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CARDIOVASCULAR ACTIVITY OF NITRO DERIVATIVES OF AZOLO[1,5-a]PYRIMIDINE

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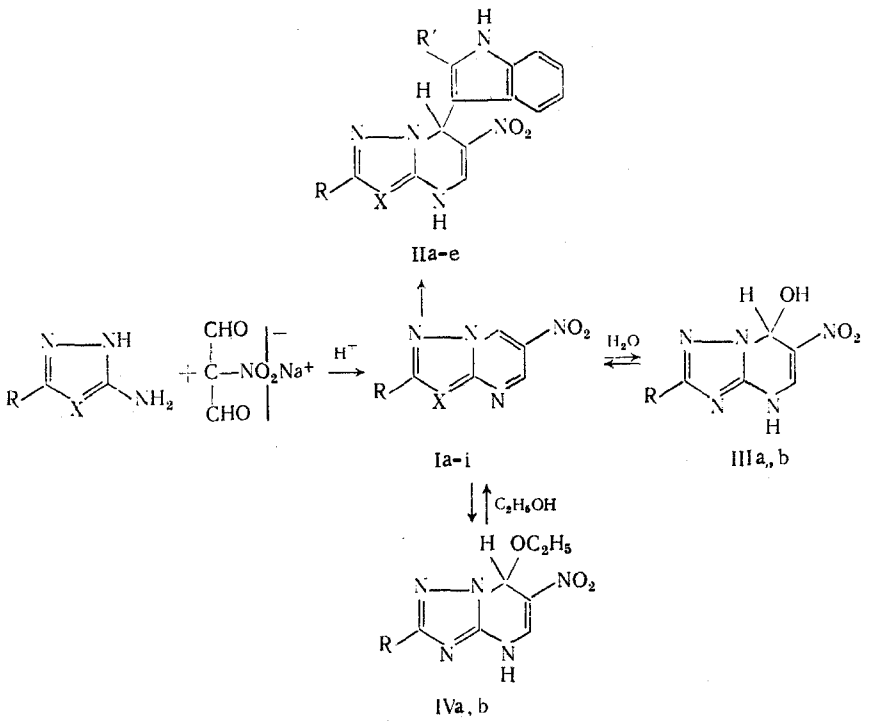
Derivatives of 7-amino-1,2,4-triazolo[1.5-a]pyrimidine exhibit vasodilator and antisclerotic activity [4, 7-9]. 5-Methyl-7-ethylamino-1,2,4-triazolo[1,5-a]pyrimidine, under the name of Trapidil, [5, 6] is used to treat atherosclerosis. The sodium salts of 6-nitro-7-oxo-4,7-dihydroazolo[1,5-a]pyrimidine were noted to have hypotensive activity [1].

As part of the continuing search for new effective cardiovascular preparations, and in order to study their structure-action relationship (the nature and position of substituents in the azole and pyrimidine segments of the molecule), we synthesized a number of nitro derivatives of azolo[1,5-a]pyrimidine (Ia-i, IIa, b, IIIa-e, IVa, b) according to the following pattern:



IIa-e

Ia-i

IIIa, b

IVa, b

Ia: X = N, R = H; Ib: X = N, R = CH_3; Ic: X = $CCOOC_2H_5$, R = H; Id: X = CH, R = H; Ie: X = N, R = SCH_3; If: X = N, R = C_6H_5; Ig: X = N, R = SC_3H_7; Ih: X = N, R = NH_2; Ii: X = N, R = $N(CH_3)_2$; IIa: X = N, R = R′ = H; IIb: X = N, R = H, R′ = CH_3; IIc: X = $CCOOC_2H_5$, R = R′ = H; IId: X = N, R = SCH_3, R′ = H; IIe: X = N, R = SCH_3, R′ = CH_3; IIIa: R = H; IIIb: R = CH_3; IVa: R = H; IVb: R = CH_3.

3-R-(Ic, d) and the 2-R-nitro derivatives (Ia, b, e-i) were produced by method [2] by the condensation of 3-R-5-aminopyrazoles and 3-R-5-amino-1, 2,4-triazoles with nitromalonic dialdehyde. The higher π-deficiency of 6-nitroazolo[1,5-a]pyrimidines I leads to their easy addition of nucleophils with the formation of σ-adducts. Thus, 2-R-6-nitro-7-indolyl-4,7-dihydroazolo-

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TABLE 1. Physicochemical and Spectral Characteristics of 6-Nitroazolo[1,5-a]Pyrimidines

Compound	mp, °C	Found, %		Empirical formula	Calculated, %		Infrared spectra; ν, cm^{-1}	Mass spectrum, M^+	PMR spectra (DMSO-d_6, HMDS), δ ppm	Yield, %
		C	H		C	H				
Ic	150—60	45,5	3,3	$C_9H_8N_4O_4$	45,8	3,4	1355, 1570 (NO_2) 1700 (CO)	—	10,40 (1H, d 45); 9,40 (1H, d, H7); 1,30 (3H, t, HCH_3); 4,36 (2H, q H cH2); 8,75 (1H, s, H2)	82
If	246—8	55,2	3,2	$C_{11}H_7N_5O_2$	54,8	2,9	1350, 1560 (NO_2)	—	7,6—8,4 (5H, mult., Hphe.), 9,65 (1H, d, H7) 10,60 (1H, d H5)	78
Ig	110—2	39,9	3,8	$C_8H_9N_5O_2$	40,2	3,8	1560, 1355 (NO_2)	—	10,46 (1H, d, H5); 9,51 (1H, d, H7); 3,27 (2H, t, H CH_2); 1,8 (2H, sext, H CH_2); 1,2 (3H, t, H CH_3)	76
Ii	202—4	40,1	3,9	$C_7H_8N_6O_2$	40,4	3,8	1550, 1340 (NO_2)	—	3,10 (6H, s, H CH_3); 9,22 (1H, d, H7); 10,05 (1H, d. H5)	79
IIc	265	57,7	4,4	$C_{17}H_{15}N_5O_4$	58,0	4,0	1595, 1313 (NO_2) 3420 (NH) 1710 (CO)	353	1,2 (3H, t, H CH_3); 4,3 (2H, q., H CH_2); 7,09 (1H, s, H7); 7,0—7,6 (5H, mult., H ind); 8,55 (1H, C, H5); 11,3 (1H, c, H NH ind); 12,84 (1H, s, H4)	85
IId	220—1	51,0	3,7	$C_{14}H_{12}N_6O_2S$	51,3	3,7	1590, 1335 (NO_2) 3350 (NH)	328	2,51 (3H, s, H CH_3); 6,92 (1H, s, H7); 6,91—7,50 (5H, mult., H ind); 8,50 (1H, s, H5); 11,3 (1H, s, H HN ind); 12,85 (1H, s, H4)	85
IIe	237	52,6	4,2	$C_{15}H_{14}N_6O_2S$	52,6	4,0	1585, 1340 (NO_2) 3400 (NH)	342	2,50 (6H, s, H CH_3); 6,90 (1H, s, H7); 6,9—7,4 (4H, mult., H ind); 8,51 (1H, s, H5); 11,12 (1H, s, H HN ind); 12,80 (1H, s H4)	95
IIIa	165—7 with decomp.	33,1	2,9	$C_5H_5N_5O_3$	32,8	2,7	1590, 1330 (NO_2) 3250—2800 (OH, NH)	183	6,84 (1H, s, H7); 8,55 (1H, C, H5), 9.77 (1H, s, H2); 12,74 (1H, s, H4)	84
IIIb	165—6 with decomp.	36,5	3,6	$C_6H_7N_5O_3$	36,5	3,5	1585, 1335 (NO_2) 3300—2950 (OH, NH)	197	2,22 (3H, s, H CH_3); 6,80 (1H, s, H7); 8,41 (1H, s, H5); 12,85 (1H, s, H4)	95
IVa	166—8	33,7	3,7	$C_8H_8N_6O_3$	34,0	3,8	1550, 1350 (NO_2) 3340 (NH)	211	—	95
IVb	166—8	42,4	4,9	$C_8H_{11}N_5O_3$	42,6	4,9	1560, 1340 (NO_2) 3300 (NH)	225	—	98

[1,5-a]pyrimidines were produced by the reaction with indoles by method [3]. When compounds I are boiled in water or alcohol, the resultant formations are 2-R-6-nitro-7-hydroxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines (IIIa, b) and 2-R-6-nitro-7-ethoxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines (IVa, b), respectively. In contrast to IIa-e, the addition products IIIa, b and IVa, b are unstable and split off water or alcohol when they are heated up to 150°C, and dissociate into their original components when dissolved in DMSO.

The structure of the synthesized compounds was confirmed by infrared-, UV-, PMR-spectroscopy, and mass spectrometry. The spectral and physicochemical characteristics of the new substances are given in Table 1. Stretching vibration bands of the nitro group were present in the infrared spectra of all the compounds produced. Molecular ion peaks were observed in the mass spectra of adducts II-IV. The position of the proton $C_{(5)}$ and $C_{(7)}$ signals of the pyrimidine fragment in the PMR spectra as well as the UV-spectra of the indole adducts of compounds IIc-e coincide with the corresponding data for the compounds IIa, b that were described previously [3]. This indicates the addition of indole in position $C_{(7)}$ of the nitro derivatives of azolo[1,5-a]pyrimidine Ic-e.

The addition products of water (IIIa, b) and alcohol (IVa, b) dissociate when dissolved in DMSO, and the signals of both adducts IIIa, b, IVa, b, as well as the original pyrimidines Ia, b are present in the PMR spectra of these compounds. The addition of D_2O to the spectrometer cell made it possible to suppress the dissociation so that the resultant recorded PMR spectra corresponded with the structure of adducts IIIa, b, IVa, b (see Table 1).

EXPERIMENTAL (CHEMICAL PART)

The UV-spectra of the alcohol solutions were obtained on a Specord UV-Vis instrument (GDR). The infrared spectra in petroleum jelly were obtained on a UR-20 (GDR) instrument, and the PMR spectra of solutions in DMSO-d_6 were recorded on a Perkin-Elmer R-12B instrument (USA) (60 MHz, HMDS internal standard). Mass spectra were recorded on a Varian MAT-311-A instrument with direct feed of material to the ion source. Exposure conditions: Acceleration voltage — 3 kW, ionization voltage — 70 W, cathode emission current — 300 μA.

6-Nitroazolo[1,5-a]pyrimidines (Ia-i). A 0.01 mole solution of the corresponding aminoazole in 15 ml of 2 N H_2SO_4 was mixed with a solution containing 1.6 g (0.01 mole) of sodium malonate dialdehyde in 15 ml of water. The solutions were then agitated for 30 min at 20-25°C. The resultant precipitate was filtered off, crystallized from alcohol, and dried over P_2O_5 at 150°C. The basic characteristics of compounds Ia, b, d, e, and h correspond to those described in [2]. The characteristics for compounds Ic, f, g, and i are given in Table 1.

6-Nitro-7-indolyl-4,7-dihydroazolo[1,5-a]pyrimidines (IIa-e). A mixture containing 0.01 moles of the corresponding 6-nitroazolo[1,5-a]pyrimidine, 0.01 mole of indole or 2-methylindole was boiled in 30 ml of butyl alcohol for 30 min, then cooled. The precipitate was filtered off, washed in ether and dried over P_2O_5 at 150°C. The basic characteristics of compounds IIa, b correspond to those described in [3]. The characteristics of compounds IIc-e are given in Table 1.

2-R-6-Nitro-7-hydroxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines (IIIa, b). A 0.01 mole solution of 2-R-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine in 50 ml of water was boiled for 30 min and filtered. After cooling, the precipitate IIa, b was separated and dried at 100°C.

2-R-6-Nitro-7-ethoxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines (IVa, b). A solution of 0.01 mole 2-R-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine in 50 ml of alcohol was boiled for 30 min, filtered, and vacuum evaporated to 20 ml. After cooling, the precipitate IVa, b was separated and dried at 100°C.

EXPERIMENTAL (PHARMACOLOGICAL PART)

The effect that 6-nitroazolo[1,5-a]pyrimidines (Ia-i, IIa, b, IIIa-e, and IVa, b) have on arterial pressure was studied in white rats of both sexes weighing 200-250 g, under Nembutal narcosis (50 mg/kg).

Systemic arterial pressure (SAP) was recorded in the common carotid artery in the usual manner. Aqueous solutions of the test substances Ia and IIIa, b were injected into the external jugular vein at doses of 10, 25, and 50 mg/kg. Compounds Ic, f, g, and h were injected intravenously in a DMSO solution (into the external jugular vein) at doses of 10, 25, and 50 mg/kg. Parallel control tests were made by the intravenous injection of DMSO only, at the same volume as was used with the test substances. Compounds Ib, i, IIa-e, and IVa, b, dis-

TABLE 2. Cardiovascular Activity of 6-Nitroazolo[1,5-a]Pyrimidine Derivatives

Compound	Solvent	of administration	Dose, mg/kg	Change in SAP, % of initial pressure			
				after 5 min	after 15 min	after 30 min	after 60 min
Ia	H_2O	IV	10	−15,5	−11,4	−18,9	−35,5
			25	−35,1	−32,4	−29,9	−35,1
			50	−37,5	−35,5	−31,2	−45,8
Ib	$C_2H_5OH + H_2O$	IP	10	−1,3	−12,2	−16,6	−15,9
			25	−13,1	−18,6	−20,3	−11,3
			50	−4,2	−19,6	−28,6	−26,3
Ic	DMSO	IV	10	+21,1	+8,2	+29,5	−10,1
			25	+13,7	+16,5	+34,3	+18,1
			50	−6,3	−13,8	−6,9	−6,3
Id	$C_2H_5OH + H_2O$	IP	10	−1,5	+2,8	−8,3	−11,4
			25	−5,7	−15,4	−19,0	−27,5
			50	−4,6	−15,7	−23,2	−33,3
Ie	$C_2H_5OH + H_2O$	IP	10	+2,7	+2,8	−1,8	−0,1
			25	+2,7	0	−6,1	−1,3
			50	−8,1	−10,5	−14,8	−11,3
If	DMSO	IV	10	+13,5	+7,2	+32,1	+3,7
			25	−31,3	−41,3	Death of animals	
			50	Death after 5-10 min			
Ig	DMSO	IV	10	+11,8	+2,7	+25,4	−27,3
			25	−53,5	−51,8	Death of animals	
			50	Death after 5-10 min			
Ih	DMSO	IV	10	−42,6	+0,4	+17,8	−6,2
			25	−18,5	−28,5	−5,4	Death
			50	+4,8	+5,4	+23,9	+11,5
Ii	$C_2H_5OH + H_2O$	IP	10	−9,6	−17,3	−17,8	−17,9
			25	+7	+0,1	+4,7	−9,1
			50	+2,8	−6,9	−5,7	−27,7
IIa	$C_2H_5OH + H_2O$	IP	10	−2,3	−16,4	−24,9	−28,4
			50	+3,2	−19,4	−26,5	−25,1
			100	−14,1	−32,1	−22,8	−24,4
IIb	$C_2H_5OH + H_2O$	IP	10	−22,4	−40,0	−40,4	−35,8
			50	−9,7	−54,6	−42,2	−37,4
			100	−4,7	−7,7	−18,3	−37,3
IIc	$C_2H_5OH + H_2O$	IP	10	+2,9	+1,8	−5,3	−11,3
			50	−12,4	−13,6	−19,3	−24,2
			100	+2,7	+5,7	−10,6	−10,3
IId	$C_2H_5OH + H_2O$	IP	10	+11,4	−1,1	−26	−5,9
			50	+4,4	+4,9	−6,4	−12,1
			100	−11,3	−25,4	−26,2	−31,9
IIe	$C_2H_5OH + H_2O$	IP	10	+5,6	−5,2	−15,2	−20,1
			50	+5,6	−3,4	−2	−7,6
			100	+7	+0,3	−5,4	−10,9
IIIa	H_2O	IV	10	−12,0	−12,0	−12,0	−12,0
			25	−41,8	−39,2	−31;1	−32,4
			50	Death after 15 min			
IIIb	H_2O	IV	10	−10,2	−7,2	−5,8	−13
			25	−10,6	−13,4	−22,6	−38,6
			50	−60,4	−47,9	−47,9	−37,5
IVa	$C_2H_5OH + H_2O$	IP	10	−3,7	−5,4	−1	0
			25	−6,8	−4,8	−16,7	−15,1
			50	0	−9,5	−12,5	−18,9
IVb	$C_2H_5OH + H_2O$	IP	10	−10,5	−7,7	−7,3	−10,9
			25	−4,3	−8,5	−13	−17,2
			50	−1,4	−4,2	−6,7	−19

Note. Plus − increase, minus − decrease in SAP, IV − intravenously, IP − intraperitoneally.

solved in alcohol, were administered intraperitoneally in water-alcohol solutions. Parallel controls consisted of a water-alcohol solution only injected intraperitoneally in the same volume as in the test substance samples.

RESULTS AND DISCUSSION

Data on the effect that the examined substances have on arterial pressure are given in Table 2. As the test results indicate, the most active compounds were Ia, b, which at a dose of 10 mg/kg reduced the SAP by 11-20% and which exhibited a greater hypotensive effect as the dosage was increased. At a dose of 50 mg/kg the substances reduced the SAP by 26-40% (see Table 2).

Compounds IIa, b caused a 20-35% drop in SAP and their effect was enhanced by increased dosage. These compounds were administered intraperitoneally in water-alcohol solutions because of their pool solubility in water. In view of the fact that water-alcohol solutions alone re-

duced the SAP by 7-23%, the hypotensive activity of compounds IIa, b should be evaluated with considerable caution. The SAP was not significantly affected by the remaining 14 substances. None of those substances' hypotensive effect was enhanced by increased dosage.

Thus, our study of the pharmacological properties of 6-nitroazolo[1,5-a]pyrimidines has demonstrated that all the examined compounds are capable of influencing the cardiovascular system. In analyzing the results obtained in the animal experiments, certain characteristic changes in the biological activity of 6-nitroazolo[1,5-a]pyrimidines were found to be related to their structure.

One can see from Table 2 that the introduction of a methyl group in position 2 of the azole part of compound Ia (the most active of all) results in a 15-25% reduction in hypotensive activity (compound Ib).

The presence of such groups as SCH_3, $N(CH_3)_2$, and NH_2 (Ie, h, i) results in a twofold effect, i.e., first a reduction, then an increase in SAP, or vice versa. If the residues SC_3H_7 and Ph are introduced in position 2 of the azole part of compounds If, g, they exhibit a pressor action.

It should be noted that the hypotensive effect of these substances increases at an average of 5-10% when they are changed to indolyl-substituted azolo[1,5-a]pyrimidines (Ic → IIc, Ia → IIb, Ie → IId, Ie → IIe). Moreover, the introduction of a methyl group in the indole fragment (IIb, e) renders an even greater hypotensive effect than is exhibited by compounds that have an unsubstituted indole in position 7 (IIa, d).

Thus, in none of the examined cases, do the 6-nitroazolo[1,5-a]pyrimidines exhibit as high a hypotensive effect as the preparations that are presently used in therapeutic practice (Apressin, Klofelin, and others). Nevertheless, our analysis of the biological activity of the substances obtained demonstrates that the hypotensive action of 6-nitroazolo[1,5-a]pyrimidines can be enhanced by selective structural changes.

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