REACTIONS OF METHYL ESTER OF 5-AMINO-2-FURANCARBOXYLIC ACID WITH ETHYL ESTERS OF ORTHOACIDS

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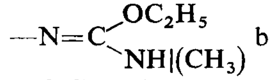
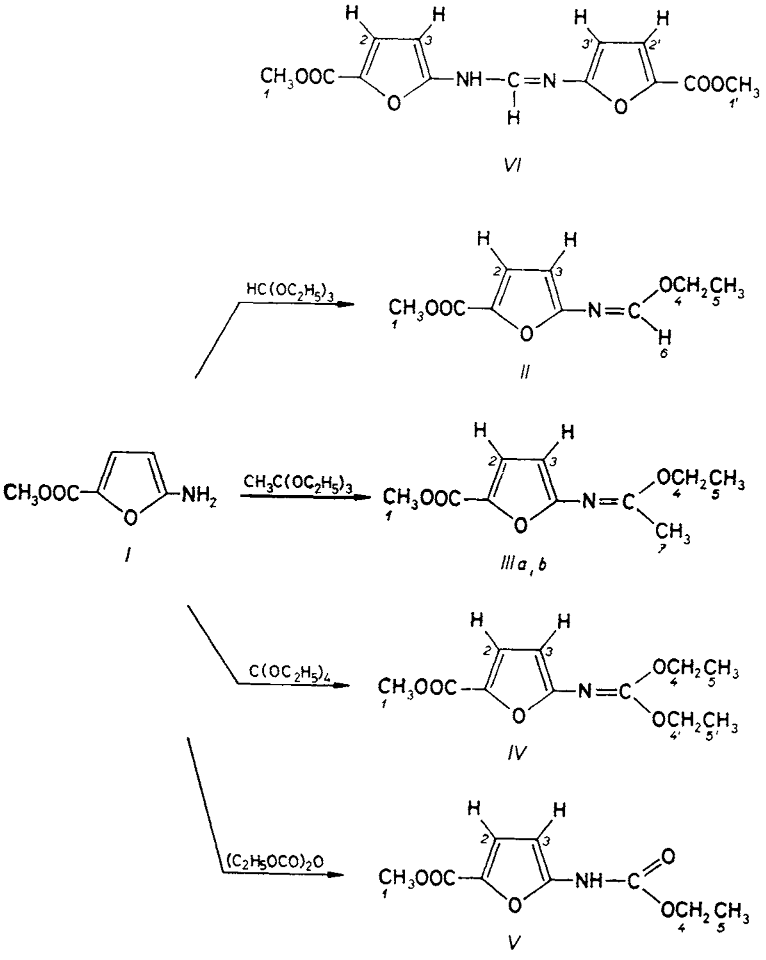
By the reaction of the title compound with ethyl esters of orthoformic, orthoacetic, orthocarbonic, and pyrocarbonic acids, respectively, formimidate *II*, acetimidate *III*, imidocarbonate *IV* and carbamides *V* were prepared. IR, UV spectra were measured and ^{1}H NMR and mass spectra were interpreted.

Reactions of aromatic amines with esters of orthoacetic and orthoformic acids are known, which, according to the conditions of the reaction, give either respective acetimidates, or formimidates[1] or in the case of excess of amine give N,N'-disubstituted amidines[2]. Methylester of 5-amino-2-furancarboxylic acid (*I*) belongs to a small number until now synthetized aminofuranes. The reactions of this compound with aldehydes[3], acylation of amino group[4], and the reaction with nitrous acid[5] were studied.

In this work the reactions of ester *I* with ethyl orthoformiate, ethyl orthoacetate ethyl carbonate, and with ethyl ester of pyrocarbonic acid (Scheme 1) were studied. The reactions were carried out by heating *I* in argon atmosphere in closed tubes using an excess of reaction agent. While the reactions of ethyl orthoacetate, ethyl orthoformiate, and of ethyl ester of pyrocarbonic acid proceed without catalyst, it is necessary to catalyze the reactions of the orthoester of carbonic acid by trifluoroacetic acid. The esters prepared in this way, ethyl-N-(5-methoxycarbonyl-2-furyl)-formimidate (*II*), ethyl-N-(5-methoxycarbonyl-2-furyl)acetimidate (*III*), diethyl-N-(5-methoxycarbonyl-2-furyl) imidocarbonate (*IV*), and ethyl-N-(5-methoxycarbonyl-2-furyl)carbaminate (*V*), represent new precursors for the synthesis of other furan derivatives.

The planar arrangement can be supposed in the case of formimidate *II* and acetimidate *III*. The group  $—\mathrm{N{=}C}\begin{smallmatrix}\mathrm{OC_2H_5} \\ \mathrm{NH|(CH_3)}\end{smallmatrix}$ bound to the heterocycle can exist in four conformations (see refs[6-8]). In ^{1}H NMR spectra of the compounds *II*, *III*, *IV*, and *V* a characteristic triplet of methylene group in the region δ 1·31 – 1·37 ppm and a quartet of methylene group of ethoxyl in the region δ 4·26 – 5·55 ppm can be found. The largest chemical shift of methylene protons signal was found at the derivative *V*.

To this fact corresponds the presence of carbonyl group, to which the ester rest is bound. Further, doublets in spectra can be found characteristic for furan protons with the constant of interaction $J_{3,4} = 3{\cdot}5-3{\cdot}6$ Hz and for proton 2-H δ 7·14 to 7·32 ppm and 3-H δ 5·74–6·32 ppm. The largest chemical shift exhibits the compounds *II* and *V*. This can be explained by anisotropic effect of the carbonyl group at the compound *V* and of the —C=N— amidine group at the compound *VI*. Signals of methoxy carbonyl group can be found as sharp singlets in the region δ 3·81 to 3·87 ppm. In the case of compound *II* proton 6-H can be found as a sharp singlet at 8·29 ppm. This is in good agreement with the signals of derivatives of formic



SCHEME 1

acid, for instance for dimethylformamide is δ 8·02 ppm and for formamide 8·1 ppm[9]. The protons of methylene group of acetamidate of the compound *III* exhibit sharp singlet with δ 2·15 ppm. In the case of NH protones with the compounds *V* and *VI*, the expected signals could not be identified in the ^{1}H NMR spectra. While the protons 2-H and 2-H′ produced awaited doublets, signals of furan protons 3-H and 3-H′ were very weakly distinct and they produced only low multiplet without separation. In the spectra of the compound *VI* which was formed as a by-product in the preparation of *II*, even these proton doublets were obtained, although with a considerably less intensity. They were obtained by measuring ^{1}H NMR spectra in deuterioacetonitrile at 100°C and with a maximum amplification of the spectrometer. In ^{1}H NMR spectra of the compound *VI* also a one proton singlet with the value of δ 8·31 ppm was observed, which corresponded to the 8-H proton of amidine. From the simplicity of the spectra, it can be concluded that in the case of the compound *VI* a planar molecule is concerned, with the rapidly exchanging nitrogen atom protons. This is simultaneously reflected on protons 3-H and 3′-H of the furan ring and these consequently exhibit only a little distinctive diffusive band in hexadeuteriodimethylsulfoxide. In a detailed study of ^{1}H NMR spectra of *III* it was found that ethoxy group gives two signals, only slightly different, less than 0·5 Hz. It was possible to conclude indirectly therefrom that *III* exists in the form of two isomers of different arrangement of ethoxy group in space. This was proved by the separation of the isomers. ^{1}H NMR spectra are comprised in Table I. The

TABLE I

^{1}H NMR spectra of compounds *II*–*IV*, chemical shift (scale δ, ppm, *J*(Hz))

Compound	H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8
II	3·86 s	7·14 d (3·5)	5·95 d (3·5)	4·33 q	1·36 t	8·29 s	—	—
III	3·82 s	7·16 d (3·5)	5·74 d (3·5)	4·26 q	1·31 t	—	2·15 s	—
IV	3·87 s	7·17 d (3·6)	6·01 d (3·6)	4·37 q	1·31 t	—	—	—
V	3·80 s	7·27 d (3·6)	6·25 d (3·6)	5·55 q	1·31 t	—	—	—
VI[a]	3·81 s	7·32 d (3·6)	6·32[b]	—	—	—	—	8·31 s

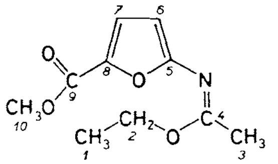
[a] Hexadeuteriodimethylsulfoxide; [b] diffusive band.

matter with m.p. 37° – 39°C was a pure compound (gas chromatography). Analysis of ^{13}C NMR spectra has proved that the crystalline matter is a pure isomer *IIIa*. In a detailed study of these spectra and after assignment of the respective signals, (Table II), it is obvious that the carbon atom $C_{(2)}$ of the methylene group displays two values of chemical shift. Simultaneously this fact was observed in a smaller degree at atom $C_{(1)}$ of ethoxy group and atoms $C_{(6)}$ and $C_{(7)}$ of furan ring. The change of the value of chemical shift of $C_{(2)}$ is up to 2 ppm. This fact can be explained by anisotropic effect of oxygen atom of furan ring, which gets to its proximity by eventual rotation of ethoxy group at *Z-trans* conformation. As a result of the magnetic anisotropic effect through space, it shields atom $C_{(2)}$ and shifts the signal upfield. In *Z-cis* conformation the atoms $C_{(6)}$ and $C_{(7)}$ of furan ring are affected by the oxygen atom of the ethoxy group. The distance of the oxygen atom of furan ring and of atom $C_{(2)}$ (*Z-trans* conformation) is smaller, on the basis of the study of the Dreiding's models, than that between the atom of oxygen of ethoxy group and the atoms $C_{(6)}$ and $C_{(7)}$ of the furan skeleton. To this fact corresponds also the smaller difference in the chemical shifts of these atoms of carbon.

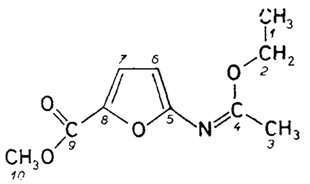
We have observed intensive molecular ion $M^{+\bullet}$ in the mass spectra of all compounds. It was possible to observe also the fragmentation, characteristic for methoxycarbonyl group, formation of the fragment ion ($M^{+\bullet}$ – 31), which corresponds to the splitting off the methoxy radical (Scheme 2). While in mass spectra of all studied

TABLE II

^{13}C NMR spectra of compound *III*

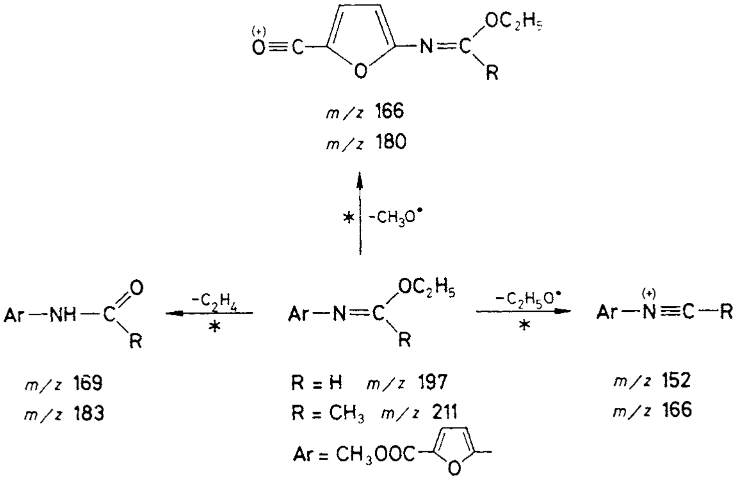


Z-trans IIIa



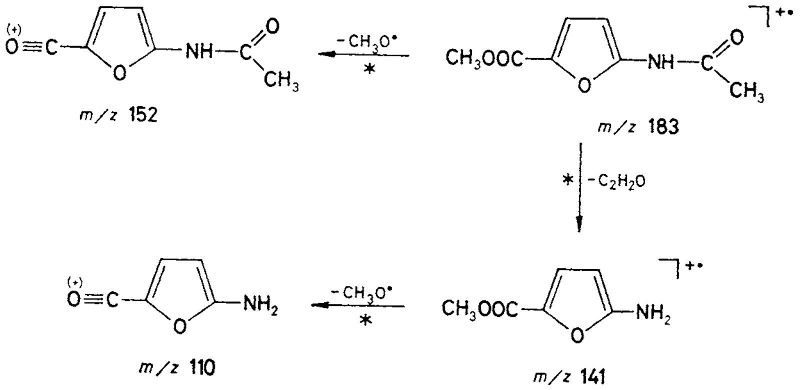
Z-cis IIIb

Atom	*IIIa* (*Z-trans*)	*IIIb* (*Z-cis*)	Atom	*IIIa* (*Z-trans*)	*IIIb* (*Z-cis*)
$C_{(1)}$	13·64	14·03	$C_{(6)}$	138·06	138·40
$C_{(2)}$	62·57	60·10	$C_{(7)}$	120·39	120·13
$C_{(3)}$	18·19	18·13	$C_{(8)}$	158·76	158·79
$C_{(4)}$	97·85	97·78	$C_{(9)}$	166·2	166·14
$C_{(5)}$	157·63	157·56	$C_{(10)}$	51·13	51·13



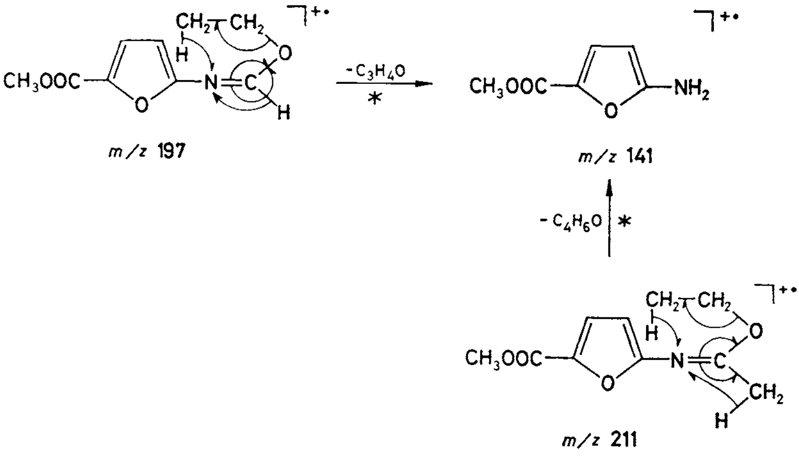
SCHEME 2

compounds an ion with m/z 141 occured, we have prepared a model compound methyl ester of 5-acetylamino-2-furancarboxylic acid for the confirmation of the structure. The mass spectra of this compound have been measured. At the studied compound, a very characteristic ion ($M^{+\bullet} - 42$) with m/z 141 can be observed by splitting the molecular ion $M^{+\bullet}$ with m/z 183, which is formed by splitting off $CH_2{=}C{=}O$ (metastable ion maximum 108·6). Further, an ion with m/z 83 is formed by splitting off the group $CH_2COO^\bullet$ (metastable ion maximum 44·8). An ion with m/z 110 (metastable ion maximum 85·5) is formed by splitting off $CH_3O^\bullet$ from the ion with m/z 141 (Scheme 3).



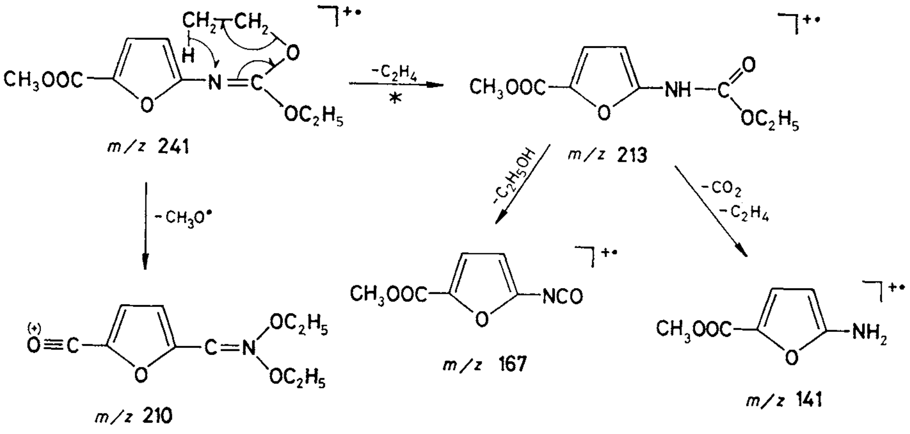
SCHEME 3

Intensivefragment ions peaks with m/z 141 are formed at compounds *II* and *III*. Their formation can be explained by splitting off the neutral molecule C_3H_4O ($M^{+\bullet} - 56$) or C_4H_6O ($M^{+\bullet} - 70$), resp. The splitting off is confirmed in both cases by the presence of metastable ion maximum with m/z 109·9 and 94·2, resp. This reflects the transfer of both protons on amidine nitrogen atom (Scheme 4).



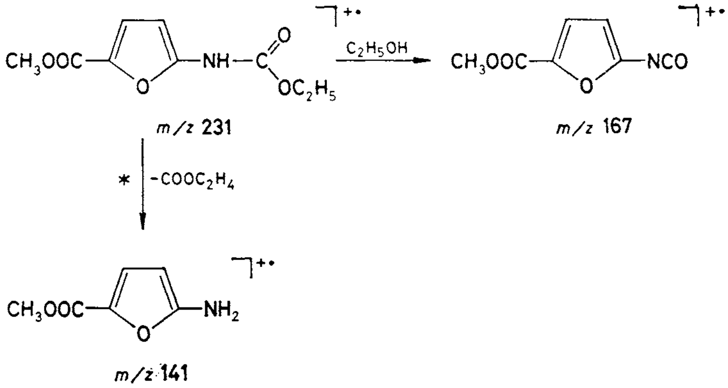
SCHEME 4

It is possible to observe the McLafferty's rearrangement at ethoxy group, the splitting off neutral molecule C_2H_4 ($M^{+\bullet} - 28$) m/z 169 and m/z 183, resp., both confirmed by metastable ion maxima 158·7 and 144·9, resp., (Scheme 2). Further it is possible



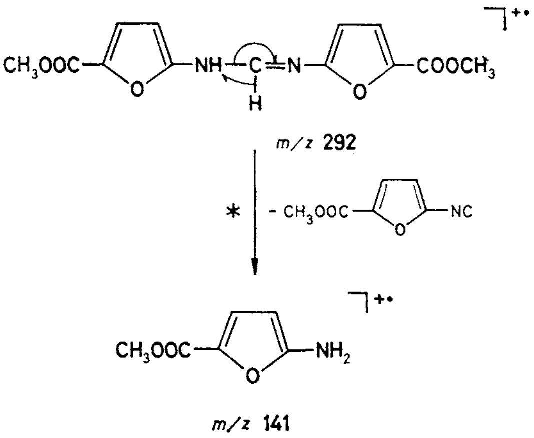
SCHEME 5

to observe fragment ions with m/z 152 and with m/z 166, which are formed from the molecular ion by splitting off the radical $C_2H_5O^{\bullet}$ ($M^{+\bullet} - 45$), which is confirmed by the presence of metastable ion maximum 117·2 (Scheme 2).



SCHEME 6

The compound *IV* and *V*, resp., are distinguished by different fragmentation. At the compound *IV* in the first stage a fragment ion with m/z 213 is formed, metastable ion maximum 188·2, by splitting off ethylene ($M^{+\bullet} - 28$), (McLafferty's rearrangement of the hydrogen atom of the ethoxy group). Fragment ion with m/z 167 is formed by splitting off ethanol, or an ion with m/z 141, already known, by splitting off ethylene and CO_2 (Scheme 5). Similarly, at *V*, by splitting off neutral molecule $COOC_2H_5$ together with the transfer of hydrogen atom (McLafferty's



SCHEME 7

rearrangement), a fragment ion with 141 is formed, metastable ion maximum 93·3, (Scheme 6). Fragment ion with *m/z* 141 is formed by splitting off (M^+ – 151) at the derivative *VI*. This is confirmed by metastable ion maximum 60·08 (Scheme 7).

EXPERIMENTAL

Melting points of synthetised compounds are uncorrected. They were measured on Kofler's block. UV spectra were measured on Specord UV VIS in methanol, the values of ε are given in $m^2 mol^{-1}$. IR spectra were measured on IR 71 by KBr technique and in chloroform. ^1H NMR spectra of all synthetised compounds were measured on spectrophotometer Tesla BS 487 C in deuteriochloroform with tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured on FX-100 (JEOL) in deuteriochloroform. Gas chromatography of the matter *III* was carried out on 7620 A Research Chromatograph Hewlett–Packard on the column DC 550 at the injection temperature of 270°C, the temperature of the column 150°C, the temperature of the detector 270°C. Methyl ester of 5-acetylamino-2-furancarboxylic acid was prepared according to[3].

Ethyl-N-(5-methoxycarbonyl-2-furyl)formimidate (*II*)

Methyl ester *I* (10 g, 70 mmol) was suspended in orthoethyl ester of formic acid (60 ml). The mixture was heated with stirring, until ester *I* was not dissolved and then heated at 80°C for 24 hours in closed tube in argon atmosphere. When the reaction was finished, the mixture was distilled under vacuum. 11 g of *II* (79%) was obtained, m.p. 37—39°C, b.p. 70—72°C at 2·6 kPa. IR spectra (cm^{-1}, KBr): 3 112, 2 911, 1 620, 1 495, 1 310, 1 262, 1 123, 910, 135, (chloroform): 2 985, 1 732, 1 629, 1 511, 1 312, 1 200. UV spectra λ_{max} (log ε): 300 nm (3·29). For $C_9H_{11}NO_4$ (197·2) calculated: 54·81% C, 5·6% H, 7·10% N; found: 54·74% C, 5·65% H, 7·11% N.

Ethyl-N-(5-methoxycarbonyl-2-furyl)acetimidate (*III*)

The conditions of the reaction were the same as at *II*, at isolation n-hexane (15 ml) was added to the residue after distilling off the orthoester. The product crystallized in the refrigerator. 14·9 g (88%) *III* was obtained, m.p. 38—40°C (n-hexane). IR spectra (cm^{-1}, KBr): 3 389, 2 971, 1 709, 1 642, 1 491, 1 433, 1 309, 1 285, 1 197, 1 143, 1 029, 981, 745, (chloroform): 2 987, 1 709, 1 650, 1 579, 1 511, 1 432, 1 381, 1 298, 1 124, 1 043, 1 008, 910, 834. UV spectra: λ_{max} (log ε): 300 nm (3·54). For $C_{10}H_{13}NO_4$ (211·2) calculated: 56·86% C, 6·20% H, 6·63% N; found: 56·83% C, 6·30% H, 6·70% N. Through repeated crystallization of *III* from n-hexane crystalline *IIIa* was obtained, which is less soluble in n-hexane. *IIIb*, which is well soluble in n-hexane, cumulated in mother liquors. It was obtained after thickening of the mother liquors in the form of light yellow oil.

N-(5-Methoxycarbonyl-2-furyl)imidocarbonate (*IV*)

To the mixture of *I* (3 g, 20 mmol) and orthoethyl ester of carbonic acid (10 ml), three drops of trifluoroacetic acid were added. The mixture was heated at 80°C under argon atmosphere for 24 hours. The excess ester was distilled off and the product was obtained either by chromatography on column (Al_2O_3 Brockman neutral, diethyl ether), or by vacuum sublimation at the pressure 13 Pa. 3 g (88%) of *IV* was obtained, m.p. 49—50°C (ether–n-hexane). IR spectra cm^{-1}, chloroform): 2 940, 1 699, 1 622, 1 570, 1 497, 1 377, 1 304, 1 075, 1 019, 911. UV spectra: λ_{max} (log ε): 305 nm (4·49). For $C_{11}H_{15}NO_5$ (241·3) calculated: 54·77% C, 6·22% H, 6·81% N; found: 55·12% C, 6·53% H, 5·86% N.

Ethyl-N-(5-methoxycarbonyl-2-furyl)carbaminate (*V*)

The mixture of *I* (3 g, 20 mmol) and orthoester of pyrocarbonic acid (5 ml) was stirred and heated at 60°C under argon atmosphere for 24 hours. The orthoester in excess was distilled off under vacuum and the residue was crystallized from the mixture benzene–cyclohexane. 2·55 g (56%) of *V* was obtained, m.p. 90—92°C. IR spectra (cm^{-1}, KBr): 3 262, 1 714, 1 694, 1 600, 1 574, 1 439, 1 317, 1 277, 1 140, 1 110, 793, 753. UV spectra: λ_{max} ($\log \varepsilon$): 297 (4·20). For $C_9H_{11}NO_5$ (213·2): calculated 50·70% C, 5·16% H, 6·57% N; found: 50·50% C, 5·35% H, 6·38% N.

Amidine *VI* was obtained from the residue of the distillation, after preparation of *II*, by the crystallization from acetonitrile as a yellow hardly soluble matter. The yield was 5—10% relative to the used ester *I*, m.g. 203—205°C (acetonitrile). IR spectra (cm^{-1}, KBr): 3 152, 2 975, 1 721, 1 660, 1 498, 1 442, 1 309, 1 134, 986, 795. UV spectra λ_{max} ($\log \varepsilon$): 277 nm (3·01), 360 (3·57). For $C_{13}H_{12}N_2O_6$ (292·3) calculated: 53·42% C, 4·14% H, 9·59% N; found: 52·98% C, 4·28% H, 9·36% N.

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