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Reactions of Alkyl (Halomethyl)furancarboxylates with Hexamethylenetetramine

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Abstract — All isomers of (aminomethyl)furancarboxylic acids were prepared by the Delepine reaction from alkyl (halomethyl)furancarboxylates. Treatment of the initially formed quaternary salt with an ethanolic HCl solution yielded the salts of the corresponding unstable amino acid esters. A procedure for their purification to a high degree of purity was developed. Hydrolysis of the crude esters yielded stable amino acid salts.
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Aminomethyl derivatives of the furan series are studied for a considerably long time as intermediates in the synthesis of biologically active compounds. Among them are precursors of muscarine and muscarine-like compounds [1]. Introduction of aminomethyl group into the furan fragment of a diterpenoid, lambertianic acid, led to the development of a new group of nootropic remedies [2]. Aminomethylfurans are used as convenient intermediates in the synthesis of biologically active compounds of perhydroazine and perhydroazole series [3]. 6-(Furfurylamino)purine was the first discovered compound stimulating the cell fission [4].

Thus, aminomethyl derivatives of furans are promising precursors for preparing new biologically active compounds and drugs.

At the same time, existing methods for preparing amines of the furan series have certain limitations concerning the structure of the furan moiety, because in most cases either the aminoalkylation of furans having free α-position and an electron-donating substituent in the ring or the reduction of furfural derivatives is used [5–7]. Furthermore, most of the amines obtained are tertiary, which strongly limits the application sphere of these compounds in the reactions involving the amino group.

It was shown previously [8] that the halomethyl group can be introduced into any position of the furancarboxylic acid heteroring. This fact allowed preparation of a series of compounds that we decided to use as starting substances in the synthesis of (aminomethyl)furancarboxylic acids with primary amino group, which are presently the most poorly studied.

Among methods for preparing primary amines, the Delepine reaction is distinguished by the availability of the starting substances, high selectivity, and mild reaction conditions. In the furan series, it was used for preparing 2-aminomethylfuran-5-carboxylic acid and 2-aminomethyl-5-benzoylfuran [9], but these studies were not developed further. We decided to apply the Delepine reaction tn a series of substituted (halomethyl)furancarboxylic acid esters with different mutual arrangement of the halomethyl and alkoxycarbonyl groups in the ring.

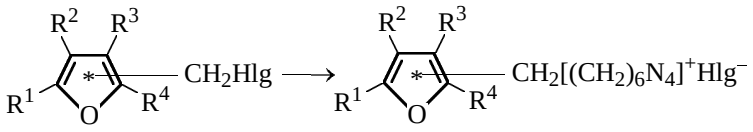
The Delepine reaction consists of two steps. In the first step, one of hexamethylenetetramine nitrogen atoms is alkylated to form a quaternary salt. The possibility and conditions of performing this step depend on the substrate electrophilicity.

In the second step, acid-catalyzed alcoholysis of this salt is performed to obtain the amine hydrochloride. In the course of this process, intermediate electrophilic species are formed, which can enter the substitution reactions with, e.g., phenolic ethers [10] and the simplest furans [11]. Therefore, the possibility of successful alcoholysis will be determined by the hydrolytic stability of the furan ring and its inertness to oxonium cations formed by alcoholysis of the hexamethylenetetramine fragment. Both these factors primarily depend on the nature and location of substituents in the furan ring.

Finally, formation of the amine competes with the redox process yielding the aldehyde (Sommelet reaction). The occurrence of the reaction along one or another pathway is determined by acidity of the medium.

Thus, the first and the second steps of the Delepine

Table 1. Alkylation of hexamethylenetetramine with alkyl halomethylfurancarboxylates



Starting comp. no.	R^1	R^2	R^3	R^4	Reaction time, h	Hexamethylene-tetramine salt	Yield, %	mp, °C (solvent)
I	$COOC_2H_5$	H	H	CH_2Cl	4	**XIII** [a]	82	219 (chloroform)
II	$COOC_2H_5$	H	CH_2Cl	CH_3	2	**XIV** [b]	88	215 (petroleum ether)
III	$COOCH_3$	CH_2Br	H	H	8	**XV** [c]	83	182–183 (chloroform–hexane)
IV	$COOCH_3$	H	CH_2Cl	*t*-C_4H_9	10	**XVI**	54	248 (ethyl acetate)
V	CH_2Br	$COOC_2H_5$	H	H	2	**XVIII**	89	186 (ethyl acetate)
VI	CH_2Br	H	$COOC_2H_5$	H	4	**XIX**	79	184–185 (petroleum ether)
VII	CH_3	CH_2Cl	$COOC_2H_5$	CH_3	11	**XX** [d]	94	189–190 (ethyl acetate)
VIII	*i*-C_4H_9	CH_2Cl	$COOC_2H_5$	CH_3	2	**XXI**	71	221 (petroleum ether)
IX	*t*-C_4H_9	H	$COOC_2H_5$	CH_2Br	2	**XXII**	74	141 (ethyl acetate)
X	C_6H_5	H	$COOC_2H_5$	CH_2Br	2	**XXIII**	92	217 (ethyl acetate–petroleum ether)
XI	CH_2Br	H	$COOC_2H_5$	C_6H_5	2	**XXIV**	78	209 (ethyl acetate–petroleum ether)

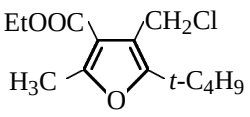
[a] Found, %: C 50.65; H 6.26; N 16.82. $C_{14}H_{21}ClN_4O_3$. Calculated, %: C 51.14; H 6.39; N 17.05. [b] Found, %: C 52.45; H 6.64; N 16.32. $C_{15}H_{23}ClN_4O_3$. Calculated, %: C 52.55; H 6.72; N 16.35. [c] Found, %: C 44.01; H 5.68; N 15.24. $C_{13}H_{19}BrN_4O_3$. Calculated, %: C 43.45; H 5.29; N 15.60. [d] Found, %: C 53.59; H 7.11; N 15.61. $C_{16}H_{25}ClN_4O_3$. Calculated, %: C 53.86; H 7.01; N 15.71.

reation are independent processes. Their character is determined by different factors, and they must be considered separately.

Alkylation of hexamethylenetetramine with (halomethyl)furancarboxylic acid esters was performed in chloroform at 1 : 1 molar ratio of the reactants [12]. The structure of the starting products, the reaction time, the isolation conditions, and the yields of the quaternary salts are listed in Table 1. The character of the process was determined by location of the halomethyl group in the furan ring and the kind of the halogen.

The reactions of α-(bromomethyl)furans **V**, **VI**, and **IX**–**XI** are strongly exothermic. Without efficient heat removal, 3-4 min after the start of the process the reaction mixture comes to boil. In the case of α-chloromethyl- and β-bromomethylfurans, the reaction mixture temperature increases by 10–15°C. For the reaction completion, the mixture was refluxed for a time given in Table 1. For compounds of the furan series, the reaction progress cannot be monitored by TLC on silica gel because of their high lability under these conditions. Therefore, the optimal reaction time was found from a series of experiments using the hexamethylenetetramine salt yield as a criterion.

Table 1 shows that the halomethyl group position and the kind of the halogen do not significantly affect the hexamethylenetetramine salt yield. In all the cases, they are high and in some cases almost quantitative. We found that the volume of the substituent in the position adjacent to the halomethyl group plays an important role. Introduction of the *tert*-butyl group into the α-position of the furan ring (compound **IV**) decreases the quaternary salt yield from 88% for **II** to 54%. Similar trend was observed in a series of compounds **VII**, **VIII**, **XII** with α-methyl, α-isobutyl, and α-*tert*-butyl substituents, respectively. For the first two compounds, the quaternary salt yield decreases from 94 to 71%, and in the case of **XII** the reaction does not occur at all.



XII

Hexamethylenetetramine salts were decomposed to amines by treatment with ethanolic HCl. Similarly to the previous step, the reaction time was found from the series of experiments because monitoring of the reaction progress appeared to be unreliable.

Variation of the HCl to quaternary salt molar ratio showed that at the stoichiometric ratio (3 : 1) the target product yield is relatively low. At the molar ratio increased to (4.5–5) : 1, it reaches the highest value, and further increase in the hydrogen chloride amount does not affect the reaction progress.

Amino ester hydrochlorides are crystalline compounds. They may be isolated from ethanol or some other organic solvents, but, as a rule, they contain residual ammonium chloride. For example, amino ester hydrochlorides prepared from hexamethylenetetramine salts **XIV**, **XV**, **XIX**, and **XX**, according to ^{1}H NMR data, contain 11, 7.7, 14, and 6.5% ammonium chloride, respectively. Removal of this impurity appeared to be labor-consuming and was accompanied by the target product losses. Therefore, the yields of the amino ester hydrochlorides cannot be used for characterizing the efficiency of the decomposition of hexamethylenetetramine salts.

Free amino esters, similarly to the native amino acid esters, slowly enter polycondensation in the cold, and at approximately 100°C this reaction is complete in several minutes. Therefore, purification of these substances, which are viscous oils, by vacuum distillation was unfeasible.

To characterize the chemical properties of the amino group in the aminomethyl compounds prepared, we involved these substances in acylation reactions typical of amines. Accessible furancarboxylic acid chlorides were used as acylating agents. With the majority of them, the amines under study form well crystallizing compounds. Although amino ester hydrochlorides were not purified to remove the residual ammonium chloride, we obtained pure (furoylaminomethyl)furancarboxylic acids.

Further studies showed that, after the base hydrolysis of the esters, aminofurancarboxylic acids readily precipitate from aqueous-ethanol solutions as free acids at pH 6.5–7 and as hydrochlorides at pH below 4. Therefore, the amino acid yield in the second step of the Delepine reaction can be most reliably estimated from the overall yield of the acid alcoholysis of the quaternary salt and of the base hydrolysis of the resulting amino ester hydrochloride.

Preparation of the target product in the form of the amino acid or its hydrochloride was performed either with isolation of the crude crystalline amino ester hydrochloride or without it. Base hydrolysis was carried out in aqueous ethanol for 2.5–3 h. Aminofurancarboxylic acids are colorless high-melting crystalline compounds which are poorly soluble in water and organic solvents, but give difficultly settling suspensions.

With the aim to obtain the compounds more suitable for identification, we have converted the amino acids into their hydrochlorides. These salts are colorless crystalline compounds readily soluble in water and DMSO and usually only moderately soluble in methanol and ethanol. When heated, amino acid hydrochlorides start to sublime at ~180°C, and at 250–260°C they carbonize without melting. The yields of amino acid hydrochlorides and their ^{1}H NMR characteristics are listed in Table 2.

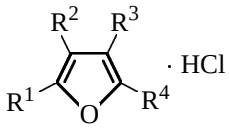
In the synthetic practice, the reactions involving the amino group require protection of the carboxy group by esterification. In this connection, we attempted to carry out esterification of the amino acid hydrochlorides obtained with the aim to prepare samples of these compounds free from the ammonium chloride impurity.

We tested three esterification procedures: in the methanol–thionyl chloride system at 0 and 65°C [13], the procedure involving intermediate formation of a mixed anhydride by treating the amino acid with trifluoroacetic anhydride [14, 15], and the reaction of the amino acid with triethyl orthoformate [16]. Amino acid hydrochlorides **XXVII** and **XXXIII** were used as substrates.

We found that the amino acid conversion with the first system does not exceed 15–20% according to the ^{1}H NMR data, and the amino ester hydrochloride cannot be separated from the corresponding amino acid salt. The second and third systems appeared to be ineffective. In both cases, only the starting acid hydrochloride was recovered.

Therefore, the development of a procedure for purification of amino ester hydrochlorides to remove residual ammonium chloride is a practically important problem. We have developed the following procedure. Contaminated amino ester hydrochloride was suspended in toluene and treated with a saturated potassium carbonate solution. Free amino ester dissolved in toluene, and the impurity remained in the aqueoeus phase. After the extraction with toluene, the aqueous layer was rejected. The toluene solution was dried for a short time over sodium sulfate and acidified with an ethanolic HCl solution. Evaporation of the solvents gave the product free from ammonium chloride. The yields of purified amino ester hydrochlorides vary

Table 2. Yields and spectral characteristics of (aminomethyl)furancarboxylic acids



Comp. no.	R^1	R^2	R^3	R^4	Yield, %	^{1}H NMR spectrum, δ, ppm
XXVII	COOH	H	H	CH_2NH_2	42	4.13 s (CH_2N), 6.69 d (H^4-furan), 7.22 s (H^3-furan), 8.75 br.s (NH_3)
XXVIII[a]	COOH	H	CH_2NH_2	CH_3	72	2.35 s (CH_3), 3.85 s (CH_2N), 7.30 s (H^5-furan), 8.34 br.s (NH_3)
XXIX	COOH	CH_2NH_2	H	H	63	4.16 s (CH_2N), 6.97 s (H^4-furan), 7.84 s (H^5-furan), 8.73 br.s (NH_3)
XXX	COOH	H	CH_2NH_2	*t*-C_4H_9	24	1.29 s [$(CH_3)_3C$], 4.00 s (CH_2N), 7.37 s (H^3-furan), 8.59 br.s (NH_2)
XXXI	CH_2NH_2	COOH	H	H	48	4.27 s (CH_2N), 6.74 s (H^4-furan), 7.79 s (H^5-furan), 8.72 br.s (NH_3)
XXXII	CH_2NH_2	H	COOH	H	42	4.07 s (CH_2H), 6.81 s (H^3-furan), 8.44 s (H^5-furan), 8.63 br.s (NH_3)
XXXIII[b]	CH_3	CH_2NH_2	COOH	CH_3	77	2.13 s (CH_3^2-furan), 2.49 s (CH_3^5-furan), 3.95 s (CH_2N), 8.25 br.s (NH_3)
XXXIV	*i*-C_4H_9	CH_2NH_2	COOH	CH_3	60	0.90 d (CH_2-isobutyl), 1.90 m (CH-isobutyl), 2.50 br.s (CH_3-furan + CH_2-furan + residual DMSO), 3.94 s (CH_2N), 8.05 br.s (NH_3)
XXXV	*t*-C_4H_9	H	COOH	CH_2NH_2	67	1.27 s [$(CH_3)_3C$], 4.26 s (CH_2N), 6.33 s (H^4-furan), 8.81 br.s (NH_3)
XXXVI[c]	C_6H_5	H	COOH	CH_2NH_2	69	4.39 s (CH_2N), 7.08 s (H^4-furan), 7.32 t (H_p-phenyl), 7.41 t (H_m-phenyl), 7.81 d (H_o-phenyl), 8.98 br.s (NH_3)
XXXVII	CH_2NH_2	H	COOH	C_6H_5	44	4.15 s (CH_2N), 6.86 s (H^3-furan), 7.50 m (H_p + H_m-phenyl), 8.00 d (H_o-phenyl), 8.63 br.s (NH_3)
XXXVIII	*t*-C_4H_9	H	CH_2NH_2	COOH	35	1.24 s [$(CH_3)_3C$], 4.12 s (CH_2N), 6.63 s (H^4-furan), 8.61 br.s (NH_3)

[a] Found, %: C 39.88; H 5.35; N 6.74. $C_7H_{11}NO_4 \cdot HCl$. Calculated, %: C 40.10; H 5.73; N 6.68. [b] Found, %: C 46.15; H 5.77; N 6.56. $C_8H_{11}NO_3 \cdot HCl$. Calculated, %: C 46.72; H 5.84; N 6.81. [c] Found, %: C 65.94; H 5.28; N 6.44. $C_{12}H_{11}NO_3$. Calculated, %: C 66.36; H 5.07; N 6.45 (for the free amino acid).

from 50 to 76%. The product loss in this operation is evidently caused by the amino ester hydrolysis in an alkaline medium.

Thus, application of the Delepine reaction to alkyl (halomethyl)furancarboxylates allows preparation of aminomethyl derivatives of furancarboxylic acids with any mutual arrangement of the carboxy and aminomethyl groups in the furan ring. Among the simplest alkyl substituents under study, only the adjacent *tert*-butyl group prevents the reaction. The process may be directed toward formation of both amino acids and hydrochlorides of their esters. The latter fact is of special value, because aminomethyl derivatives of furancarboxylic acid are poorly esterified with commonly used systems.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WM-250 spectrometer in DMSO-d_6. Chemical shifts were measured relative to internal TMS.

Alkylation of hexamethylenetetramine with alkyl (halomethyl)furancarboxylates *(general procedure).* To a solution of hexamethylenetetramine in chloroform (5 ml of chloroform per gram of hexamethylenetetramine), an equivalent amount of alkyl

(halomethyl)furancarboxylate was added, and the mixture was refluxed for the required time (Table 1). Then the mixture was left overnight, after which the hexamethylenetetrammonium salt was filtered off, or chloroform was removed and the residue was crystallized from a mixture of solvents indicated in Table 1. The crystals obtained were dried at 40–50°C. The structures of the starting compounds, reaction conditions, and melting points of the salts obtained are given in Table 1.

Hydrolysis of hexamethylenetetramine salt to amino acid *(general procedure). a. Without isolation of the amino ester hydrochloride.* Hexamethylenetetramine salt **XVI**, **XVIII**, **XXI**, or **XXV** was dissolved on heating in ethanol to prepare an almost saturated solution, and then a saturated solution of HCl in ethanol was added (4.5 mol per mole of the salt). The mixture was refluxed with stirring for 2.5–3 h and then filtered while hot to separate the ammonium chloride precipitate. The major part of the solvent was distilled off at reduced pressure, and the residue was dissolved in water and alkalized with a 20% NaOH solution to pH 8.5–9. After that, the same solution (2 mol per mole of the starting hexamethylenetetramine salt) was added, and the resulting mixture was boiled with stirring for 3 h. After removing the residual ethanol, the solution was acidified with HCl to pH 1–2. The amino acid hydrochloride crystallized from the solution within certain time.

b. With isolation of the crystalline amino ester hydrochloride. **A nearly saturated solution of hexamethylenetetramine salt XIII–XV**, **XIX**, **XX**, or **XXII–XXIV** was prepared by heating it in ethanol. After that, a saturated solution of HCl in ethanol (4.5 mol per mole of the salt) was added, and the mixture was refluxed for 2.5–3 h. Then the mixture was filtered while hot, and the ammonium chloride precipitate was washed with hot ethanol. The combined filtrate was concentrated at reduced pressure by a factor of 2–2.5, until the crystallization started, and was left in the refrigerator (–6°C). Usually on the next day, crystals of the amino ester hydrochloride were filtered off and washed with a small amount of acetone or ethyl acetate. In the case of the synthesis of the amino ester hydrochloride from hexamethylenetetramine salt **XXIV**, the solution obtained after removing ammonium chloride must be concentrated and triturated with ethyl acetate before cooling. The crystals of the amino ester hydrochloride dried at 40–50°C were dissolved in a small amount of ethanol, and 3 equiv of 20% aqueous NaOH solution was added. The resulting mixture was boiled with stirring for 3 h. After removing the residual ethanol, the reaction mixture was acidified with HCl to pH 6.5–7. The precipitated amino acid was filtered off and dried at 40–50°C. The structures of the compounds obtained, yields of amino acids, and ^{1}H NMR data for their hydrochlorides are listed in Table 2.

Purification of amino ester hydrochlorides. Crude amino ester hydrochloride obtained from hexamethylenetetramine salt **XIV**, **XV**, **XX**, **XXII**, or **XXIV** was suspended in toluene (5 ml per gram of salt), and the saturated aqueous solution of potassium carbonate was added (2 mol of K_2CO_3 per mole of salt). The resulting mixture was stirred for 10–15 min, the organic layer was separated, and the aqueous layer was washed with toluene. The combined toluene solutions were dried over sodium sulfate and acidified to pH 1 with a saturated solution of HCl in ethanol. The acidified solution was evaporated at reduced pressure until the onset of crystallization. Hydrochlorides **XIV**, **XV**, and **XX** were filtered off, and compounds **XXII** and **XXIV** were preliminarily triturated with a small amount of petroleum ether. The obtained crystals of amino ester hydrochlorides were dried at 40–50°C.

Ethyl 4-aminomethyl-5-methylfuran-2-carboxylate hydrochloride. Yield 59%, mp 188°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (CH_3-ethyl), 2.40 s (CH_3^5-furan), 3.81 s (CH_2N), 4.25 q (CH_2O), 7.39 s (H^3-furan), 8.57 s (NH_3^+).

Ethyl 3-aminomethylfuran-2-carboxylate hydrochloride. Yield 59%, mp 154–156°C. ^{1}H NMR spectrum, δ, ppm: 1.28 t (CH_3-ethyl), 4.16 s (CH_2N), 4.23 q (CH_2O), 6.97 s (H^4-furan), 7.89 s (H^5-furan), 8.72 br.s (NH_3^+).

Ethyl 5-aminomethyl-2-phenylfuran-3-carboxylate hydrochloride. Yield 60%, mp 128°C. ^{1}H NMR spectrum, δ, ppm: 1.27 s (CH_3-ethyl), 4.15 s (CH_2N), 4.22 q (CH_2O), 6.86 s (H^4-furan), 7.51 m (H_p + H_m), 8.01 m ($2H_o$), 8.63 br.s (NH_3^+).

Ethyl 2-aminomethyl-5-*tert*-butylfuran-3-carboxylate. Yield 59%, mp 125°C. ^{1}H NMR spectrum, δ, ppm: 1.28 br.s [$(CH_3)_3C$ + CH_3-ethyl], 4.22 m (CH_2O + CH_2N), 6.33 s (H^4-furan), 8.82 br.s (NH_3^+).

Ethyl 4-aminomethyl-2,5-dimethylfuran-3-carboxylate. Yield 76%, mp 218°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (CH_3-ethyl), 2.47 s (CH_3^2-furan + residual DMSO), 2.99 s (CH_3^5-furan), 3.92 s (CH_2N), 4.24 q (CH_2O), 7.99 s (NH_3^+).

Acylation of alkyl (aminomethyl)furancarboxylates *(general procedure).* A weighed portion of alkyl (aminomethyl)furancarboxylate hydrochloride was dissolved in a small amount of acetonitrile, and 2 equiv of triethylamine was added with stirring. The resulting mixture was treated with 1 equiv of furan-

carboxylic acid chloride (50% solution in acetonitrile). The mixture was stirred for 2 h at room temperature and then left overnight. After that, triethylamine hydrochloride was filtered off, the filtrate was evaporated, and the residue was dissolved in chloroform and washed with water. The resulting solution was dried over calcium chloride and then evaporated. If no crystalline acylated aminomethylfurancarboxylic acid ester could be obtained, the residue was hydrolyzed with aqueous-ethanolic alkali. For this purpose, a weighed portion of the acylated ester was dissolved in a small amount of ethanol, and 2 equiv of 50% KOH solution was added. The resulting mixture was refluxed for 6 h, and then, if necessary, ethanol was distilled off at reduced pressure. After that, the mixture was acidified with an HCl solution to pH 2. The crystals that formed were filtered off and dried at 40–50°C.

5-[*N*-(5-*tert*-Butyl-2-methyl-3-furoyl)amino]-methylfuran-2-carboxylic acid: mp 172°C. ^{1}H NMR spectrum, δ, ppm: 1.24 s [$(CH_3)_3C$], 2.48 m (CH_3^2), 4.41 s (CH_2N), 6.38 s (H^4-furan), 6.43 s (H^4-furan), 7.07 s (H^3-furan), 8.33 s (NH), 12.7 br.s (COOH). Found, %: C 63.96; H 6.28; N 4.54. $C_{16}H_{19}NO_5$. Calculated, %: C 62.95; H 6.23; N 4.59.

2-[*N*-(3-Methyl-2-furoyl)amino]methylfuran-3-carboxylic acid: mp 130°C. ^{1}H NMR spectrum, δ, ppm: 2.31 s (CH_3), 4.75 s (CH_2N), 6.45 s (H^4-furan), 6.62 s (H^4-furan), 7.60 d.s ($2H^5$-furan), 8.39 s (NH), 12.73 br.s (COOH).

5-[*N*-(4-Carboxy-3-furoyl)amino]methylfuran-2-carboxylic acid: mp 222°C. ^{1}H NMR spectrum, δ, ppm: 4.55 s (CH_2N), 6.48 s (H^4-furan), 7.09 s (H^3-furan), 8.38 d.s (H^2 and H^5-furan), 9.89 s (NH). Found, %: C 51.37; H 3.64; N 5.00. $C_{12}H_9NO_7$. Calculated, %: C 51.61; H 3.23; N 5.02.

5-[*N*-(2-Methyl-3-furoyl)amino]methylfuran-2-carboxylic acid: mp 176°C. ^{1}H NMR spectrum, δ, ppm: 2.51 m (CH_3^2), 4.42 s (CH_2N), 6.39 s (H^4-furan), 6.84 d (H^4-furan), 7.18 s (H^3-furan), 7.42 s (H^5-furan), 8.48 m (NH), 12.72 br.s (COOH). Found, %: C 57.11; H 4.56; N 5.60. $C_{12}H_{11}NO_5$. Calculated, %: C 57.83; H 4.42; N 5.62.

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