NITROSATION AND BROMINATION OF 6-(2'-FURYL)IMIDAZO[2,1-b]THIAZOLE AND ITS DERIVATIVES

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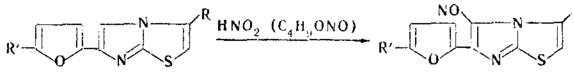
The action of nitrosating agents and bromine on 6-(2'-furyl)imidazo[2,1-b]thiazole and its 3-methyl, 5'-bromo, and 5'-nitro derivatives was studied. The structures of the products were proved by UV, IR, and PMR spectroscopy and thin-layer chromatography.

In a continuation of our study of the electrophilic substitution reactions of furylimidazo heterocycles [1, 2], we have investigated the nitrosation and bromination of 6-(2'-furyl)imidazo[2,1-b]thiazole (Ia) and its 3-methyl (Ib) and 5'-nitro derivatives (IXe and IXf). In analogy with 2-(2'-furyl)imidazo[1,2-*a*]pyridine [1, 2], in Ia one can assume the presence of two centers that are reactive with respect to electrophilic substitution – the 5' position of the furan ring and the 5 position of the imidazothiazole system.

As in the case of 2-(2'-furyl)imidazo[1,2-*a*]pyridine [2], the nitrosation of 6-(2'-furyl)imidazo[2,1-b]thiazole (Ia) and its 3-methyl derivative (Ib) with sodium nitrite in acetic acid or butyl nitrite in benzene led to mononitroso derivatives IIa and IIb, respectively. The structure of IIa is confirmed by the PMR spectrum, in which the signals of α-substituted furan (three multiplets, δ 6.78, 7.65, and 7.99 ppm with an integral intensity ratio of 1 : 1 : 1) are observed. The chemical shifts and spin–spin coupling constants are in good agreement with those previously measured [3, 4]. The two doublets at 7.55 and 8.33 ppm, which form an AB system, can be assigned to the 2-H and 3-H protons of the imidazothiazole system.



I a-d

II a-d

I, II a R = R' = H; b R = CH_3, R' = H; c R = H, R' = Br; d R = CH_3, R' = Br

The direction of nitrosation is also confirmed by the fact that when the 5' position in the furan ring is occupied, as, for example, in Ic and Id, nitrosation nevertheless occurs smoothly to also form mononitroso derivatives IIc and IId, respectively.

New (as compared with the starting compounds) maxima appear in the UV spectra of the nitroso compounds in the long-wave region at 370-380 nm (see Table 1). Absorption bands at ~1510-1530 cm^{-1}, which correspond to the C–N=O group, are observed in the IR spectra of the nitrosation products.

An attempt to nitrosate 5'-nitro derivatives IXe and IXf was unsuccessful; this can be explained by the electron-acceptor effect of the nitro group, which leads to a sharp decrease in the electron density in the 5 position of the imidazothiazole system.

A study of the bromination reaction showed that when 1 mole of bromine was added to a solution of Ia in chloroform and the isolated hydrobromide of bromo derivative IIIe was subsequently neutralized, 5-

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TABLE 1. Thin-Layer Chromatography and UV Spectra of 6-(2'-Furyl)imidazo[2,1-b]thiazole and Its Derivatives

Compound	$R_f \times 100$ in systems[a]		Color of the fluorescence on the chromatograms	UV spectra in alcohol[b]	
	1	2		λ_{max}, nm	lg ε
Ia	44	56	Blue	258	4,17
Ib	53	64	Blue	257	4,42
Ic	54	62	Blue	270, 276, 283	4,46; 4,46; 4,46
Id	60	69	Blue	270, 277, 284	4,38; 4,38; 4,39
IIa	45	60	Green	250, 370	4,19; 4,27
IIb	46	66	Green	245, 385	4,27; 4,32
IIc	40	55	Green	328, 380	4,24; 4,43
IId	63	73	Green	358, 377	4,18; 4,20
Ve	59	68	Blue	270	4,34
VIIe	66	75	Blue	260	4,29
VIIf	69	78	Blue	265	4,29
IXe	40	51	Green	240, 370	3,90; 3,91
IXf	50	61	Green	241, 370	3,99; 3,97
XIIe	54	65	Green	370	4,15
XIIf	58	70	Green	380	3,57

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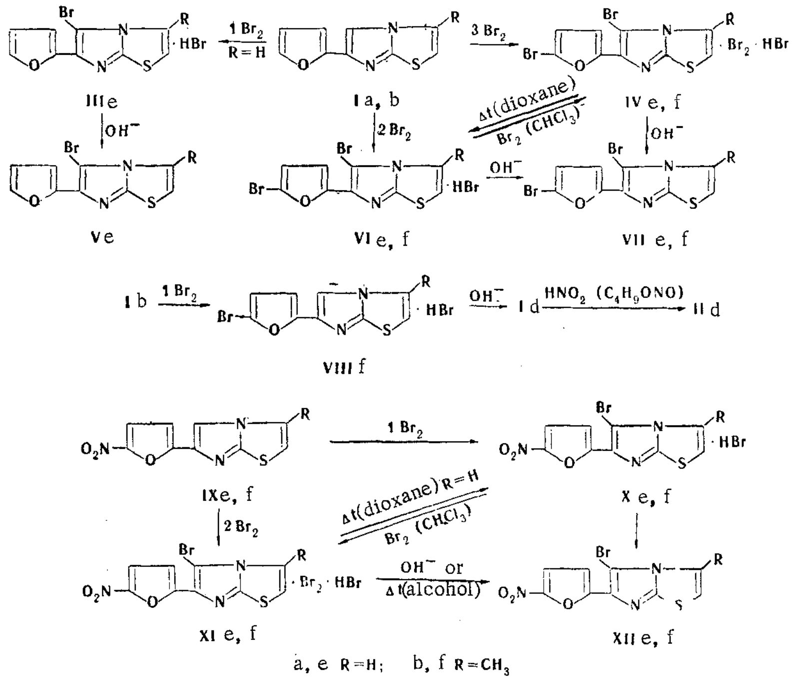
[a] On Silufol UV_{254} plates; systems: 1) benzene–ethyl acetate (1 : 1), 2) chloroform–acetone (5 : 1).

[b] The spectra of IIc and IId in acetone were recorded.

bromo-6-(2'-furyl)imidazo[2,1-b]thiazole (Ve) was formed exclusively, as confirmed by the PMR spectrum presented below and the fact that it was impossible to accomplish nitrosation.



In analogy with 2-(2'-furyl)imidazo[1,2-*a*]pyridine [1], Ia reacts with 2 moles of bromine to give the hydrobromide of dibromo derivative VIe, in which the second bromine atom enters the 5' position of the furan ring. The action of three or more moles of bromine on Ia leads to the perbromide (IVe) of the hydrobromide of the dibromo derivative.

The direction of the bromination of 3-methyl-Ia (Ib) differs substantially from the direction of bromination of Ia. The action of an equimolecular amount of bromine on Ib leads to predominant bromination in the 5' position of the furan ring to give a hydrobromide (VIIIf), which is converted to Id after treatment with aqueous alkali. Traces of dibromo derivative VIIf were also detected chromatographically. The structure of the product of the monobromination of Ib as Id is confirmed by a comparison of it with an authentic sample of Id, obtained from 2-bromoacetyl-5-bromofuran via the method described in [5]. In ad-

TABLE 2. Data from the PMR Spectra of 6-(2'-furyl)imidazo[2,1-b]thiazole and Its Derivatives

Compound	Solvent	Chemical shifts, δ, ppm							J, Hz			
		2-H	3-H	5-H	3'-H	4'-H	5'-H	CH₃	$J_{2,3}$	$J_{3',4'}$	$J_{4',5'}$	$J_{3',5'}$
Ia	Acetone	7,12	7,79	7,87	6,69	6,50	7,51	—	4,4	3,0	1,6	0,7
Ib	Acetone	6,64	—	7,75	6,70	6,48	6,49	—	0,6	3,1	1,5	0,7
	CCl_4	6,24	—	7,34	6,62	6,35	6,26	2,31	—	3,2	1,6	0,6
Ic	Acetone	7,14	7,81	7,91	6,68	6,49	—	—	4,4	3,1	—	—
Id	Acetone	6,72	—	7,79	6,67	6,48	—	—	0,8	3,3	—	—
	CCl_4	6,26	—	7,41	6,27	6,60	—	2,35	—	3,1	—	—
IIa	Acetone	7,55	8,38	—	7,65	6,78	7,99	—	4,4	3,3	1,6	0,6
Ve	Acetone	7,31	7,69	—	6,84	6,56	7,61	—	4,3	3,1	1,6	0,7
VIIe	Acetone	7,30	7,68	—	6,81	6,53	—	—	4,1	3,6	—	—
VIIf	Acetone	6,78	—	—	6,81	6,53	—	—	0	3,6	—	—
	CCl_4	6,30	—	—	6,67	6,28	—	2,66	0,8	3,0	—	—

dition, we made a comparison of the product of nitrosation of Id, obtained by bromination of Ib, with the product of nitrosation of authentic Id; this comparison showed that the nitroso derivatives obtained in both cases were identical and were IId.

As in the case of Ia, bromination of Ib with 2 moles of bromine leads to the hydrobromide VIf the dibromo derivative, while the perbromide (IVf) of the hydrobromide of the dibromo derivative is formed in the presence of more than a twofold excess of bromine.

The PMR spectra of the starting Ia and Ib and their bromination products (see Table 2) were studied to confirm the structures of the bromo derivatives obtained.

In analogy with the PMR spectrum of nitroso compound IIa, three multiplets of the AMX type, which correspond to the protons of the furan ring, are observed in the PMR spectra of the starting Ia and Ib. The certain difference in the chemical shifts as compared with IIa is explained by the effect of the nitroso group. The 2-H and 3-H protons of the imidazothiazole system also form two AB doublets with characteristic $^3J = 4.4$ Hz. The singlet at 7.8-7.9 ppm can be assigned to the single proton of the imidazole ring. A study of the PMR spectra of bromo derivatives Ia and Ib makes it possible to unambiguously establish the site of entry of the bromine. A sharp change in the characteristic absorption of the furan ring is observed for Ic and Id. As a consequence of the introduction of bromine, the remaining two protons form an AB multiplet. The J values (3.1 and 3.3 Hz), which are characteristic for the interaction between the 3'-H and 4'-H protons, make it possible to conclude that the bromine atom enters the 5' position. Similar changes in the absorption of the furan ring are observed in dibromo derivatives VIIe and VIIf, and the signals at 7.87 and 7.34 ppm also vanish, which indicates entry of the bromine atom into the 5 and 5' positions.

Depending on the amount of bromine used in the reaction, the 5-bromo derivatives are formed as the hydrobromides (Xe and Xf) or the perbromides (XIe and XIf) of the hydrobromides in the bromination of 6-(5'-nitro-2'-furyl)imidazo[2,1-b]thiazole (IXe) and its 3-methyl analog (IXf). The perbromides (IVe, IVf, XIe, and XIf) of the hydrobromide are also obtained by trituration of hydrobromides VIe, VIf, Xe, and Xf with bromine in chloroform.

Perbromides IVe, IVf, XIe, and XIf liberate iodine from aqueous potassium iodide solutions; when perbromides IVe, IVf, and XIe are heated briefly in dioxane, a bromine molecule is split out, and hydrobromides VIe, VIf, and Xe are formed. When perbromides IVe, IVf, XIe, and XIf are treated with aqueous alkali solutions, bases VIIe, VIIf, XIIe, and XIIf are formed. The nitrofuryl-substituted hydrobromide perbromides (XIe and XIf) are converted to bases XIIe and XIIf on heating with alcohol, water, and pyridine, or even on prolonged storage in air.

Treatment of hydrobromides VIe, VIf, Xe, and Xf with aqueous alkali solutions gives bases VIIe, VIIf, XIIe, and XIIf. In addition, traces of monobromo derivative Id are noted on the chromatograms during isolation of dibromo derivative VIIf, which again confirms the considerably lower activity of hydrogen in the 5 position of the imidazothiazole system as compared with hydrogen in the 5' position of the furan ring of Ib.

In contrast to the starting Ia and Ib, which give a carmine-red coloration with concentrated sulfuric acid, their monobromo derivatives (with respect to the imidazothiazole or furan rings) (Ve and Id) give a

TABLE 3. Products of the Bromination of 6-(2'-Furyl)imidazo[2,1-b]thiazole and Its Derivatives

Compound	R	R′	R″	Type of compound	mp, °C	Empirical formula	Found, %^{a}				Calc., %				Yield, % (synthetic method)
							C	H	Br	N	C	H	Br	N	
V^{e}	H	Br	H	Base^{b}	150—151^{c,d}	$C_9H_5BrN_2OS$	40,0	1,8	29,9	10,1	40,2	1,9	29,7	10,4	76 (H)
III^{e}				Hydrobromide	220—221	$C_9H_5BrN_2OS \cdot HBr$	30,6	1,7	45,2	7,9	30,9	1,7	45,6	8,0	87 (A)
VII^{e}	H	Br	Br	Base^{e}	163—164^{c,d}	$C_9H_4Br_2N_2OS$	31,1	1,1	46,3	7,9	31,0	1,1	45,9	8,1	83 (H), 70 (I)
VI^{e}				Hydrobromide	222—224	$C_9H_4Br_2N_2OS \cdot HBr$	25,5	1,2	—	6,6	25,2	1,2	—	6,5	96 (C), 75 (D)
IV^{e}				Hydrobromide perbromide	178—180	$C_9H_4Br_2N_2OS \cdot Br_2 \cdot HBr \cdot H_2O$	17,5	1,1	65,3	4,6	17,8	1,2	65,6	4,6	98 (E),, 95 (G)
XII^{e}				Base	240—242^{f}	$C_9H_4BrN_3O_3S$	34,2	1,4	—	13,7	34,4	1,3	—	13,4	95 (H), 65 (I), 95 (J)
X^{e}	H	Br	NO_2	Hydrobromide	200—203	$C_9H_4BrN_3O_3S \cdot HBr \cdot H_2O$	26,4	1,7	39,0	—	26,2	1,7	38,7	—	80 (A), 78 (D)
XI^{e}				Hydrobromide perbromide	170—172	$C_9H_4BrN_3O_3S \cdot Br_2 \cdot HBr \cdot H_2O$	19,8	1,2	59,0	—	20,0	1,3	59,1	—	90 (F), 93 (G)
Id	CH_3	H	Br	Base	108—109^{g}	$C_{10}H_7BrN_2OS$	42,2	2,6	28,0	9,7	42,4	2,5	28,2	9,9	80 (H)
VIII^{f}				Hydrobromide	230—232	$C_{10}H_7BrN_2OS \cdot HBr$	32,7	2,1	—	7,5	33,0	2,2	—	7,7	89 (B)
VII^{f}	CH_3	Br	Br	Base	145—146^{h}	$C_{10}H_6Br_2N_2OS$	32,9	1,6	43,9	7,5	33,2	1,7	44,1	7,7	75 (H), 94 (I)
VI^{f}				Hydrobromide	235—236	$C_{10}H_6Br_2N_2OS \cdot HBr$	27,3	1,9	53,7	6,1	27,1	1,6	54,1	6,3	93 (C), 72 (D)
IV^{f}				Hydrobromide perbromide	151—152	$C_{10}H_6Br_2N_2OS \cdot Br_2 \cdot HBr$	19,7	1,4	65,1	—	19,9	1,2	66,2	—	81 (E), 92 (G)
XII^{f}	CH_3	Br	NO_2	Base	230—232	$C_{10}H_6BrN_3O_3S$	36,7	1,7	—	13,1	36,6	1,8	—	12,8	97 (H), 73 (J)
X^{f}				Hydrobromide	210—212	$C_{10}H_6BrN_3O_3S \cdot HBr$	29,2	1,6	—	10,0	29,4	1,7	—	10,3	85 (A)
XI^{f}				Hydrobromide perbromide	187—188	$C_{10}H_6BrN_3O_3S \cdot Br_2 \cdot HBr$	21,0	1,2	56,7	7,3	21,1	1,2	56,2	7,4	91 (F), 94 (G)

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[a] The results of elementary analyses are presented for the first-indicated methods, while the results of analyses for the remaining methods coincide with the calculated values within the limits of allowable error.

[b] The picrate had mp 189-190°.

[c] From aqueous alcohol.

[d] Vacuum sublimation.

[e] The picrate had mp 163-164°.

[f] From dimethylformamide.

[g] The melting point of authentic Id, obtained via the method in [5], was 109-111° (mp 102-103° [6]).

[h] From alcohol.

violet coloration, dibromo derivative VIIe gives a bright-blue coloration, VIIf gives a blue-green coloration, while nitrofuryl derivatives IXe and IXf and their bromination products have a stable yellow color. All of the nitroso derivatives of the compounds listed above give a dark-red coloration under the same conditions.

A study of the bacteriostatic action in vitro with respect to *Escherichia coli*, *Shigella sonnei*, *Salmonella paratyphi*, *Salmonella typhi*, and *Salmonella typhimurium* demonstrated that monobromo derivatives Ve and Id are about five times more active than the starting Ia and Ib (20 μg/ml), dibromo derivative VIIe is less active than Ve, while nitroso derivative IIa and nitrofurylimidazothiazoles IXe and IXf are active in concentrations of 3-12 μg/ml.

EXPERIMENTAL

The UV spectra were recorded with an automatic UV-2 spectrophotometer designed by the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR. The IR spectra of samples in hexachlorobutadiene (2000-3600 and 1500-1300 cm^{-1}) and in Nujol (800-2000 cm^{-1}) were obtained with a UR-20 spectrometer. The PMR spectra of 5% solutions in acetone and CCl_4 were recorded with a Perkin Elmer R-12A spectrometer (60 MHz) with cyclohexane as the internal standard.

5-Nitroso-6-(2'-furyl)imidazo[2,1-b]thiazole (IIa). A solution of 2.07 g (30 mmole) of sodium nitrite in 10 ml of water was added to a solution of 3.8 g (20 mmole) of Ia in 15 ml of acetic acid at 0-5° in the course of 10 min. After 15 min the reaction mass was diluted with 50 ml of water, and the precipitate was removed by filtration to give 3.2 g (86%) of bright-green crystals with mp 162-163° (from benzene–petroleum ether). Found: C 49.7; H 2.5; N 19.7%. $C_9H_5N_3O_2S$. Calculated: C 49.3; H 2.3; N 19.2%.

3-Methyl-5-nitroso-6-(2'-furyl)imidazo[2,1-b]thiazole (IIb). This compound was similarly obtained in 81% yield from Ib by the action of sodium nitrite. The shiny light-green crystals had mp 172-174° (from benzene–petroleum ether). Found: C 51.7; H 3.2; N 18.0%. $C_{10}H_7N_3O_2S$. Calculated: C 51.5; H 3.0; N 18.0%.

5-Nitroso-6-(5'-bromo-2'-furyl)imidazo[2,1-b]thiazole (IIc). This compound was similarly obtained in 97% yield from Ic by the action of sodium nitrite. The green crystals had mp 250-252° (dec., from benzene–petroleum ether). Found: C 37.2; H 1.6; N 13.8%. $C_9H_4BrN_3O_2S$. Calculated: C 36.3; H 1.4; N 14.1%.

3-Methyl-5-nitroso-6-(5'-bromo-2'-furyl)imidazo[2,1-b]thiazole (IId). A 3.09-g (30 mmole) sample of butyl nitrite was added with stirring to a solution of 5.66 g (20 mmole) of Id in 30 ml of benzene. After 1.5 h the reaction mass was diluted with 100 ml of petroleum ether, and the precipitate was removed by filtration to give 4.94 g (79%) of dark-green crystals with mp > 300° (dec., from benzene–petroleum ether). Found: C 38.5; H 2.0; N 13.3%. $C_{10}H_6BrN_3O_2S$. Calculated: C 38.5; H 1.9; N 13.5%.

Bromination of Imidazothiazoles

Preparation of Hydrobromides. Method A. A solution of 10 mmole of bromine in 10 ml of chloroform was added with stirring in the course of 0.5 h to a solution of 10 mmole of Ia in 15 ml of chloroform, and the mixture was stirred for 1 h. The precipitate was removed by filtration, washed with chloroform, and dried at 80-100°. Nitro derivatives IXe and IXf (10 mmole) were brominated as suspensions in 200 ml of chloroform.

Method B. A solution of 10 mmole of bromine in 10 ml of chloroform was added with stirring in the course of 0.5 h to a solution of 10 mmole of Ib in 15 ml of chloroform, and the mixture was stirred for 1 h. The solvent was removed by distillation, and the residue was washed with chloroform.

Method C. The bromination was carried out as in method A but with the addition of 20 mmole of bromine to Ia or Ib.

Method D. A 10-mmole sample of hydrobromide perbromides IVe, IVf, and XIe was briefly refluxed in 20 ml of dioxane.

Preparation of Hydrobromide Perbromides. Method E. The procedure was the same as in method A, but 30-40 mmole of bromine was added to Ia or Ib.

Method F. The procedure was the same as in method A, but 20 mmole of bromine was added to IXe or IXf.

Method G. The products were obtained from the hydrobromides of bromo-substituted VIe, VIf, Xe, and Xf by trituration with bromine in chloroform.

Preparation of the Bases of Brominated Imidazothiazoles. Method H. The bases were obtained from the hydrobromides by neutralization with aqueous alkali.

Method I. The products were obtained from hydrobromide perbromides IVe, IVf, XIe, and XIf by the action of aqueous alkali solutions.

Method J. The products were obtained from hydrobromide perbromides XIe and XIf by refluxing with alcohol, pyridine, and water (50 ml of solvent per gram of substance).

See Table 3 for data on the bromination products.

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