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SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTI-AGGREGATION ACTIVITY OF 2-[3-METHYL-1-ETHYLXANTH-8-YLTHIO]ACETATE SALTS CONTAINING THIETANYL AND DIOXOTHIETANYL RINGS

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Reactions of 2-[1-ethyl-3-methyl-7-(thietan-3-yl)- and 2-[1-ethyl-3-methyl-7-(1,1-dioxothietan-3-yl)xanth-8-ylthio]acetic acids with amines (diethylamine, monoethanolamine, diethanolamine, triethanolamine, piperidine, cyclohexylamine, and benzylamine) gave 42 – 89% yields of 2-[1-ethyl-3-methyl-xanth-8-ylthio]-acetate salts containing thietanyl and dioxothietanyl rings. The structures of the synthesized compounds were confirmed using IR and PMR spectroscopy. The synthesized compounds exhibited anti-aggregation activity.

Keywords: xanthines, thietanes, anti-aggregation activity.

The xanthine derivative pentoxifylline is used to correct disturbances of blood rheological properties, suppress erythrocyte and platelet aggregation, lower blood viscosity, and increase erythrocyte elasticity [1]. The salt cyclohexylammonium 2-[3-methyl-1-propyl-7-(1-oxothietan-3-yl)xanth-8-ylthio]acetate exhibited anti-aggregation properties of platelets and was reported by us [2]. Research on the anti-aggregation activities of a series of thietane-containing salts of 2-(3-methyl-1-ethylxanth-8-ylthio)acetic acids has begun [3]. In continuation of the search for xanthine derivatives with anti-aggregation activity, we synthesized new salts of 2-(3-methyl-1-ethylxanth-8-ylthio)acetic acids containing thietanyl and dioxothietanyl rings.

The starting compounds were 2-[3-methyl-7-(thietan-3-yl)- and 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetic acids (**1a** and **1b**), which were synthesized by the literature methods [3]. Salts were produced using the amines diethylamine, monoethanolamine, diethanolamine, triethanolamine, piperidine, cyclohexylamine, and benzylamine. Reactions of **1a** with the amines in Me_2CO gave 54 – 89% yields of the salts of 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetic acid (**IIa-g**). By analogy, **1b** gave 42 – 89% yields of salts of 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetic acid (**IIh-n**).

IR spectra of **IIa-n** exhibited absorption bands for N^+–H stretching vibrations at 2200 – 3580 cm^{-1}. Furthermore, spectra of **IIh-n** contained strong absorption bands for symmetric and asymmetric stretching vibrations of SO_2 groups at 1134 – 1147 and 1307 – 1324 cm^{-1}.

PMR spectra confirmed formation of the salts and contained characteristic resonances of the thietanyl or dioxothietanyl rings and alkyl substituents. The SCH_2 singlets of the thioglycolic acid appeared at ~4 ppm. Resonances of the amine protons were also observed. For example, triplets and quartets centered at 1.3 and 3.0 ppm with spin—spin coupling constants (SSCCs) 7.3 Hz in spectra of **IIa** and **IIh** belonged to ethyl moieties of protonated diethylamine. Spectra of monoethanolammonium salts **IIb** and **IIi** contained trip-

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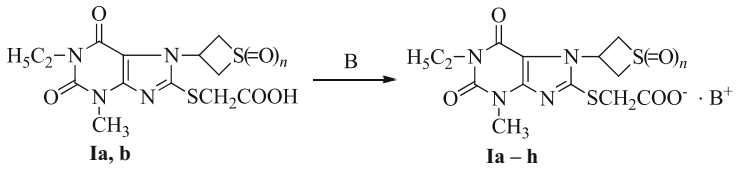

n = 0 (**Ia, IIa – g**), 2 (**Ib, IIh – n**);

$B^+ = H_2\overset{+}{N}(C_2H_5)_2$ (**IIa, h**), $H_3\overset{+}{N}CH_2CH_2OH$ (**IIb, i**), $H_2\overset{+}{N}(CH_2CH_2OH)_2$ (**IIc, j**),

$H_3\overset{+}{N}C(CH_2OH)_3$ (**IId, k**), $H\overset{+}{N}$ (**IIe, l**), $H_3\overset{+}{N}$ (**IIf, m**), $H_2\overset{+}{N}$-H_2C (**IIg, n**)

lets for the NCH_2 and OCH_2 groups at 2.8 and 3.6 ppm with SSCC 5.3 Hz.

The newly synthesized salts of the 2-(3-methyl-1-ethylxanth-8-ylthio)acetic acids containing thietanyl and dioxothietanyl rings exhibited anti-aggregation activities of various strengths. In contrast to pentoxifylline and acetylsalicylic acid, they were characterized by anti-aggregation activity for collagen-induced platelet aggregation. Compounds **IIf**, **-h**, and **-i** were the most potent (Table 1). Salts **IIf** and **-h** inhibited adenosine-diphosphate (ADP)-induced platelet aggregation by ~20% as compared to the control. Compound **IIm** at the studied concentration suppressed completely ADP- and collagen-induced platelet aggregation. A patent was obtained for compound **IIm** [4]. Thus, compounds exhibiting broad spectra of high anti-aggregation activity were found among the newly synthesized salts of 2-[3-methyl-1-ethylxanth-8-ylthio)acetic acids containing thietanyl and dioxothietanyl rings.

EXPERIMENTAL CHEMICAL PART

IR spectra of the compounds in KBr pellets were taken on an Infralum FT-02 instrument. PMR spectra were recorded on a Bruker AM-300 instrument at operating frequency 300 MHz. The solvents were deuterated $CDCl_3$ and DMSO-d_6; internal standards, solvent resonances.

The purities of the synthesized compounds were determined by TLC on Sorbfil plates using $CHCl_3$–EtOH (1:3, v/v). Spots were detected by I_2 vapor in a humid chamber. Elemental analyses of the synthesized compounds agreed with those calculated. Table 2 presents the characteristics of the synthesized compounds.

Diethylammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIa). A hot solution of **Ia** (1.07 g, 3 mmol) in Me_2CO (50 mL) was treated with diethylamine (0.29 g, 3.9 mmol) and cooled. The resulting precipitate was filtered off, rinsed with Me_2CO, dried, and purified by crystallization from Me_2CO–C_6H_6 (1:6, v/v). IR spectrum (KBr), ν_{max}, cm^{-1}: 1661, 1698 (C=C, C=N, C=O), 2200 – 3100 (N^+H_2). PMR spectrum ($CDCl_3$), δ, ppm: 1.26 (t, 3H, J 7.0 Hz, CH_3); 1.34 (t, 6H, J 7.3 Hz, $2CH_3$); 2.97 (q, 4H, J 7.3 Hz, $N(CH_2)_2$); 3.25 – 3.33 (m, 2H, $S(CH)_2$); 3.51 (s, 3H, 3-CH_3); 4.09 (s, 2H, 8-SCH_2); 4.07 – 4.17 (m, 4H, 1-CH_2 and 8-SCH_2); 4.34 – 4.42 (m, 2H, $S(CH)_2$); 5.90 – 6.04 (m, 1H, 7-CH).

Monoethanolammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIb) was prepared analogously to **IIa** from monoethanolamine (0.24 g, 3.9 mmol) and purified by crystallization from Me_2CO–C_6H_6 (1:3, v/v). IR spectrum (KBr), ν_{max}, cm^{-1}: 1607, 1662, 1694 (C=C, C=N, C=O), 2380 – 3200, 3420 – 3550 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.13 (t, 3H, J 7.0 Hz, CH_3); 2.83 (t, 2H, J 5.3 Hz, NCH_2); 3.28 – 3.35 (m, 2H, $S(CH)_2$); 3.39 (s, 3H, 3-CH_3); 3.57 (t, 2H, J 5.3 Hz, OCH_2); 3.86 (s, 2H, 8-SCH_2); 3.94 (q, 2H, J 7.0 Hz, 1-CH_2); 4.18 – 4.27 (m, 2H, $S(CH)_2$); 5.84 – 5.98 (m, 1H, 7-CH).

Diethanolammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIc) was prepared analogously to **IIa** from diethanolamine (0.41 g, 3.9 mmol) and purified by crystallization from *i*-PrOH. IR spectrum (KBr), ν_{max}, cm^{-1}: 1634, 1660, 1698 (C=C, C=N, C=O), 2380 – 3520 (N^+H_2). PMR spectrum ($CDCl_3$), δ, ppm: 1.27 (t, 3H, J 7.0 Hz, CH_3); 3.12 – 3.18 (m, 4H, $N(CH_2)_2$); 3.27 – 3.33 (m, 2H, $S(CH)_2$); 3.53 (s, 3H, 3-CH_3); 3.88 – 3.94 (m, 4H, $2OCH_2$); 4.06 (s, 2H, 8-SCH_2); 4.13 (q, 2H, J 7.0 Hz, 1-CH_2); 4.34 – 4.42 (m, 2H, $S(CH)_2$); 5.90 – 6.03 (m, 1H, 7-CH).

Triethanolammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IId). A hot solution of **Ia** (1.07 g, 3 mmol) in Me_2CO (50 mL) was treated with triethanolamine (0.47 g, 3.9 mmol) in H_2O (1 mL) and cooled. The resulting precipitate was filtered off, rinsed with Me_2CO, dried, and purified by crystallization from dioxane. ν_{max}, cm^{-1}: 1663, 1708 (C=C, C=N, C=O), 2780 – 3580 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.13 (t, 3H, J 7.0 Hz, CH_3); 3.40 – 3.50 (m, 11H, 3-CH_3, $S(CH)_2$, $C(CH_2)_3$); 3.83 (s, 2H, 8-SCH_2); 3.93 (q, 2H, J 7.0 Hz, 1-CH_2); 4.10 – 4.19 (m, 2H, $S(CH)_2$); 6.29 – 6.43 (m, 1H, 7-CH).

Piperidinium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIe) was prepared analogously to **IIa** from piperidine (0.29 g, 3.9 mmol) and purified by crys-

TABLE 1. Influence of Synthesized Compounds and Reference Drugs on ADP- and Collagen-induced Platelet Aggregation, Me (25 – 75)

Compound	ADP-induced platelet aggregation, % inhibition of control level	*p*	Collagen-induced platelet aggregation, % inhibition of control level	*p*
IIa	2.8 (0.9 – 4.3)	$p_1 = 0.001$ $p_2 = 0.0006$ $p_3 = 0.000007$ $p_4 = 0.0007$	3.9 (3.1 – 6.2)	$p_1 = 0.5$ $p_2 = 0.2$
IIb	6.8 (2.7 – 11.2)	$p_1 = 0.5$ $p_2 = 0.004$ $p_3 = 0.00002$ $p_4 = 0.0001$	2.3 (1.1 – 4.2)	$p_1 = 0.3$ $p_2 = 0.004$
IIc	2.3 (1.1 – 4.2)	$p_1 = 0.07$ $p_2 = 0.0008$ $p_3 = 0.000009$ $p_4 = 0.0007$	3.6 (2.7 – 4.5)	$p_1 = 0.03$ $p_2 = 0.8$
IId	3.2 (1.2 – 5.1)	$p_1 = 0.0003$ $p_2 = 0.006$ $p_3 = 0.00008$ $p_4 = 0.0003$	4.7 (2.7 – 5.8)	$p_1 = 0.4$ $p_2 = 0.8$
IIe	14.3 (9.5 – 17.3)	$p_1 < 0.0001$ $p_2 = 0.3$ $p_3 = 0.007$ $p_4 = 0.4$	3.6 (1.3 – 5.2)	$p_1 = 0.7$ $p_2 = 0.4$
IIf	19.3 (16.7 – 24.9)	$p_1 < 0.0001$ $p_2 = 0.002$ $p_3 = 0.0005$ $p_4 = 0.003$	3.6 (2.1 – 4.8)	$p_1 = 0.5$ $p_2 = 0.6$
IIg	10.1 (7.2 – 13.3)	$p_1 = 0.03$ $p_2 = 0.006$ $p_3 = 0.00003$ $p_4 = 0.0005$	6.4 (4.2 – 7.9)	$p_1 = 0.002$ $p_2 = 0.4$
IIh	20.4 (17.5 – 24.6)	$p_1 < 0.0001$ $p_2 = 0.002$ $p_3 = 0.0008$ $p_4 = 0.003$	4.6 (3.1 – 5.4)	$p_1 = 0.2$ $p_2 = 0.7$
IIi	6.2 (5.2 – 8.6)	$p_1 = 0.6$ $p_2 = 0.002$ $p_3 = 0.000005$ $p_4 = 0.0004$	7.3 (5.4 – 8.7)	$p_1 = 0.0003$ $p_2 = 0.02$
IIj	7.4 (6.3 – 8.5)	$p_1 = 0.6$ $p_2 = 0.002$ $p_3 = 0.001$ $p_4 = 0.0003$	8.4 (6.5 – 9.3)	$p_1 = 0.002$ $p_2 = 0.03$
IIk	9.1 (8.1 – 10.6)	$p_1 = 0.8$ $p_2 = 0.002$ $p_3 = 0.0005$ $p_4 = 0.0004$	4.2 (3.1 – 6.2)	$p_1 = 0.002$ $p_2 = 0.6$
IIl	2.3 (2.1 – 3.7)	$p_1 = 0.6$ $p_2 = 0.003$ $p_3 = 0.0005$ $p_4 = 0.0001$	3.8 (3.2 – 4.7)	$p_1 = 0.3$ $p_2 = 0.1$
IIm	100.0 (100.0 – 100.0)	$p_1 = 0.0002$ $p_2 = 0.001$ $p_3 = 0.0004$ $p_4 = 0.0003$	100.0 (100.0 – 100.0)	$p_1 = 0.0001$ $p_2 = 0.0002$

TABLE 1. Continued

Compound	ADP-induced platelet aggregation, % inhibition of control level	*p*	Collagen-induced platelet aggregation, % inhibition of control level	*p*
IIn	1.7 (1.1 – 2.4)	$p_1 = 0.003$ $p_2 = 0.001$ $p_3 = 0.0006$ $p_4 = 0.001$	2.8 (1.2 – 3.4)	$p_1 = 0.8$ $p_2 = 0.002$
Euphyllin	7.4 (5.6 – 9.3)	-	2.5 (0.8 – 4.2)	-
Caffeine-sodium benzoate	14.7 (10.3 – 17.9)	-	5.3 (3.9 – 7.2)	-
Pentoxifylline	48.4 (42.7 – 56.5)	-	0.0 (0.0 – 0.0)	-
Acetylsalicylic acid	13.7 (10.8 – 16.4)	-	0.0 (0.0 – 0.0)	-

Statistical significance of differences vs. euphyllin (p_1), caffeine-sodium benzoate (p_2), pentoxifylline (p_3), and acetylsalicylic acid (p_4), $n = 7$.

tallization from Me_2CO–dioxane (1:1, v/v). IR spectrum (KBr), ν_{max}, cm^{-1}: 1604, 1635, 1662, 1694 (C=C, C=N, C=O), 2200 – 3100 (N^+H_2).

Cyclohexylammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIf) was prepared analogously to **IIa** from cyclohexylamine (0.39 g, 3.9 mmol) and purified by crystallization from Me_2CO–dioxane (1:1, v/v). IR spectrum (KBr), ν_{max}, cm^{-1}: 1662, 1698 (C=C, C=N, C=O), 2400 – 3150 (N^+H_3).

Benzylammonium 2-[3-methyl-7-(thietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIg) was prepared analogously to **IIa** from benzylamine (0.42 g, 3.9 mmol) and purified by crystallization from Me_2CO–dioxane (1:1, v/v). IR spectrum (KBr), ν_{max}, cm^{-1}: 1608, 1662, 1697 (C=C, C=N, C=O), 2400 – 3200 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.14 (t, 3H, J 6.9 Hz, CH_3); 3.27 – 3.36 (m, 2H, $S(CH)_2$); 3.39 (s, 3H, 3-CH_3); 3.87 (s, 2H, 8-SCH_2); 3.90 – 4.00 (m, 4H, 1-CH_2 and NCH_2); 4.19 – 4.28 (m, 2H, $S(CH)_2$); 5.84 – 5.99 (m, 1H, 7-CH); 7.29 – 7.47 (m, 5H, C_6H_5).

Diethylammonium 2-[3-methyl-7-(1, 1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIh) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using diethylamine (0.48 g, 6.5 mmol) and purified by crystallization from dioxane. IR spectrum (KBr), ν_{max}, cm^{-1}: 1139, 1308 (SO_2 str), 1601, 1658, 1698 (C=C, C=N, C=O), 2230 – 3100 (N^+H_2). PMR spectrum ($CDCl_3$), δ, ppm: 1.22 (t, 3H, J 7.0 Hz, CH_3); 1.31 (t, 6H, J 7.3 Hz, $2CH_3$); 2.99 (q, 4H, J 7.3 Hz, $N(CH_2)_2$); 3.51 (s, 3H, 3-CH_3); 4.05 (s, 2H, 8-SCH_2); 4.03 – 4.14 (m, 4H, 1-CH_2 and 8-SCH_2); 4.31 – 4.41 (m, 2H, $S(CH)_2$); 5.16 – 5.26 (m, 2H, $S(CH)_2$); 5.55 – 5.69 (m, 1H, 7-CH).

Monoethanolammonium 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIi) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using monoethanolamine (0.40 g, 6.5 mmol) and purified by crystallization from dioxane. IR spectrum (KBr), ν_{max}, cm^{-1}: 1147, 1307 (SO_2 str), 1608, 1665, 1698 (C=C, C=N, C=O), 2400 – 3500 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.13 (t, 3H, J 6.8 Hz, CH_3); 2.82 (t, 2H, J 5.3 Hz, NCH_2); 3.41 (s, 3H, 3-CH_3); 3.56 (t, 2H, J 5.3 Hz, OCH_2); 3.82 (s, 2H, 8-SCH_2); 3.93 (q, 2H, J 6.8 Hz, 1-CH_2); 4.49 – 4.59 (m, 2H, $S(CH)_2$); 5.00 – 5.11 (m, 2H, $S(CH)_2$); 5.50 – 5.64 (m, 1H, 7-CH).

Diethanolammonium 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIj) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using

TABLE 2. Characteristics of Synthesized **IIa-n**

Compound	Yield, %	mp, °C	Empirical formula
IIa	60	166 – 169	$C_{17}H_{27}N_5O_4S_2$
IIb	74	192 – 194	$C_{15}H_{23}N_5O_5S_2$
IIc	74	135 – 137	$C_{17}H_{27}N_5O_6S_2$
IId	54	199 – 200	$C_{17}H_{27}N_5O_7S_2$
IIe	84	198 – 201	$C_{18}H_{27}N_5O_4S_2$
IIf	89	209 – 211	$C_{19}H_{29}N_5O_4S_2$
IIg	77	181 – 183	$C_{20}H_{25}N_5O_4S_2$
IIh	84	199 – 201	$C_{17}H_{27}N_5O_6S_2$
IIi	84	198 – 201	$C_{15}H_{23}N_5O_7S_2$
IIj	42	195 – 197	$C_{17}H_{27}N_5O_8S_2$
IIk	67	169 – 173	$C_{17}H_{27}N_5O_9S_2$
IIl	86	219 – 222	$C_{18}H_{27}N_5O_6S_2$
IIm	89	223 – 225	$C_{19}H_{29}N_5O_6S_2$
IIn	80	201 – 203	$C_{20}H_{25}N_5O_6S_2$

diethanolamine (0.68 g, 6.5 mmol) and purified by crystallization from *i*-PrOH. IR spectrum (KBr), ν_{max}, cm^{-1}: 1147, 1308 (SO_2 str), 1618, 1668, 1698 (C=C, C=N, C=O), 2600 – 3550 (N^+H_2). PMR spectrum (DMSO-d_6), δ, ppm: 1.13 (t, 3H, J 6.7 Hz, CH_3); 2.94 (t, 4H, J 5.2 Hz, $N(CH_2)_2$); 3.41 (s, 3H, 3-CH_3); 3.60 (t, 4H, J 5.2 Hz, $2OCH_2$); 3.85 (s, 2H, 8-SCH_2); 3.93 (q, 2H, J 6.7 Hz, 1-CH_2); 4.49 – 4.59 (m, 2H, $S(CH)_2$); 5.00 – 5.10 (m, 2H, $S(CH)_2$); 5.49 – 5.62 (m, 1H, 7-CH).

Triethanolammonium 2-[3-methyl-7-(1, 1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIk) was prepared analogously to **IId** from **Ib** (1.16 g, 3 mmol) and purified by crystallization from *i*-PrOH. IR spectrum (KBr), ν_{max}, cm^{-1}: 1138, 1324 (SO_2 str), 1670, 1712 (C=C, C=N, C=O), 2750 – 3550 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.13 (t, 3H, J 6.9 Hz, CH_3); 3.41 (s, 3H, 3-CH_3); 3.44 (s, 6H, $N(CH_2)_3$); 3.82 (s, 2H, 8-SCH_2); 3.93 (q, 2H, J 6.9 Hz, 1-CH_2); 4.49 – 4.58 (m, 2H, $S(CH)_2$); 5.00 – 5.09 (m, 2H, $S(CH)_2$); 5.51 – 5.64 (m, 1H, 7-CH).

Piperidinium 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (III) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using piperidine (0.56 g, 6.5 mmol) and purified by crystallization from dioxane. IR spectrum (KBr), ν_{max}, cm^{-1}: 1134, 1311 (SO_2 str), 1642, 1655, 1662, 1697 (C=C, C=N, C=O), 2220 – 3100 (N^+H_2). PMR spectrum (DMSO-d_6), δ, ppm: 1.08 (t, 3H, J 6.9 Hz, CH_3); 1.45 – 1.72 (m, 6H, $(CH_2)_3$); 2.91 – 3.02 (m, 4H, $N(CH_2)_2$); 3.37 (s, 3H, 3-CH_3); 3.77 (s, 2H, 8-SCH_2); 4.03 – 4.14 (m, 4H, 1-CH_2 and 8-SCH_2); 4.95 – 5.04 (m, 2H, $S(CH)_2$); 5.48 – 5.62 (m, 1H, 7-CH).

Cyclohexylammonium 2-[3-methyl-7-(1, 1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIm) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using cyclohexylamine (0.64 g, 6.5 mmol) and purified by crystallization from dioxane. IR spectrum (KBr), ν_{max}, cm^{-1}: 1136, 1320 (SO_2 str), 1662, 1699 (C=C, C=N, C=O), 2400 – 3150 (N^+H_3). PMR spectrum (DMSO-d_6), δ, ppm: 1.09 – 1.31 (m, 9H, CH_3 and $(CH_2)_3$); 1.61 – 1.91 (m, 4H, $(CH_2)_2$); 2.82 – 2.93 (m, 1H, NCH); 3.42 (s, 3H, 3-CH_3); 3.79 (s, 2H, 8-SCH_2); 3.94 (q, 2H, J 6.9 Hz, 1-CH_2); 4.50 – 4.61 (m, 2H, $S(CH)_2$); 5.00 – 5.11 (m, 2H, $S(CH)_2$); 5.52 – 5.65 (m, 1H, 7-CH).

Benzylammonium 2-[3-methyl-7-(1,1-dioxothietan-3-yl)-1-ethylxanth-8-ylthio]acetate (IIn) was prepared analogously to **IIa** from **Ib** (1.94 g, 5 mmol) using benzylamine (0.70 g, 6.5 mmol) and purified by crystallization from dioxane. IR spectrum (KBr), ν_{max}, cm^{-1}: 1143, 1311 (SO_2 str), 1666, 1701 (C=C, C=N, C=O), 2380 – 3050, 3270 (N^+H_3).

EXPERIMENTAL BIOLOGICAL PART

Anti-aggregation activities of the newly synthesized compounds and reference drugs were studied *in vitro* using human donor blood on a Thromlite-1006A aggregometer using the Born method [5]. The experiments used blood from healthy male donors aged 18 – 24 years. Blood was collected from cubital veins using a BD Vacutainer® vacuum collection system (Dickinson and Co., USA). Venous blood was stabilized by sodium citrate solution (3.8%) in a 9:1 ratio. All tests used platelet-rich and platelet-poor plasmas. Platelet-rich plasma was produced by centrifuging citrated blood at 100 g for 10 min; platelet-poor plasma, at 300 g for 15 min on an OPN-3.02 centrifuge (OAO TNK Dastan, Kyrgyz Rep.). Platelets were aggregated using the inductors ADP at a concentration of 20 μg/mL and collagen at a concentration of 5 mg/mL (Technology Standard, Barnaul).

The reference drugs were pentoxifylline (solution for injection, 20 mg/mL, 5 mL, OJSC Borisov Plant of Medical Preparations, Borisov, Belarus), batch No. 290715, exp. date Aug. 2018, produced July 2015; caffeine-sodium benzoate (solution for injection, 200 mg/mL, 1 mL, OJSC Borisov Plant of Medical Preparations, Borisov, Belarus), batch No. 040609, exp. date Aug. 2017, produced June 4, 2015; euphyllin (solution for i.v. injection, 24 mg/mL, 10 mL, OJSC Novosibkhimfarm, Novosibirsk, Russia), batch No. 10416, exp. date May 2019, produced Apr. 1, 2016; and acetylsalicylic acid (Shandong Pharmaceutical Plant, Xinhua Pharmaceutical Co. Ltd., China), batch No. 10E16, exp. date Apr. 2017, produced Nov. 10, 2015.

Results were processed using Statistica 10.0 software (StatSoft Inc., USA). Normal distributions of actual data were checked using the Shapiro—Wilk criterion. Data were given as medians and 25 and 75 percentiles. Dispersion analysis used the Kruskal—Wallis criterion. The critical significance level *p* for statistical criteria was 0.05.

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