Among arenesulfonamides V, the meta-derivative Vb also showed the highest activity. The corresponding para-isomer is much less active.

Among the acylhydrazides of dioxamic acids VI, VII, the arenesulfonyl derivatives VII display the highest activity. The nitro derivative VIIg has equivalent anti-exudative activity to that of mephenamic acid.

It should be noted that, on the whole, the anti-inflammatory activity of the dioxamic acid derivatives is less than that of the corresponding oxamic acid derivatives [1, 2], but among phenylenedioxamic acids, compounds may possibly be found with a high activity.

The acute toxicity of the compounds was determined on white mice, weighing 20-22 g each, with peroral administration of suspension of the compound on Tween-80 by the method of I. V. Sanotskii [6]. The LD_{50} of the compounds studied is greater than 5000 mg/kg, and according to the K. K. Sidorov classification, they can be grouped as being practically nontoxic compounds (the LD_{50} of mephenamic acid is 620 mg/kg).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF MONO- AND TRICYCLIC DERIVATIVES OF 2-AMINO-3-CYANOPYRIDINE

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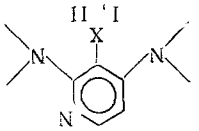
The broad spectrum of biological activity of bradykinin (BK) in the presence of common types of pathology (cardiovascular, inflammatory and other diseases), in which activated kininogenesis is observed, prompts the search for new compounds which restrict the activity of this peptide [2]. One of the promising paths for restricting the activity of BK is the use of its antagonists, i.e., compounds which selectively block its interaction with a receptor in tissues. This suggestion is based on abundant data on the use of antagonists of various biologically active compounds which restrict the activity of the corresponding biochemical systems in the organism (in particular, blocking agents or adrenergic, cholinergic and other systems).

Examination of the literature data shows that in order to have antikinin activity, low-molecular-weight compounds should contain one or several aromatic rings in their struc-



Va: R = H, R′ = CH_2Ph; Vb: NRR′ = $N(CH_2)_5$; Vc: R = R′ = H; Vd: RR′N = $N(CH_2CH_2)_2O$; Ve: R = H, R′ = $PhCH_2CH(CH_3)$; Vf: R = H, R′ = $3,4\text{-}(OMe)_2C_6H_2CH_2CH_2$.

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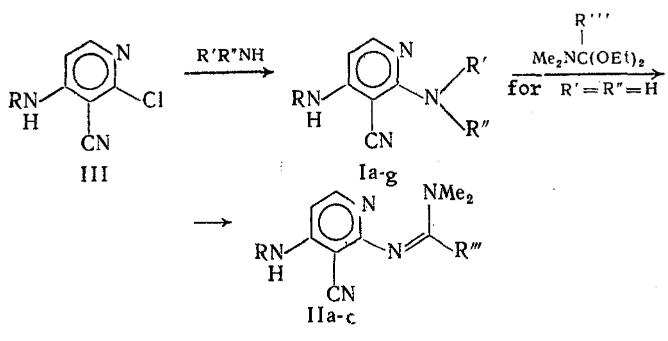
TABLE 1. Physical Constants, Yields, and Analytical Characteristics of Compounds I and II

Compound	mp, °C (solvent)	Yield, % (method)	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N
Ia	185—7 (ethanol)	88	64,13	6,01	18,63	$C_{16}H_{18}N_4O_2$	64,43	6,04	18,79
Ib	172—4 (ethanol)	75	71,55	6,30	22,17	$C_{15}H_{16}N_4$	71,43	6,35	22,22
Ic	166—8 (benzene)	87	66,73	7,31	26,24	$C_{12}H_{16}N_4$	66,67	7,41	25,93
Id	122—4 (heptane)	79	69,11	7,20	15,36	$C_{21}H_{26}N_4O_2$	68,85	7,10	15,30
Ie	99—100 (hexane)	97	75,17	7,27	17,49	$C_{20}H_{24}N_4$	75,00	7,50	17,50
If	105—7 (heptane)	84	74,56	7,27	18,42	$C_{19}H_{22}N_4$	74,51	7,19	18,30
Ig	70—1 (hexane)	54	70,94	8,20	21,00	$C_{20}H_{27}N_5$	71,22	8,01	20,77
IIa	124—6 (heptane)	42 (A) 36 (B)	64,36	6,55	20,05	$C_{19}H_{23}N_5O_2$	64,59	6,52	19,83
IIb	99—101 (heptane)	66	70,27	6,90	22,95	$C_{18}H_{21}N_5$	70,36	6,84	22,80
IIc	112—4 (heptane)	67	70,95	7,17	22,02	$C_{19}H_{23}N_5$	71,03	7,17	21,81

ture, as well as groups capable of forming a hydrogen bond or of undergoing ion—ion interaction with negatively charged domains of the receptor [3, 6].

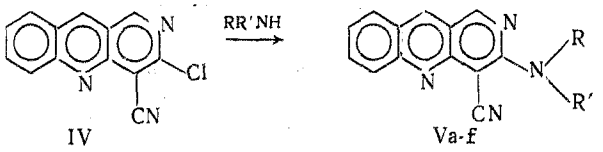
In the present work we have therefore carried out the synthesis of several derivatives of 2,4-diaminipyridine (I, II), in which the presence of basic groups in positions 2 and 4 of the pyridine ring can ensure binding with the corresponding parts of the kinin receptor carrying a full or partial negative charge (N —H...$^-$X interaction or $\geq N^+$—H ...$^-$X interaction).

We have previously described the synthesis of various derivatives of 2-chloro-4-aminopyridine (III) from substituted enaminoamides and dimethylformamide diethyl acetal [1]. In these compounds, the chlorine atom is fairly mobile and can be replaced by an amino group and residues of primary and secondary amines; several diamino derivatives of pyridine (Ia-g) were synthesized in this way. Reaction of compound Ia, having a primary amino group with dimethylformamide and dimethylacetamide diethyl acetals, led to the synthesis of amidines (IIa-c).



Ia: R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$; Ib: R = $PhCH_2CH(CH_3)$; Ic: R = C_6H_{11}; Ia-c R′ = R″ = H; Id R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$; Ie: R = $PhCH_2CH(CH_3)$; If: R = $PhCH_2CH_2$; I e-f R′R″N=$N(CH_2)_5$; Ig: R = $PhCH_2CH_2$, R′ = H, R″ = $CH_2CH_2NEt_2$; IIa: R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$; IIb: R = $PhCH_2CH(CH_3)$; IIa, b: R‴ = H; IIc: R = $PhCH_2CH(CH_3)$, R‴ = CH_3.

It has recently been found that when heated with phosphorus oxychloride, 3-cyano-4-anilino-5-formyl-2-pyridone undergoes cyclization with a simultaneous replacement of the 2-oxo group by chlorine and formation of 3-chloro-4-cyanobenzo[b]-1,6-naphthyridine (IV). This compound reacts very readily with different amines with the formation of the corresponding 3-amino derivatives (Va-f).



IV Va-f

From the above structure of compounds V, it is seen that the compounds have a definite similarity to compounds of type I, since they contain an amino group in the pyridine ring and a quinoline nitrogen atom in the 4-position of this ring, whose protonation may lead to a system capable of reacting with the kinin receptor by the scheme described above. Therefore, this group of compounds was studied as potential antibradykinin compounds. Their anti-inflammatory and analgesic properties were also studied.

EXPERIMENTAL (CHEMICAL)

4-Homoveratrylamino-3-cyano-2-aminopyridine (Ia). A mixture of 1 g of compound III [R = $(MeO)_2C_6H_3CH_2CH_2$] and 15 ml of alcoholic ammonia is heated at 220-240°C in a bomb for 9 h, and then evaporated, the residue is ground with 5 ml of iso-propanol, and 0.8 g of compound Ia is filtered.

Compounds Ib, c are obtained in a similar way.

4-β-Phenylethylamino-3-cyano-2-piperidinopyridine (If). A mixture of 5 g of compound III (R = $PhCH_2CH_2$) and 50 ml of piperidine is heated at 180-185°C in a bomb for 15 h, then evaporated, the residue is ground with water, and 4.7 g of compound If are filtered.

Compounds Id, e, g are obtained in a similar way.

4-Homoveratrylamino-3-cyano-2-[N-(N',N'-dimethylaminomethylene)amino]pyridine (IIa). A 2.5 ml portion of 70% N,N-dimethylformamide acetal is added to a mixture of 1 g of compound Ia and 0.15 g of $AlCl_3$ in 10 ml of dry xylene, and the mixture is boiled for 6 h (every 2 h, 2 ml portions of the acetal are added). The reaction mixture is filtered (from $AlCl_3$), the filtrate is evaporated and the residue is extracted with 250 ml of boiling hexane, cooled, and the precipitate that separates, is filtered. Yield, 0.5 g of compound IIa, M^+ 353.

B. A mixture of 1 g of compound Ia and 2.5 ml of 70% N,N-dimethylformamide acetal in 15 ml of DMFA is heated at 110°C for 5 h (after 3 h, 2 ml of the acetal are added), then evaporated, and the residue is extracted by 250 ml of boiling hexane. The extract is cooled, and the precipitate that separates is filtered. Yield 0.4 g of compound IIa.

Compounds IIb, c are obtained in a similar way, according to method A.

The physical constants, yields and analytical characteristics of compounds I and II are listed in Table 1.

3-N-Benzylamino-4-cyanobenzo[1,6-g]naphthyridine (Va). A mixture of 2 g (8.4 mmoles) of chlorine derivative IV and 3.2 g (30 mmoles) of benzylamine in 40 ml of DMFA is heated at 65°C for 1.5 h, then evaporated to dryness in vacuo, and the residue is ground with water, and filtered to yield 2 g of Va.

Compounds Vb-f are obtained in a similar way.

The physical constants, yields and analytical characteristics of compounds Va-f are listed in Table 2.

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds I, II, V were studied with respect to several factors characterizing the antibradykinin activity.

The influence of the compounds on the spasmogenic effect of BK ($1\cdot10^{-9}$ to $1\cdot10^{-8}$ g/ml) was studied on isolated sections of thin intestines of guinea pigs of both sexes, weighing 250-400 g each. the influence of the compounds on the depressant effect of BK (1-3 μg/kg, intravenously) was studied on urethane-narcotized (1.2 g/kg, intraperitoneally) rats of both sexes, weighing 170-200 g each. The pressure in the principal carotid artery was re-

TABLE 2. Physicochemical Properties of Compounds V Synthesized

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
Va	79	254—6	77,66	4,61	18,20		$C_{20}H_{14}N_4$	77,42	4,52	18,06	
Vb	91	154—7	74,80	5,60	19,46		$C_{18}H_{16}N_4$	75,00	5,55	19,44	
Vc	86	310—5	60,48	3,29	21,89	14,06	$C_{13}H_8N_4 \cdot HCl$	60,82	3,51	21,83	13,84
Vd	88	226—8	70,56	5,08	19,49		$C_{17}H_{14}N_4O$	70,34	4,83	19,31	
Ve	63	189—91	77,85	5,25	16,53		$C_{22}H_{18}N_4$	78,11	5,33	16,57	
Vf	56	188—92	71,87	5,19	14,52		$C_{23}H_{20}N_4O_2$	71,88	5,21	14,58	

Note. Compound Va is crystallized from DMFA, Vb from EtOH, Vc from a 1:1 mixture of DMFA and alcohol, Vd-f from isopropanol; compounds Va, c, e are obtained at a reaction temperature of 65-70°C, compound Vb at room temperature, compounds Vd, f at 50°C.

TABLE 3. Pharmacological Properties of 2,4-Diamino-Substituted Cyanopyridine Derivatives

Compound	LD_{50} for mice (perorally), mg/kg	Inhibition of spasmogenic effect of BK ($1 \cdot 10^{-5}$ g/ml), % with respect to initial value	Influence of depressant effect of BK in rats in a dose of 10 mg/kg intravenously (decrease, % with respect to initial value)	Inhibiting effect in a dose of 1/10 LD_{50} on paw edema in rats, %		Analgetic activity in mice (decrease in number of spasms)
				BK-induced	carrageen-induced	
Ia	1200	63	0	0	37	31
Ib	>1000	52	0	22	16	17
Ic	355	53	0	24	25	40
Id	>1000	95	0	26	0	26
Ie	1000	45	0	16*	0	14
If	>1000	60	0	19	0	16*
Ig	75	76	20—25	36	26	0
IIa	1000	55	0	34	0	11
IIb	250	83	0	47	0	40
IIc	355	53	0	24	25	40
Va	>1000	5*	0	7*	8	0
Vb	890	80	0	16	7*	0
Vc	>1000	67	0	26	17	19
Vd	>1000	52	0	11	20	15*
Ve	>1000	48	0	0	20	9*
Vf	>1000	63	0	17	28	29
Parmidine	3100	95—100	30—40	64	37	60

*Differences from control unreliable.

corded by mercury manometer. The compounds, dissolved in an isotonic solution of sodium chloride (to facilitate the dissolution of water-insoluble compounds, 1-3 drops of Tween-80 were used) were introduced thorugh a catheter into a jugular vein. The influence of the compounds during oral administration in doses of 10% of LD_{50} on paw edema, induced by introducing 0.1 ml of a 0.01% BK solution or 0.1 ml of a 1% solution of carrageenin, was studied on male rats [7]. The volume of the foot was determined plethymometrically, before, and 15, 30, 60, and 120 min after the introduction of BK and 1, 2, 3 h after the introduction of carrageen. The influence of the compounds on the pain reductions (spasms) induced by intraperitoneal administration of acetic acid [4] and the pain sensitivity threshold (PST) upon thermal pain stimulation (the "hot plate" method) [8], were studied on male mice, weighing 18-22 g each. The compounds were administered orally 1 h before the pain stimulation in doses of 10% of LD_{50}.

The acute toxicity was determined on male mice weighing 16-17 g each, with oral administration. The LD_{50} was calculated by the method in [5]. The investigations showed that all the cyanopyridine derivatives tested decrease the spasmogenic effect of BK in experiments on an isolated section of intestinum ileum of guinea pig. In the intensity of action, compounds Id, IIb, and Vb approach that of the specific BK antagonist – parmidine (Table 3). At the same time, even compound IIb, which is most active in experiments on isolated organs, is less active than parmidine by a factor of 2 in its influence on the parmidine-induced edema of rat paws. This effect was even more weakly pronounced in compounds Id, IIa, IIc, Vc.

With the exception of compound Ig, the cyanopyridine derivatives did not exhibit influence on the BK-induced depressant reaction in narcotized mice, thus differing from parmidine, which is a dose of 10 mg/kg decreased this reaction by 30-40%.

The anti-inflammatory and analgesic properties were manifested to a lesser extent in the cyanopyridine derivatives than in parmidine. They are more toxic than parmidine.

The data obtained show that the pyridine derivatives can display antibradykinin properties, whose degree of manifestation may vary substantially, depending on the structure of the substituents. 2,4-Substituted pyridines giving a β-arylethylamino group (Ig) in the 4- position, and various basic groups such as diethylaminoethyl (Ig), piperidinyl (Id-f), unsubstituted amino group, acetamidinyl group (IIb), display the highest activity. Tricyclic compounds V are more active in experiments on isolated organs, while on whole animals, their antibradykinin activity substantially decreases, possibly because of biopharmaceutical features.

Our investigatons showed that it is expedient to carry out further search for BK antagonists in the series of pyridine derivatives with a monocyclic structure, characterized by the presence of basic and NH-containing groupings in meta-position with respect to one another.

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SYNTHESIS OF 2,4-BISHEXAMETHYLENIMINO- AND 2,4-BISHEXAMETHYLENEIMINOMETHYL-1,5-BISARYL-1,5-PENTANEDIONE DIHYDROCHLORIDES AND AN EXAMINATION OF THEIR BIOLOGICAL PROPERTIES

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It has been shown [10, 11] that aminomethyl derivatives of hexanediones possess weak sympatholytic, antitumor, and antibacterial activity. Relatively high levels of conductive anesthesia have been demonstrated in α-aminoketones containing the hexamethylenimine residue as the amine moiety [6].

Continuing these studies, we have now synthesized the dihydrochlorides of 2,4-bishexamethylenimino (I-IV)- and 2,4-bishexamethyleniminomethyl-1,5-bisaryl-1,5-pentanediones (V-VIII), and examined their biological properties.

Reaction of 1,5-bisaryl-2,4-dibromo-1,5-pentanediones (IX-XII) with hexamethylenimine gives 1,5-bisaryl-2,4-bishexamethylenimino-1,5-pentanediones (XIII-XVI). Treatment of the latter with ethereal hydrogen chloride affords the dihydrochlorides (I-IV). Dihydrochlorides (V-VIII) were obtained by the previously-described condensation of diketones (XVII-XX) with paraformaldehyde and hexamethylenimine hydrochloride in dioxane [10].

$(4\text{-}R\ C_6H_4COCHR')_2CH_2$ (V—XX) $\qquad$ $(PhCHOHCH(N(CH_2)_6)_2CH_2$ (XXI)

I = XIII·2HCl: R = H, R′ = $N(CH_2)_6$; II = XIV·2HCl: R = OMe, R′ = $N(CH_2)_6$; III = XV·2HCl: R = OEt, R′ = $N(CH_2)_6$; IV = XVI·2HCl- R = OPr, R′ = $N(CH_2)_6$; V·2HCl: R = H, R′ $CH_2N(CH_2)_6$; VI·2HCl: R = OMe, R′ = $CH_2N(CH_2)_6$; VII·2HCl: R = OEt, R′ = $CH_2N(CH_2)_6$; VIII·2HCl: R = OPr, R′ = $CH_2N(CH_2)_6$; IX: R = H, R′ = Br; X: R = OMe, R′ = Br; XI: R = OEt, R′ = Br; XII: R = OPr, R′ = Br; XVII: R = R′ = H; XVIII: R = OMe, R′ = H; XIX: R = OEt, R′ = H; XX: R = OPr, R′ = H.

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