CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Synthesis and biological activity of 5-acetyl- and 5-hydroxyalkyl-1,3-dioxane derivatives

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Abstract

Objectives. *To synthesize derivatives of 5-acetyl- and 5-hydroxyalkyl-1,3-dioxanes and evaluate their effect on platelet aggregation and plasma hemostasis.*

Methods. *To determine the qualitative and quantitative composition of the reaction masses, gas chromatography-, chromate mass spectrometry-, and ^{1}H and ^{13}C nuclear magnetic resonance spectrometry methods were used.*

Results. *Derivatives of 5-acetyl- and 5-hydroxyalkyl-1,3-dioxanes were obtained under thermal heating conditions in order to evaluate their effect on platelet aggregation and plasma hemostasis.*

Conclusions. *Derivatives of 5-acetyl- and 5-hydroxyalkyl-1,3-dioxanes were synthesized in high yields. Their effect on platelet aggregation and plasma hemostasis was established.*

Keywords: *5-acyl-1,3-dioxane, alkylation, ethers, isoniazid, 2,4-dinitrophenyl hydrazine*

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НАУЧНАЯ СТАТЬЯ

Синтез и биологическая активность производных 5-ацетил- и 5-оксиалкил-1,3-диоксанов

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Аннотация

Цели. *Синтезировать производные 5-ацетил- и 5-оксиалкил-1,3-диоксанов и оценить их влияние на агрегацию тромбоцитов и плазменное звено гемостаза.*
Методы. *Для определения качественного и количественного состава реакционных масс были использованы газовая хроматография, хромато-масс-спектрометрия и спектроскопия ядерного магнитного резонанса ^{1}H и ^{13}C.*
Результаты. *В условиях термического нагрева получены производные 5-ацетил- и 5-оксиалкил-1,3-диоксанов, произведена оценка их влияния на агрегацию тромбоцитов и плазменное звено гемостаза.*
Выводы. *С высокими выходами синтезированы производные 5-ацетил- и 5-оксиалкил-1,3-диоксанов, установлено их влияние на агрегацию тромбоцитов и плазменное звено гемостаза.*

Ключевые слова: *5-ацил-1,3-диоксан, алкилирование, простые эфиры, изониазид, 2,4-динитрофенил-гидразин*

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INTRODUCTION

Substituted cyclic acetals and their analogs are known to support a wide spectrum of biological activity [1–5]. Thus, 5-hydroxymethi-1,3-dioxanes obtained from commercial 1,1,1-trioxymethylalkanes and their derivatives exhibit herbicidal, anticoagulant, and other activities [6–11].

In previous work we demonstrated the possibility of reducing that available 5-acyl-1,3-dioxanes to the corresponding secondary alcohols using metal-containing catalysts [12]. According to this approach, a highly efficient heterogeneous Pd/Al_2O_3 catalyst (0.25% Pd; hydrogenation temperature 40–90°C) was studied at the Ya.K. Syrkin Department of Physical Chemistry of RTU MIREA by the research group led by V.R. Flid [13].

In this connection, the synthesis of new reagents of the class of cyclic acetals based on available petrochemical products seems important and promising.

MATERIALS AND METHODS

The analysis of the reaction masses of the compounds was carried out on the Chromatec-Crystal 5000M hardware-software

complex (*Chromatec*, Russia) with the installed base NIST MS Search 2020 (*National Institute of Standards and Technology*, USA). A CR-5ms capillary quartz column (*Chromatec*, Russia) of 30 m length, 0.25 mm diameter, and 0.25 μm phase thickness was used under the following analysis conditions: duration of analysis is 20 min; temperature of ion source is 260°C; temperature of the transition line is 300°C; pressure is 37–43 mTorr; carrier gas is helium; heating rate is 20°C/min). The mass spectra of the compounds were obtained using the electron impact ionization method with an ionization energy of 70 eV; the scanning range was 30–300 Da. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-500 spectrometer (*Bruker Corporation*, USA) with operating frequencies of 500 and 125 MHz, respectively; the solvent used was $CDCl_3$. Chemical shifts are given in δ (ppm) scale relative to tetramethylsilane as an internal standard. The spin-spin coupling constants (*J*) are given in Hz.

Compounds **1a** and **1b** were obtained according to the procedure described in [14]. The physicochemical characteristics correspond to those previously presented in work [14].

Compounds **3a** and **3b** were obtained according to the procedures listed in [15, 16].

***N*-[1-(5-isopropyl-1,3-dioxan-5-yl)ethylidene]-benzohydrazone (3a).** White powder. $T_{m.p.}$ = 138–140°C. Yield 90%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.13 (t, 6H, 2 CH_3, *J* = 8.8 Hz), 2.13 (s, 3H, CH_3), 2.65 (q, 1H, CH, *J* = 7.03, 14.0 Hz), 3.51 (d, 2H, CH_a, *J* = 12 Hz), 4.35 (d, 2H, CH_b, *J* = 11.52 Hz), 4.47 (d, 1H, CH, *J* = 6.11 Hz), 4.90 (d, 1H, CH, *J* = 6.05 Hz), 7.50–9.00 (5H, Ph-). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 17.93 (CH_3), 17.95 (CH_3), 31.29 (CH), 42.39 (CH_3), 72.95 (2 CH_2), 94.16 (CH_2), 120.91–150.45 (Ph-), 162.37 (N=C).

1-(5-isopropyl-1,3-dioxan-5-yl)ethanone (2,4-dinitrophenyl)(methyl)hydrazone (3b). Light yellow powder. $T_{m.p.}$ = 138–140°C. Yield 88%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.43 (t, 6H, 2 CH_3, *J* = 7.3 Hz), 2.13 (s, 3H, CH_3), 2.51 (q, 1H, CH, *J* = 7.06, 13.8 Hz), 3.88 (d, 2H, CHa_a, *J* = 12 Hz), 4.24 (d, 1H, CH_b, *J* = 11.88 Hz), 4.47 (d, 1H, CH, *J* = 6.02 Hz), 4.90 (d, 1H, CH, *J* = 6.01 Hz), 7.50–9.00 (5H, Ph-). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 19.68 (CH_3), 19.87 (CH_3), 31.22 (CH), 42.23 (CH_3), 73.63 (2 CH_2), 94.24 (CH_2), 120.91–145.28 (Ph-), 162.39 (N=C).

The basic deacetalization technique is presented in the work [17].

3,3-bis-(hydroxymethyl)-4-methylpentan-2-one (3c). Colorless liquid. Yield 89%. $T_{b.p.}$ = 108–110°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.02 (t, 6H, 2 CH_3, *J* = 7.1 Hz), 1.88 (q, 1H, CH, *J* = 7.01, 13.2 Hz), 2.23 (s, 3H, CH_3), 3.96 (d, 2H, CH_a, *J* = 10.55 Hz), 4.02 (d, 1H, CH_b, *J* = 10.43 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 19.69 (CH_3), 19.88 (CH_3), 22.51 (CH_3), 30.83 (CH), 63.49 (2 CH_2), 207.23 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (159)/(14), (145)/(60), (99)/(76), (41)/(100).

The basic acylation procedure is presented in the work [18].

1-(5-isopropyl-1,3-dioxan-5-yl)-ethylchloroacetate (7a). Colorless viscous liquid. Yield 90%. $T_{b.p.}$ = 125–127°C (5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.95 (t, 6H, 2 CH_3, *J* = 7.75 Hz), 1.35 (t, 3H, CH_3, *J* = 7.01 Hz), 1.88–1.98 (m, 1H, CH), 3.66 (d, 2H, CH_a, *J* = 11 Hz), 3.99 (d, 2H, CH_b, *J* = 11 Hz), 4.05 (s, 2H, CH_2), 4.15 (d, 1H, CH, *J* = 6 Hz). 4.66 (d, 1H, CH, *J* = 6 Hz), 4.92 (d, 1H, CH, *J* = 6 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.94 (CH_3), 21.49 (CH_3), 21.68 (CH_3), 29.69 (CH), 40.77 (CH_2), 68.21 (2 CH_2), 71.26 (CH), 93.87 (CH_2), 166.94 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (251/253)/(5/2), (99)/(30), (87)/(100), (43)/(60).

Bis-[1-(5-isopropyl-1,3-dioxan-5-yl)ethyl]-terephthalate (7b). Colorless viscous liquid. Yield 70%. $T_{b.p.}$ = 131–133°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.99 (t, 12H, 4 CH_3, *J* = 11.67 Hz), 1.23 (t, 6H, 2 CH_3, *J* = 10 Hz), 1.73–1.84 (m, 2H, 2 CH), 3.74 (d, 4H, 4 CH_a, *J* = 11.3 Hz), 3.99 (d, 4H, 4 CH_b, *J* = 11.04 Hz), 4.43 (d, 2H, 2 CH, *J* = 6 Hz), 4.59 (d, 2H, 2 CH, *J* = 6 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.12 (2 CH_3), 21.42 (2 CH_3), 21.47 (2 CH_3), 31.66 (CH), 68.91 (4 CH_2), 71.23 (2 CH), 92.99 (2 CH_2), 121.49–153.41 (Ph-), 171.03 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (487/1), (335)/(20), (87)/(100), (77)/(50), (51)/(10).

The basic alkylation procedure is presented in the work [18].

5-[1-(allyloxy)ethyl]-5-isopropyl-1,3-dioxane (8a). Colorless viscous liquid. Yield 98%. $T_{b.p.}$ = 131–133°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.98 (t, 6H, 2 CH_3, *J* = 7 Hz), 1.35 (d, 3H, CH_3, *J* = 7 Hz), 1.82–1.93 (m, 1H, CH), 3.28 (d, 1H, CH, *J* = 7 Hz), 3.74 (d, 2H, CH_a, *J* = 10.2 Hz), 3.83 (d, 2H, CH_b, *J* = 11 Hz), 3.94 (d, 1H, CH, *J* = 7 Hz), 4.04 (d, 1H, CH, *J* = 7.4 Hz), 4.63 (d, 1H, CH, *J* = 6 Hz), 4.88 (d, 1H, CH, *J* = 6 Hz), 5.74 (d, 1H, CH,

J = 10.2 Hz), 5.81 (d, 1H, CH, *J* = 7 Hz), 5.83–5.91 (m, 1H, CH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.92 (CH_3), 21.42 (CH_3), 21.46 (CH_3), 29.67 (CH), 68.27 (2 CH_2), 71.44 (CH), 73.39 (CH_2), 93.89 (CH_2), 113.99 (CH_2), 136.73 (CH).

Mass spectrum *m*/*z*, (I_{rel}, %): (213/1), (186)/(30), (157)/(80), (87)/(100), (41)/(40).

5-[1-(benzyloxy)ethyl]-5-isopropyl-1,3-dioxane (8b). Colorless liquid. Yield 83%. $T_{b.p.}$ = 122–123°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.97 (t, 6H, 2 CH_3, *J* = 7.8 Hz), 1.30 (d, 3H, CH_3, *J* = 8 Hz), 1.76–1.83 (m, 1H, CH), 3.05 (d, 1H, CH, *J* = 10 Hz), 3.59 (d, 2H, CH_a, *J* = 10 Hz), 3.74 (d, 2H, CH_b, *J* = 11 Hz), 4.75 (s, 2H, CH_2), 4.89 (d, 1H, CH, *J* = 6 Hz), 4.95 (d, 1H, CH, *J* = 6 Hz), 7.05–7.94 (Ph-). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.87 (CH_3), 21.39 (CH_3), 21.41 (CH_3), 29.49 (CH), 68.22 (2 CH_2), 71.41 (CH_2), 72.31 (CH), 92.05 (CH_2), 126.99–139.93 (Ph-).

Mass spectrum *m*/*z*, (I_{rel}, %): (263/1), (187)/(50), (91)/(30), (87)/(100), (77)/(60), (51)/(30).

The basic procedure for condensation with phenyl isocyanate is presented in the work [18].

1-(5-isopropyl-1,3-dioxan-5-yl)ethylcarbamate (5a). White powder. Yield 92%. $T_{m.p.}$ = 101–103°C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.90 (t, 6H, 2 CH_3, *J* = 8 Hz), 1.17 (d, 3H, CH_3, *J* = 8 Hz), 1.73–1.86 (m, 1H, CH), 3.67 (d, 2H, CH_a, *J* = 11 Hz), 3.78 (d, 2H, CH_b, *J* = 11 Hz), 4.01 (d, 1H, CH, *J* = 8 Hz), 4.93 (d, 1H, CH, *J* = 6.3 Hz), 4.96 (d, 1H, CH, *J* = 6.6 Hz), 7.05–7.92 (Ph-). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.77 (CH_3), 21.41 (CH_3), 21.44 (CH_3), 29.41 (CH), 68.12 (2 CH_2), 75.33 (CH), 91.09 (CH_2), 127.92–138.91 (Ph-), 163.66 (C=O).

The method for the condensation of alcohol **1b** with vinyl ethyl ether **10** is presented in [19].

5-[1-(1-diethoxy]ethyl-5-isopropyl-1,3-dioxane (11a). Colorless liquid. Yield 65%. $T_{b.p.}$ = 134–135°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.96 (t, 6H, 2 CH_3, *J* = 8 Hz), 1.01 (t, 3H, CH_3, *J* = 9 Hz), 1.12 (s, 3H, CH_3), 1.28 (t, 3H, CH_3, *J* = 8.1 Hz), 1.62–1.73 (m, 1H, CH), 3.63 (d, 1H, CH, *J* = 9.1 Hz), 3.69 (d, 2H, CH_a, *J* = 11.7 Hz), 3.92 (d, 2H, CH_b, *J* = 11.5 Hz), 4.02 (d, 1H, CH, *J* = 9.2 Hz), 4.12 (d, 1H, CH, *J* = 6.4 Hz), 4.23 (d, 1H, CH, *J* = 6.3 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.18 (CH_3), 17.73 (CH_3), 20.99 (CH_3), 21.44 (CH_3), 29.32 (CH), 64.55 (CH_2), 68.37 (2 CH_2), 76.31 (CH), 93.21 (CH_2), 99.21 (CH).

5,5-[ethane-1,1-diylbis(oxyethane-1,1-diyl)]-bis-(5-isopropyl-1,3-dioxane) (11b). Colorless liquid. Yield 65%. $T_{b.p.}$ = 154–156°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.96 (t, 12H, 6 CH_3, *J* = 8.1 Hz), 1.01 (t, 6H, 2 CH_3, *J* = 9.5 Hz), 1.18 (t, 3H, CH_3, *J* = 8.9 Hz), 1.71–1.81 (m, 2H, 2 CH), 3.69 (d, 2H, 2 CH, *J* = 9.1 Hz), 3.78 (d, 2H, CH_a, *J* = 11 Hz), 3.83 (d, 2H, CH_b, *J* = 11 Hz), 4.28 (d, 2H, 2 CH, *J* = 8 Hz), 4.32 (d, 2H, 2 CH, *J* = 6.4 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.54 (CH_3), 17.33 (CH_3), 20.92 (CH_3), 21.31 (CH_3), 29.49 (CH), 64.23 (CH_2), 68.85 (2 CH_2), 76.98 (CH), 93.96 (CH_2), 99.21 (CH).

Methodology for conducting a biological experiment

The basic method for determining anticoagulant and aggregation activity is presented in [19].

Optical measurements. The results were recorded by optical density with the calculation of hemolysis according to the formula: % of hemolysis = $((E_{op} - E_c)/E_{100}) \times 100$, where E_{op} is the optical density of the experimental sample; E_c is the optical density of the control sample; E_{100} is the optical density of water with a suspension of erythrocytes with 100% hemolysis (optical density: 0.8–1.0).

Statistical processing. The check for the normality of the distribution of actual data was performed using the Shapiro–Wilk test. Analysis of variance was performed using the Kruskal–Wallis test. The critical significance level *p* for statistical tests was taken as equal to 0.05.

RESULTS AND DISCUSSION

Previously, we showed [12] that the condensation of methyl isobutyl ketone with paraform leads to ketone **1a** in high yield. By carrying out hydrogenation of **1a** under homo- and heterogeneous conditions, it is possible to pass to cyclic alcohol **1b** [12]. Continuing these studies, we obtained some derivatives of ketone **1a** and alcohol **1b**, as well as determining the assessment of their effect on platelet aggregation and plasma hemostasis.

By breaking the ring in compound **1a** with refluxing in 2% sulfuric acid, ketodiol **3c** was obtained in 60% yield. Condensation of ketone **1a** with compounds containing a primary amino group, isoniazid **2a** and 2,4-dinitrophenylhydrazine **2b**, gave Schiff bases **3a** and **3b** in quantitative yields (Fig. 1).

The corresponding complex mono-**7a** and di-**7b** esters were obtained *via* esterification of secondary alcohol **1b** with mono-**6a** and di-**6b** acid chlorides (Fig. 2).

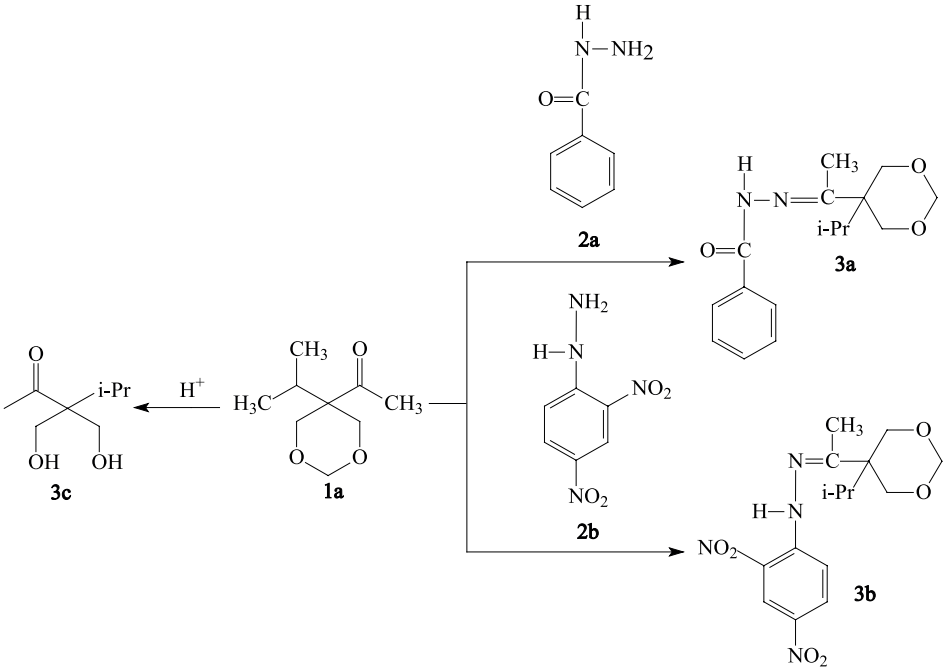

Fig. 1. Scheme of reactions of 1-(5-isopropyl-1,3-dioxan-5-yl)ethanone **1a**.

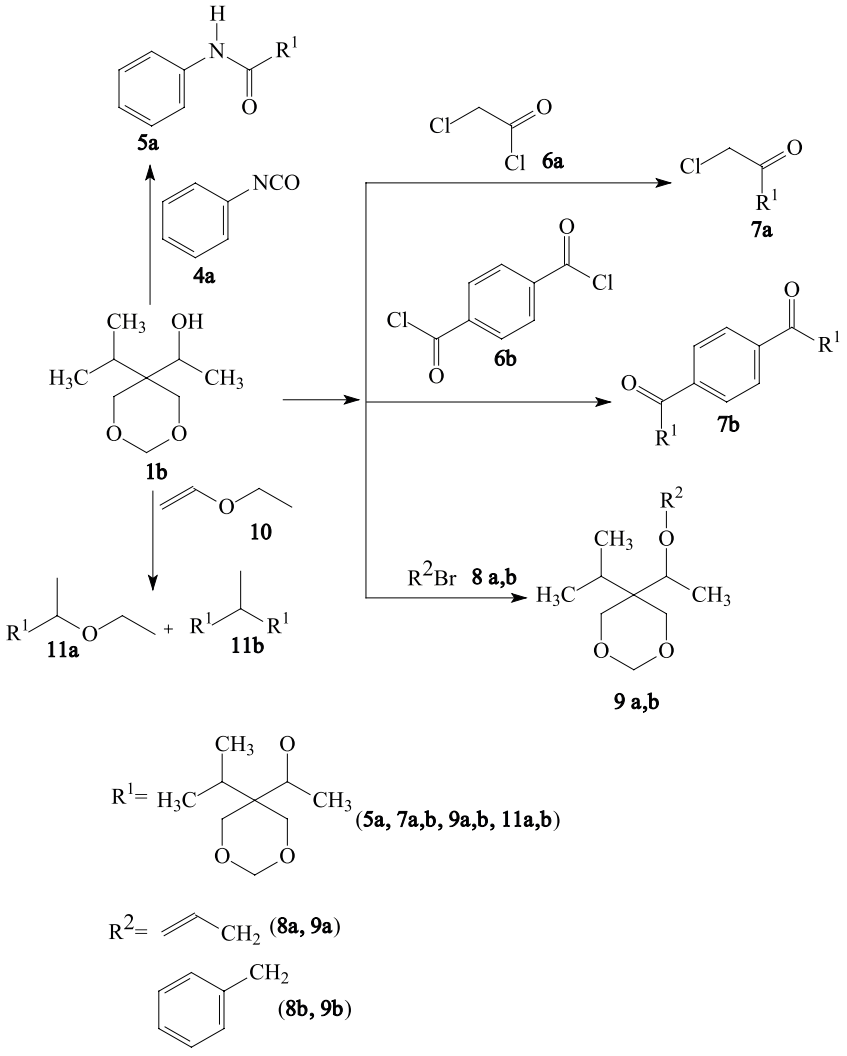

Fig. 2. Scheme of reactions of 1-(5-isopropyl-1,3-dioxan-5-yl)ethanol **1b**.

Table 1. Effect of the ether : alcohol molar ratio on the yield of reaction products (0.5 wt % KU-2-8, 0–5°C, 3 h)

Ether : alcohol mole ratio	Yield of acetals, %
10 : **1b** = 1 : 10	**11a** = 12%, **11b** = 72%
10 : **1b** = 10 : 1	**11a** = 70%, **11b** = 15%
10 : **1b** = 1 : 1	**11a** = 30%, **11b** = 65%

Ethers **9a** and **9b** were obtained by alkylation of alcohol **1b** allyl-**8a** and benzyl-**8b** bromides (70–90% yield of the corresponding derivatives).

The addition of 1-(5-isopropyl-1,3-dioxan-5-yl)ethanol **1b** to ethyl vinyl ether **10** resulted in a mixture of mono-**11a** and di-**11b** acetals (Table 1).

At a 10-fold excess of alcohol **1b**, almost complete substitution of the ethoxy group is observed with a more than 70% yield of symmetrical acetal **11b**. In the absence of alcohol, the main product is unsymmetrical acetal **11a** at a yield 4–5 times higher than that of acetal **11b**. The equimolar ratio of the reactants ether : alcohol leads to a mixture of unsymmetrical and symmetrical acetals **11a** and **11b**, the latter being dominant.

It was of interest to determine the effect of the synthesized compounds on anticoagulation and antiaggregation activity *in vitro* according to the method presented in the recommendation [20].

The indicators of the effect of compounds on the hemostasis system under *in vitro* conditions are presented in Table 2.

Table 2. Effect of newly synthesized compounds and reference drugs on platelet aggregation, Me (0.25–0.75)

Compound	Latent period, % to control	Maximum amplitude, % to control	Aggregation rate, % to control	Time to reach maximum amplitude, % to control
1a	+4.7 (3.8–5.8)††, #	−6.3 (5.2–7.4)*, ††, ##	−3.2 (2.6–4.1)††, #	+11.5 (10.3–12.4)*, †
1b	+15.1 (13.4–16.5)*, †, ##	−3.4 (2.3–5.6)††, #	−11.4 (9.6–12.5)*, ††	−17.4 (15.7–18.6)*, ††, ##
7a	−2.3 (0.5–3.1)††	−1.2 (0.6–1.8) ††, #	−3.9 (1.4–5.2)††, ##	−8.1 (5.8–9.1)*, ††, ##
7b	+14.7 (14.3–18.1)*, †, ##	−19.4 (16.5–20.2)**, ††, #	−13.6 (12.8–17.4)*, †, #	−23.0 (22.6–27.8)**, ††, ##
Acetylsalicylic acid	−2.1 (1.1–2.6)††	−13.7 (10.8–16.4)*, ††	−10.5 (7.6–12.3)*, ††	+10.5 (8.7–13.4)*, ††
Pentoxifylline	+32.4 (28.7–35.6)**, ##	−48.4 (42.7–56.5)**, ##	−34.9 (28.7–39.6)**	+32.1 (27.6–36.4)**, #

Note: *$p \le 0.05$; **$p \le 0.001$ in comparison with the control; † $p \le 0.05$, †† $p \le 0.001$ in comparison with pentoxifylline; # $p \le 0.05$, ## $p \le 0.001$ in comparison with acetylsalicylic acid, $n = 6$.

Table 3. Influence of the newly synthesized compounds and the reference drug on the parameters of the plasma hemostasis link, Me (0.25–0.75)

Compound	Elongation of activated partial thromboplastin time, % to control	Elongation of prothrombin time, % to control	Change in fibrinogen concentration, g/L
1a	+ 10.2 (9.4–11.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
1b	+ 11.7 (9.2–12.3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
7a	+ 9.3 (8.1–11.9)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
7b	+ 12.4 (9.5–12.9)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Sodium heparin	20.3 (19.7–21.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)

Note: † $p > 0.05$ in comparison with the control; compounds versus sodium heparin at $p \leq 0.05$, $n = 6$.

Ester **7a** exhibited antiaggregation activity exceeding the values of acetylsalicylic acid (Table 2). At the same time, **7a** significantly prolonged the latent period, lengthening the reaction of platelet release relative to the control. It should be noted that compounds **1a** and **1b** also reduce the rate of platelet aggregation; however, they are inferior to acetylsalicylic acid in terms of antiaggregation activity, and their antiaggregation activity values are in the range of 3.4–10.4%. Among the studied derivatives of this series, no compounds with a proaggregant effect were found.

All compounds induced hypocoagulation, increasing the activated partial thromboplastin time (APTT) by 6.2–12.4% compared with the control (Table 3); however, the fibrinogen concentration and prothrombin time were not affected. The severity of the effect of the studied compounds was significantly inferior to the effect of heparin, which increased APTT by 20.3%.

CONCLUSIONS

After obtaining derivatives of 5-acetyl- and 5-hydroxyalkyl-1,3-dioxanes under thermal heating conditions, their antiaggressive and anticoagulant activity was studied. Among the synthesized series of compounds, the ester of monochloroacetic acid was found to have the maximum effect on platelet aggregation and the plasma link of hemostasis.

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Sh. Sh. Dzhumaev – conducting research;

N.S. Khusnutdinova – processing of biological research results;

Yu.G. Borisova – collection and processing of the material and writing the text of the article;

R.M. Sultanova – consultations on planning;

S.S. Zlotskii – development of the concept of scientific work, critical revision with the introduction of valuable intellectual content.

The authors declare no conflicts of interest.

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