

SYNTHESIS AND REACTIONS OF TRIMETHYLAMMONIUM SALTS OF ETHYLENE DERIVATIVES OF FURAN

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The paper deals with direct quaternization of trimethylamine with 5-bromo-2-furylethylene derivatives *Ia–Ig* which contain strong electron acceptor substituents. New variants are described of the synthesis of 5-N,N-dimethylamino-2-furylethylene compounds *III* and 5-azido-2-furylethylene derivatives *IV*.

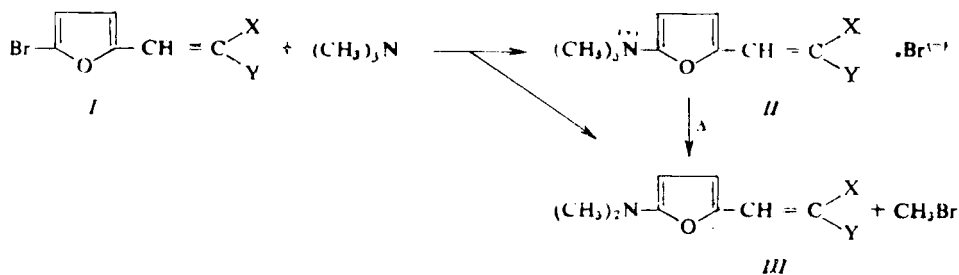
In preceding papers we have presented^{1,2} syntheses of trimethylammonium salts of furan by the Menshutkin reaction³. On the basis of successful quaternization of trimethylamine with 5-halo-2-furaldehydes¹ and 5-nitro-2-bromofuran² the study of preparation of trimethylammonium salts of furylethylene derivatives was approached. The research in this field is supported by the fact that analogical 5-nitro-2-furylethylene compounds exhibit high antibacterial activity, but they are only weakly soluble in water. The replacement of the nitro group by trimethylammonium group practically does not change the electron effects in the molecule which in such way obtains necessary solubility in water.

In the presented paper, a study of direct quaternization of trimethylamine with 5-bromo-2-furylethylene derivatives *Ia–Ig* is described.

The condensation of 5-bromo-2-furaldehyde⁴ with compounds containing an active methylene group was carried out according to ref.^{5,6} on the catalysis with methanolate anion, piperidine or glycine⁷, resp. While at *Ib* and *Ic* only (*E*) isomer is obtained, *Ie* and *If* produce both (*E*) and (*Z*) isomers. By a fractionation crystallization from methanol *Ie* and *If* are obtained as pure (*E*) isomers.

Substituents X and Y in the compounds *Ia–Ic* activate strongly enough the halogen in the position 5 of the furane ring and quaternization of trimethylamine proceeds sufficiently quickly, resulting in the formation of quaternary ammonium salts *IIa–IIc* with 80 to 90 per cent yields. Reactions were proceeded at 20 to 25°C in aprotic solvents, where *IIa–IIc* are practically insoluble. The best results were obtained when the reaction was carried out in benzene, 1,2-dimethoxyethane and acetone.

Mother liquors, after filtering the insoluble trimethylammonium salts, contained 5-N,N-dimethylamino-2-furylethylene derivatives *IIIa–IIIc*, as the products of the decomposition of trimethylammonium salts. The amount of formed 5-N,N-dimethylamino furan derivative is affected by the temperature, the solvent and by the amount of trimethylamine. A small amount of water or other protic components in the solvent lowers very considerably the yield of trimethylammonium salts *II*



<i>I–III</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>
X	CN	CN	CN	COOC ₂ H ₅	COOCH ₃	COOC ₂ H ₅	COCH ₃
Y	CN	CONH ₂	COOCH ₃	COOC ₂ H ₅	COCH ₃	COCH ₃	COCH ₃

Trimethylammonium salts *IIa–IIc* (according to ¹H NMR spectroscopy) begin to decompose already at 40°C. Because the decomposition is a monomolecular S_N1 reaction⁸ polar protic solvents help very strongly to the formation of 5-N,N-dimethylamino furan derivatives *III*. Efforts for quaternization of *Ia–Ic* derivatives in these solvents (*e.g.* methanol, ethanol) unambiguously result in the formation of *IIIa–IIIc* derivatives. Analogically, crystallization of trimethylammonium salts from protic solvents (methanol, ethanol, water *etc.*) leads to a partial or even total decomposition of these compounds to dimethylamino derivatives *IIIa–IIIc*. The efforts for quaternization of trimethylamine with 5-bromo-2-furylethylene derivatives *Id–If*, carried out at analogical condition resulted in obtaining only a slight amount of trimethylammonium salts *IId–IIf*. Longer time of quaternization (50 to 200 hours) is necessary for compounds *Id–If*, while trimethylammonium salts *IId–IIf* so formed are contaminated by the products of the decomposition *IIId–IIIf* and mainly by tetramethylammonium bromide. With respect to the lowered reactivity of halogen compounds, *Id–If* give in the quaternization preferentially products *IIId–IIIf* as the result of the effect of temperature and media. At quaternization of trimethylamine with derivatives *Ie–If* in the mixture of (*E*) and (*Z*) isomers in benzene was on the basis of ¹H NMR spectra found the retention of the original configuration of molecules with the formation of relatively equal ratio of (*Z*) and (*E*) isomers *IIf* and *IIIe* or *IIIe* and *IIIe*, resp. as was in the original com-

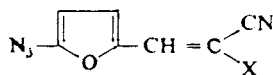
pound *Ie* and *If*. The least reactive derivative *Ig* gave even after 240 hours at ambient temperature no trimethylammonium salt *IIg* but only *IIIg*, the product of decomposition.

By the reaction of *Ia–Ig* with trimethylamine in methanol, ethanol, and water or in their mixtures with water, dimethylaminofuran derivatives *IIIa–IIIc* in 90 to 95% yield and *IIId–IIIg* in 35 to 60% yield are formed. The temperature decomposition of trimethylammonium salts in aprotic and protic solvents give high yields of *IIIa–IIIc*.

Temperature dependence of the decomposition of compounds *IIa–IIg* in hexa-deuteriodimethyl sulfoxide at 20°, 40°, 60°, 80° and 100°, resp., was determined on the basis of ¹H NMR spectroscopy. The decomposition of *IIa* and *IIf* was detected already after 10 minutes at 40°. All derivatives *IIa–IIf* decompose quantitatively at 100° after 30 to 60 minutes and only derivatives *IIIa–IIIf* can be identified in the spectra together with a small amount of until now unidentified compounds which do not contain furan ring. Two doublets, corresponding to H₃ and H₄ of the furan ring (see Table III) and a singlet of a proton H_{CH=} can be identified in ¹H NMR spectra of synthesized compounds *IIa–IIf* and *IIIa–IIIg*. While the position of H₃ signal changes only less distinctly for all compounds by the influence of the substituent in the position 5 of the furan ring (it occurs in the region 6.9 to 7.6 ppm), the position of H₄ signal shifts distinctly to the lower values of ppm as a result of effect of electron donor substituent (CH₃)₂N. At trimethylammonium compounds occurs H₄ in the region 7.06–7.28 ppm and at 5-N,N-dimethylamino derivatives *IIIa–IIIg* in the region 5.25–5.62 ppm. Monitoring thermal decomposition of compounds *IIa–IIf* by means of ¹H NMR spectroscopy is highly persuasive. Analogically, highly sensitive is also the monitoring of thermal decomposition of *IIa–IIf* by means of UV-spectroscopy in methanol, where strong bathochromic shift from values λ_{max} (300 to 325 nm) for *IIa–IIf* to λ_{max} (427–455 nm) for *IIIa–IIIg* can be observed.

Trimethylammonium salts *IIa–IIf* react easily with nucleophilic reagents and give products of nucleophilic substitution of a good leaving⁹ trimethylammonium group.

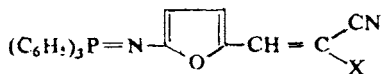
Especially reactions with slightly basic and good nucleophilic azide anion are highly selective^{1,2,10}. Nucleophilic substitution of trimethylammonium group in *IIa–IIc* by the azide anion in water proceeds even at ambient temperature with the formation of azides *IVa–IVc* in a 75 to 95% yield.



IVa, X = CN

IVb, X = CONH₂

IVc, X = COOCH₃



Va, X = CN

Vb, X = CONH₂

Vc, X = COOCH₃

By the reaction of azides with triphenylphosphine iminotriphenylphosphoranes, new precursors of aminofuran compounds, are obtained practically in quantitative yield.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. The IR spectra were measured by the KBr technique with a UR-20 (Zeiss, Jena) spectrophotometer. The UV spectra were measured in methanol with a UV VIS (Zeiss, Jena) spectrophotometer. The ^1H NMR

TABLE I
Physico-chemical properties of compounds *Iib*–*Iif*, *IVa*–*IVc* and *Va*–*Vc*

Compound	Formula (mol. weight)	M.p. (°C) yield (%)	Calc./Found		λ_{max} , nm, (log ϵ)
			% N	% Br	
<i>Iib</i>	$\text{C}_{11}\text{H}_{14}\text{BrN}_3\text{O}_2$ (300.1)	218–224 (215–217) ^a 90	13.99 13.81	26.62 26.09	323 (4.19)
<i>Iic</i>	$\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{O}_3$ (315.1)	164–167 (181–185) ^a 82	8.88 9.08	25.35 25.17	323 (4.19)
<i>Iid</i>	$\text{C}_{15}\text{H}_{22}\text{BrNO}_5$ (376.2)	182–187 — 25	3.72 3.99	21.24 21.99	314 (4.07)
<i>Iie</i>	$\text{C}_{13}\text{H}_{18}\text{BrNO}_4$ (332.2)	132–133 (187–192) ^a 37	4.21 4.48	24.08 24.48	302 (4.02)
<i>Iif</i>	$\text{C}_{14}\text{H}_{20}\text{BrNO}_4$ (346.2)	137–139 (184–186) ^a 35	4.04 4.47	23.10 23.87	302 (4.45)
<i>IVa</i>	$\text{C}_8\text{H}_3\text{N}_5\text{O}$ (185.1)	117–119 — 90	37.81 37.62	—	230 (3.87), 355 (3.89)
<i>IVb</i>	$\text{C}_8\text{H}_5\text{N}_5\text{O}_2$ (203.1)	172–177 — 75	34.46 34.22	—	226 (3.68), 350 (3.99)
<i>IVc</i>	$\text{C}_9\text{H}_6\text{N}_4\text{O}_3$ (218.1)	98–102 — 75	25.68 25.99	—	242 (4.14), 391 (4.23)
<i>Va</i>	$\text{C}_{26}\text{H}_{18}\text{N}_3\text{OP}$ (419.4)	185–187 — 98	10.02 10.23	—	227 (4.59), 482 (4.87)
<i>Vb</i>	$\text{C}_{26}\text{H}_{20}\text{N}_3\text{O}_2\text{P}$ (437.4)	123–128 — 89	9.60 9.83	—	226 (4.09), 481 (3.97)
<i>Vc</i>	$\text{C}_{27}\text{H}_{21}\text{N}_2\text{O}_3\text{P}$ (452.3)	119–122 — 90	6.19 6.40	—	228 (4.51), 488 (4.65)

^a Melting point of a picrate.

spectra were measured in hexadeuteriodimethyl sulfoxide with Tesla BS 487C spectrometer with tetramethylsilane as an internal reference.

N-[5-(2',2'-Dicyanovinyl)-2-furyl]trimethylammonium bromide (*Ila*) was prepared according to¹; yield 75%, m.p. 180–183°C (decomp.).

Quaternization of Trimethylamine with 5-Bromo-2-furfurylidene malonic Compounds *Ib–Ig*

A solution of 0.01 mol 5-bromo-2-furfurylidene malonic derivative *Ib–Ig* in 25 ml of benzene was mixed with a solution of 0.012 mol trimethylamine in 25 ml of benzene. The precipitate, at *Ib* and *Ic* after one hour and at *Id–If* after 48 hours, was filtered off with exclusion of air moisture and several times washed with dry ether. Physico-chemical constants can be found in Table I and III.

5-N,N-Dimethylamino-2-furfurylidene Derivatives *IIIa–IIIg*

a) Derivatives *IIIa–IIIg* can be isolated from mother liquors after quaternization of trimethylamine with *Ia–Ig*. After filtration and washing the trimethylammonium salts *Ila–IIg*, the filtrate and the washing solutions are evaporated *in vacuo*. Crude dimethylammonium com-

TABLE II
Physico-chemical properties of compounds *IIIa–IIIg*

Compound	Formula	M.p. (°C) yield (%) ^a			Calc./Found			λ_{max} , nm, (log ϵ)
		<i>a</i>	<i>b</i>	<i>c</i>	% C	% H	% N	
<i>IIIa</i>	C ₁₀ H ₉ N ₃ O (187.2)	191–193 10	95	95	64.16 64.11	4.85 4.90	22.25 22.37	233 (4.17), 465 (4.83)
<i>IIIb</i>	C ₁₀ H ₁₁ N ₃ O ₂ (205.2)	224–227 7	90	95	58.53 58.00	5.36 5.07	20.48 20.88	230 (4.10), 460 (4.35)
<i>IIIc</i>	C ₁₁ H ₁₂ N ₂ O ₃ (220.2)	162–163 35	40	95 ^b	60.00 60.17	5.49 5.46	12.72 12.84	230 (4.38), 462 (5.00)
<i>III d</i>	C ₁₄ H ₁₉ NO ₅ (281.3)	102–107 30	35	77 ^b	66.83 66.04	6.75 6.34	4.97 5.12	231 (4.02), 427 (4.44)
<i>III e</i>	C ₁₂ H ₁₅ NO ₄ (237.3)	105–107 25	65	85 ^b	60.76 60.41	6.37 6.42	5.90 5.96	235 (4.00), 450 (4.40)
<i>III f</i>	C ₁₂ H ₁₇ NO ₄ (251.4)	107–108 30	65	85 ^b	62.01 61.92	6.76 6.64	5.57 5.49	237 (3.97), 453 (4.41)
<i>III g</i>	C ₁₀ H ₉ NO ₃ (191.1)	109–112 30	60	—	62.82 62.76	4.75 4.82	7.33 7.41	— 448 (4.40)

^a Yields of the particular ways of preparation; ^b yield determined by ¹H NMR.

pounds *IIIa–IIIg* are purified by column chromatography on SiO_2 column. Yields and other physical properties are given in Table II.

b) 0.01 mol of *Ia–Ig* is dissolved under heating in 50 ml of CH_3OH or $\text{C}_2\text{H}_5\text{OH}$ and 0.012 mol of trimethylamine in 20 ml of the respective alcohol is added. The mixture is stirred for 8 hours and 150 ml of ether is added to it. The precipitated compound is filtered off and properly washed. The combined organic solutions are evaporated *in vacuo*. The residue is purified in the same way as ad a).

c) 0.01 mol of trimethylammonium salt *IIa–IIg* is dissolved in 50 ml of CH_3OH and heated to 50°C . The mixture is stirred at this temperature for 4 hours; 100 ml of ether are added, the precipitate is filtered off and the filtrate is processed as ad a).

5-Azido-2-furfurylidemalonic Derivatives *IV–IVc*

0.005 mol of ammonium salt *IIa–IIc* was dissolved in 80 ml of water and mixed with 0.7 g of NaN_3 in 10 ml of water. After 10 minutes was the forming azide several times extracted with ether. The combined ethereal solutions were evaporated *in vacuo*. The yields and other physico-chemical constants can be found in Tables I and II.

TABLE III

^1H NMR spectral data of compounds *IIa–IIg*, *IIIa–IIIg* and *IVa–IVc*

Compound	H_3^a	H_4^a	H_A	$-\text{CH}_3$	$-\text{OCH}_3$	$-\text{COCH}_3$	$-\text{OCH}_2$	$-\text{N}(\text{CH}_3)_2$
<i>IIa</i>	7.55	7.28	8.40	—	—	—	—	3.69
<i>IIb</i>	7.45	7.22	8.10	—	—	—	—	3.71
<i>IIc</i>	7.55	7.21	8.21	—	3.82	—	—	3.72
<i>IIId</i>	7.25	7.12	7.57	1.30	—	—	4.25	3.68
<i>IIe</i>	7.40	7.11	7.68	1.30	—	2.53	4.38	3.68
<i>IIIf</i>	7.23	7.14	7.72	—	3.90	2.56	—	3.68
<i>IIIa</i>	7.45	5.91	7.13	—	—	—	—	3.17
<i>IIIb</i>	7.34	5.63	7.49	—	—	—	—	3.11
<i>IIIc</i>	7.06	5.42	7.41	—	3.83	—	—	3.19
<i>IIIId</i>	6.98	5.25	7.17	1.32	—	—	4.35	3.07
<i>IIIe (E)</i>	6.98	5.25	7.30	1.36	—	2.30	4.36	2.98
<i>IIIe (Z)</i>	6.99	5.25	7.33	1.36	—	2.46	4.36	3.00
<i>IIIIf (E)</i>	6.99	5.26	7.17	—	3.86	2.30	—	3.00
<i>IIIIf (Z)</i>	6.99	5.26	7.31	—	3.79	2.48	—	3.03
<i>IIIg</i>	6.95	5.22	7.33	—	—	2.45	—	3.07
<i>IVa</i>	7.50	6.36	7.81	—	—	—	—	—
<i>IVb</i>	7.36	6.94	7.91	—	—	—	—	—
<i>IVc</i>	7.34	6.02	7.84	—	3.80	—	—	—

$^a J_{\text{H}_3, \text{H}_4} = 4 \text{ Hz}$.

5-N-Iminotriphenylphosphorano-2-furfurylidemalonic Derivatives *Va–Vc*

0.01 mol of triphenylphosphine is added to the ether solution of azides *IVa–IVc* at ambient temperature and the mixture is left to boil for 10 minutes. After evaporation of the solvent, *Va–Vc* is obtained. Yields and other physico-chemical constants are given in Table I.

REFERENCES

1. Végh D., Kováč J., Dandárová M.: This Journal 47, 961 (1982).
2. Végh D., Kováč J., Dandárová M.: This Journal 48, 1885 (1983).
3. Menshutkin N.: Z. Phys. Chem. (Leipzig) 5, 589 (1890).
4. Nazarova Z. N.: Dokl. Akad. Nauk. Uzb. SSR. 4, 40 (1963); Chem. Abstr. 49, 10 261 (1955).
5. Považanec F., Kováč J., Piklerová A.: Zb. Pr. Chemickotechnol. Fak. Slov. Vys. Šk. Tech. Bratislava, 1975–1976, 55.
6. Kříž M.: Thesis. Slovak Institute of Technology, Bratislava 1985.
7. Bastús B. J.: Tetrahedron Lett. 1963, 955.
8. Klötzer W.: Monatsch. Chem. 87, 326, 536 (1956).
9. Stirling Ch. J. M.: Accounts Chem. Res. 12, 198 (1979).
10. Horwitz J. P., Tomson A. J.: J. Org. Chem. 26, 3392 (1961).

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