DIFFERENT SPECIFICITIES IN THE BROMINATION OF 6-(2-FURYL)IMIDAZO[2,1-b]THIAZOLE AND ITS DERIVATIVES WITH 1 MOLE OF BROMINE

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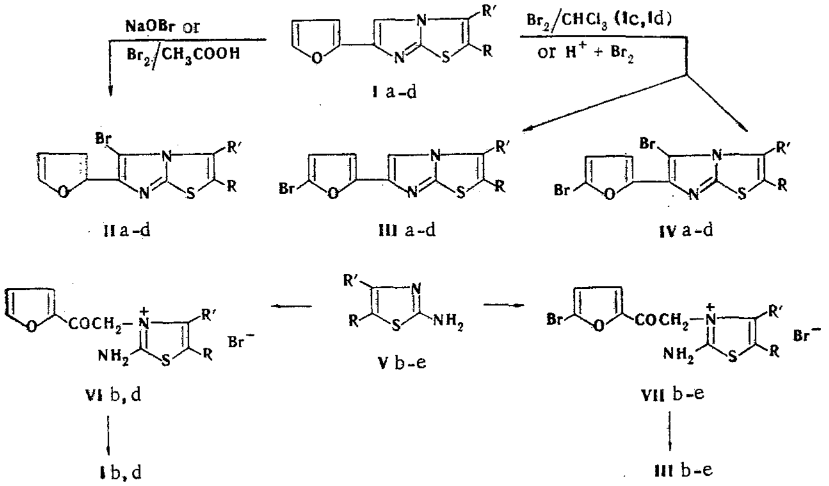
The action of 1 mole of bromine on 6-(2'-furyl)imidazo[2,1-b]thiazole, its 2-methyl-, 3-methyl-, and 2,3-dimethyl-substituted derivatives, and their hydrobromides in chloroform and glacial acetic acid was studied. The bromination of bases containing a methyl group in the 3 position leads primarily to the 5'-derivatives with respect to the furan ring in chloroform, whereas in the remaining cases 5-bromo derivatives with respect to the imidazothiazole system are formed. Compounds of the latter type are formed by the action of bromine in glacial acetic acid or of sodium hypobromite in alkaline media on the bases. The hydrobromides are brominated in both acetic acid and chloroform, regardless of the substituents in the thiazole ring, primarily in the 5' position of the furan ring. The structures of the bromination products were proved by means of alternative syntheses, thin-layer chromatography, and the PMR spectra.

It has been found [1] that 6-(2'-furyl)imidazo[2,1-b]thiazole (Ia) is brominated primarily in the 5 position of the imidazothiazole system by the action of 1 mole of bromine in chloroform, whereas its 3-methyl-substituted derivative (Ic) is brominated primarily in the 5' position of the furan ring.



I-V a R=R'=H; I-VII b R=CH_3, R'=H; c R=H, R'=CH_3; d R=R'=CH_3; e R=Br, R'=H

This difference has served as a premise for a more detailed study of the products of the reaction of Ia and its possible methyl-substituted derivatives with respect to the thiazole ring (Ib-d) with 1 mole of

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TABLE 1. Composition of the Products of Bromination of 6-(2'-Furyl)imidazo-[2,1-b]thiazole and Its Methyl-Substituted Derivatives with 1 Mole of Bromine

Starting compound	Bromination method*	Composition of the products from the PMR spectra (%) for TLC data
Ia	A	IIa+Ia
	B	IIa
	C	IIa (~100%)
	D	IIIa
	E	IIIa
Ib	B	IIb
	C	IIb
	D	IIb (~100%)
	E	IIIb (55%)+IVb (33%)+Ib (12%)
Ic	A	IIc (71,5%)+Ic (28,5%)
	B	IIc (~100%)
	C	IIIc (~100%)
	D	IIIc (~100%)
	E	IIIc (75%)+Ic (25%)
Id	A	IId+Id
	B	IId (84%)+IIId (16%)
	C	IIId (50%)+IVd (50%)
	D	IIId+traces of Id
	E	IIId+traces of Id

* Symbols: A indicates $Br_2/NaOH$, B indicates Br_2/CH_3COOH, C indicates $Br_2/CHCl_3$, D indicates H^+, Br_2/CH_3COOH, and E indicates H^+, $Br_2/CHCl_3$.

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							SSCC, Hz			
		2-H	3-H	5-H	3'-H	4'-H	5'-H	CH_3	$J_{2,3}$	$J_{3',4'}$	$J_{4',5'}$	$J_{3',5'}$
Ia	Acetone	7,12	7,79	7,87	6,69	6,50	7,51	—	4,4	3,0	1,6	0,7
Ib	d_6-Acetone	—	7,56	7,70	6,59	6,43	7,50	2,40 (2-CH_3)	*	3,3	1,7	0,9
Ic	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-CH_3)	—	3,2	1,6	0,6
Id	CCl_4	—	—	7,19	6,56	6,31	7,22	2,22 (2-CH_3, 3-CH_3)	—	3,8	1,7	1,0
IIa	Acetone	7,31	7,69	—	6,84	6,56	7,61	—	4,3	3,1	1,6	0,7
IIb	d_6-Acetone	—	7,41	—	6,75	6,51	7,57	3,54 (2-CH_3)	†	3,3	1,7	0,9
IIc	Acetone	6,80	—	—	6,82	6,52	7,58	—	—	3,4	1,9	0,7
IId	CCl_4	—	—	—	6,68	6,35	7,37	2,26 (2-CH_3), 2,52 (3-CH_3)	—	3,3	1,8	0,8
IIIa	Acetone	7,14	7,81	7,91	6,68	6,49	—	—	4,4	3,1	—	—
IIIb	d_6-Acetone	—	7,50	7,75	6,57	6,44	—	2,40 (2-CH_3)	‡	3,5	—	—
IIIc	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-CH_3)	—	3,1	—	—
IIId	CCl_4	—	—	7,26	6,54	6,25	—	2,23 (2-CH_3, 3-CH_3)	—	3,3	—	—
IVa	Acetone	7,30	7,68	—	6,81	6,53	—	—	4,1	3,6	—	—
IVb	Acetone	—	7,50	—	6,79	6,59	—	2,50 (2-CH_3)	—	3,3	—	—
IVc	CCl_4	6,30	—	—	6,67	6,28	—	2,66 (3-CH_3)	0,8	3,0	—	—
IVd	CCl_4	—	—	—	6,67	6,30	—	2,26 (2-CH_3), 2,51 (3-CH_3)	—	3,2	—	—

* 1.3 (H, CH_3).

† 1.4 (H, CH_3).

‡ 1.5 (H, CH_3).

bromine under various conditions. The results of bromination of bases Ia, Ic, and Id with sodium hypobromite and of bases Ia-d and their hydrobromides in glacial acetic acid and in chloroform are presented in Table 1. The ratios of the individual substances in the bromination products were determined by means of the PMR spectra and thin-layer chromatography (TLC). The parameters of the PMR spectra for the individual compounds are presented in Table 2.

According to the quantum-chemical calculations within the Pariser–Parr–Pople approximation (Fig. 1*), the 5 position of the imidazothiazole system has the highest capacity for electrophilic substitution reactions in base Ia. In fact, this compound is brominated in this position with sodium hypobromite

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* We sincerely thank Professor V. I. Minkin for performing the calculations.

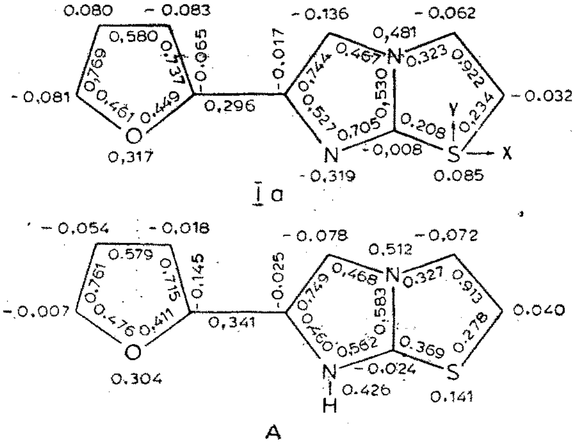


Fig. 1. Molecular diagram of base Ia and its conjugate acid (A).

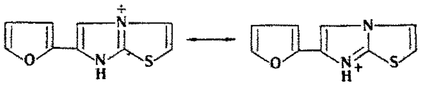
in alkaline media. In addition, quantum-chemical calculations of the dipole moment and the UV spectrum of base Ia (μ 3.20 D for α 314°; λ_{max} 265 nm, f 0.54) are in satisfactory agreement with the experimentally determined values (μ 3.53 D, λ_{max} 261 nm, and f 0.74), calculated by the method in [2]).

It follows from the data in Table 1 that the action of bromine on bases Ia-d in glacial acetic acid leads primarily to 5-substituted derivatives with respect to the imidazothiazole system, i.e., the reaction of acetyl hypobromite or its protonated form (which, according to [3, 4], are brominating agents) is realized with the unprotonated form of Ia-d, as in the case of bromination with sodium hypobromites.

However, 5'-bromo-substituted derivatives with respect to the furan ring (IIIa-d) are primarily formed in the reaction of bromine with solutions or suspensions of hydrobromides of Ia-d in glacial acetic acid or chloroform. The bromination of the hydrobromide of Ib in acetic acid, in which, in addition to the expected IIIb, IIb was detected in greater amounts, constitutes an exception to this rule.

It is apparent from Fig. 1 that the charges calculated for the conjugate acid of Ia (structure A), which was adopted in analogy with other imidazo heterocycles with an angular nitrogen atom, for example, imidazo[1,2-a]pyridine [5], are unsuitable for prediction of the direction of electrophilic substitution.

Quantum-chemical calculations of λ_{max} for A (280 and 330 nm) also do not correspond to the experimentally determined λ_{max} value (265 nm). The results that we obtained in the bromination of the hydrobromides of Ia-d lead to the assumption of predominance of the conjugate acid in structural form B with a positive charge on N_7.



Like 3-methyl-6-(2'-furyl)imidazo[2,1-b]thiazole (Ic) [1], the 2,3-dimethyl analog (Id) reacts with bromine in chloroform to give the 5'-bromo-substituted derivative with respect to the furan ring (IIId) rather than the 5-bromo-substituted derivative with respect to the imidazothiazole system (IId), just as is observed in the case of bromination in acetic acid.

2-Methyl-6-(2'-furyl)imidazo[2,1-b]thiazole (Ib), like 6-(2'-furyl)imidazo[2,1-b]thiazole (Ia), reacts with bromine in chloroform and in acetic acid to give a 5-bromo derivative with respect to the imidazothiazole system (IIb).

Starting Ib and Id were obtained by reaction of 5-methyl- (Vb) and, respectively, 4,5-dimethyl-substituted (Vd) 2-aminothiazole with 2-(bromoacetyl)furan through the thiazolium salts (VIb and VId).

Compounds IIIb, IIId, and IIIe were similarly synthesized alternatively from 5-bromo-2-(bromoacetyl)furan and the appropriate thiazole derivatives (Vb, Vd, and Ve). Compound IIIe, which contains bromine in the thiazole and furan rings, in contrast to dibromo derivatives IVa-d, is only very slightly soluble in organic solvents.

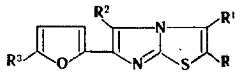
The physicochemical constants and yields of the compounds obtained by the various methods are presented in Table 3.

EXPERIMENTAL

Chromatography was accomplished on Silufol UV-254 plates in benzene–ethyl acetate (3 : 1) (system 1) and acetone–chloroform (1 : 5) (system 2); under normal exposure conditions, IIa-d show up after a few hours as dark spots, whereas all of the imidazothiazoles have a blue-violet color in UV light.

The melting points were determined with a Boetius microheater stage and were not corrected. The UV spectra were recorded with a Specord UV-vis automatic spectrophotometer; the concentration of solutions

TABLE 3



Compound	R	R¹	R²	R³	mp, °C	Empirical formula	Found, %			Calculated, %			$R_f \cdot 100$ in systems*	
							C	H	N	C	H	N	1	2
IIa	H	H	Br	H	150—151	$C_9H_5BrN_2OS$	40,0	1,8	10,1	40,2	1,9	10,4	46	48
IIb	CH_3	H	Br	H	167—169	$C_{10}H_7BrN_2OS$	42,0	2,3	9,5	42,4	2,4	9,9	49	59
IIb·HBr	CH_3	H	Br	H	156—158	$C_{10}H_7BrN_2OS \cdot HBr$	33,0	2,2	7,3	33,0	2,2	7,7	—	—
IIc	H	CH_3	Br	H	108—109	$C_{10}H_7BrN_2OS$	42,6	2,5	10,1	42,4	2,4	9,9	47	50
IIc·HBr	H	CH_3	Br	H	237—238	$C_{10}H_7BrN_2OS \cdot HBr$	33,2	2,2	7,4	33,0	2,2	7,7	—	—
IId	CH_3	CH_3	Br	H	157—159	$C_{11}H_9BrN_2OS$	44,0	2,8	9,1	44,4	3,0	9,4	50	55
IIIa	H	H	H	Br	159—160	$C_9H_5BrN_2OS$	40,1	1,8	10,4	40,2	1,9	10,4	39	40
IIIb	CH_3	H	H	Br	174—176	$C_{10}H_7BrN_2OS$	42,2	2,4	9,6	42,4	2,4	9,9	45	48
IIIc	H	CH_3	H	Br	109—111	$C_{10}H_7BrN_2OS$	42,6	2,3	9,8	42,4	2,5	9,9	48	48
IIId	CH_3	CH_3	H	Br	145—146	$C_{11}H_9BrN_2OS$	43,9	3,1	9,2	44,4	3,0	9,4	46	55
IIIe	Br	H	H	Br	175—178	$C_9H_4Br_2N_2OS$	31,0	1,3	7,6	31,0	1,1	8,0	2	0
IVa	H	H	Br	Br	163—164	$C_9H_4Br_2N_2OS$	31,1	1,1	7,9	31,0	1,1	8,0	54	57
IVb	CH_3	H	Br	Br	170—171	$C_{10}H_6Br_2N_2OS$	33,5	1,9	7,9	33,2	1,7	7,7	61	66
IVb·Br₂·HBr	CH_3	H	Br	Br	205—206	$C_{10}H_6Br_2N_2OS \cdot Br_2 \cdot HBr$	20,2	1,4	4,4	20,0	1,2	4,6	—	—
IVc	H	CH_3	Br	Br	145—146	$C_{10}H_6Br_2N_2OS$	32,9	1,6	7,5	33,2	1,7	7,7	63	67
IVd	CH_3	CH_3	Br	Br	162—164	$C_{11}H_8Br_2N_2OS$	34,9	1,9	7,4	35,1	2,1	7,5	68	79
IVd·Br₂·HBr·H₂O	CH_3	CH_3	Br	Br	202—204	$C_{11}H_8Br_2N_2OS \cdot Br_2 \cdot HBr \cdot H_2O$	20,7	1,5	4,0	21,0	1,7	4,4	—	—

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* The following are the $R_f \cdot 100$ values of the starting compounds in systems 1 and 2: 30 and 34 (Ia), 28 and 41 (Ib) 37 and 40 (Ic), and 34 and 43 (Id).

in methanol or isopropyl alcohol was $25 \cdot 10^{-6}$ M. The PMR spectra were recorded with a Perkin–Elmer R-12A spectrometer (60 MHz) from 5% solutions in acetone, hexadeuteroacetone, or carbon tetrachloride. The internal standard was cyclohexane. The dipole moment of Ia was measured with a Dipol' apparatus in dioxane solution, for which we thank I. S. Yankovskaya.

Bromination of Imidazothiazoles

Method A. Bromination with Sodium Hypobromite. A total of 25 ml of 20% sodium hydroxide was added to a cooled solution of 1.02 ml (20 mmole) of bromine in 50 ml of water, and the resulting solution of sodium hypobromite was poured with stirring in the course of 15-20 min to a suspension of 20 mmole of Ia (or, respectively, Ic and Id) in 75 ml of ice water. The aqueous mixture was stirred for 3 h, after which bromo derivative IIa (or, respectively, IIc or IId) mixed with starting material was removed by filtration.

Method B. Bromination of the Bases with Bromine in Glacial Acetic Acid. A solution of 20 mmole of bromine in 15 ml of glacial acetic acid was added with stirring in the course of 30 min to a solution of 20 mmole of bases Ia-d in 100 ml of glacial acetic acid, after which the mixture was stirred for 1 h, and the hydrobromide of the bromo derivative was precipitated by the addition of ether.

Method C. Bromination of the Bases with Bromine in Chloroform. A solution of 20 mmole of bromine in 20 ml of chloroform was added with stirring in the course of 1.5 h to a solution of 20 mmole of base Ia (or, respectively, Ib-d) in 100 ml of chloroform, after which the mixture was stirred for 2 h. The solvent was removed with a rotary vacuum evaporator to give the hydrobromides of the bromo derivatives. The yields of crude products were 77-88%.

Method D. Bromination of the Hydrobromides of Ia-d with Bromine in Acetic Acid. These experiments were carried out as in method B. The mixture obtained after addition of bromine to the hydrobromide suspension was stirred for 3 h, after which the hydrobromides of the bromo derivatives were removed by filtration. The yields were 53-76%.

Method E. Bromination of the Hydrobromides of Ia-d with Bromine in Chloroform. A solution of 20 mmole of bromine in 20 ml of chloroform was added in the course of an hour to a suspension of 20 mmole of the hydrobromide in 100 ml of chloroform, after which the mixture was stirred for 3 h. The precipitated hydrobromide of the bromo derivative was removed by filtration in the case of the reaction of hydrobromide Ic, whereas the products in the remaining cases were isolated by evaporation of the reaction mixture with a rotary vacuum evaporator.

Bases of Bromo Derivatives IIa-d, IIIa-d, and IVb, d. These compounds were isolated from their hydrobromides by the action of 10% aqueous sodium hydroxide solution, and they were subjected to analysis by means of TLC and the PMR spectra. The products were purified by crystallization from aqueous alcohol.

2-Amino-5-methyl-3-(2'-furoylmethyl)thiazolium Bromide (VIb). A 16.1-ml (0.31 mole) sample of bromine was added dropwise with stirring to a solution of 34.5 g (0.31 mole) of 2-acetylfuran in 68 ml of dioxane and 150 ml of ether. When the color of the mixture had become lighter, it was poured into 200 ml of ether and 300 ml of water, and the mixture was shaken. The ether layer was separated, washed successively with sodium carbonate solution and water, and dried with sodium sulfate. A 28.6-g (0.25 mole) sample of 2-amino-5-methythiazole (Vb) was added to the filtered ether solution of 2-bromoacetylfuran, and the mixture was allowed to stand for 24 h. It was then filtered to give 39.5 g (55%) of VIb with mp 215-217° (from alcohol–ether). Found: C 39.4; H 3.7; N 9.1%. $C_{10}H_{11}BrN_2O_2S$. Calculated: C 39.6; H 3.7; N 9.2%.

2-Amino-4,5-dimethyl-3-(2'-furoylmethyl)thiazolium Bromide (VId). This compound, with mp 230-235° (from alcohol) (mp 228-236° [6]), was similarly obtained in 89% yield.

2-Amino-5-methyl-3-(5'-bromo-2'-furoylmethyl)thiazolium Bromide (VIIb). Equivalent amounts of Vb and 2-bromoacetyl-5-bromofuran were mixed in acetone, and after 24 h the precipitate was removed by filtration to give a product with mp 205-207° (from alcohol–ether) in 74% yield. Found: C 31.3; H 2.6; N 7.2%. $C_{10}H_{10}BrN_2O_2S$. Calculated: C 31.4; H 2.6; N 7.3%.

2-Amino-4,5-dimethyl-3-(5'-bromo-2'-furoylmethyl)thiazolium Bromide (VIId). This compound, with mp 225-227° (from alcohol–ether), was obtained in 73% yield by the method used to prepare VIIb. Found: C 33.6; H 3.0; N 6.9%. $C_{11}H_{12}Br_2N_2O_2S$. Calculated: C 33.4; H 3.1; N 7.1%.

2-Methyl-6-(2'-furyl)imidazo[2,1-b]thiazole (Ib). A 39-g (0.127 mole) sample of bromide VIb was refluxed with 700 ml of water and 50 g of sodium bicarbonate, and after 24 h the precipitate was removed by filtration to give 25.4 g (94%) of a product with mp 114-116° (from aqueous alcohol). Found: C 58.5; H 3.8; N 13.8%. $C_{10}H_8N_2OS$. Calculated: C 58.6; H 3.9; N 13.7%. The hydrobromide of Ib, with mp 220-222° (from alcohol), was obtained by the action of hydrobromic acid on an acetone solution of base Ib. Found: C 41.8; H 3.1; N 9.8%. $C_{10}H_8N_2OS \cdot HBr$. Calculated: C 42.1; H 3.2; N 9.8%.

2,3-Dimethyl-6-(2'-furyl)imidazo[2,1-b]thiazole (Id). This compound, with mp 115-116° (from octane) (in agreement with the value in [6]), was obtained in 89% yield from bromide VId by the method used to prepare Ib. The hydrobromide of Id had mp 261-262° (from alcohol). Found: C 44.0; H 3.7; N 9.2%. $C_{11}H_{10}N_2OS \cdot HBr$. Calculated: C 44.1; H 3.7; N 9.4%.

2-Methyl-6-(5'-bromo-2'-furyl)imidazo[2,1-b]thiazole (IIIb). This compound, with mp 109-111° (from aqueous alcohol), was similarly obtained from VIIb. Found: C 42.6; H 2.4; N 9.7%. $C_{10}H_7BrN_2OS$. Calculated: C 42.4; H 2.5; N 9.9%.

2,3-Dimethyl-6-(5'-bromo-2'-furyl)imidazo[2,1-b]thiazole (IIId). This compound, with mp 146-147° (from aqueous alcohol), was obtained in 92% yield from VIId by the method used to obtain Ib. Found: C 44.1; H 3.1; N 9.2%. $C_{11}H_9BrN_2OS$. Calculated: C 44.4; H 3.0; N 9.4%.

2-Bromo-6-(5'-bromo-2'-furyl)imidazo[2,1-b]thiazole (IIIe). A 2.7-g (15 mmole) sample of amine Ve was added to a solution of 4.02 g (15 mmole) of 2-(bromoacetyl)-5-bromofuran in 100 ml of acetone. After 4 h, precipitated salt VIIe was removed by filtration, washed with ether, and heated with 200 ml of water and 10 g of sodium bicarbonate. Liberated base IIIe was removed by filtration to give 3 g (62%, based on the bromo ketone) of golden crystals with mp 175-178° (from nitromethane).

Hydrobromides of the Perbromides of IVb and IVd. These compounds were obtained by the action of excess bromine on, respectively, Ib and Id, in analogy with the preparation of $IVa \cdot Br_2 \cdot HBr$ [1]. The yellow-green crystals were obtained in 90-92% yield.

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