LLC was inoculated beneath the perirenal fat to female VDG hybrids (weighing 20-23 g) in 2 microfragments weighing 1-2 mg, using a stereomicroscope and microsurgical technique. The compounds were administered i/p on the third, fourth, and fifth days at the MTD, amounting to 1/3-1/2 the daily MTD for lympholeukemia P388. The numbers of mice in the test groups were three in the first test and five in the repeats.

Antitumor activity was assessed by the mean mass of the tumors on the sixth day in the LLC test, or the mean lifespan in the P388 test, expressed as the test/control (t/c) ratio as a percentage. The statistical criteria for activity ($P < 0.05$) (t/c) were 75 and 120% in the LLC and P388 tests respectively. The statistical criterion for toxicity (t/c) in the P388 test was 80%.

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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NEW SUBSTITUTED GUANIDINES AND 2-AMINO-2-IMIDAZOLINES

R. G. Glushkov, L. A. Nikolaeva, L. N. Dronova, O. V. Kozlova, B. A. Medvedev, and M. D. Mashkovskii

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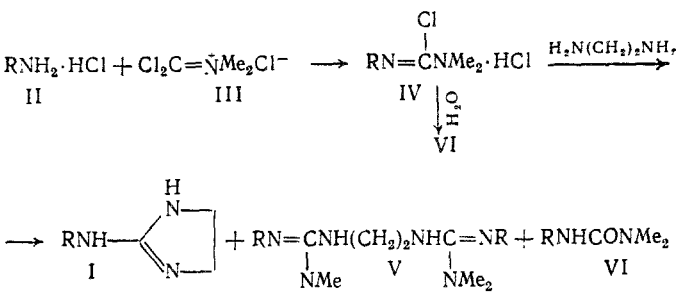
In continuation of our search for hypotensive agents [2] among the structural analogs of clofeline [1], we carried out the synthesis of new derivatives of 2-amino-2-imidazoline (I) and substituted guanidines (V, VII) containing lipophilic groups in their structure, such as p-cyclohexylphenyl and p-isobutylphenyl fragments, and studied their pharmacological activity.

The N-substituted 2-amino-2-imidazolines (Ia-c) were synthesized by a previously developed method [1] consisting in the reaction of the corresponding primary amine hydrochlorides (IIa-c) with N,N-dimethyl-N-dichloromethyleneimmonium chloride (III) [5, 6], followed by the reaction of the hydrochlorides of N-substituted N',N'-dimethyl-C-chloroformamidines (IVa-c) obtained with ethylenediamine in an acetonitrile medium.



I, II, IV—VI: a — R = p-cyclohexylphenyl, b — R = isobutylphenyl; c — R = 2-(p-isobutylphenyl)propyl.

Examination of the reaction of IVa, b with ethylenediamine showed that the process proceeds with the formation of a mixture of products, from which imidazolines Ia, b, bisguanidines

S. Ordzhonikidze All-Union Scientific Research Chemical Pharmaceutical Institute, Moscow.

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Va, b, as well as a small amount of ureas VIa, b could be isolated. It was shown that the ratio of Ia, b and Va, b in the reaction mixture greatly depends on the temperature of the process: at 0-2°C, the yield of I reaches 50%, while at 30-35°C compound V is preferentially formed. The structure of the compounds obtained was confirmed by elemental analysis and mass spectral data. Compounds VIa-c were also obtained by hydrolysis of IVa-c. When IVc was of treated with ethylenediamine, the main reaction product was Ic and no formation of Vc was observed.

Reaction of compounds IVa, c with aqueous ammonia gave the corresponding guanidine hydrochlorides (VIIa, c).

$$\text{IVa, c} \xrightarrow{NH_3} \underset{\underset{NH_2}{|}}{RN{=}CN(Me_2)\cdot HCl}\ \text{VIIa, c}$$

The starting amine IIc was obtained by the reduction of 2-(p-isobutylphenyl)propionitrile with $NaBH_4$ in the presence of Raney nickel in a methanol medium.

The yields and properties of the compounds obtained are given in Table 1.

EXPERIMENTAL (CHEMICAL)

The purity of the products was monitored by TLC on Silufol UV-254 plates (CSSR) with development of the spots in the UV light. The melting points were determined on a PTP-1 apparatus at a rate of heating of 1-3°C/min near the melting point. The electron impact mass spectra were obtained on a "Varian" MAT-112 spectrometer (GFR) with a direct introduction of the sample into the ionic source. The energy of the ionizing electrons was 70 eV, temperature of the ionization chamber 180°C.

2-(p-Cyclohexylphenylamino)-2-imidazoline (Ia). A solution of 3.01 g (0.01 mole) of IVa in 15 ml of acetonitrile is added at 1-2°C to a solution of 2.4 g (0.04 mole) of ethylenediamine in 15 ml of acetonitrile. The mixture is stirred for 4 h at 1-2°C, and then for 15-20 h at 20°C. The reaction mixture is evaporated to dryness, the residue is treated with water, and filtered to yield 1.38 g of Ia. M^+ 243.

Compound Ib is obtained in a similar manner from IVb. The product is isolated by extraction with CH_2Cl_2 from aqueous solution. M^+ 217.

Tosylates of Ia, b are obtained by adding a solution of p-toluenesulfonic acid in ethyl acetate to a solution of Ia, b in ethyl acetate at 20°C.

2-[2-(p-Isobutylphenyl)propylamino]-2-imidazoline Hemisulfate (Ic). A solution of 3.55 g (0.011 mole) of IVc in 20 ml of dry acetonitrile is added gradually at −3 to −1°C to a solution of 2.02 g (0.034 mole) of ethylenediamine in 40 ml of dry acetonitrile. The mixture is stirred for 4 h at the same temperature, and then for 24 h at 20°C. The precipitate is filtered, and the filtrate is evaporated to dryness. The residue is treated with 20 ml of water, and made alkaline with 40% of NaOH. The product is extracted with ethyl acetate, and after the evaporation of the solvent, the hemisulfate is obtained by adding H_2SO_4 to an acetone solution of Ic. An additional amount of the hemisulfate is obtained from the acetone mother liquid. M^+ 259.

2-(p-Isobutylphenyl)propylamine Hydrochloride (IIc). A 10.8 g portion of moist Raney nickel in 20 ml of methanol is added to a solution of 20.3 g (0.108 mole) of 2-(p-isobutylphenyl)propionitrile in 60 ml of methanol, and then at 20-45°C, a solution of 6.77 g of $NaBH_4$ in 22 ml of 8 N NaOH is added with stirring in the course of 1 h. The mixture is held at 45-48°C for 30 min. It is then cooled to 20°C, filtered, the filtrate is evaporated, and 6.5 g of KOH are added to the residue. The mixture is heated at 70-80°C up to the separation of layers in the mixture, which is then extracted by benzene. After the removal of solvent, the residue is dissolved in ethyl acetate and compound IIc is isolated by adding an alcoholic solution of hydrogen chloride up to pH 3.0. An additional amount of the product is isolated from the mother liquor after evaporation of the solvent and addition of a fresh portion of ethyl acetate.

N,N-Dimethyl-N'-(p-cyclohexylphenyl)-C-chloroformamidine Hydrochloride (IVa). A suspension of 5.36 g (0.033 mole) of III in 50 ml of dry CH_2Cl_2 is added at 20°C to a suspension of 6.35 g (0.03 mole) of IIa in 50 ml of dry CH_2Cl_2. The mixture is stirred for 15 min and then boiled for 1.5 h. The solvent is distilled and the residue is treated with 50 ml of ethyl

TABLE 1. Yields and Properties of Compounds Obtained

Compound	Yield, %	mp, °C (solvent for crystallization)	Found, %				Empirical formula	Calc., %			
			C	H	Cl (S)	N		C	H	Cl (S)	N
Ia	56,8	168—70 (ethylacetate)	74,21	8,38	—	17,38	$C_{15}H_{21}N_3$	74,07	8,64	—	17,28
Ia (tosylate)	92,8	184—6 (acetone)	63,79	6,77	(7,93)	10,25	$C_{22}H_{29}N_3O_3S$	63,61	6,99	(7,71)	10,12
Ib *	40,85	108—10	71,73	8,70	—	19,75	$C_{13}H_{19}N_3$	71,89	8,76	—	19,35
Ib (tosylate)	95,0	162—6 (acetone)	61,50	7,10	(8,28)	11,10	$C_{20}H_{27}N_3O_3S$	61,65	7,01	(8,21)	10,78
Ic **	65,9	208—10 (abs. isopropanol)	60,81	8,07	(5,14)	13,37	$C_{16}H_{25}N_3 \cdot 1/2H_2SO_4 \cdot 1/2H_2O$	60,55	8,57	(5,05)	13,23
IIc ***	85,33	188—90	68,46	9,98	15,66	6,30	$C_{13}H_{21}N \cdot HCl$	68,53	9,75	15,57	6,15
Va	78,3	262—2,5 (abs. ethanol)	65,08	8,65	12,13	14,27	$C_{32}H_{48}N_6 \cdot 2HCl$	65,19	8,54	12,02	14,25
Vb	53,85	240—2 (abs. isopropanol)	62,63	8,07	13,08	16,08	$C_{28}H_{44}N_6 \cdot 2HCl$	62,56	8,57	13,22	15,64
VIa	92,7	180—2 (methanol)	73,22	9,08	—	11,41	$C_{15}H_{22}N_2O$	73,13	9,01	—	11,36
VIb	88,3	108,5—10,5 (ether)	71,22	9,13	—	12,59	$C_{13}H_{20}N_2O$	70,91	9,09	—	12,73
VIc	95,0	71—3 (hexane)	73,32	9,85	—	10,49	$C_{16}H_{26}N_2O$	73,25	9,98	—	10,67
VIIa	35,6	167—9 (abs. isopropanol)	63,88	8,28	12,15	14,90	$C_{15}H_{23}N_3 \cdot HCl$	63,93	8,59	12,58	14,90
VIIc	71,0	184—6 (mixture of abs. isopropanol and ethyl acetate, 1:9)	64,65	9,57	11,94	14,20	$C_{16}H_{27}N_3 \cdot HCl$	64,53	9,47	11,91	14,10

*Compound Ib is purified by precipitation from acid solutions by alkali.
**Found, %: H_2O 2.91%, calculated, %: H_2O 2.84.
***Compound IIc is purified by reprecipitation from solutions in absolute isopropanol by ethyl acetate.

acetate to yield 8.46 g (93.6%) of IVa, which is used without purification in the preparation of compounds I, V-VII.

Compound IVb is obtained in a similar manner, yield 70.2%.

N,N-Dimethyl-N'-2-(p-isobutylphenyl)propyl-C-chloroformamidine Hydrochloride (IVc). A solution of 8.92 g (0.039 mole) of IIc in 20 ml of dry CH_2Cl_2 is added at 20°C, with stirring, to a suspension of 8.72 g (0.054 mole) of III in 70 ml of dry CH_2Cl_2. The mixture is boiled for 4 h, and treated with activated carbon. The solvent is distilled off, and the residue is treated with 200 ml of hexane. The mixture is left to stand for 2 days, and 6.88 g (55.4%) of the hygroscopic compound IVc are obtained.

1,2-bis[N,N-Dimethyl-N'-(p-cyclohexylphenyl)guanidyl]ethane Dihydrochloride (Va). A solution of 1.8 ml (0.02 mole) of ethylenediamine in 5 ml of acetonitrile is added gradually, with stirring at 20-25°C to a solution of 3.01 g (0.01 mole) of IVa in 20 ml of acetonitrile. The mixture is stirred for 4 h, and then allowed to stand for 24 h at 20°C. The solvent is distilled off from the mixture, and the residue is treated with 10 ml of water. The mixture is acidified to pH 6.0, heated to dissolution, and then extracted with $CHCl_3$. After the removal of solvent, 2.31 g of Va are obtained. M^+ 589.

Compound Vb is obtained in a similar manner. M^+ 537.

N,N-Dimethyl-N'-(p-cyclophenylphenyl)urea (VIa). A 1.5 g portion (0.005 mole) of IVa is added gradually at 20°C to a solution of 1 g of $NaHCO_3$ in 15 ml of water. The mixture is allowed to stand at this temperature for 2 days, and then the precipitate is filtered and washed with water to yield 1.13 g of VIa.

Compounds VIb, c are obtained in a similar way; VIc is isolated by extraction by ethyl acetate from the aqueous solution.

N,N-Dimethyl-N'-(p-cyclohexylphenyl)guanidine Hydrochloride (VIIa). A 15 ml portion of 25% aqueous ammonia is added at 5°C to a solution of 1.5 g (5 mmoles) of IVa in 10 ml of $CHCl_3$, and the mixture is allowed to stand for 1 h at 20°C. The organic layer is separated, and the aqueous layer is extracted with $CHCl_3$. The combined extract is evaporated, and the residue is treated with 15 ml of ethyl acetate to yield 0.5 g of VIIa.

N,N-Dimethyl-N-[2-(p-isobutylphenyl)propyl]guanidine Hydrochloride (VIIc). Compound IVc (2.4 g, 0.064 mole) is added in portions to 10 ml of 25% aqueous ammonia at 0 ± 2°C. The mixture is stirred at 0 ± 2°C for 30 min, then allowed to stand for 16 h at 20°C, and 40% NaOH is added up to a separation of layers in the mixture. The mixture is extracted with ethyl acetate, the extract is dried over Na_2SO_4, and compound VIIc is isolated by adding an alcoholic solution of hydrogen chloride. An additional amount of VIIc is obtained from the mother liquor after the removal of the solvent and addition of a fresh portion of ethyl acetate.

EXPERIMENTAL (PHARMACOLOGICAL)

The antihypertensive compounds containing a guanidine group partially substituted or included in the ring, may lower the arterial pressure by various mechanisms, in particular, by displaying a sympatholytic action (octadyne, estabal, etc.), or by exciting presynaptic α-adrenoreceptors (clofeline, guafacine, etc.). Compounds Ia-c, Va, VIIc were tested as possible hypotensive agents by methods described previously in [3, 4].

Compounds Ia-c, Va, VIIc, administered intravenously to urethane- and chlorazole-narcotized cats in doses of 2, 5, 10, and 20 mg/kg, comprising approximately 1/4 to 1/2 of LD_{50} (the LD_{50} were found in experiments on mice with intravenous administration, and were equal to 12.5 mg/kg for Va, 42 mg/kg for Ib, 83 mg/kg for Ia, 31 mg/g for Ic, and 12 mg/kg for VIIc), caused a short-term (7-12 min), lowering of the arterial pressure. Compound VIIc intensified the hypertension in narcotized cats, induced by adrenalin (5-7 μg/kg, intravenously), and reduced the increase in pressure, excitation of respiration, and contraction of third eyelid, occurring during intravenous administration of cytisine (15 μg/kg). The contraction of the third eyelid in response to electrical irritation of the postganglion part of the cervical sympathetic nerve did not change under the influence of Ia-c, Va, VIIc, i.e., the compounds did not have a sympatholytic action. At the same time, during irritation of the preganglion part of the nerve, the contraction amplitude of the third eyelid decreased under the influence of VIIc, indicating the ganglion blocking properties of this compound. In nonnarcotized rats with normal arterial pressure, and in rats with spontaneous arterial hypertension (SHR), compound VIIc administered in large doses [20-30 mg/kg, introduced by gavage (intragastic infusion)] decreased the arterial pressure during the first 2 h after administration, and then

the pressure was restored to the initial level. In rats with spontaneous hypertension, the decrease in pressure was more pronounced. The remaining compounds were inactive under these experimental conditions. In experiments on an isolated seminal duct of rats during intramural electrical irritation of adrenergic nervous extremities, compounds Ia-c, Va, VIIc at concentrations of 10^{-6}-10^{-5} g/ml did not change the contraction amplitude of the organ, i.e., did not display sympatholytic action. Under these experimental conditions, octadyne decreased the contraction amplitude of an isolated seminal duct by 50% at a concentration of $5.4 \cdot 10^{-7}$ g/ml.

The above results show that the compounds studied have no sympatholytic or adrenomimetic properties. A short-term hypotensive effect observed in experiments on rats at large doses of VIIc, is caused by gaglioblocking properties, which were previously observed in other compounds with a guanidine structure [2].

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SYNTHESIS AND CARDIOVASCULAR ACTIVITY OF 4-SUBSTITUTED 2-ALKYLTHIO-1,4-DIHYDROPYRIDINES

A. A. Krauze, R. O. Vitolinya, M. R. Romanova, and G. Ya. Dubur

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In continuation of our work on the synthesis and study of the biological activity of 1, 4-dihydropyridine-2(3H)-thiones [3], we have synthesized 4-substituted 2-alkylthio-6-methyl-5-acetyl-3-cyano-1,4-dihydropyridines, their tetrohydro- derivatives, and 4,7-dihydrothieno (2,3-b)pyridines, and studied their cardiovascular activities.

2-Alkylthio-3-cyano-1,4-dihydropyridines (III) were obtained with high yields by the alkylation of 3-cyano-1,4-dihydropyridine-2(3H)-thiolates (I) using alkylhalogenides. To obtain the 2-methylthio-1,4-dihydropyridines IIIa-d, both dimethylsulfate and methyliodide can be used with equal success [2]. The alkylation of the thiolates I by iodoacetamide is exothermic. 2-Alkylthio-1,4-dihydropyridines (III) can also be formed by dehydration of 6-oxy-2-alkylthio-1,4,5,6-tetrahydropyridines (IV) in acidic media. The 6-oxytetrahydropyridines (IV), being all unstable compounds, are produced by the action of alkylhalogenides on 6-oxy-1,4,5,6-tetrahydropyridine-2-thiolates (II) without separating the latter (the reaction mixture contains arylidenacetylacetone, cyanothioacetamide, and piperidine, or 2-cyanoacrylthioamide, acetylacetone, and piperidine). Oxidation of 1,4-dihydropyridines III and 1,4,5,6-tetrahydropyridines IV by sodium nitrite in acetic acid produces the corresponding substituted pyridines (VI). 3-Amino-2-carbamoyl-4,7-dihydrothieno(2,3-b)pyridine (V-g) was obtained by cyclization of 2-carbamoylmethylthio-3-cyano-1,4-dihydropyridine (III-g) using NaOH.

The structures of compounds III-VI were verified spectroscopically. In the IR spectra of III and IV, for substances in the crystalline state the most characteristic features are the absorption bands of the valence oscillations of the cyanogroups at 2182-2204 cm^{-1}, and also the band ν_{CO} of the acetyl group, the latter band being reduced in the dihydropyridines III to 1600-1663 cm^{-1} (relative to its position for the tetrahydropyridines IV: 1686-1704 cm^{-1}), which is characteristic for β-aminovinylketones [4]. In the case of the 1,4-dihydropyridines III ν_{CO} is also noticeably reduced due to the intermolecular hydrogen bonding which is present in the crystalline state. Also, for compound III-d, ν_{CO} is observed at 1600 cm^{-1} in Nujol, but at 1676 cm^{-1} in a dioxane solution. In the IR spectrum of 4,7-dihydrothieno-

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga.

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