 br.d (1H, NH, $J_{trans} = 9.0$ Hz), 4.65 s (2H, 5-H). Mass spectrum: m/z 293 [M]⁺. Found, %: C 73.59; H 10.63. C₁₈H₃₁NO₂. Calculated, %: C 73.68; H 10.65.

4-Heptylamino-5-methyl-3-octylfuran-2(5H)-one (L). Yield 76%, mp 25–28°C (from ethyl acetate). IR spectrum, ν , cm⁻¹: 1320, 1345, 1390, 1480, 1580, 1645 (max.), 1735, 3105, 3310. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, $J = 6.5$ Hz), 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.09–1.42 m (20H, CH₂), 1.47 d (3H, 5-CH₃, $J = 6.5$ Hz), 1.61 quint (2H, NHCH₂CH₂, $J = 7.0$ Hz), 2.16 t (2H, 3-CH₂, $J = 7.0$ Hz), 3.25 br.q (2H, NHCH₂, $J = 6.7$ Hz), 4.32 br.t (1H, NH, $J = 6.0$ Hz), 4.76 q (1H, 5-H, $J = 6.5$ Hz). Mass spectrum: m/z 323 [M]⁺. Found, %: C 74.28; H 11.49. C₂₀H₃₇NO₂. Calculated, %: C 74.25; H 11.53.

5-Methyl-3-octyl-4-octylaminofuran-2(5H)-one (LI). Yield 71%, oily substance. IR spectrum, ν , cm⁻¹: 1265, 1315, 1345, 1390, 1480, 1575, 1650 (max.),

1710 sh, 1730, 3100, 3315. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, $J = 6.5$ Hz), 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.12–1.42 m (22H, CH₂), 1.46 d (3H, 5-CH₃, $J = 6.5$ Hz), 1.52–1.68 m (2H, NHCH₂CH₂), 2.17 t (2H, 3-CH₂, $J = 7.5$ Hz), 3.24 br.q (2H, NHCH₂, $J = 6.7$ Hz), 4.36 br.m (1H, NH), 4.76 q (1H, 5-H, $J = 6.5$ Hz). Mass spectrum: m/z 337 [M]⁺. Found, %: C 74.71; H 11.71. C₂₁H₃₉NO₂. Calculated, %: C 74.72; H 11.65.

4-Benzylamino-5-methyl-3-octylfuran-2(5H)-one (LII). Yield 75%, oily substance. IR spectrum, ν , cm⁻¹: 1310, 1340, 1360, 1390, 1430, 1465, 1475 sh, 1510, 1580, 1645 (max.), 1730, 3040, 3075, 3100, 3310. ¹H NMR spectrum, δ , ppm: 0.88 t (3H, CH₃, $J = 6.0$ Hz), 1.06–1.42 m (12H, CH₂, α -chain), 1.48 d (3H, 5-CH₃, $J = 6.5$ Hz), 2.14 t (2H, 3-CH₂, $J = 7.0$ Hz), 4.47 br.d (2H, NHCH₂, $J = 6.0$ Hz), 4.67 br.t (1H, NH, $J = 6.0$ Hz), 4.81 q (1H, 5-H, $J = 6.5$ Hz), 7.20–7.46 m (5H, H_{arom}). Mass spectrum: m/z 315 [M]⁺. Found, %: C 76.21; H 9.28. C₂₀H₂₉NO₂. Calculated, %: C 76.15; H 9.27.

3-[3-(2-Furyl)propyl]-4-heptylamino-furan-2(5H)-one (LIII). Yield 36%, oily substance. IR spectrum, ν , cm⁻¹: 1350, 1380 sh, 1465 br, 1480 sh, 1640 (max.), 1730, 3110 br, 3310 br. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.12–1.44 m (8H, CH₂, ω -chain), 1.57 br.quint (2H, NHCH₂CH₂, $J = 7.0$ Hz), 1.84 quint (2H, 3-CH₂CH₂, $J = 7.0$ Hz), 2.18 t (2H, 3-CH₂, $J = 7.0$ Hz), 2.64 t (2H, CH₂CO, $J = 7.0$ Hz), 3.09 q (2H, NHCH₂, $J = 6.7$ Hz), 4.54 br.t (1H, NH, $J = 6.0$ Hz), 4.64 s (2H, 5-H), 6.03 d.d (1H, CH, furyl, $J = 3.0, 1.0$ Hz), 6.31 d.d (1H, CH, furyl, $J = 3.0, 2.0$ Hz), 7.30 m (1H, CH, furyl). Mass spectrum: m/z 305 [M]⁺.

3-[3-(2-Furyl)propyl]-4-heptylamino-5-methyl-furan-2(5H)-one (LIV). Yield 41%, oily substance. IR spectrum, ν , cm⁻¹: 1310, 1345, 1380, 1470, 1575, 1630 (max.), 1720, 3100 br, 3310 br. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.20–1.36 m (8H, CH₂, ω -chain), 1.47 d (3H, 5-CH₃, $J = 6.5$ Hz), 1.55 m (2H, NHCH₂CH₂), 1.83 quint (2H, 3-CH₂CH₂, $J = 7.0$ Hz), 2.21 t (2H, 3-CH₂, $J = 7.0$ Hz), 2.65 t (2H, CH₂CO, $J = 7.0$ Hz), 3.17 q.d (2H, NHCH₂, $J = 6.7, 2.5$ Hz), 4.20 br.t (1H, NH, $J = 6.0$ Hz), 4.78 q (1H, 5-H, $J = 6.5$ Hz), 6.03 br.d (1H, CH, furyl, $^3J = 3.0$ Hz), 6.30 d.d (1H, CH, furyl, $^3J = 3.0, 1.5$ Hz), 7.30 d (1H, CH, furyl, $^3J = 1.5$ Hz). Mass spectrum: m/z 319 [M]⁺. Found, %: C 71.55; H 9.17. C₁₉H₂₉NO₃. Calculated, %: C 71.44; H 9.15.

4-Octylamino-3-[3-(2-thienyl)propyl]furan-2(5H)-one (LV). Yield 63%, mp 47–49°C (from

diethyl ether). IR spectrum, ν , cm^{-1} : 1285, 1315, 1340, 1355, 1390, 1450, 1470, 1625 (max.), 1665 sh, 1725, 3085, 3290. ^1H NMR spectrum, δ , ppm: 0.89 t (3H, CH_3 , $J = 6.5$ Hz), 1.09–1.45 m (10H, CH_2 , ω -chain), 1.56 quint (2H, NHCH_2CH_2 , $J = 6.7$ Hz), 1.86 quint (2H, $3\text{-CH}_2\text{CH}_2$, $J = 7.5$ Hz), 2.20 t (2H, 3-CH_2 , $J = 7.5$ Hz), 2.84 t (2H, CH_2CS , $J = 7.5$ Hz), 3.07 q (2H, NHCH_2 , $J = 6.7$ Hz), 4.60 m (1H, NH), 4.63 s (2H, 5-CH), 6.80 d.d (1H, CH, thienyl, $^3J = 3.0$, $^4J = 1.0$ Hz), 6.92 d.d (1H, CH, thienyl, $^3J = 5.0$, $^4J = 1.5$ Hz), 7.12 d.d (1H, CH, thienyl, $^3J = 5.0$, $^4J = 1.5$ Hz). Mass spectrum: m/z 335 $[M]^+$. Found, %: C 68.11; H 8.70. $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{S}$. Calculated, %: C 68.02; H 8.71.

4-Heptylamino-5-methyl-3-[3-(2-thienyl)propyl]-furan-2(5H)-one (LVI). Yield 61%, oily substance. IR spectrum, ν , cm^{-1} : 1340, 1450, 1470, 1580, 1635 (max.), 1725, 3100, 3310. ^1H NMR spectrum, δ , ppm: 0.90 t (3H, CH_3 , $J = 6.5$ Hz), 1.16–1.39 m (8H, CH_2 , ω -chain), 1.45 d (3H, 5- CH_3 , $J = 6.5$ Hz), 1.54 quint (2H, NHCH_2CH_2 , $J = 7.0$ Hz), 1.86 quint (2H, $3\text{-CH}_2\text{CH}_2$, $J = 7.5$ Hz), 2.24 t (2H, 3-CH_2 , $J = 7.5$ Hz), 2.86 t (2H, CH_2CS , $J = 7.5$ Hz), 3.16 br.q (2H, NHCH_2 , $J = 6.7$ Hz), 4.48 br.t (1H, NH, $J = 5.5$ Hz), 4.76 q (1H, 5-CH, $J = 6.5$ Hz), 6.80 br.d (1H, CH, thienyl, $^3J = 3.5$ Hz), 6.92 d.d (1H, CH, thienyl, $^3J = 5.0$, $^4J = 1.0$ Hz), 7.11 d.d (1H, CH, thienyl, $^3J = 5.0$, $^4J = 1.0$ Hz). Mass spectrum: m/z 335 $[M]^+$. Found, %: C 68.13; H 8.73. $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{S}$. Calculated, %: C 68.02; H 8.71.

4-Heptylamino-3-[3-(3-methoxyphenyl)propyl]-furan-2(5H)-one (LVII). Yield 70%, oily substance. IR spectrum, ν , cm^{-1} : 1270, 1290, 1320, 1350, 1375 sh, 1445 sh, 1465, 1495, 1595 sh, 1635 br (max.), 1730, 3105, 3310. ^1H NMR spectrum, δ , ppm: 0.90 t (3H, CH_3 , $J = 6.5$ Hz), 1.14–1.43 m (8H, CH_2 , ω -chain), 1.54 quint (2H, NHCH_2CH_2 , $J = 6.7$ Hz), 1.82 quint (2H, $3\text{-CH}_2\text{CH}_2$, $J = 7.5$ Hz), 2.15 t (2H, 3-CH_2 , $J = 7.5$ Hz), 2.62 t (2H, $\text{CH}_2\text{C}_6\text{H}_4$, $J = 7.5$ Hz), 3.06 q (2H, NHCH_2 , $J = 6.7$ Hz), 3.81 s (3H, OCH_3), 4.27 br.t (1H, NH, $J = 6.0$ Hz), 4.62 s (2H, 5-H), 6.71–6.83 m (3H, H_{arom}), 7.21 m (1H, H_{arom}). Mass spectrum: m/z 345 $[M]^+$. Found, %: C 73.08; H 9.01. $\text{C}_{21}\text{H}_{31}\text{NO}_3$. Calculated, %: C 73.01; H 9.04.

4-Heptylamino-3-[3-(3-methoxyphenyl)propyl]-5-methylfuran-2(5H)-one (LVIII). Yield 64%, oily substance. IR spectrum, ν , cm^{-1} : 1270, 1325 sh, 1345, 1385 sh, 1410, 1450, 1465, 1500, 1565 sh, 1580 sh, 1595 sh, 1615 sh, 1630 br (max.), 1725, 3105, 3315. ^1H NMR spectrum, δ , ppm: 0.90 t (3H, CH_3 , $J = 6.5$ Hz), 1.12–1.40 m (8H, CH_2 , ω -chain), 1.40–1.59 m

(2H, NHCH_2CH_2), 1.45 d (3H, 5- CH_3 , $J = 6.5$ Hz), 1.81 quint (2H, $3\text{-CH}_2\text{CH}_2$, $J = 7.5$ Hz), 2.19 br.t (2H, 3-CH_2 , $J = 7.5$ Hz), 2.62 t (2H, $\text{CH}_2\text{C}_6\text{H}_4$, $J = 7.5$ Hz), 3.14 q.d (2H, NHCH_2 , $J = 6.7$, 2.0 Hz), 3.80 s (3H, OCH_3), 4.07 m (1H, NH), 4.76 q (1H, 5-H, $J = 6.5$ Hz), 6.67–6.81 m (3H, H_{arom}), 7.12–7.24 m (1H, H_{arom}). Mass spectrum: m/z 359 $[M]^+$. Found, %: C 73.62; H 9.22. $\text{C}_{22}\text{H}_{33}\text{NO}_3$. Calculated, %: C 73.50; H 9.25.

Reactions of enol ethers XXXVIII–XLVIII with amines. A mixture of 0.001 mol of enol ether XXXVIII–XLVIII and 0.003 mol of the corresponding amine was stirred at room temperature or at 35–40°C until the initial enol ether disappeared (TLC). The mixture was cooled and treated with 2 N hydrochloric acid until strongly acidic reaction (indicator paper). The aqueous phase was extracted with diethyl ether, the extract was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel or aluminum oxide using chloroform as eluent.

5-Cyclohexylamino-4-octylfuran-3(2H)-one (LIX). Yield 80%, oily substance. IR spectrum, ν , cm^{-1} : 1255, 1310, 1355, 1370, 1460, 1475, 1495, 1545 sh, 1555 sh, 1575 br (max.), 1685, 1735, 3210 br. ^1H NMR spectrum, δ , ppm: 0.88 t (3H, CH_3 , $J = 6.5$ Hz), 1.07–1.50 m (16H, CH_2), 1.57–1.72 m (2H, CH_2), 1.72–1.86 m (2H, CH_2), 1.92–2.14 m (4H, CH_2 , 4- CH_2), 3.56–3.78 m (1H, NHCH), 4.52 br.s (2H, 2-H), 4.96 br.m (1H, NH). Mass spectrum: m/z 293 $[M]^+$. Found, %: C 73.70; H 10.69. $\text{C}_{18}\text{H}_{31}\text{NO}_2$. Calculated, %: C 73.68; H 10.65.

5-Heptylamino-2-methyl-4-octylfuran-3(2H)-one (LX). Yield 72%, oily substance. IR spectrum, ν , cm^{-1} : 1260, 1295 sh, 1315, 1365 sh, 1380, 1450, 1470, 1505, 1545 sh, 1565, 1580 br (max.), 1690, 3080–3160, 3215. ^1H NMR spectrum, δ , ppm: 0.88 t (3H, CH_3 , $J = 6.5$ Hz), 0.90 t (3H, CH_3 , $J = 6.5$ Hz), 1.10–1.40 m (20H, CH_2), 1.45 d (3H, 2- CH_3 , $J = 7.0$ Hz), 1.50–1.68 m (2H, NHCH_2CH_2), 2.05 t (2H, 4- CH_2 , $J = 7.5$ Hz), 3.36 q (2H, NHCH_2 , $J = 6.7$ Hz), 4.54 q (1H, 2-H, $J = 7.0$ Hz), 5.06 t (1H, NH, $J = 6.0$ Hz). Mass spectrum: m/z 323 $[M]^+$. Found, %: C 74.17; H 11.53. $\text{C}_{20}\text{H}_{37}\text{NO}_2$. Calculated, %: C 74.25; H 11.53.

5-Benzylamino-2-methyl-4-octylfuran-3(2H)-one (LXI). Yield 64%, mp 59–62°C (from ethyl acetate). IR spectrum, ν , cm^{-1} : 1265, 1310, 1365, 1370, 1440, 1460, 1475, 1505, 1545 sh, 1560 br (max.), 1595 sh, 1625, 3040, 3210–3280. ^1H NMR spectrum, δ , ppm: 0.88 t (3H, CH_3 , $J = 6.5$ Hz), 1.08–1.40 m (12H, CH_2 ,

α -chain), 1.44 d (3H, 2-CH₃, J = 7.0 Hz), 2.07 t (2H, 4-CH₂, J = 7.0 Hz), 4.54 q (1H, 2-H, J = 7.0 Hz), 4.56 d (2H, CH₂Ph, J = 6.0 Hz), 5.62 br.t (1H, NH, J = 6.0 Hz), 7.24–7.46 m (5H, H_{arom}). Mass spectrum: m/z 315 [M]⁺. Found, %: C 75.94; H 9.36. C₂₀H₂₉NO₂. Calculated, %: C 76.15; H 9.27.

Ethyl 7-(2-heptylamino-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (LXII). Yield 81%, oily substance. IR spectrum, ν , cm⁻¹: 1255, 1270 sh, 1305, 1355 sh, 1375, 1445, 1465, 1495, 1505, 1540 sh, 1555 sh, 1570 br (max.), 1680, 1740, 3210 br. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, J = 7.0 Hz), 1.18–1.48 m (14H, CH₂), 1.28 t (3H, OCH₂CH₃, J = 7.5 Hz), 1.61 quint (4H, CH₂CH₂CO₂Et, NHCH₂CH₂, J = 7.0 Hz), 2.06 t (2H, 3-CH₂, J = 7.0 Hz), 2.30 t (2H, CH₂CO₂Et, J = 7.0 Hz), 3.37 q (2H, NHCH₂, J = 7.0 Hz), 4.12 q (2H, OCH₂CH₃, J = 7.5 Hz), 4.48 s (2H, 5-H), 5.57 t (1H, NH, J = 6.0 Hz). Mass spectrum: m/z 353 [M]⁺. Found, %: C 67.97; H 9.97. C₂₀H₃₅NO₄. Calculated, %: C 67.95; H 9.98.

Methyl 7-(2-heptylamino-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (LXIII). Yield 66%, mp 46–48°C (from ethyl acetate). IR spectrum, ν , cm⁻¹: 1260, 1295, 1315, 1365 sh, 1375, 1445, 1470, 1505, 1545 sh, 1565 sh, 1575 br (max.), 1625, 1650 sh, 1685, 1750, 3175 sh, 3215, 3250 sh. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, J = 6.5 Hz), 1.10–1.50 m (14H, CH₂), 1.50–1.72 m (4H, CH₂CH₂CO₂Me, NHCH₂CH₂), 2.06 t (2H, 3-CH₂, J = 7.0 Hz), 2.31 t (2H, CH₂CO₂Me, J = 7.0 Hz), 3.37 q (2H, NHCH₂, J = 6.7 Hz), 3.68 s (3H, OCH₃), 4.48 s (2H, 5-H), 5.81 br.t (1H, NH, J = 6.0 Hz). Mass spectrum: m/z 339 [M]⁺. Found, %: C 67.16; H 9.78. C₁₉H₃₃NO₄. Calculated, %: C 67.22; H 9.80.

Methyl 7-(2-octylamino-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (LXIV). Yield 62%, mp 105–107°C (from ethyl acetate). IR spectrum, ν , cm⁻¹: 1260, 1280, 1315, 1375, 1445, 1475, 1505, 1545 sh, 1560 sh, 1575 br (max.), 1625 sh, 1650, 1690, 1750, 3210 br, 3310. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, J = 6.5 Hz), 1.13–1.48 m (16H, CH₂), 1.61 quint (4H, CH₂CH₂CO₂Me, NHCH₂CH₂, J = 7.0 Hz), 2.06 t (2H, 3-CH₂, J = 7.0 Hz), 2.32 t (2H, CH₂CO₂Me, J = 7.0 Hz), 3.36 q (2H, NHCH₂, J = 6.7 Hz), 3.67 s (3H, OCH₃), 4.48 s (2H, 5-H), 5.43 br.t (1H, NH, J = 6.0 Hz). Mass spectrum: m/z 353 [M]⁺. Found, %: C 67.91; H 9.96. C₂₀H₃₅NO₄. Calculated, %: C 67.95; H 9.98.

Methyl 7-(2-benzylamino-4-oxo-4,5-dihydrofuran-3-yl)heptanoate (LXV). Yield 60%, mp 92–

94°C (from ethyl acetate). IR spectrum, ν , cm⁻¹: 1260, 1275, 1310, 1330, 1370, 1390, 1435 br, 1460, 1505, 1545 sh, 1560 sh, 1580 br (max.), 1605 sh, 1690, 1745, 3035, 3100, 3125, 3175, 3210. ¹H NMR spectrum, δ , ppm: 1.18–1.48 m (6H, CH₂, α -chain), 1.58 quint (2H, CH₂CH₂CO₂Me, J = 7.0 Hz), 2.08 t (2H, 3-CH₂, J = 7.0 Hz), 2.28 t (2H, CH₂CO₂Me, J = 7.0 Hz), 3.63 s (3H, OCH₃), 4.48 s (2H, 5-H), 4.58 d (2H, CH₂Ph, J = 6.0 Hz), 5.96 br (1H, NH), 7.20–7.46 m (5H, H_{arom}). Mass spectrum: m/z 331 [M]⁺. Found, %: C 68.95; H 7.57. C₁₉H₂₅NO₄. Calculated, %: C 68.86; H 7.60.

4-[3-(2-Furyl)propyl]-5-heptylamino-furan-3(2H)-one (LXVI). Yield 36% (calculated on the crude β -dicarbonyl compound XXIV), oily substance. IR spectrum, ν , cm⁻¹: 1285, 1310, 1380, 1435, 1480, 1505, 1540–1580 br (max.), 1625, 1690, 3080, 3165, 3200. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, J = 6.5 Hz), 1.12–1.40 m (8H, CH₂, ω -chain), 1.55 quint (2H, NHCH₂CH₂, J = 6.5 Hz), 1.78 quint (2H, 3-CH₂CH₂, J = 7.0 Hz), 2.14 t (2H, 3-CH₂, J = 7.0 Hz), 2.62 t (2H, CH₂CO, J = 7.0 Hz), 3.31 q (2H, NHCH₂, J = 6.7 Hz), 4.48 s (2H, 2-H), 5.70 br (1H, NH), 6.02 br.d (1H, CH, furyl, ³ J = 3.0 Hz), 6.29 d.d (1H, CH, furyl, ³ J = 3.0, 2.0 Hz), 7.29 br.d (1H, CH, furyl, ³ J = 2.0 Hz). Mass spectrum: m/z 305 [M]⁺.

4-[3-(2-Furyl)propyl]-5-heptylamino-2-methylfuran-3(2H)-one (LXVII). Yield 40% (calculated on the crude β -dicarbonyl compound XXV), oily substance. IR spectrum, ν , cm⁻¹: 1200, 1230, 1295 sh, 1310, 1365 sh, 1380, 1450, 1510, 1550 sh, 1565 sh, 1580 (max.), 1690, 3030 br, 3220 br. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, J = 6.5 Hz), 1.10–1.40 m (8H, CH₂, ω -chain), 1.45 d (3H, 2-CH₃, J = 7.0 Hz), 1.58 quint (2H, NHCH₂CH₂, J = 6.5 Hz), 1.78 quint (2H, 3-CH₂CH₂, J = 7.0 Hz), 2.13 t (2H, 3-CH₂, J = 7.0 Hz), 2.62 t (2H, CH₂CO, J = 7.0 Hz), 3.34 q (2H, NHCH₂, J = 6.7 Hz), 4.56 q (1H, 2-H, J = 7.0 Hz), 5.70 br (1H, NH), 6.02 br.d (1H, CH, furyl, ³ J = 3.0 Hz), 6.29 d.d (1H, CH, furyl, ³ J = 3.0, 2.0 Hz), 7.29 br.d (1H, CH, furyl, ³ J = 2.0 Hz). Mass spectrum: m/z 319 [M]⁺. Found, %: C 71.40; H 9.13. C₁₉H₂₉NO₃. Calculated, %: C 71.44; H 9.15.

5-Octylamino-4-[3-(2-thienyl)propyl]furan-3(2H)-one (LXVIII). Yield 71%, mp 72–74°C (from diethyl ether). IR spectrum, ν , cm⁻¹: 1285, 1310, 1380, 1435, 1480, 1505, 1540–1580 br (max.), 1625, 1690, 3080, 3165, 3200. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, J = 6.5 Hz), 1.16–1.44 m (10H, CH₂, ω -chain), 1.56 quint (2H, NHCH₂CH₂, J = 6.5 Hz), 1.82 quint (2H, 4-CH₂CH₂, J = 7.0 Hz), 2.15 t (2H,

4-CH₂, $J = 7.0$ Hz), 2.84 t (2H, CH₂CS, $J = 7.0$ Hz), 3.33 q (2H, NHCH₂, $J = 6.7$ Hz), 4.48 s (2H, 2-H), 5.26 br.m (1H, NH), 6.80 br.d (1H, CH, thienyl, $^3J = 3.0$ Hz), 6.93 d.d (1H, CH, thienyl, $^3J = 5.0, 3.0$ Hz), 7.12 br.d (1H, CH, thienyl, $^3J = 5.0$ Hz). Mass spectrum: m/z 335 [M]⁺. Found, %: C 68.07; H 8.67. C₁₉H₂₉NO₂S. Calculated, %: C 68.02; H 8.71.

5-Heptylamino-2-methyl-4-[3-(2-thienyl)propyl]furan-3(2H)-one (LXIX). Yield 77%, oily substance. IR spectrum, ν , cm⁻¹: 1295, 1310, 1380, 1450, 1460, 1475 sh, 1505, 1565 sh, 1575 (max.), 1685, 3080, 3220. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.14–1.40 m (8H, CH₂, ω -chain), 1.46 d (3H, 2-CH₃, $J = 7.0$ Hz), 1.56 quint (2H, NHCH₂CH₂, $J = 7.0$ Hz), 1.82 quint (2H, 4-CH₂CH₂, $J = 7.0$ Hz), 2.14 t (2H, 4-CH₂, $J = 7.0$ Hz), 2.84 t (2H, CH₂CS, $J = 7.0$ Hz), 3.34 q (2H, NHCH₂, $J = 6.7$ Hz), 4.65 br.q (1H, 2-CH, $J = 7.0$ Hz), 5.34 br.s (1H, NH), 6.81 br.d (1H, CH, thienyl, $^3J = 3.5$ Hz), 6.92 d.d (1H, CH, thienyl, $^3J = 5.0, 3.5$ Hz), 7.11 d.d (1H, CH, thienyl, $^3J = 5.0, ^4J = 1.0$ Hz). Mass spectrum: m/z 335 [M]⁺. Found, %: C 68.10; H 8.66. C₁₉H₂₉NO₂S. Calculated, %: C 68.02; H 8.71.

5-Heptylamino-4-[3-(3-methoxyphenyl)propyl]furan-3(2H)-one (LXX). Yield 79%, mp 74–76.5°C (from diethyl ether). IR spectrum, ν , cm⁻¹: 1275, 1290, 1310, 1320, 1375, 1385, 1430, 1455, 1475, 1500, 1540–1590 br (max.), 1625 sh, 1685, 3065, 3165, 3195. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, CH₃, $J = 6.5$ Hz), 1.16–1.40 m (8H, CH₂, ω -chain), 1.55 quint (2H, NHCH₂CH₂, $J = 6.7$ Hz), 1.77 quint (2H, 4-CH₂CH₂, $J = 7.5$ Hz), 2.11 t (2H, 4-CH₂, $J = 7.5$ Hz), 2.62 t (2H, CH₂C₆H₄, $J = 7.5$ Hz), 3.31 q (2H, NHCH₂, $J = 6.7$ Hz), 3.80 s (3H, OCH₃), 4.49 s (2H, 2-H), 4.73 br.s (1H, NH), 6.70–6.83 m (3H, H_{arom}), 7.21 m (1H, H_{arom}). Mass spectrum: m/z 345 [M]⁺. Found, %: C 73.02; H 9.00. C₂₁H₃₁NO₃. Calculated, %: C 73.01; H 9.04.

5-Cyclohexylamino-4-[3-(3-methoxyphenyl)propyl]furan-3(2H)-one (LXXI). Yield 65%, oily substance. IR spectrum, ν , cm⁻¹: 1270, 1290, 1320, 1355, 1370, 1445 sh, 1460, 1495, 1545 sh, 1570 br (max.), 1680, 3055 br, 3205–3250. ¹H NMR spectrum, δ , ppm: 1.03–1.47 m (5H), 1.54–1.86 m (5H), 1.86–2.01 m (2H), 2.11 t (2H, 4-CH₂, $J = 7.0$ Hz), 2.60 t (2H, CH₂C₆H₄, $J = 7.0$ Hz), 3.51–3.72 m (1H, NHCH), 3.80 s (3H, OCH₃), 4.56 br.s (2H, 2-H), 5.17 br (1H, NH), 6.68–6.82 m (3H, H_{arom}), 7.19 br.t (1H, H_{arom}, $J = 8.0$ Hz). Mass spectrum: m/z 329 [M]⁺. Found, %: C 72.88; H 8.23. C₂₀H₂₇NO₃. Calculated, %: C 72.92; H 8.26.

5-Heptylamino-4-[3-(3-methoxyphenyl)propyl]-2-methylfuran-3(2H)-one (LXXII). Yield 70%, oily substance. IR spectrum, ν , cm⁻¹: 1270, 1285 sh, 1315, 1365 sh, 1380, 1450, 1465, 1475, 1500, 1565 sh, 1580 (max.), 1685, 3215. ¹H NMR spectrum, δ , ppm: 0.90 t (3H, CH₃, $J = 6.5$ Hz), 1.12–1.41 m (8H, CH₂, ω -chain), 1.45 d (3H, 2-CH₃, $J = 7.0$ Hz), 1.55 m (2H, NHCH₂CH₂), 1.76 quint (2H, 4-CH₂CH₂, $J = 7.5$ Hz), 2.12 t (2H, 4-CH₂, $J = 7.5$ Hz), 2.60 t (2H, CH₂C₆H₄, $J = 7.5$ Hz), 3.31 q (2H, NHCH₂, $J = 6.7$ Hz), 3.80 s (3H, OCH₃), 4.56 q (1H, 2-H, $J = 7.0$ Hz), 5.22 br.m (1H, NH), 6.68–6.81 m (3H, H_{arom}), 7.19 br.t (1H, H_{arom}, $J = 7.5$ Hz). Mass spectrum: m/z 359 [M]⁺. Found, %: C 73.45; H 9.22. C₂₂H₃₃NO₃. Calculated, %: C 73.50; H 9.25.

9-Oxa-7-aza prostanoids LXXIII and LXXIV. A freshly prepared solution of sodium methoxide [from 0.15 g (0.0065 mol) of metallic sodium and 8 ml of methanol] was added under stirring and cooling (0°C) to 1.18 g (0.0065 mol) of methyl 6-amino-hexanoate hydrochloride. The mixture was stirred for 5–10 min at room temperature and was added to 0.001 mol of ethoxy derivative XLV or XLVII. The resulting mixture was stirred at 35–40°C until the initial enol ether disappeared (TLC), the solvent was distilled under reduced pressure, the residue was cooled and treated with 2 N hydrochloric acid to strongly acidic reaction (indicator paper), the aqueous phase was extracted with diethyl ether, the extract was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel or aluminum oxide using chloroform as eluent.

Methyl 6-{4-oxo-3-[3-(2-thienyl)propyl]-4,5-dihydrofuran-2-ylamino}hexanoate (LXXIII). Yield 34%, oily substance. IR spectrum, ν , cm⁻¹: 1210, 1250, 1310, 1375, 1450, 1505, 1545 sh, 1565 sh, 1585 br (max.), 1690, 1750, 3090 br, 3220 br. ¹H NMR spectrum, δ , ppm: 1.25–1.46 m [2H, NH(CH₂)₂CH₂-(CH₂)₂CO₂Me], 1.50–1.74 m (4H, CH₂CH₂CO₂Me, NHCH₂CH₂), 1.81 m (2H, 3-CH₂CH₂), 2.18 m (2H, 3-CH₂), 2.34 t (2H, CH₂CO₂Me, $J = 7.0$ Hz), 2.83 br.t (2H, CH₂CS, $J = 7.0$ Hz), 3.36 br.q (2H, NHCH₂, $J = 6.7$ Hz), 3.67 s (3H, OCH₃), 4.60 br.s (2H, 5-H), 6.12 br (1H, NH), 6.78 br.d (1H, CH, thienyl, $^3J = 3.0$ Hz), 6.90 d.d (1H, CH, thienyl, $^3J = 5.0, 3.0$ Hz), 7.10 d (1H, CH, thienyl, $^3J = 5.0$ Hz). Mass spectrum: m/z 351 [M]⁺.

Methyl 6-{3-[3-(3-methoxyphenyl)propyl]-4-oxo-4,5-dihydrofuran-2-ylamino}hexanoate (LXXIV).

Yield 39%, oily substance. IR spectrum, ν , cm^{-1} : 1260, 1285 sh.w, 1310 w, 1360 sh, 1365, 1440, 1455 br.sh, 1495, 1545 sh, 1555 sh, 1570–1585 br (max.), 1600 sh, 1660, 1740, 3230 br. ^1H NMR spectrum, δ , ppm: 1.24–1.44 m [2H, $\text{NH}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{Me}$], 1.50–1.86 m (6H, $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$, NHCH_2CH_2 , 3- CH_2CH_2), 2.12 t (2H, 3- CH_2 , $J = 7.5$ Hz), 2.34 t (2H, $\text{CH}_2\text{CO}_2\text{Me}$, $J = 7.5$ Hz), 2.62 t (2H, $\text{CH}_2\text{C}_6\text{H}_4$, $J = 7.5$ Hz), 3.34 q (2H, NHCH_2 , $J = 6.5$ Hz), 3.68 s (3H, OCH_3), 3.80 s (3H, OCH_3), 4.48 s (2H, 5-H), 5.16 t (1H, NH, $J = 6.0$ Hz), 6.68–6.82 m (3H, H_{arom}), 7.20 d.t (1H, H_{arom} , $J = 7.5$, 2.0 Hz). Mass spectrum: m/z 375 [M] $^+$. Found, %: C 67.12; H 7.74. $\text{C}_{21}\text{H}_{29}\text{NO}_5$. Calculated, %: C 67.18; H 7.78.

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REFERENCES

- Pashkovskii, F.S., Katok, Ya.M., Shchukina, E.M., Koroleva, E.V., and Lakhvich, F.A., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 230.
- Lakhvich, F.A., Pashkovskii, F.S., and Koroleva, E.V., *Usp. Khim.*, 1992, vol. 61, p. 457.
- Venton, D.L., Enke, S.E., and Le Breton, G.C., *J. Med. Chem.*, 1979, vol. 22, p. 824; Le Breton, G.C., Venton, D.L., Enke, S.E., and Halushka, P.V., *Proc. Natl. Acad. Sci. USA*, 1979, vol. 76, p. 4097.
- Lakhvich, F.A., Lis, L.G., Pashkovskii, F.S., Kuz'mitskii, B.B., Mizulo, N.A., and Ignat'eva, T.N., *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk*, 1988, no. 6, p. 53.
- Lakhvich, F.A., Pashkovskii, F.S., and Lis, L.G., *Zh. Org. Khim.*, 1992, vol. 28, p. 1626.
- Kuz'mitskii, B.B., Malaeva, L.P., Pashkovskii, F.S., Lis, L.G., and Lakhvich, F.A., *Vestsi Nats. Akad. Navuk Belarusi, Ser. Khim. Navuk*, 1992, no. 2, p. 88; Malaeva, L.P., Pashkovskii, F.S., and Kuz'mitskii, B.B., *Vestsi Nats. Akad. Navuk Belarusi, Ser. Biyal. Navuk*, 1993, no. 2, p. 59.
- Konoplya, N.A., Mizulo, N.A., Pashkovskii, F.S., Romanova, V.N., Shafranskaya, G.A., and Kuz'mitskii, B.B., *Vestsi Nats. Akad. Navuk Belarusi, Ser. Biyal. Navuk*, 1993, no. 3, p. 75.
- Dad'kov, I.G., Kuz'mitskii, B.B., Kondratenkova, E.M., Pashkovskii, F.S., and Lakhvich, F.A., *Dokl. Nats. Akad. Navuk Belarusi*, 1998, vol. 42, no. 3, p. 77.
- Pashkovskii, F.S., Katok, Ya.M., Khlebnikova, T.S., Koroleva, E.V., and Lakhvich, F.A., *Russ. J. Org. Chem.*, 2003, vol. 39, p. 998.
- Lakhvich, F.A., Pashkovskii, F.S., and Lis, L.G., *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk*, 1987, no. 5, p. 53.
- Pashkovskii, F.S., Shchukina, E.M., and Lakhvich, F.A., *Vestsi Nats. Akad. Navuk Belarusi, Ser. Khim. Navuk*, 2002, no. 4, p. 67.
- Duncanson, L.A., *J. Chem. Soc.*, 1953, p. 1207.
- De Keukeleire, D., De Taeye, L., and Verzele, M., *Tetrahedron*, 1976, vol. 32, p. 2923.
- Jacobsen, J.P., Reffstrup, T., and Boll, P.M., *Acta Chem. Scand., Ser. B*, 1977, vol. 31, p. 756.
- Akhrem, A.A., Lakhvich, F.A., Lis, L.G., Khripach, V.A., Fil'chenkov, N.A., Kozinets, V.A., and Pashkovskii, F.S., *Dokl. Akad. Nauk SSSR*, 1990, vol. 311, p. 1381.
- Pashkovskii, F.S., Lokot', I.P., and Lakhvich, F.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2001, p. 309; Pashkovsky, F.S., Lokot, I.P., and Lakhvich, F.A., *Synlett*, 2001, p. 1391.
- Parnes, Z.N., Bolestova, G.I., Belen'kii, L.I., and Kursanov, D.N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1973, p. 1918; Kursanov, D.N., Parnes, Z.N., Bolestova, G.I., and Belen'kii, L.I., *Tetrahedron*, 1975, vol. 31, p. 311.
- Jaffer, H.J. and Pauson, P.L., *J. Chem. Res., Synop.*, 1983, p. 244; Buendia, J. and Schalbar, J., *Tetrahedron Lett.*, 1977, p. 4499.
- Freimanis, Ya.F., *Khimiya enamino-ketonov, enamino-iminov, enamino-otimionov* (Chemistry of Enamino Ketones, Enamino Imines, and Enamino Thiones), Riga: Zinatne, 1974.
- Azzaro, M., Geribaldi, S., and Videau, B., *Synthesis*, 1981, p. 880.
- Dixon, K. and Greenhill, J.V., *J. Chem. Soc., Perkin Trans. 1*, 1976, p. 2211; Greenhill, J.V., *Chem. Soc. Rev.*, 1977, p. 277.
- Wengel, A.S., Reffstrup, T., and Boll, P.M., *Tetrahedron*, 1979, vol. 35, p. 2181.
- Cone, E.J., Garner, R.H., and Hayes, A.W., *J. Org. Chem.*, 1972, vol. 37, p. 4436.