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To the memory of Prof. B.I. Ionin

Furan-Containing *gem*-Bromonitroethenes: Synthesis and Reaction with Morpholine

S. S. Eliseenko, S. V. Makarenko, and V. M. Berestovitskaya

Herzen State Pedagogical University, nab. reki Moiki 48, St. Petersburg, 191186 Russia
e-mail: kohrgpu@yandex.ru

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Abstract—The first time the representative of furan-containing *gem*-bromonitroethenes 5-nitro-2-(2-bromo-2-nitro-ethenyl)furan was synthesized by bromination of 5-nitro-2-(2-nitroethenyl)furan followed by dehydrohalogenation of the dibromide. Morpholine adducts of the synthesized β-substituted *gem*-bromonitroethene and its analog with a 5-bromo-2-furyl substituent were obtained. The structures of the *gem*-bromonitroethenes and aza adducts were characterized by spectral methods (IR, UV, ^{1}H, and ^{13}C–{^{1}H} NMR, including ^{1}H–^{13}C HMQC and HMBC).

Keywords: furan, *gem*-bromonitroethene, morpholine, nucleophilic addition

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The chemistry of *gem*-halonitroethenes has attracted increased interest due to their high reactivity [1]. Especially interesting among compounds of this class are those containing a furan ring [2–5], because furan is the key structure of many medicines, including the antibiotics Furacilin and cefuroxime, antiulcer drug ranitidine, diuretic furosemide, and anticancer drug lapatinib [6], and 5-bromo-2-(2-bromo-2-nitroethenyl)-furan[1] (Furvina) is use in the therapy of dermatological infections [7].

We report here the first synthesis of 5-nitro-2-(2-bromo-2-nitroethenyl)furan (**III**) by bromination of 5-nitro-2-(2-nitroethenyl)furan (**I**) followed by dehydrohalogenation of dibromide **II** with alcoholic melted potassium acetate (Scheme 1). This preparatively convenient procedure features high yields of the intermediate dibromide **II** (99%) and final *gem*-bromonitroethene **III** (97%) can be realized in one pot (i.e. without isolation of dibromide). It should be noted that compound **III** was previously obtained by nitration of furan- and 5-bromofuran-containing *gem*-bromonitroethenes in yields of 88 and 39%, respectively [8].

The advantages of the method proposed here is not only a high yield of the target product, but also that it has much in common with the known synthesis of its structurally related analog, specifically 5-bromo-2-(2-bromo-2-nitroethenyl)furan (**V**) [8]. The published procedure of synthesis of compound **V** [8] was modified by replacing aqueous potassium hydroxide (molar ratio 1 : 4.3) at the dehydrohalogenation stage by alcoholic melted potassium acetate (molar ratio 1 : 1.6), which allowed the yield of the product to be increased to 68% (64% [8]).

We performed detailed combined structural analysis of 5-nitro- and 5-bromo-2-(2-bromo-2-nitroethenyl)-furans (**III**, **V**) by modern spectral methods (IR, UV, ^{1}H, and ^{13}C–{^{1}H} NMR, including ^{1}H–^{13}C HMQC and HMBC) (Table 1). It should be noted that the obtained spectral characteristics are agree well with the IR and UV data presented in part [9] for *gem*-bromonitroethene **III**, as well as more complete IR [9, 10], UV [9], ^{1}H [10, 11], and ^{13}C NMR data [10] for *gem*-bromonitroethene **V**.

The chemical shift of the vinyl proton signal in the ^{1}H NMR spectra of *gem*-bromonitroethenes **III** and **V**

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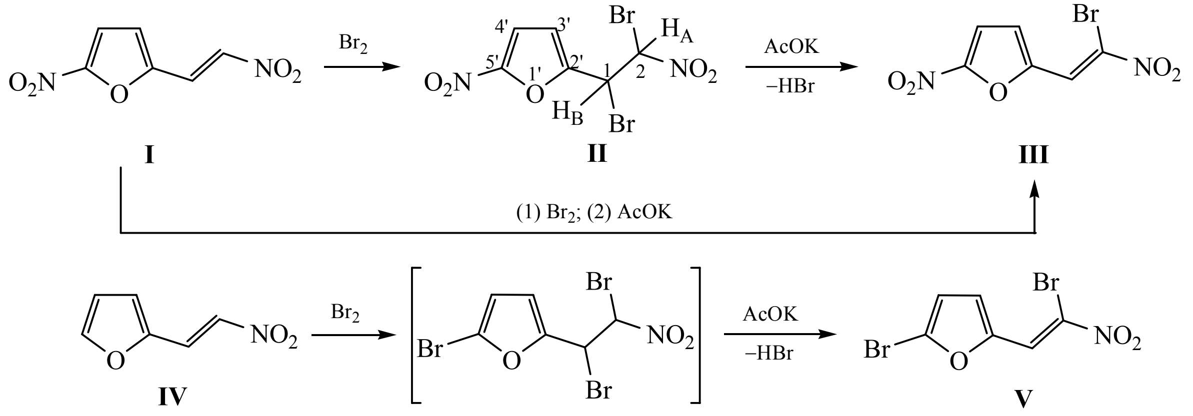
[1] For convenience in discussion, we used the same heteroring atom numbering in structurally similar *gem*-bromonitroethenylfurans.

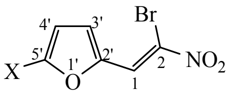
Scheme 1.



(8.55 and 8.49 ppm) suggests *Z* configuration. As known, the downfield position of the signal of the vinyl proton arranged cis to the nitro group (due to its anisotropic effect) is one of the important criteria for the configuration assessment of nitroalkenes. For example, the olefin proton signal in the spectrum of the *E* isomer of 1-bromo-1-nitro-2-phenylethene (the proton is *trans* to the nitro group) appears at 7.02 ppm, whereas the respective signal of the *Z* isomer (the proton is *cis* to the nitro group), at 8.60 ppm [12, 13].

In the $^{13}C-\{^1H\}$ NMR spectra of *gem*-bromonitroethenes **III** and **V**, the carbon signals of the bromonitrovinyl fragment are observed at 123.00, 123.88 (C^1) and 131.10, 124.95 ppm (C^2), and the furan ring gives a series of signals at 147.79, 148.49 ($C^{2'}$), 119.72, 122.08 ($C^{3'}$), 112.55, 115.64 ($C^{4'}$), and 153.24, 129.48 ppm ($C^{5'}$) (Table 1); the signals were assigned on the basis of $^1H-^{13}C$ HMQC and HMBC experiments (Fig. 1). Specifically, the HMBC spectrum of compound **III** contains cross peaks between the downfield vinyl proton signal (δ_H = 8.55 ppm) and the signals of the furan carbons $C^{3'}$ (δ_C = 119.72, ^3J) and $C^{2'}$ (δ_C = 147.79, ^2J), and the carbon atom of the bromonitrovinyl substituent C^2 (δ_C = 131.10, ^2J), whereas the doublet signals of the furan hydrogens $C^{4'}H$ (δ_H = 7.45)

Table 1. Yields, melting points, and spectral characteristics of 5-nitro- and 5-bromo-2-(2-bromo-2-nitroethenyl)furans **III** and **V**



Comp. no.	X	Yield, %	mp, °C	δ, ppm (*J*, Hz)						ν, cm^{-1}			UV spectrum (EtOH)	
				^1H			$^{13}C-\{^1H\}$			C=C (Fur)	NO_2 (Fur-NO_2)		λ_{max}, nm	ε, L mol^{-1} cm^{-1}
				$C^{4'}H$	$C^{3'}H$	C^1H	$C^{5'}(C^{2'})$	$C^{4'}(C^{3'})$	$C^1(C^2)$		ν_{as}	ν_s		
III	NO_2	97	89–90	7.45 d [^3J 4.0]	7.53 d	8.55 s	153.24 (147.79)	112.55 (119.72)	123.00 (131.10)	1620	1534 (1550)	1311 (1352)	250 360	5600 20200
V	Br	68	90–91	6.60 d [^3J 3.7]	7.37 d	8.49 s	129.48 (148.49)	115.64 (122.08)	123.88 (124.95)	1611 1623 (1460)	1533	1305	243 371	6400 19500

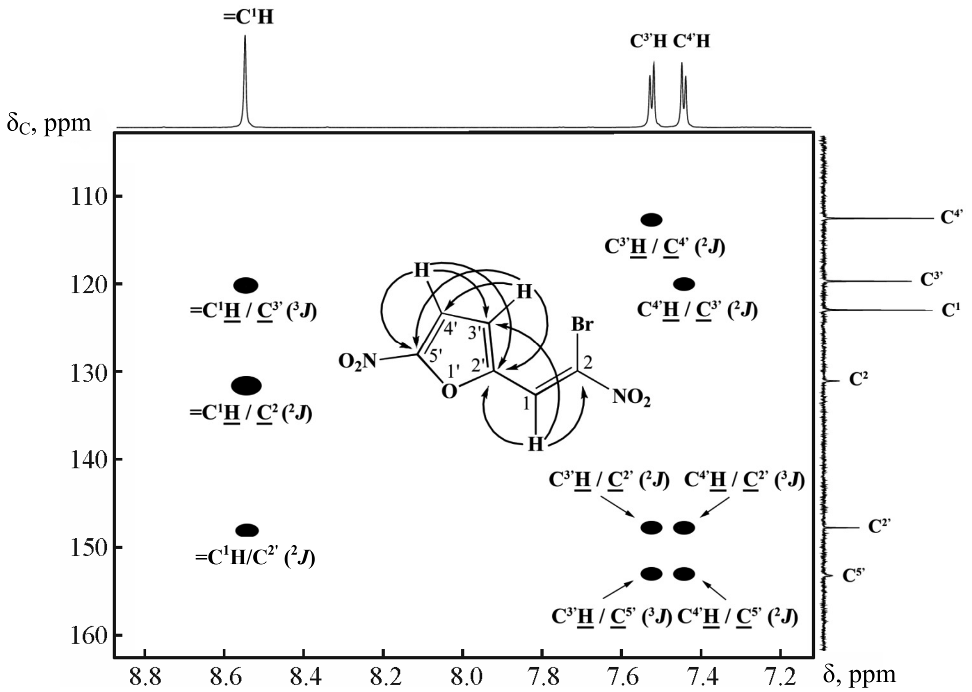


Fig. 1. ^1H–^{13}C HMBC spectrum of *gem*-bromonitroethene **III**.

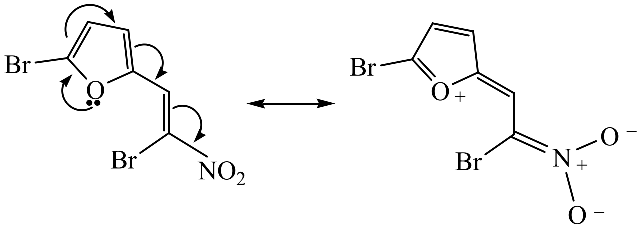
and $C^{3'}H$ (δ_H = 7.53) give cross peaks (^3J and ^2J) with the signals of the furan carbons $C^{2'}$ (δ_C = 147.79) and $C^{5'}$ (δ_C = 153.24), as well as, separately, $C^{4'}H/C^{3'}$ (δ_C = 119.72, ^2J) and $C^{3'}H/C^{4'}$ (δ_C = 112.55, ^2J).

The IR spectra of bromonitroethenes **III** and **V** in $CHCl_3$ differ from each other (Table 1). Thus, the spectrum of 5-nitrofuran-containing compound **III** contains strong bands of the conjugated nitro group of the bromonitrovinyl fragment (ν_{as} = 1534, ν_s = 1311 cm^{-1}, $\Delta\nu$ = 223 cm^{-1}) and of the furan ring (ν_{as} = 1550, ν_s = 1352 cm^{-1}, $\Delta\nu$ = 198 cm^{-1}), as well as a weak C=C band at 1620 cm^{-1}. The spectrum of 5-bromofuran-containing bromonitroethene **V** displays absorption bands of the C=C bond (1611 and 1623 cm^{-1}), furan ring (1460 cm^{-1}), and covalent conjugated nitro group (ν_{as} = 1533 cm^{-1}, ν_s = 1305 cm^{-1}, $\Delta\nu$ = 228 cm^{-1}). It would be noted that the IR spectra of compounds **III** and **V** in a chloroform solution agree with the IR spectra measured for suspensions of these compounds in mineral oil. The electronic absorption spectra of furan-containing bromonitroethenes **III** and **V** show strong long-wave bands at λ_{max} = 360–371 nm, ε = 19500–20200 (Table 1), whose position does contradict the data in [9] and may suggest considerable polarization of the molecules (Scheme 2).

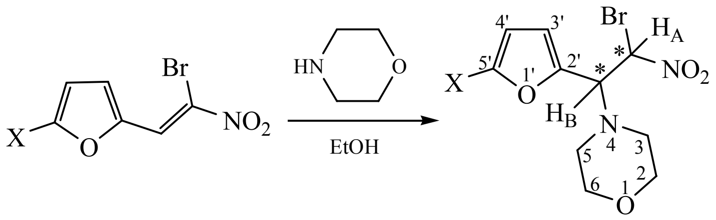
Note that according to the X-ray diffraction data in [14], 5-bromofuran-containing *gem*-bromonitroethene **V** in crystal exists as an *s-trans* isomer.

Bromonitroethenes **III** and **V** were reacted with morpholine in ethanol for 1 h at –10 to –5°C to obtain furan-containing 4-(2-bromo-2-nitroethyl)morpholines **VI** and **VII** (aza-Michael adducts) in yields of up to 88%; the products are crystalline substances stable on storage at a low temperature. Previously Gruntfest et al. [9] reported the preparation of compound **VII** in more rigid conditions (heating in an alcohol solution at 40–80°C) but provided no details of the synthesis and physicochemical characteristics of the product (Scheme 3).

Scheme 2.



Scheme 3.



III, V **VI, VII**

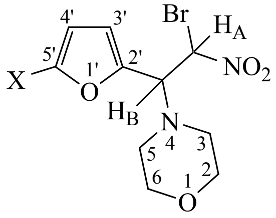
X = NO_2 (**III, VI**); Br (**V, VII**).

The ^1H NMR spectra of aza adducts **VI** and **VII** show similar sets of signals, implying diastereohomogeneity of these compounds (Table 2). For example, in the spectrum of compound **VII** the morpholine ring proton signals appear as multiplets at 2.16–2.48, 2.52–2.75, and 3.50–3.77 ppm, the H_A and H_B methine protons form two doublets at 6.25 and 4.31 ppm (^3J = 10.9 Hz), and the furan ring protons resonate as two doublets at 6.34 and 6.36 ppm (^3J = 3.3 Hz), which does not contradict the data for structurally related 2,5-disubstituted furan [15] and *N*-substituted morpholines [16].

The ^{13}C–{^1H} NMR spectra of aza adducts **VI** and **VII** contain sets of signals at 112.32–147.92 (**VII**) and 111.77–152.69 ppm (**VI**) from furan ring carbons. The morpholine ring carbons appear at 50.27, 50.34 ($\underline{C}H_2N$) and 66.93, 66.82 ppm ($\underline{C}H_2O$), and the $\underline{C}H_A$ and $\underline{C}H_B$ signals are observed at 76.24, 75.13 and 67.30, 67.43 ppm, respectively (Table 2). Such assignment of the ^{13}C–{^1H} NMR spectra was confirmed by the ^1H–^{13}C HMQC and ^1H–^{13}C HMBC experiments (Fig. 2 and 3). For example, in the HMBC spectrum of compound **VII** the H_A signal forms cross peaks with the $\underline{C}H_B$ (^2J) and $C^{2'}$ (^3J) signals, and the H_B signal forms gross peaks with the $\underline{C}H_2N$ (^3J), $\underline{C}H_A$ (^2J), $C^{3'}$ (^3J), and $C^{2'}$ (^2J) signals.

The IR spectra of aza adducts **VI** and **VII** contain strong absorption bands of the unconjugated nitro group (1575–1576, 1356–1358 cm^{-1}). In the IR spectrum of compound **VI** the nitro group conjugated with the furan ring gives a ν_{as} band at 1535 cm^{-1}, and the band of symmetric stretching vibrations appears at

Table 2. Yields, melting points, and spectral characteristics of aza adducts **VI** and **VII**



Comp. no.	X	Yield, %	mp, °C	δ, ppm (*J*, Hz)									ν, cm^{-1}
				^1H					^{13}C–{^1H}				CHBrNO2 (Fur-NO2)
				CH_2O	CH_2N	$C^{4'}H$, $C^{3'}H$	H_A	H_B	CH_2O	CH_2N	CH_B (CH_A)	$C^{4'}$, $C^{3'}$, $C^{5'}$, $C^{2'}$	
VI	NO_2	88	106–107 (decomp.)	3.57–3.68 m	2.30–2.38 m, 2.69–2.74 m	7.34 d, 6.62 d [^3J 3.7]	6.32 d [J_{AB} 10.9]	4.49 d	66.82	50.34	67.43 (75.13)	111.77, 114.82, 152.69, 149.52	1576 s, 1356 s (1535 m, 1356 s)
VII	Br	83	102–104 (decomp.)	3.50–3.77 m	2.16–2.48 m, 2.52–2.75 m	6.34 d, 6.36 d [^3J 3.3]	6.25 d [J_{AB} 10.9]	4.31 d	66.93	50.27	67.30 (76.24)	112.32, 114.63, 123.23, 147.92	1575 s, 1358 w

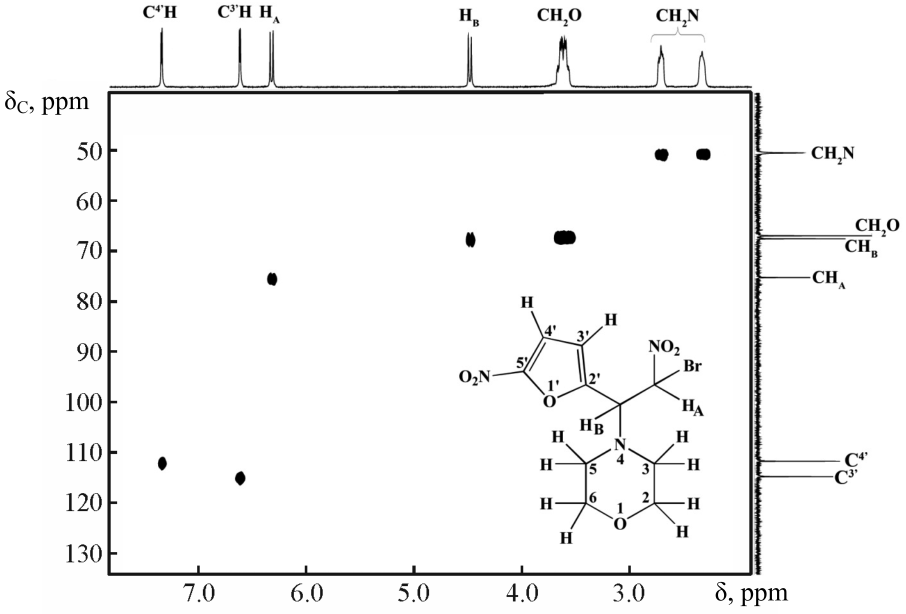


Fig. 2. ^{1}H–^{13}C HMQC spectrum of compound **VI**.

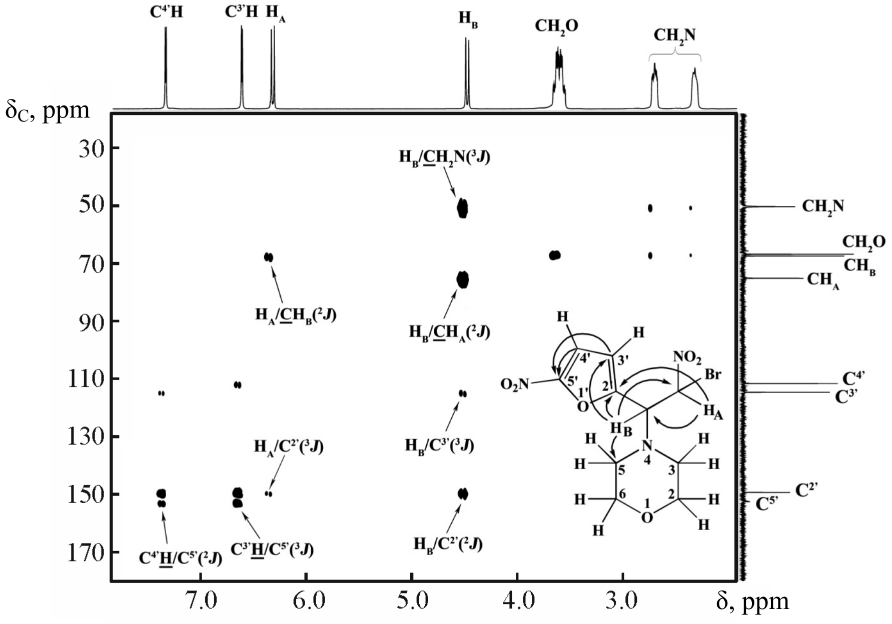


Fig. 3. ^{1}H–^{13}C HMBC spectrum of compound **VI**.

the same position as the same band of the unconjugated nitro group (1356 cm^{-1}).

Thus, we developed a convenient method of synthesis of 2-(2-bromo-2-nitroethenyl)-5-nitrofuran. This nitroalkene and its analog with a 5-bromofuryl substituent were used to obtain amination products with morpholine.

EXPERIMENTAL

Physicochemical measurements were performed at the Center for Collective Use, Department of Chemistry, Herzen State Pedagogical University of Russia.

The ^{1}H, ^{13}C–{^{1}H}, and ^{1}H–^{13}C HMQC and HMBC NMR spectra were obtained on a Jeol ECX400A instrument at 399.78 (^{1}H) and 100.53 MHz (^{13}C) in chloroform-*d* and referenced based on the residual proton signals of the deuterated solvent. The IR spectra were recorded on a Shimadzu IRPrestige-21 FTIR spectrometer in chloroform (*c* = 40 mg/mL). The electronic absorption spectra were measured on a Shimadzu UV2401PC spectrophotometer in ethanol in quartz cells (*l* = 1.01 mm). Elemental analysis was performed on a EuroVector EA3000 (CHN Dual) analyzer.

Nitroethenes **I** and **IV** were prepared by the procedures described in [17] and [18], respectively.

2-(1,2-Dibromo-2-nitroethyl)-5-nitrofuran (II). A solution of 10.67 mL (33.11 g, 207 mmol) of bromine in 20 mL chloroform was added dropwise to a suspension of 7.63 g (41 mmol) of 5-nitro-2-(2-nitroethenyl)furan (**I**) в 85 mL chloroform. The reaction mixture allowed to stand for 24 h at 18–20°C, and the solvent and excess bromine were evaporated in a Petri dish to obtain 14.10 g (99%) of compound **II** as colorless crystals, mp 105–108°C (CCl_4) (mp 110–111°C [19]). IR spectrum, ν, cm^{-1}: 1580, 1354 (C–NO_2), 1541, 1354 (Fur–NO_2), 1507 (Fur). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.65 d (1H, H_B, ^3J 10.7), 6.46 d (1H, H_A, ^3J 10.7), 6.80 d (1H, $C^{3'}H$, ^3J 3.7), 7.31 d (1H, $C^{4'}H$, ^3J 3.7). ^{13}C–{^{1}H} NMR spectrum, δ_C, ppm: 30.09 (CH_B), 75.59 (CH_A), 112.03, 114.36, 149.20, 152.40 ($C^{3'}$, $C^{4'}$, $C^{2'}$, $C^{5'}$). Found, %: C 20.64; H 1.31. $C_6H_4Br_2N_2O_5$. Calculated, %: C 20.95; H 1.17.

2-(2-Bromo-2-nitroethenyl)-5-nitrofuran (III). *a*. A solution of 4.08 g (41.5 mmol) of melted potassium acetate in 55 mL of ethanol was added dropwise to a suspension of 8.93 g (26 mmol) of 2-(1,2-dibromo-2-nitroethyl)-5-nitrofuran (**II**) in 55 mL of ethanol at 18–20°C. The reaction mixture was stirred for 15 min at 18–20°C, poured onto ice chips, and the precipitate that formed was filtered off to obtain 6.62 g (97%) of compound **III** as yellow crystals, mp 89–90°C (ethanol) (mp 88–89°C [9]).

b. A solution of 2.2 mL (6.94 g, 43 mmol) of bromine in 8 mL of chloroform was added to a suspension of 1.6 g (8.7 mmol) of 5-nitro-2-(2-nitroethenyl)furan (**I**) in 15 mL of chloroform. The reaction mixture was stirred for 24 h at 18–20°C, and the solvent and excess bromine were evaporated in a Petri dish to leave a solid residue which, without additional treatment, was mixed with 15 mL of ethanol. A solution of 1.36 g (14 mmol) of melted potassium acetate in 15 mL of ethanol was added to the resulting suspension at 18–20°C. The reaction mixture was allowed to stand for 10 min at 18–20°C, poured onto ice chips, and the precipitate that formed was filtered off to obtain 2.22 g (97%) of compound **III** as yellow crystals, mp 89–90°C (ethanol). Mixed sample with the compound obtained by procedure *a* showed no melting point depression.

5-Bromo-2-(2-bromo-2-nitroethenyl)furan (V). A solution of 3.7 mL (11.55 g, 72 mmol) of bromine in 10 mL of chloroform was added dropwise to a solution of 5.03 g (36 mmol) of 2-(2-nitroethenyl)furan (**IV**) in 20 mL of chloroform at –7 to –5°C. The reaction mixture was stirred for 3.5 h at 18–20°C, and the solvent and excess bromine were evaporated in a Petri dish to leave a light yellow oil which, without additional treatment, was dissolved in 80 mL of ethanol. A solution of 5.67 g (57.8 mmol) of melted potassium acetate in 80 mL of ethanol was added to the resulting solution at 18–20°C. The reaction mixture was allowed to stand for 10 min at 18–20°C, poured onto ice chips, and the precipitate that formed was filtered off to obtain 7.28 g (68%) of compound **V** as dark yellow crystals, mp 90–91°C (hexane) (mp 87–89°C [10]).

4-[2-Bromo-2-nitro-1-(5-nitrofuran-2-yl)ethyl]-morpholine (VI). A solution of 0.16 mL (0.16 g, 1.83 mmol) of morpholine in 13 mL of ethanol was added to a suspension of 0.48 g (1.83 mmol) of compound **III** in 15 mL of ethanol at –10 to –8°C. The reaction mixture was allowed to stand for 1 h at –10 to –6°C. The precipitate was filtered off. Yield 0.31 g (49%), mp 106–107°C (decomp., ethanol).

The mother liquor was poured onto ice chips, and an additional 0.25 g (39%) of compound **VI** was filtered off, mp 106–107°C (decomp., ethanol). Mixed sample with the substance isolated from the reaction solution showed no melting point depression. Total yield 88%. Found, %: C 33.99, 33.82; H 3.43, 3.40; N 11.95, 12.03. $C_{10}H_{12}BrN_3O_6$. Calculated, %: C 34.30; H 3.45; N 12.00.

4-[2-Bromo-1-(5-bromofuran-2-yl)-2-nitroethyl]-morpholine (VII) was prepared in a similar way from 1.41 g (4.75 mmol) of compound **V** and 0.41 mL (0.41 g, 4.75 mmol) of morpholine in 30 mL of ethanol at –8 to –5°C for 1 h. Yield 1.51 g (83%), mp 102–104°C (decomp., ethanol). Found, %: C 31.05, 31.32; H 3.33, 3.31; N 7.13, 7.26. $C_{10}H_{12}Br_2N_2O_4$. Calculated, %: C 31.28; H 3.15; N 7.29.

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