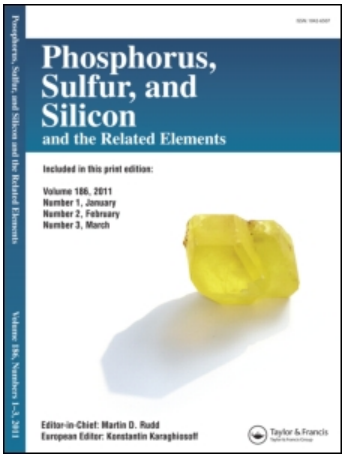

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SYNTHESIS OF NEW 5-SUBSTITUTED 1,2,4-TRIAZOLE-3-THIONE DERIVATIVES

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SYNTHESIS OF NEW 5-SUBSTITUTED 1,2,4-TRIAZOLE-3-THIONE DERIVATIVES

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In the present paper we describe the preparation of series of new derivatives of 1,2,4-triazole-3-thiol. As starting materials methyl 3-acyldithiocarbazates were used, which on reaction with amines gave the corresponding 4,5-disubstituted 1,2,4-triazole-3-thiol derivatives (**3**). Into the 4-position of the 1,2,4-triazole-3-thiol system a β-hydroxyethyl substituent was introduced (compounds **4**). These compounds were alkylated with methyl iodide to from **6**, with N-substituted amides of chloroacetic acid (products **7** and **8**), and aminomethylated with formation of Mannich bases (**10**). Some of the thiols **4** were desulfurized to **9**. The new compounds were tested for their circulatory activity, but found not pharmacologically active.

Keywords: 1,2,4-triazole-3-thiones; alkylation; Mannich bases; desulfurization

INTRODUCTION

In continuation of our previous studies we report in this paper on the synthesis of new compounds with potential influence on the circulatory system. Since many 1,2,4-triazole-3-thiols derivatives were described in the chemical literature as biologically active[1,2], it seemed to be interesting to obtain new 4,5-disubstituted derivatives of this heterocyclic system and determine their circulatory activity.

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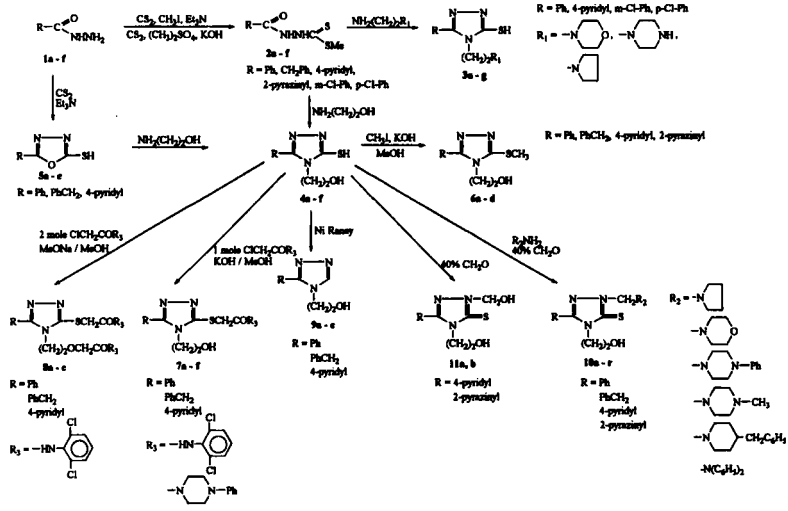
RESULTS AND DISCUSSION

The starting materials **2** for the target compounds were prepared from acid hydrazides **1** by addition of carbon disulfide and followed by methylation with methyl iodide (**2a** – **c**) or dimethylsulphate (**2a** – **f**)[3]. The methyl dithiocarbazates **2a, c, e, f** were caused to react with 2-morpholino-, 2-piperazino- and 2-pyrrolidinoethylamine to afford the 4-substituted 1,2,4-triazole-3-thiol derivatives **3**. These reactions proceeded with difficulty and the expected products formed with low yields. However, the best yields of **3** were found when **2** was refluxed with excess of amine.

As the β-hydroxyethyl moiety is present in mamy compounds with high circulatory activity, we introduced it to the triazole system and synthesized compound **4** by reaction of esters **2** with excess of β-ethanoloamine (Scheme).



SCHEME

Some of the compounds **4** were obtained by another method. The corresponding acid hydrazides **1** treated with carbon disulphide in the presence of triethylamine gave oxadiazolinethiones **5**[3], and the latter compounds were converted to derivatives **4a** – **c** when refluxed whith ethanoloamine.

The reaction yields were not high, since the aminooxadiazole derivatives formed as by products.

The derivatives **4a – c** obtained by these two methods possessed identical melting points, IR and NMR spectra.

Compounds **4** (**a – c, f**) were earlier obtained by Malbec[4] in the reaction of the corresponding thiosemicarbazide esters with ethanoloamine. Compounds **4d – e** were not described before and their characteristic data are given in the Table I.

Afterwards the 5-substituted 4-(2-hydroxyethylo)-1,2,4-triazole-3-thiols **4a – d** were alkylated with methyl iodide to give the S-methyl derivatives **6a – d**, and treatment with N-substituted chloroacetic acid amides yielded **7**[4].

When equimolar quantities of substrates were used and the reaction of derivatives **4** (**a – c**) was carried out in methanolic solution of potassium hydroxide, the S-substituted derivatives **7a – f** were obtained. Whereas in the presence of sodium ethanolate and excess of amide, S,N-disubstituted derivatives **8a – c** were formed.

Desulfurization of the 5-substituted-4-(2-hydroxyethyl)-1,2,4-triazole-3-thiols **4a – c** was carried out by reacting the thiols with Raney – nickel at boiling temperature[5] to afford 4,5-disubstituted-1,2,4-triazole **9a – c**.

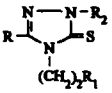
Aminomethylation of compounds **4a – d** led to the corresponding Mannich bases **10**, while reaction with formalin gave 2-hydroxymethyl-4-(2-hydroxyethyl)-1,2,4-triazole-3-thiols **11a – b**.

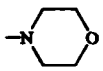
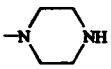
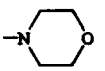
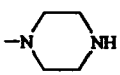
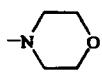
The compounds **6a-c; 7a-d, f; 8c; 9a, c; 10a, c, j, k, m, o; 11c** did not show any measurable pressor or antipressor activity in rats *in vitro*.

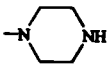
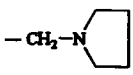
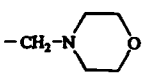
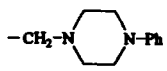
EXPERIMENTAL

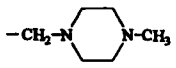
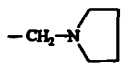
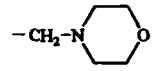
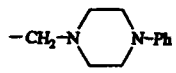
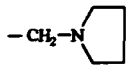
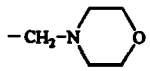
Chemistry

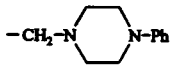
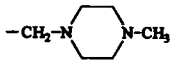
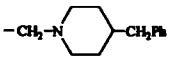
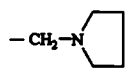
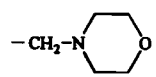
Melting points of obtained compounds were determined on a Boetius apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Tesla-Brno 80 MHz spectrometer. Chemical schifts are given in ppm (δ) relative to tetramethylsilane and as solvents were used DMSO-d_6, TFA and $CDCl_3$. The IR spectra were obtained with a Specord TL 80. The ν_{max} are given in cm^{-1}; all compounds were examined as potassium bromide pellets.

TABLE I Physical preperties of 

R	*R_1*	*R_2*	*M.p. °C (solvent)*	*Yield (%)*	*^1H NMR 80 MHz δ (ppm)*
h		H	182 – 185 methanol + H_2O	40	2,45(m, H, morphol.); 2,7 (m, 4H, morphol.); 3,4- 3 4H, CH_2CH_2); 4,15(m, NH); 7,85–8,2 (m, 5H arom
		H	222 – 227 methanol	35	2,3–2,8(m, 8H, piperaz.); 3,1–3,47(m, NH); 4,1–4,5 4H, CH_2CH_2); 7,72(m, 5H arom.)
-pyridyl		H	195 – 200 ethanol + H_2O	45	2,3(m, 4H, morphol.); 2,65 (m, 4H morphol.); 3,3–3 4H, CH_2CH_2); 4,3–4,55(m, NH); 8 i 8,9 (d, 4H pyr
-pyridyl		H	85 – 100 methanol + H_2O	45	2,4(m, 4H piperaz.); 2,7 (m, 4H piperaz.); 4,45(2H, 2×NH); 5,7 (m, 4H CH_2CH_2); 8 i 8,9(d, 5H pyrid.)
-Cl-Ph		H	150 – 153 water	50	2,5(m, 4H morphol.); 2,9 (m, 4H morphol.); 3,5- 3,5 4H, CH_2CH_2); 7,4–7,8(m, 4H arom.)

R	*R_1*	*R_2*	*M.p. °C (solvent)*	*Yield (%)*	*^1H NMR 80 MHz δ (ppm)*
-Cl-Ph		H	123 – 133 methanol + H_2O	45	1,05–1,7(m, 8H piperaz.); 3,3–3,8(m, CH_2CH_2); 7,(7,8(m, 4H arom.)
-Cl-Ph		H	72 – 76 water	45	1,7(m, 4H pyrrol.); 2,5 (m, 4H pyrrol.); 3,5(t, CH_2): 7,75(m, 4H arom.)
pyrazinyl	OH	H	159 – 160 methanol + H_2O	55	3,45–4(m, 4H CH_2CH_2); 4,15(m, OH); 8,85–9,25 (pyraz.)
-Cl-Ph	OH	H	150 – 160 methanol	60	3,4–4,2(m, CH_2CH_2); 4,12 (m, OH); 7,4–8,01 (m, 4 arom.)
	OH		97 – 99 cyclohex.	27	1,64–1,8(4H pyrrol.); 2,72–2,90(4H pyrrol.); 3,96 (CH_2N); 4,20 (2H, CH_2O); 4,80(1H, OH)5,24 (2H, 7,48–7,72(5H arom.)
	OH		167 – 170 methanol + H_2O 1:1	31	3,67–3,92(m, 4H mor- phol.); 2,80–3,0(4H, morpho 4,85(1H, OH); 4,17–4,50(4H, CH_2CH_2); 5,30(s, 2H 7,75–8,15(5H arom.)
n	OH		70 – 72 water	17	3,93–4,4(4H, CH_2CH_2); 2,61(m, 4H piperaz.); 3,07 4H piperaz.); 4,8(OH); 6,96–7,45 (10H, arom.)

R	*R_1*	*R_2*	*M.p. °C (solvent)*	*Yield (%)*	*^1H NMR 80 MHz δ (ppm)*
h	OH		86 – 89 methanol	40	2,9(m, 4H piperaz.); 2,45 (m, 4H piperaz); 3,95(t, CH_2CH_2); 1,02 (s, CH_3); 4,02(t, CH_2); 5,12(s, CH_2 7,55–7,7 (m, 5H arom.)
h	OH	$-CH_2-N(C_6H_5)_2$	112 – 115 methanol	35	3,9(t, CH_2); 4,15(t, CH_2) 6,07(s, CH_2); 7,35–7,55 (r arom.)
hCH_2	OH		119 – 123 water	12	2,0–2,25(m, 4H pyrrol.) 2,80–3,05(m, 4H pyrrol.); 4,20(2H, CH_2O); 3,37–3,95(2H, CH_2N); 4,45(2H, C 5,90 (2H, CH_2); 4,95(1H, OH); 7,37–7,62 (5H, aro
hCH_2	OH		110 – 115 water	16	2,60–2,82(4H morphol.); 3,50–3,75(4H morphol.); 4,25 (4H, CH_2CH_2); 5,0(1H, OH); 4,07(2H, CH_2); 7,37(5H, arom.)
hCH_2	OH		49 – 53 water	18	2,95–3,31(4xCH_2 pipe- raz.); 3,73–4,20(4H pipe- r 4,40(2H, CH_2N); 4,07(2H, CH_2); 7,04–7,27 (5H ar 7,31–7,50 (5H arom.)
-pyridyl	OH		75 – 79 cyclohex + H_2O	19	2,40–2,68(4H pyrrol.); 1,85–2,05(4H pyrrol.); 4,16- 4,32(2H, CH_2O); 3,80–4,0(2H, CH_2N); 4,60 (2H, C 8,40- 8,56(2H, pyrid.); 8,9–9,1 (2H pyrid.)
-pyridyl	OH		115 – 117 water	16	2,45–3,55(4xCH_2 mor- phol.); 3,70–7,20(4H, CH_2 5,0(1H, OH); 6,70(2H, CH_2N); 7,75 (2H pyrid.); 8, pyrid.)

R	R_1	R_2	*M.p. °C (solvent)*	*Yield (%)*	*^{1}H NMR 80 MHz δ (ppm)*
-pyridyl	OH		146 – 147 water	15	2,68–3,24(4xCH_2 pipe- raz.); 3,84–4,32(4H, CH_2C 5,20(1H, OH); 6,80(2H, CH_2); 7,01–7,36 (5H arom. (2H pyrid.); 8,71 (2H pyrid.)
-pyridyl	OH		107 – 109 methanol	40	1,15(3H, CH_3); 2,75(m, 4H pyraz.); 3,92(t, 2H, CH 4,7(t, 2H, CH_2); 8,62(d, 2H pyrid.); 5,12 (s, 2H, CH 9,15 (d, 2H pyrid.)
-pyridyl	OH	-$CH_2N(C_6H_5)_2$	53 – 58 cyclohex + H_2O	14	3,85(1H, CH_2N); 4,52(1H, CH_2O); 5,02(1H, OH); 6,8(-NCH_2N-); 7,10–7,50 (10H, arom.); 7,80(2H py 8,90 (2H pyrid.)
-pyridyl	OH		132 – 135 methanol	45	0,8(m, 1H piperid.); 1,17 (m, 4H piperid.); 2,35(m, piperid.); 3,1(d, 2H, CH_2); 3,9–4,3 (m, 4H, CH_2CH_2 (s, CH_2); 7,15(m, 5H arom.); 7,3(d, 2H pyrid.); 8,7(pyrid.)
-pyrazinyl	OH		143 – 146 methanol + H_2O	16	2,0–2,3(4H pyrrol.); 2,75–2,97(4H pyrrol.); 4,85 (1 OH); 3,90–4,20 (4H, -CH_2-CH_2-); 8,85- 9,2(3H, pi
-pyrazinyl	OH		135 – 145 methanol	14	2,72–2,92(4H morphol.); 3,50–3,82(4H morphol.); 4,85(1H, OH); 5,20(2H, CH_2); 3,87–4,20(4H, CH_2- 9,30(1H py- raz.); 8,67(2H, pyraz.)

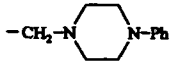
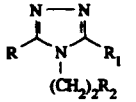
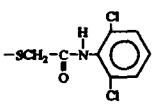
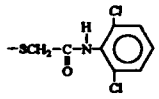
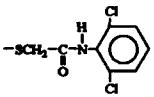
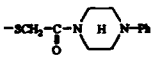
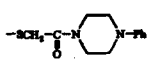
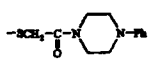
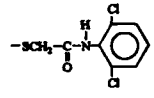
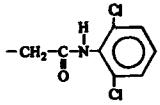
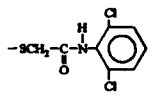
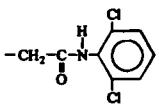
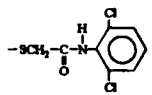
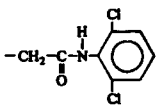
R	R_1	R_2	*M.p. °C (solvent)*	*Yield (%)*	*^{1}H NMR 80 MHz δ (ppm)*
pyrazinyl	OH		64 – 65 methanol	28	4,01–4,25(4H, CH_2CH_2); 5,1(1H, OH); 7,1–7,40 (5 arom.); 8,70(2H pyraz.); 9,21(1H pyraz.)
pyridyl	OH	$-CH_2OH$	146 – 149 methanol + H_2O	17	3,60–3,80(2H, CH_2N); 4,04–4,20(2H, CH_2O); 5,40 5,60(2H, CH_2OH); 5,0(1H, OH); 7,04(1H, CH_2OH 7,84(2H py- rid.); 8,80(2H pyrid.)
pyrazinyl	OH	$-CH_2OH$	226 – 230 methanol	12	3,85(CH_2N); 4,75(2H, CH_2O); 4,97(1H, OH); 6,95 OH); 5,70–5,82 (CH_2O); 8,95(3H pyraz.)

TABLE II Physical preperties of 

R	R_1	R_2	*M.p. °C (solvent)*	*Yield (%)*	*IR (KBr) cm^{-1}*	*^1H NMR δ – ppm*
n	-SCH_3	OH	120 – 124 water	70		3,75(3H, CH_3); 4,08 (C 3,03(2H, CH_2N); 7,55– (5H arom.)
nCH_2	-SCH_3	OH	116 – 118 water	64		3,43(2H, CH_2N); 4,15(CH_2O); 3,81 (3H, 7,85(5H arom.); 4,2(2H
pyri- dyl	-SCH_3	OH	85 – 86 methanol + water 1:1	53		4,3(CH_2O); 3,75 (3H, 2,85 (2H, CH_3N); 7,92 8,9(4H pyrid.)
pyra- zinyl	-SCH_3	OH	174 – 175 water	57		3,51(2H, CH_2N); 4,02(CH_2O); 3,78 (3H, 8,95(3H pyraz.)
h		OH	137 – 139 methanol + water 1:1	25	1680 (C=O) 3100–3200 (OH) 2920 (NH)	3,51(2H, CH_2N); 3,71(CH_2O); 7,85(5H arom. 7,7(3H arom.); 4,42(2H CH_2O)

R	*R_1*	*R_2*	*M.p. °C (solvent)*	*Yield (%)*	*IR (KBr) cm^{-1}*	*^1H NMR δ – ppn*
hCH$_2$		OH	144 – 147 water	30	1675 (C=O) water 3100–3200 (OH) 2940 (NH)	
pyridyl		OH	194 – 197 methanol	33	1690 (C=O) 3100–3200 (OH) 2920 (NH)	
		OH	198 – 200 water	30	1660 (C=O) 3120–3200 (OH)	
hCH$_2$		OH	176 – 179 methanol	17	1680 (C=O) 3100–3200 (OH)	
pyridyl		OH	175 – 177 water	21	1650 (C=O) 3100–3200 (OH)	4,3(CH_2O); 3,45 (2H, C 3,85 (2H, CH_2CO); 7,8 pyrid.); 8,80 (2H pyrid. (1H piper.); 1,17 (4H p
h			165 – 167 methanol + water 1:1	23	1690 (C=O) 2910 (NH)	2,35(4H piper.); 3,1 (2H CH_2)

R	*R_1*	*R_2*	*M.p. °C (solvent)*	*Yield (%)*	*IR (KBr) cm^{-1}*	*^1H NMR δ – ppm*
nCH_2			171 – 173 methanol	16	1670 (C=O) 2900 (NH)	3,45(2H, CH_2N); 3,95(CH_2O); 4,45(4H, CH_2 7,7(5H arom.); 4,2(2H, 7,55-7,6(6H arom.)
pyridyl			189 – 192 dioxan	28	1690 (C=O) 2900 (NH)	3,5(2H, CH_2N); 3,82(CH_2O); 4,42(4H, CH_2 7,97(2H pyrid.); 8,9(2H pyrid.); 7,6(6H arom.)
n	H	OH	102 – 103 methanol + water 1:1	48		3,42(2H, CH_2N); 3,79(CH_2O); 7,87(5H arom.
nCH_2	H	OH	76 – 79 methanol + water	40		3,37(2H, CH_2N); 3,82(CH_2O); 4,07(2H, CH_2 7,25(5H arom.)
pyridyl	H	OH	151 – 153 methanol + water	42		3,92(2H, CH_2N); 4,5(CH_2O); 7,95(2H pyrid. 8,95(2H pyrid.)

The results of elemental analyses (%C, H) for all the compounds obtained were in a good agreement with the data calculated. Reaction yields and the physical constants of the new compounds are given in Tables I and II.

1. Methyl 2-acylodithiocarbazates (2a – f)

A) compounds 2a – c

To a suspension of 50 mmole of hydrazide **1a – e** in 15 ml of ethanol 50 mmole of Et_3N was added. Then, 50 mmole of carbon disulphide was added dropwise through a reflux condenser. After the reaction mixture cleared, 50 mmole of methyl iodide was added drop by drop. The mixture was allowed to stay overnight at room temperature. The precipitated ester was filtered off and recrystallized.

B) compounds 2d – f

To a solution of 15 mmole of KOH in 20 ml of water and 10 ml of ethanol was added 15 mmole of hydrazide **1d – f** and then, through a reflux condenser 15 mmole of carbon disulfide was added with stirring. After the oily drops of carbon disulfide disappeared, 15 mmole of dimethyl sulfate was added portionwise with stirring. After 30 minutes the solution was acidified with acetic acid and the precipitated esters **2d – f** were collected, washed with water and recrystallized.

2. 4,5-Disubstituted S-triazole-3-thiol derivatives (3a – g)

2-Morpholino-, 2-pyrrolidino- and 2-piperazinoethylamine (3 ml), respectively, were added to the corresponding ester **2a, c, e, f** (10 mmole) and the reaction mixture was refluxed for 0,5 – 2 h. After cooling the oily mixture was dissolved in 20 ml of water and acidified with acetic acid; the precipitated products were filtered off and recrystallized (Table I).

3. 5-Substituted-4-(2-hydroxyethylo)-1,2,4-triazolo-3-thiols (4a – f)

Method A

Compounds **4a – f** were obtained in a similar manner as described in 2 for thiols **3**, but the methyl esters **2** were caused to react with β-ethanoloamine. Characteristic data of compounds **4d – e** are given in Table I.

Method B

a) Hydrazide **1a – c** (25 mmole) was refluxed with an equimolar quantity of CS_2 and Et_3N in 10 ml of methanol until H_2S liberation ceased. After evaporation under vacuum, the solid residue was dissolved in a small volume of water and acidified with concentrated hydrochloric acid. Precipitated oxadiazolothiones **5a – c** were filtered off and recrystallized.

b) Oxadiazolothiones **5a – c** were refluxed with an excess of ethanoloamine (10 – 30 min.), then to the thick mixture, 10 ml of water was added and the precipitated aminooxadiazoles were filtered off, the filtrates were acidified with concentrated hydrochloric acid The obtained compounds **4a – c** were recrystallized.

4. Methylation of 5-substituted 4-(2-hydroxyethyl)-s-triazole-3-thioles – compounds (6a – d)

Derivative **4a – d** (30 mmole) was dissolved in methanolic solution of potassium hydroxide (0,1 g KOH in 10 ml of methanol), then 0,2 ml of methyl iodide was added dropwise. The reaction mixture was refluxed for 0,5 – 3 hours. After the precipitated KCl was filtered off, methanol was evaporated in vacuo, and the resulting oily residue was treated with ethyl ether and allowed to stand until crystalls were formed. The precipitate was separated and purified by recrystallization (Table II).

5. Alkylation of 5-substituted 4-(2-hydroxyethyl)-s-triazole-3-thiols with N-substituted chloroacetic acid amides – compounds (7a – f) and (8a – c)

A) N-substituted amides of chloroacetic acid

To a solution of chloroacetic chloride in 50 ml of dry ethyl ether or benzene the appropriate amine (2,6-dichloroaniline or N-phenylpiperazine) was added dropwise with cooling in icewater. The reaction mixture was kept at room temperature for 24 h. The precipitated amides were filtered off.

B) Synthesis of alkylated products 7a-f

Derivative **4a – c** (2 mmole) was dissolved in methanolic solution of potassium hydroxide (0,2 g KOH in 10 ml of methanol – for the

2,6-dichloroaniline derivative and 0,4 g KOH – for the N-phenylpiperazine derivative), and treated with an equimolar quantity of N-substituted chloroamide. The reaction mixture was refluxed for 30 min., the precipitated salt was filtered, and the filtrate evaporated. The oily residue solidified after treating with ethyl ether or petroleum ether. Obtained derivatives **7a – f** were purified by recrystallization (Table II).

C) Synthesis of alkylated products 8a – c

Compounds **4a – c** were refluxed with N-substituted chloroamide (1:2) in methanol (10 ml) with sodium methanolate (0,23 g Na) for 3 hours. The precipitated salt was filtered and the methanolic solution was evaporated. The oily residue solidified after treating with ethyl ether. Derivatives **8a – c** were finally purified by recrystallization (Table II).

6. 5-Substituted-4-(2-hydroxyethyl)-s-triazoles (9a – c)

Appropriate triazole-3-thione **4a – c** (3 mmole) was dissolved in 10 ml of ethanol, Raney Nickel (2,3 g) was added and the mixture was refluxed for 4 hours. Then nickel was filtered off and the filtrate evaporated, the oily residue was treated with ethyl ether and allowed to stand till a precipitate separated (Table II).

7. Synthesis of Mannich bases (10a – r)

Appropriate compound **4a – d** was dissolved in 5 ml of methanol, the corresponding amine (1:1) and 0,3 ml of 40% formalin was added. The reaction mixture was refluxed for 3 hours, the solvent was evaporated and the oily residue treated with ethyl ether or petroleum ether and kept in a refrigerator. After some time the Mannich bases precipitated. Products were purified by crystallization (Table I).

8. Synthesis of 2-hydroxymethyl derivatives (11a – b)

Appropriate compound **4c – d** (2,5 mmole) the was refluxed with 3 ml of 40% formalin for 2 hours. The resulting solution was evaporated and the oily residue treated with ethyl ether till solidifying. The obtained solid crude products were recrystallized (Table I).

PHARMACOLOGY

Perfused artery experiment

Experiments were performed on male Wistar rats, weighing 200 ± 20 g bred in the Central Animal Farm of the Silesian Medical University. The rats were housed in an animal room at a constant temperature (21 – 24 °C), humidity (50 – 60%), and alternative 12/12-hr light-dark cycle. The animals had a free access to a standard diet and tap water. The rats were killed under ether anesthesia.

The tail artery was prepared for perfusion according to the method of Nicholas[6]. The proximal segment (2 – 3 cm) of the tail artery was excised, cannulated and mounted vertically under 0,5 g tension in an organ bath with Krebs solution. The constriction of tail artery in response to the tested compounds (10^{-6} – 10^{-5}M) or in response to noradrenaline (10^{-7} – 10^{-5}M) with presence of the compounds (10^{-6} – 10^{-5}M) was measured as an increase in perfusion pressure (Statham P23 ID transducer) at a constant flow Krebs solution (4 ml/min.).

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