1-AMINO-4-(5-ARYLOXAZOL-2-YL)-1,3-BUTADIENES: SYNTHESIS AND STUDY OF SPECTRAL AND PHARMACOLOGICAL PROPERTIES

D. A. Maiboroda,[1] E. V. Babaev,[2] and L. V. Goncharenko[2]

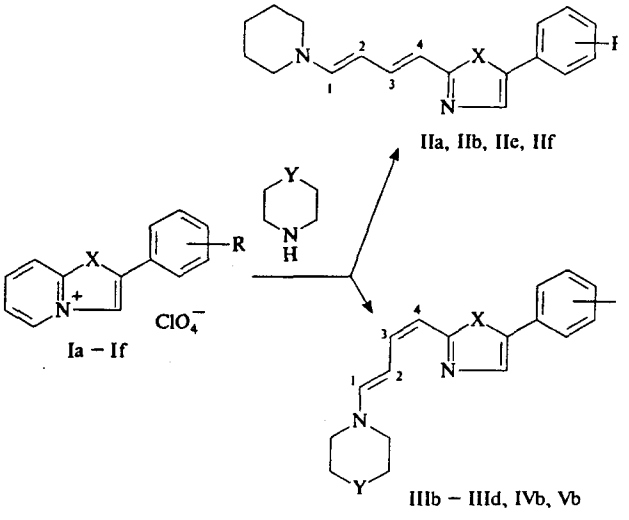
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 32, No. 6, pp. 24 – 28, June, 1998.

Original article submitted July 29, 1997.

Recently we have reported [1] that reaction with piperidine leads to opening of the pyridine ring in the 2-phenyloxazolo[3, 2-a]pyridinium (Ia) cation with the formation of 1(piperid-1-yl)-4-(5-phenyloxazol-2-yl)-1*E*,3*E*-butadiene (IIa). It was also found that the *p*-nitrophenyl-substituted cation (Ib) may be converted, depending on the reaction conditions, into both 1*E*,3*E* (IIb) and 1*E*,3*Z* (IIIb) stereomers [2]. The formation of dienes of the latter type is rather unusual for reactions involving secondary amines. Indeed, a related system of bridged azolopyridinium compounds [3, 4] features only the 1*E*,3*E* isomers; the 1*E*,3*Z* configuration can be obtained only using alkaline amine salts.

The purpose of this work was to study the possibility of synthesizing the 1*E*,3*Z* stereomers of 1-amino-4-(azol-2-yl)butadienes (III – V), using reactions of cations Ib – If with free secondary amines, and to investigate the spectral and pharmacological properties of the synthesized compounds.

Experiments showed that the treatment of salts Ib – If (Table 1) with cyclic secondary amines leads to compounds representing (by the data of mass spectrometry and elemental analysis) 1 : 1 adducts between the initial heterocyclic system and the secondary amines. Their IR spectra (Table 2) exhibit absorption bands in the region of 1630 – 1620 cm^{-1} characteristic of the conjugated dienes, while the ^{13}C NMR spectra (Table 3) are missing the signals of tertiary and quaternary aliphatic carbon atoms.



a: X = O, R = H;
b: X = O, R = 4-NO_2;
c: X = O, R = 3-NO_2;
d: X = S, R = 4-NO_2;
e: X = NMe, R = 4-NO_2;
f: X = O, R = Br.
Y = CH_2 (II, III); CH_2CH_2 (IV); O (V).

This evidence is sufficient to classify the synthesized compounds as products resulting from opening of the six-mem-

[1] Moscow State University, Moscow, Russia.
[2] All-Russia Scientific Center for Safety Testing of Biologically Active Substances, Ministry of Health of the Russian Federation, Staraya Kupavna, Moscow Region, Russia.

TABLE 1. Characteristics of Azolopyridinium Salts Ic – Ie

Compound	M.p., °C	Yield, %	Empirical formula	^1H NMR spectrum in CF_3COOH: δ, ppm and J, Hz								
				(s, 3-H)	(d, 5-H)	(dd, 6-H)	(dd, 7-H)	(d, 8-H)	2-aryl	J_{56}	J_{67}	J_{78}
Ic	201 – 202	68	$C_{13}H_9ClN_2O_7$	8.87	9.00	7.95*	8.53*	8.23	8.88, 8.51, 8.33, 7.90	6.4	7.8	9.0
Id	249 – 250	75	$C_{13}H_9ClN_2O_6S$	8.38	8.66	7.36*	7.69	7.91*	7.90 – 7.82, 7.45 – 7.38	6.6	7.5	9.1
Ie**	235 – 236	70	$C_{14}H_{12}ClN_3O_6$	8.16	8.64	7.56	8.08	7.91	8.51 – 8.45, 7.85 – 7.78	7.0	7.1	9.3

* Overlap with the signal from 2-aryl substituent.
** δ(N–CH_3) = 4.00 ppm.

0091-150X/98/3206-0310$20.00

TABLE 2. Characteristics of 1-Amino-4-(5-arylazol-2-yl)butadienes

Compound	M.p., °C	Yield, %	Empirical formula	Mass spectrum: m/z (I_{rel}, %)	IR spectrum: $\nu_{C=C}$, cm^{-1} (nujol mulls)	UV spectrum ($CHCl_3$): λ_{max}, nm (log ε)
IIa	–*	67	–*	280 (34) M^+, 196 (100)	1628	268 (3.99), 281 (4.05), 382 (4.38)
IIb	179 – 180**	88	–**	325 (62) M^+, 241 (100), 195 (63)	1640, 1625	259 (3.80), 287 (3.80), 350 (4.32), 462 (4.36)
IIIb	160 – 161**	81	–**	325 (63) M^+, 241 (100), 195 (65)	1622	259 (4.46), 287 (4.41), 346 (4.88), 464 (4.88)
IVb	147 – 148	96	$C_{19}H_{21}N_3O_3$	339 (63) M^+, 241 (100), 195 (39)	1625	260 (4.00), 350 (4.35), 475 (4.33)
Vb	193 – 194	62	$C_{17}H_{17}N_3O_4$	327 (40) M^+, 241 (100), 195 (57)	1623	259 (3.94), 335 (4.26), 439 (4.34)
IIIc	120 – 121	68	$C_{18}H_{19}N_3O_3$	325 (47) M^+, 241 (100), 195 (23)	1630	277 (4.23), 400 (4.37)
IIId	128 – 129	81	$C_{18}H_{19}N_3O_2S$	341 (24) M^+, 257 (100), 211 (40)	1625	270 (4.03), 360 (4.15), 483 (4.42)
IIe	162 – 163	47	$C_{19}H_{22}N_4O_2$	338 (17) M^+, 254 (100), 208 (38)	1630	258 (3.96), 352 (4.25), 454 (4.25)
IIf	148 – 150	70	$C_{18}H_{19}BrN_2O$	360/358 (46/40) M^+, 276/274 (94/100), 195 (12)	1628	240 (3.97), 287 (4.15), 391 (4.47)

* [1].
** [2].

bered cycle of the initial cations with the formation of a butadiene system (IIe, IIf, IIIc, IIId, IVb, and Vb).

Previously we have demonstrated that the isomer formed at room temperature has a 1*E*,3*Z* configuration, while the same reaction at a higher temperature leads to the 1*E*,3*E* isomer (configurations of the 1*E*,3*E* and 1*E*,3*Z* isomers IIb and IIIb were assigned on the basis of their NOESY spectra) [2].

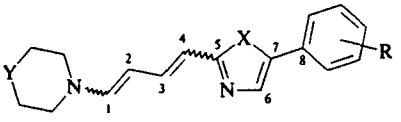
The results of our quantum-chemical MNDO calculations [5] of the heats of formation of the isomeric butadienes IIb (ΔH_f = 49.54 kcal/mole) and IIIb (ΔH_f = 55.15 kcal/mole) showed evidence of a somewhat greater thermodynamic stability of the 1*E*,3*E* stereomer IIb. Therefore, we may expect that reactions proceeding under the kinetically controlled conditions will yield the 1*E*,3*Z* stereomers (similar to butadiene IIIb), whereas the process under more rigid conditions (thermodynamic control) would favor the formation of 1*E*,3*E* isomers.

Indeed, it was established that a short-term treatment of perchlorates Ib – Id with cyclic secondary amines at room temperature leads to the 1*E*,3*Z* stereomers IIIc, IIId, IVb, and Vb. The ^1H NMR spectra of these compounds (Table 4) in the region of signals from butadiene protons are virtually identical to the spectrum of established 1*E*,3*Z* isomer IIIb and differ from the the spectrum of the 1*E*,3*E* isomer IIb (Table 5).

It should be noted that the opening of a pyridine fragment with 1*E*,3*Z* stereomer (IIId) formation under mild conditions was also observed for 2-(4-nitrophenyl)thiazolo[3,2-a]pyridinium (Id) (according to the published data, the products of room-temperature interactions between 3-(4-bromophenyl)thiazolo[3,2-apyridinium and secondary amines were assigned the structure of adducts with bridging 8a-carbon atom [3]).

Replacement of the oxygen atom in compound Ib by the MeN group increases the stability of the system with respect to the cycle opening. Indeed, in contrast to the oxa and thia

TABLE 3. Chemical Shifts (δ, ppm) in the ^{13}C NMR Spectra ($CDCl_3$) of 1-Amino-4-(5-arylazol-2-yl)-1,3-butadienes



Compound	C_1, C_3 (CH)	C_2, C_4 (CH)	C_5 (C)	C_6 (CH)	C_7, C_8, C–R (C)	C_{aryl} (CH)	C_{aryl} (CH_2)
IIa	148.08, 139.35	104.37, 98.01	163.78	123.65	149.19, 129.05, 127.84	124.65, 123.88	49.79, 25.75, 24.58
IIb	148.41, 140.78	103.01, 97.50	165.26	127.38	146.64, 146.02, 134.29	124.39 123.39	49.59, 25.38, 24.07
IIe*	146.88, 137.22	104.04, 98.47	151.55	130.08	136.97, 130.73, 126.33	127.38, 124.13	49.44, 25.21, 24.12
IIf	148.28, 139.75	104.03, 97.90	164.09	124.37	148.17, 128.09, 121.25	132.28, 125.38	49.93, 25.78, 24.58
IIIb	150.14, 140.11	98.98, 96.77	165.15	127.34	146.13, 146.00, 134.32	124.38, 123.37	49.70, 25.36, 24.06
IVb	150.31, 140.22	98.07, 95.92	165.46	127.37	146.08, 145.91, 134.40	124.39, 123.25	54.04, 28.85, 27.50, 27.18
Vb	150.35, 140.10	98.73, 96.82	165.07	127.36	146.22, 146.03, 134.35	124.40, 123.38	66.07, 50.37
IIIc	149.86, 139.25	99.51, 96.73	164.53	129.72	148.67, 146.11, 130.16	128.76, 125.26, 121.55, 117.87	49.72, 25.38, 24.11
IIId	150.33, 141.08	107.80, 96.86	146.03	137.59	138.74, 138.60, 126.96	125.96, 124.36	49.78, 25.36, 24.05

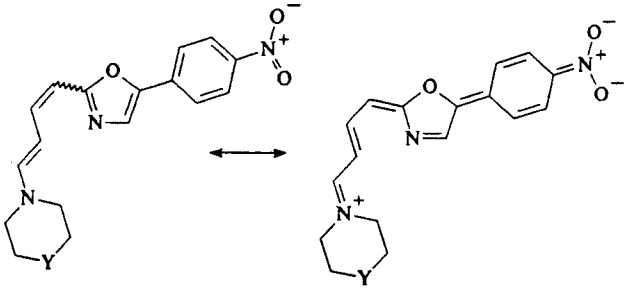
* δ(N – CH_3) = 31.43 ppm.

analogs, 1-methyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridinium perchlorate (Ie) remained unchanged under the action of piperidine at room temperature. Treatment under more rigid conditions (boiling in acetonitrile) led to the formation of the 1*E*,3*E* isomer IIe. Thus, it is practically impossible to obtain a 1*E*,3*Z* stereomer under kinetic control in this system.

Previously we have demonstrated that a reaction of 2-phenyloxazolo[3,2-a]pyridinium perchlorate (Ia) with piperidine at 20°C leads to the formation of only 1*E*,3*E*-butadiene isomer (IIa) [1]. A similar result was obtained upon opening of a salt of 2-(bromophenyl)oxazolo[3,2-apyridinium (If), whereby only the 1*E*,3*E* isomer IIf was isolated from the reaction mixture. The absence of the 1*E*,3*Z* isomer among the products in these systems can be explained by certain features of the treatment of reaction mixtures. In both cases, the primary reaction products have the form of a viscous amorphous mass and require additional chromatographic purification, during which a transformation of the 1*E*,3*Z* butadienes into thermodynamically more stable 1*E*,3*E* isomers is not excluded.

In the crystalline state, the 1*E*,3*Z*-butadienes IIIc, IIId, IVb, and Vb are sufficiently stable with respect to the stereoizomerization process. At the same time, the 1*E*,3*Z* isomers in solution are slowly transformed into the 1*E*,3*E* isomers. For example, the ^{1}H NMR spectrum of the initially pure 1*E*,3*Z* isomer IIIb in $CDCl_3$, measured after a 1-day storage of the solution at room temperature, shows evidence of the appearance of IIb with the IIIb / IIb isomer ratio of approximately 3 : 1. Moreover, even an increase in the time of the reaction mixture stirring from 0.5 – 1 to 3 – 4 h during the synthesis of compound IIIb results, according to the ^{1}H NMR spectrum, in the formation of a significant amount of the 1*E*,3*E* isomer IIb.

Butadienes IIb, IIIb, IIId, IIIe, IVb, and Vb, containing *p*-nitrophenyl substituents, have the form of almost absolutely black fine-crystalline powders, while their solutions in benzene and chloroform have a crimson-red color. The electronic absorption spectra (Table 2) contain two intense (log ε > 4) absorption bands in the visible range (λ_{max} = 330 – 350 and 440 – 480 nm). In contrast, butadiene IIa, IIf, and IIIc have an orange color and their spectra contain a single absorption band in the visible range at 380 – 400 nm. We may suggest that the second, longwave absorption band in the spectra of compounds containing *p*-nitrophenyl groups is due to the intramolecular charge transfer:



This substitution is apparently impossible for the isomeric *m*-nitrophenyl-substituted butadiene IIIc; accordingly, the corresponding absorption band is missing from the UV spectrum of this compound.

An interesting feature is observed in the mass spectra of IIa, IIb, IIe, IIf, IIIb – IIId, IVb, and Vb: each of these contains only three peaks with the relative intensity exceeding

TABLE 4. Chemical Shifts (δ, ppm) in the ^{1}H NMR Spectra ($CDCl_3$) of 1-Amino-4-(5-arylazol-2-yl)-1*E*,3*Z*-butadienes

Compound	(3H, diene)	(1H, diene)	(4H, azolyl)	(4H, 2-aryl)	1-dialkylamino
IIIb*	6.65 – 6.40 m	5.70 – 5.57 m	7.56	8.28 – 8.19, 7.75 – 7.66	3.4 – 3.2 (4H), 1.7 – 1.5 (6H)
IVb	6.78 (d, 1H), 6.60 – 6.30 (m, 2H)	5.52 d	7.49	8.30 – 8.20, 7.76 – 7.66	3.5 – 3.3 (4H), 1.9 – 1.5 (8H)
Vb	6.71 – 6.46 m	5.80 – 5.70 m	7.58	8.30 – 8.15, 7.80 – 7.68	3.8 – 3.6 (4H), 3.4 – 3.2 (4H)
IIIc	6.64 – 6.38 m	5.70 – 5.57 m	7.46	8.41, 8.05, 7.84, 7.51	3.3 – 3.1 (4H), 1.7 – 1.5 (6H)
IIId	6.63 (d, 1H), 6.51 – 6.32 (m, 2H)	6.00 d	8.04	8.28 – 8.15, 7.70 – 7.57	3.3 – 3.1 (4H), 1.7 – 1.5 (6H)

* For ^{1}H NMR spectrum measured in C_6D_6 see [2].

TABLE 5. Chemical Shifts (δ, ppm) and Spin – Spin Coupling Constants (J, Hz) in the ^{1}H NMR Spectra ($CDCl_3$) of 1-Amino-4-(5-arylazol-2-yl)-1*E*,3*E*-butadienes

Compound	(d, 1-H)	(dd, 2-H)	(dd, 3-H)	(d, 4-H)	(s, H_{azolyl})	(H_{aryl})	J_{12}	J_{23}	J_{34}	($H_{dialkylamino}$)
IIa [1]	6.53	5.31	7.21	5.97	7.25	7.64 – 7.59, 7.41 – 7.35	13.1	11.2	15.2	3.2 – 3.0 (4H), 1.7 – 1.5 (6H)
IIb*	6.59	5.34	7.30	5.98	7.49	8.30 – 8.20, 7.78 – 7.68	13.0	11.5	15.5	3.3 – 3.1 (4H), 1.7 – 1.5 (6H)
IIe**	6.48	5.36	7.33	5.98	7.22	8.32 – 8.20, 7.57 – 7.45	13.0	11.4	14.9	3.2 – 3.0 (4H), 1.7 – 1.5 (6H)
IIf	6.54	5.31	7.21	5.92	7.26	7.54 – 7.46	13.0	11.3	15.2	3.2 – 3.0 (4H), 1.7 – 1.5 (6H)

* For ^{1}H NMR spectrum measured in C_6D_6 see [2].
** δ(N–CH_3) = 3.61 ppm.

10% (M^+, 20 – 60%; $[M^+ - NR_2]$, 100%; and $[M^+–NR_2–R]$, 20 – 60%; here, NR_2 is the secondary amine fragment and R is the substituent in the benzene ring). The most intense peak corresponds to fragments formed upon splitting of the secondary amine fragment NR^2 from the initial molecule. We may suggest that these fragments represent a stable aromatic system, 2-arylazolo[3,2-apyridinium cation, which may account for the absence of intense peaks corresponding to further decomposition.

A potential pharmacological activity of compounds IIb, IIIb – IIId, IVb, and Vb was estimated using a computer program PASS 4.2 (Prediction of Activity Spectrum for a Substance) [6], which is capable of predicting some types of activity of a given compound upon analysis of its structural formula. The prognosis is based on the structure – activity relationships established by analysis of the data for more than 10,000 compounds forming the learning sample set. The PASS system either predicts the possible type of pharmacological activity or indicates a possible mechanism of the biological action. The activity prognosis has the form of a probability of the corresponding manifestations or their absence, since the learning sample set contains data on both definitely active and definitely inactive compounds.

As an example, we will consider the prognosis for the spectrum of pharmacological activity of compound III (Table 6). The data are sufficiently representative for the entire series, since the substances have very similar structures.

An analysis of the prognosis suggests the possible antimicrobial activity of compounds of the series studied. The experimental investigation showed that compounds IIb, IIIb – IIId, IVb, and Vb exhibited weak antibacterial activity with respect to both the Gram-positive and Gram-negative species. The minimum bacteriostatic concentration for the compounds studied is 100 – 200 μg / ml. The further search in the series of compounds with analogous structures will probably reveal more active agents.

There is also a sufficiently high probability that the compounds studied have the properties of reversible inhibitors of the monoamine oxidase (MAO). However, this is accompanied with a relatively high probability of carcinogen and mutagen manifestations. This circumstance hinders using substances of the series studied as potential neurotropic agents.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Germany) using samples prepared as nujol mulls. The UV spectra were recorded with a Varian K325 instrument. The ^1H NMR spectra were measured on the Bruker M-400 and AC-200 spectrometers with TMS as the internal standard. The course of the reactions was monitored by TLC on Silufol UV-254 plates. The chromatographic separations were effected with the aid of Silpearl columns. The data of elemental analyses agree with the results of calculations according to the empirical formulas.

2-Aryloxazolo- and thiazolo[3,2-a]pyridinium perchlorates (Ib – Id). To a solution of 0.106 mole of substituted phenacyl bromide in 100 – 150 ml acetonitrile was added 10 ml (12.03 g, 0.106 mole) of 2-chloropyridine and the mixture was boiled for 18 – 22 h. The precipitated crystals were filtered and washed with acetonitrile (2 × (1 – 2) ml) to obtain: (a) **2-chloro-1-(4-nitrophenacyl)pyridinium bromide**; yield, 54%; m.p., 202 – 203°C (decomp.); $C_{13}H_{10}BrClN_2O_3$; (b) **2-chloro-1-(3-nitrophenacyl)pyridinium bromide**; yield, 51%; m.p., 191 – 192°C (decomp.); $C_{13}H_{10}BrClN_2O_3$.

To 2-chloro-1-phenacylpyridinium salt (2 g) dissolved at 60 – 70°C in 20 – 30 ml of the EtOH – H_2O mixture (1 : 1) was added with stirring 20 ml of a saturated aqueous $NaHCO_3$ solution. The mixture was kept at this temperature for 5 – 10 min and allowed to cool. The precipitate was filtered to obtain (a) **1-(4-nitrophenacyl)-2-pyridone**; yield, 80%; m.p., 234 – 235°C (reported m.p., 236 – 238°C [7]); IR spectrum ($\nu_{C=O}$, cm^{-1}): 1711, 1665; $C_{13}H_{10}N_2O_4$; (b) **1-(3-nitrophenacyl)-2-pyridone**; yield, 92%; m.p., 167 – 168°C; IR spectrum ($\nu_{C=O}$, cm^{-1}): 1711, 1667; $C_{13}H_{10}N_2O_4$.

To 2-chloro-1-(4-nitrophenacyl)pyridinium salt (2 g) dissolved at 40 – 50°C in 15 ml of the EtOH – H_2O mixture (1 : 1) was added dropwise with stirring 2 ml of a 20% aqueous Na_2S solution until precipitation ceases (in excess of the latter reagent, the precipitate partly dissolves and the solution acquires a dark-red color). The mixture was kept at this tem-

TABLE 6. Spectrum of Pharmacological Activity Predicted for Compound IIIb by PASS 4.2 Program

Activity type	Probability, %	
	active	inactive
Antimicrobial	78	1
Carcinogenic	75	5
Reversible MAO inhibitor	71	3
Antihelminthic	63	4
Antifungal	60	3
Antihypoxic	52	14
Dopaminergic receptor stimulator	41	9
Antitrichomonacidal	35	5
Mutagenic	40	12
Antituberculous	36	13
Myorelaxant	36	15
MAO inhibitor	30	17
Antiallergic	30	17
H_2-histamine receptor blocking	21	9
Antiviral	34	23
Antiprotozoal	24	13
Reversible acetylcholinesterase inhibitor	27	17
Antispirochetal	23	14
Antiparkinsonic	32	27
Immunomodulator	31	26
Antiandronogenic	24	23

perature for 5 – 10 min and allowed to cool. The precipitate was filtered to obtain **1-(4-nitrophenacyl)-2-thiopyridone**; yield, 74%; m.p., 194 – 195°C; IR spectrum ($\nu_{C=O}$, cm^{-1}): 1719; $C_{13}H_{10}N_2O_3S$.

N-substituted pyridone or thiopyridone (1 g) was carefully dissolved in 2 ml of concentrated H_2SO_4 and the solution was allowed to stand overnight. Then was added 50 – 100 ml of water and the mixture was heated to 60 – 80°C and, if necessary, filtered hot. To the filtrate was added 5 ml of 70% $HClO_4$. The resulting precipitate was recrystallized from the EtOH – H_2O mixture (1 : 1) to obtain perchlorates Ib – Id. Characteristics of salts Ic and Id, perchlorate Ib were described previously [2].

1-Methyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridinium perchlorate (Ie). To 2 g (8.37 mmole) of 2-(4-nitrophenyl)imidazo[1,2-a]pyridine [8] was added 8 ml (84 mmole) of freshly distilled dimethylsulfate and the mixture was heated for 2 – 3 h on a water bath. The resulting homogeneous mixture was cooled and shaken with 50 ml ether and the ether solution was decanted. To the residue was added 100 ml water, and the mixture was heated to 80°C and filtered hot. To the filtrate was added 10 ml of 70% $HClO_4$, and the precipitate was recrystallized from the EtOH – H_2O mixture (1 : 1) to obtain perchlorates Ie (Table 1).

Perchlorate If was obtained as described in [9, 10].

Butadienes IIf, IIIb – IIId, IVb, and Vb (Table 2). To 0.2 g of the corresponding 2-arylazolopyridinium perchlorate was added 1 ml piperidine, hexamethyleneimine, or morpholine and the mixture was stirred for 0.5 – 1 h at room temperature. Then was added 50 – 100 ml water. The precipitate was filtered, washed with water, and dried in air. Compound IIf was additionally purified by chromatography on a short column filled with silica gel and eluted with ether.

Butadienes IIb and IIe (Table 2). To a solution of 0.2 g of the corresponding 2-arylazolopyridinium perchlorate in 5 – 10 ml acetonitrile was added 0.5 ml amine and the mixture was boiled with reflux for 2 – 3 h and cooled. Then was added 50 – 100 ml water. The precipitate was filtered, washed several times with water, and dried in air.

EXPERIMENTAL BIOLOGICAL PART

The bacteriostatic activity of compounds IIb, IIIb – IIId, IVb, and Vb was studied at the Laboratory of Antibacterial Preparations (All-Russia Scientific Center for Safety Testing of Biologically Active Substances) by the method of double serial dilutions in a liquid nutrient medium (meat-infusion broth). The test cultures were Gram-positive *St. aureus* ATCC 6538 and Gram-negative *E. coli* ATCC 25922 species at a concentration of 2.5×10^5 cells / ml.

ACKNOWLEDGMENTS

One of the authors (E. V. B.) gratefully acknowledges the support from the Russian Foundation for Basic Research (project No. 96 – 03 – 32935), the Center for Fundamental Natural Sciences (project No. 95 – 0.9.4 – 222), and the Volkswagen – Stiftung foundation.

REFERENCES

1. E. V. Babaev, K. Yu. Pasichnichenko, and D. A. Maiboroda, *Khim. Geterotsikl. Soedin.*, No. 3, 397 – 402 (1997).
2. E. V. Babaev, A. V. Efimov, D. A. Maiboroda, and K. Jug, *Liebigs Annalen (Eur. J. Org. Chem.)*, No. 1, 193 – 196 (1998).
3. G. Hajos and A. Messmer, *J. Heterocycl. Chem.*, **21**, 809 – 811 (1984).
4. A. Messmer, G. Hajos, and G. Timari, *Tetrahedron*, **48**, 8451 – 8458 (1992).
5. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 – 4907 (1977).
6. D. A. Filimonov and V. V. Poroikov, *Bioactive Compounds Design: Possibilities for Industrial Use*, BIOS Scientific Publishers Ltd., Oxford (1996), pp. 47 – 56.
7. U. M. Teotino, L. Polo-Friz, A. Gandini, and D. D. Bella, *Farmaco Ed. Sci.*, **17**, 988 – 999 (1962); *Chem. Abstr.*, **64**, 9676h (1966).
8. E. S. Hand and W. W. Paudler, *Tetrahedron*, **38**, 49 – 55 (1982).
9. C. K. Bradsher and M. F. Zinn, *J. Heterocycl. Chem.*, **4**, 66 – 70 (1967).
10. E. V. Babaev, A. V. Efimov, and D. A. Maiboroda, *Khim. Geterotsikl. Soedin.*, No. 8, 1104 – 1111 (1995).