1-(OXOALKYL)-3,7,8-TRIALKYL-3,7-DIHYDRO-1*H*-PURINE-2,6-DIONES

Alfonz RYBÁR[a], Peter TURČÁNI[b] and Juraj ALFÖLDI[a]

[a]*Institute of Chemistry, Slovak Academy of Sciences, 842 38 Bratislava, The Slovak Republic*
[b]*Department of Neurology, School of Medicine, Comenius University, 813 64 Bratislava, The Slovak Republic*

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1-(2-Oxopropyl)-, 1-(3-oxobutyl)-, and 1-(5-oxohexyl)-3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones (*Ia – Xa*, *Ib – Xb*, and *Ic – Xc*, respectively) were prepared by alkylation of alkali metal salts of 3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *XI – XX* with chloroacetone or 6-chloro-2-hexanone or by addition of the starting diones *XI – XX* to methyl vinyl ketone. The effect of the final compounds *I – X* on aggregation of thrombocytes and erythrocytes was investigated.

Pentoxifylline (1-(5-oxohexyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) and, more recently, propentofylline (1-(5-oxohexyl)-3-methyl-7-propyl-3,7-dihydro-1*H*-purine-2,6-dione) belong to drugs improving microcirculation of blood[1]. Generally, this effect may be achieved by vasodilatation and reduction of peripheral blood flow, increase of the perfusion pressure or lowering blood viscosity[2]. The mentioned purine derivatives improve the microcirculation not only by vasodilatation but predominantly by lowering blood viscosity as a result of higher flexibility and reduced aggregation of erythrocytes and other blood elements.

Pentoxifylline and propentofylline have hydrogen in the position 8 of the purine skeleton. It was of interest how the introduction of an alkyl group into position 8 affects the mentioned properties in the presence of variously long alkyl groups in positions 3 and 7 and an oxoalkyl group in position 1 of the purine nucleus.

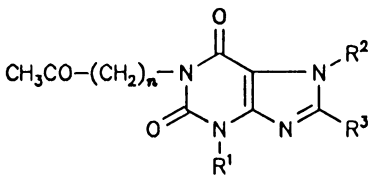
1-(Oxoalkyl)-3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *I – X* were prepared from the corresponding 3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *XI – XX*, described in our previous paper[3], by alkylation with functionalized methyl ketones. The obtained compounds *I – X* were pharmacologically tested. As alkylation reagents we used chloroacetone, methyl vinyl ketone and 6-chloro-2-hexanone.

In the preparation of the 1-(2-oxopropyl) derivatives *Ia – Xa*, the starting purine diones *XI – XX* were first converted in their sodium salts which were then subjected to nucleophilic substitution with chloroacetone in dimethylformamide. A complete reaction of the sodium salts required 20% excess of chloroacetone at 125 °C, the

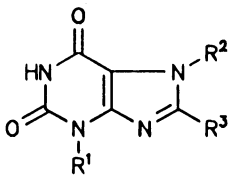
reaction time being 3 h. In preparations of some 1-(2-oxopropyl) derivatives we used successfully the free purinediones in the presence of potassium carbonate in dimethylformamide instead of their sodium salts.

1-(5-Oxohexyl) derivatives *Ic* – *Xc* were prepared analogously by heating the corresponding sodium salts and 6-chlorohexanone at 125 °C for 4 h.

Preparation of 1-(3-oxobutyl) derivatives *Ib* – *Xb* consisted in base-catalyzed nucleophilic addition of purinediones *XI* – *XX* to methyl vinyl ketone. Of the bases tried (alkali metal alkoxides, trimethylbenzylammonium hydroxide), sodium methoxide appeared to be the reagent of choice. Even when 5 equivalents of methyl vinyl ketone were used, the starting compounds *XI* – *XX* did not react completely because of polymerization of the ketone. In order to achieve quantitative conversion, it was necessary to repeat the reaction with another portion (5 equivalents) of methyl vinyl ketone.



I – *X*



XI – *XX*

	R^1	R^2	R^3
I, *XI*	CH_3	CH_3	CH_3
II, *XII*	CH_3	C_2H_5	CH_3
III, *XIII*	CH_3	C_3H_7	CH_3
IV, *XIV*	CH_3	C_4H_9	CH_3
V, *XV*	CH_3	$CH_2C_6H_5$	CH_3
VI, *XVI*	CH_3	CH_3	C_2H_5
VII, *XVII*	CH_3	CH_3	C_3H_7
VIII, *XVIII*	CH_3	CH_3	C_5H_{11}
IX, *XIX*	C_2H_5	CH_3	CH_3
X, *XX*	C_3H_7	CH_3	CH_3

In formulae *I*–*X*: a, $n = 1$; b, $n = 2$; c, $n = 4$

As shown by monitoring the reaction by TLC, for introduction of a given oxoalkyl group, the magnitude of the groups R^1, R^2 and R^3 has only a negligible effect on the reaction rate. The yields and analytical data of the obtained 1-(oxoalkyl) derivatives *I* – *X* are listed in Table I.

The structure of the compounds was confirmed by their analytical data as well as mass and ^1H and ^{13}C NMR spectra. The chemical shifts in ^1H and ^{13}C NMR spectra are given in Table II. The individual signals were assigned on the basis of their multiplicity and in cases of more complicated substituents the ^{13}C NMR signals were assigned using the DEPT and selective decoupling techniques. In addition to the values given in Table II, the spectra of all compounds *I* – *X* exhibit signals due to the purine skeleton (δ_C for C-2 150.1 – 155.0, for C-4 149.3 – 151.3, for C-5 106.5 – 107.4, for C-6 154.1 – 155.4 and for C-8 147.3 – 148.4 ppm).

Compounds *I* – *X* were tested for their effect on aggregation of thrombocytes in full blood as well as in thrombocyte-rich plasma, and for the effect on erythrocyte aggregation. In the first test, the aggregation of thrombocytes was measured by the impedance method on an electronic aggregometer which recorded dependence of the increase in impedance between electrodes (as the result of aggregation of thrombocytes) on time. In the second test, the same parameter was followed by the turbidimetric method on the same instrument; the changes in transmittance due to thrombocyte aggregation were transformed by the aggregometer into voltage changes and recorded as function of time[4].

Both kinds of the thus-obtained aggregation curves were digitized and their amplitudes in % transmission or in Ohms were calculated.

In the third test we made use of erythrocyte aggregometer[5] which registered changes in optical density of the flowing blood due to the presence or absence of erythrocyte aggregates. The formation of aggregates leads to decrease in optical density of blood which is registered as a function of time[6]. The obtained curve has an exponential character and therefore the magnitude of erythrocyte aggregation was expressed as its rate constant in the tenth second. The results of all the three tests are given in Table III as percentage of a control.

The results show that in full blood compounds *IIa*, *IIIa*, *IXa* and *Xa* show the same inhibition of thrombocyte aggregation as propentofylline whereas compounds *IXc*, *Xb* and *Xc* are more effective. Comparison of their structure with the found effectiveness indicates that in full blood the inhibition of thrombocyte aggregation increases with increasing length of the alkyl group at the N-3 atom. Aggregation of thrombocytes in thrombocyte-rich plasma is not inhibited by the purinediones. As concerns the inhibition of erythrocyte aggregation, only compounds *IIa* and *IIIb* show activity nearing to that of propentofylline.

TABLE I
Yields and analytical data of 1-(oxoalkyl)-3,7,8-trisubstituted 3,7-dihydro-1*H*-purine-2,6-diones *I* – *X*

Compound	Yield, % (Method)	M. p., °C Solvent[a]	Formula (M. w.)	Calculated/Found % C	% H	% N	M^+ *m/z*
Ia	79 (*A*)	160 – 161	$C_{11}H_{14}N_4O_3$	52.79	5.64	22.39	250
	76 (*B*)	MeOH	(250.3)	52.78	6.07	22.72	
Ib	49	189 – 191	$C_{12}H_{16}N_4O_3$	54.53	6.10	21.20	264
		THF	(264.3)	54.60	6.13	21.47	
Ic	86	105 – 106	$C_{14}H_{20}N_4O_3$	57.52	6.90	19.17	292
		MeOH	(292.3)	57.26	6.99	19.14	
IIa	65 (*A*)	140 – 142	$C_{12}H_{16}N_4O_3$	54.53	6.10	21.20	264
	50 (*B*)	MTBE–MeOH	(264.3)	54.52	6.27	21.39	
IIc	91	129 – 131	$C_{15}H_{22}N_4O_3$	58.80	7.24	18.29	306
		MTBE–MeOH	(306.4)	58.64	7.34	18.24	
IIIa	77 (*A*)	136 – 138	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13	278
	71 (*B*)	MTBE–MeOH	(278.3)	56.12	6.76	20.26	
IIIb	48	90 – 91	$C_{14}H_{20}N_4O_3$	57.52	6.90	19.17	292
		MTBE–MeOH	(292.3)	57.44	7.15	19.26	
IVa	67 (*A*)	135 – 136	$C_{14}H_{20}N_4O_3$	57.52	6.90	19.17	292
		MTBE–MeOH	(292.3)	57.56	7.03	19.22	
IVc	49	55 – 57	$C_{17}H_{26}N_4O_3$	61.05	7.84	16.75	334
		MTBE	(334.4)	60.87	7.99	16.57	
Va	45 (*A*)	152 – 153	$C_{17}H_{18}N_4O_3$	62.56	5.56	17.17	326
	53 (*B*)	THF–MTBE	(326.3)	62.41	5.68	17.00	
Vb	79	114 – 115	$C_{18}H_{20}N_4O_3$	63.51	5.92	16.46	340
		THF–MTBE	(340.4)	63.51	5.94	16.35	
Vc	45	89 – 90	$C_{20}H_{24}N_4O_3$	65.20	6.56	15.21	368
		THF–MTBE	(368.4)	65.11	6.72	15.10	
VIa	81 (*A*)	159 – 160	$C_{12}H_{16}N_4O_3$	54.53	6.10	21.20	264
	72 (*B*)	MeOH	(264.3)	54.74	6.15	21.33	
VIb	57	175 – 176	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13	278
		THF	(278.3)	56.42	6.53	19.91	
VIc	60	120 – 123	$C_{15}H_{22}N_4O_3$	58.80	7.24	18.29	306
		MTBE–MeOH	(306.4)	58.85	7.23	18.30	
VIIa	88 (*A*)	128 – 130	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13	278
	83 (*B*)		(278.3)	56.29	6.84	20.34	

TABLE I
(*Continued*)

Compound	Yield, % (Method)	M. p., °C Solvent[a]	Formula (M. w.)	Calculated/Found			M^+ *m/z*
				% C	% H	% N	
VIIb	46	132 – 133	$C_{14}H_{20}N_4O_3$	57.52	6.90	19.17	292
		THF	(292.3)	57.50	7.08	19.41	
VIIc	53	83 – 85	$C_{16}H_{24}N_4O_3$	59.98	7.55	17.49	320
		MTBE	(320.4)	59.83	7.41	17.73	
VIIIa	73 (*A*)	105 – 107	$C_{15}H_{22}N_4O_3$	58.80	7.24	18.29	306
	69 (*B*)	MeOH	(306.4)	58.92	7.42	18.41	
IXa	68 (*A*)	149 – 151	$C_{12}H_{16}N_4O_3$	54.53	6.10	21.20	264
	64 (*B*)	THF–MTBE	(264.3)	54.21	6.28	21.50	
IXb	66	166 – 167	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13	278
		THF	(278.3)	56.14	6.57	19.73	
IXc	89	89 – 90	$C_{15}H_{22}N_4O_3$	58.80	7.24	18.29	306
		THF–MTBE	(306.4)	58.71	7.38	18.42	
Xa	68 (*A*)	176 – 178	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13	278
		EtOH	(278.3)	56.20	6.46	19.90	
Xb	48	178 – 180	$C_{14}H_{20}N_4O_3$	57.52	6.90	19.17	292
		THF	(292.3)	57.52	7.10	19.06	
Xc	85	85 – 86	$C_{16}H_{24}N_4O_3$	59.98	7.55	17.49	320
		EtOH	(320.4)	59.86	7.77	17.43	

[a] MTBE methyl tert-butyl ether.

EXPERIMENTAL

The melting points are uncorrected. Depending on their melting points, analytical samples were dried over phosphorus pentoxide at 40 °C/65 Pa for 10 h or at 100 °C/65 Pa for 8 h. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 (300 MHz and 75 MHz, respectively) instrument in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were taken on a Jeol 100 D spectrometer (ionizing energy 70 eV). The reactions were monitored by TLC on Silufol UV_{254} (Kavalier, The Czech Republik) in chloroform–methanol 9 : 1. The purity of the compounds *I* – *X* was checked by HPLC on a 15 × 0.3 cm column Separon SGX RPS (Tessek Ltd., The Czech Republic), mobile phase water–acetonitrile 7 : 3, flow rate 0.3 ml/min, detection at 278 nm. The purity of the compounds for the farmacological testing was at least 99.9%.

TABLE II
NMR spectra of compounds *I* – *X*

Compound	Spectrum	δ, ppm
Ia	^{1}H	2.26 s, 3 H (CH_3CO); 2.48 s, 3 H (C(8)–CH_3); 3.55 s, 3 H (N(3)–CH_3); 3.88 s, 3 H (N(7)–CH_3); 4.82 s, 2 H (N(1)–CH_2)
	^{13}C	13.0 (C(8)–CH_3); 27.1 (CH_3CO); 29.6 (N(3)–CH_3); 49.9 (N(1)–CH_2); 201.1 (CH_3CO)
Ib	^{1}H	2.19 s, 3 H (CH_3CO); 2.48 s, 3 H (C(8)–CH_3); 2.81 t, 2 H (N(1)–CH_2); 3.54 s, 3 H (N(3)–CH_3); 3.90 s, 3H (N(7)–CH_3); 4.26 t, 2 H ($COCH_2$)
	^{13}C	12.9 (C(8)–CH_3); 29.3 (CH_3CO); 29.7 (N(3)–CH_3); 31.6 (N(7)–CH_3); 36.2 ($COCH_2$); 41.5 (N(1)–CH_2); 206.4 (CH_3CO)
Ic	^{1}H	1.65 m, 4 H (N(1)–$CH_2CH_2CH_2$); 2.15 s, 3 H (CH_3CO); 2.47 s, 3 H (C(8)–CH_3); 2.50 t, 2 H (N(1)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 3.92 s, 3 H (N(7)–CH_3); 4.00 t, 2 H ($COCH_2$)
	^{13}C	13.0 (C(8)–CH_3); 20.9 (N(1)–CH_2CH_2); 27.4 (N(1)–$CH_2CH_2CH_2$); 27.4 (CH_3CO); 29.9 (N(3)–CH_3); 31.8 (N(7)–CH_3); 40.6 (N(1)–CH_2); 43.1 ($COCH_2$); 208.0 (CH_3CO)
IIa	^{1}H	1.40 t, 3 H (N(7)–CH_2CH_3); 2.27 s, 3 H (CH_3CO); 2.48 s, 3 H (C(8)–CH_3); 3.55 s, 3 H (N(3)–CH_3); 4.28 q, 2 H (N(7)–CH_2); 4.82 s, 2 H (N(1)–CH_2)
	^{13}C	13.0 (C(8)–CH3); 15.8 (N(7)–CH_2CH_3); 27.1 (CH_3CO); 29.7 (N(3)–CH_3); 40.5 (N(7)–CH_2); 49.9 (N(1)–CH_2); 201.2 (CH_3CO)
IIc	^{1}H	1.35 t, 3 H (N(7)–CH_2CH_3); 1.60 m 4 H (N(1)–$CH_2CH_2CH_2$); 2.18 s, 3 H (CH_3CO); 2.43 s, 3 H (C(8)–CH_3); 2.45 t, 2 H (N(1)–CH_2); 3.48 s, 3 H (N(3)–CH_3); 3.95 t, 2 H ($COCH_2$); 4.26 q, 2 H (N(7)–CH_2)
	^{13}C	13.0 (C(8)–CH_3); 15.9 (N(7)–CH_2CH_3); 21.0 (N(1)–CH_2CH_2); 27.4 (N(1)–$CH_2CH_2CH_2$); 29.5 (CH_3CO); 29.9 (N(3)–CH_3); 40.4 (N(7)–CH_2); 40.6 (N(1)–CH_2); 43.1 ($COCH_2$); 208.5 (CH_3CO)
IIIa	^{1}H	0.90 t, 3 H (N(7)–$CH_2CH_2CH_3$); 1.78 sc, 2 H (N(7)–CH_2CH_2); 2.22 s, 3 H (CH_3CO); 2.45 s, 3 H (C(8)–CH_3); 3.52 s, 3 H (N(3)–CH_3); 4.15 t, 2 H (N(7)–CH_2); 4.78 s, 2 H (N(1)–CH_2)
	^{13}C	10.8 (N(7)–$CH_2CH_2CH_3$); 13.2 (C(8)–CH_3); 23.9 (N(7)–CH_2CH_2); 27.1 (CH_3CO); 29.6 (N(3)–CH_3); 46.9 (N(7)–CH_2); 201.1 (CH_3CO)
IIIb	^{1}H	0.97 t, 3 H (N(7)–$CH_2CH_2CH_3$); 1.82 sc, 2 H (N(7)–CH_2CH_2); 2.19 s, 3 H (CH_3CO); 2.48 s, 3 H (C(8)–CH_3); 4.28 t, 2 H ($COCH_2$); 3.55 s, 3 H (N(3)–CH_3); 4.20 t, 2 H (N(7)–CH_2); 2.81 t, 2 H (N(1)–CH_2)
	^{13}C	10.7 (N(7)–$CH_2CH_2CH_3$); 13.1 (C(8)–CH_3); 23.8 (N(7)–CH_2CH_2); 29.4 (N(3)–CH_3); 29.7 (CH_3CO); 36.4 (CH_2CO); 41.6 (N(1)–CH_2); 46.8 (N(7)–CH_2); 206.4 (CH_3CO)
IVa	^{1}H	0.96 t, 3 H (N(7)–$CH_2CH_2CH_2CH_3$); 1.39 sc, 2 H (N(7)–$CH_2CH_2CH_2$); 1.76 qi, 2 H (N(7))–CH_2CH_2); 2.26 s, 3 H (CH_3CO); 2.48 s, 3 H (C(8)–CH_3); 3.56 s, 3 H (N(3)–CH_3); 4.21 (N(7)–CH_2); 4.82 s, 2 H (N(1)–CH_2)
	^{13}C	13.2 (C(8)–CH_3); 13.8 (N(7)–$CH_2CH_2CH_2CH_3$); 19.7 (N(7)–$CH_2CH_2CH_2$); 27.1 (N(7)–CH_2CH_2); 27.1 (CH_3CO); 29.6 (N(3)–CH_3); 45.3 (N(7)–CH_2); 49.9 (N(1)–CH_2); 201.1 (CH_3CO)

TABLE II
(*Continued*)

Compound	Spectrum	δ, ppm
IVc	^{1}H	0.96 t, 3 H (N(7)–$CH_2CH_2CH_2CH_3$); 1.38 se, 2 H (N(7)–$CH_2CH_2CH_2CH_3$); 1.65 m, 4 H (N(1)–$CH_2CH_2CH_2CH_3$); 1.77 qi, 2 H (N(7)–$CH_2CH_2CH_3$); 2.14 s, 3 H (CH_3CO); 2.47 s, 3 H (C(8)–CH_3); 2.50 t, 2 H (N(1)–CH_2); 3.55 s, 3 H (N(3)–CH_3); 4.01 t, 2 H ($COCH_2$); 4.23 t, 2 H (N(7)–CH_2)
	^{13}C	13.2 (C(8)–CH_3); 13.6 (N(7)–$CH_2CH_2CH_2CH_3$); 19.7 (N(7)–$CH_2CH_2CH_2CH_3$); 21.0 (N(1)–$CH_2CH_2CH_3$); 27.4 (N(1)–$CH_2CH_2CH_2CH_3$); 29.5 (N(3)–CH_3); 29.8 (CH_3CO); 32.7 (N(7)–$CH_2CH_2CH_3$); 40.7 (N(1)–CH_2); 43.1 ($COCH_2$); 45.3 (N(7)–CH_2); 208.6 (CH_3CO)
Va	^{1}H	2.25 s, 3 H (CH_3CO); 2.42 s, 3 H (C(8)–CH_3); 3.57 s, 3 H (N(3)–CH_3); 4.82 s, 2 H (N(1)–CH_2); 5.49 s, 2 H (N(7)–CH_2); 7.15 – 7.30 m, 5 H (C_6H_5)
	^{13}C	13.5 (C(8)–CH_3); 27.1 (CH_3CO); 29.6 (N(3)–CH_3); 48.3 (N(7)–CH_2); 49.9 (N(1)–CH_2); 126.8, 128.0, 128.9, 135.3 (C_6H_5); 201.0 (CH_3CO)
Vb	^{1}H	2.17 s, 3 H (CH_3CO); 2.42 s, 3 H (C(8)–CH_3); 2.81 t, (N(1)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 4.28 t, 2 H ($COCH_2$); 5.51 s, 2 H (N(7)–CH_2); 7.19 – 7.33 m, 5 H (C_6H_5)
	^{13}C	13.4 (C(8)–CH_3); 29.5 (N(3)–CH_3); 29.8 (CH_3CO); 36.4 ($COCH_2$); 41.6 (N(1)–CH_2); 48.2 (N(7)–CH_2); 126.9, 127.9, 128.8, 135.1 (C_6H_5); 206.4 (CH_3CO)
Vc	^{1}H	1.65 m, 4 H (N(1)–$CH_2CH_2CH_2$); 2.12 s (CH_3CO); 2.42 s, 3 H (C(8)–CH_3); 2.49 t, 2 H (N(1)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 4.01 t, 2 H ($COCH_2$); 5.23 s, 2 H (N(7)–CH_2); 7.18 – 7.30 m, 5 H (C_6H_5)
	^{13}C	13.6 (C(8)–CH_3); 21.0 (N(1)–CH_2CH_2); 29.6 (N(3)–CH_3); 29.9 (CH_3CO, N(1)–$CH_2CH_2CH_2$); 40.7 (N(1)–CH_2); 43.2 ($COCH_2$); 48.3 (N(7)–CH_2); 126.9, 128.1, 129.0, 135.6 (C_6H_5); 208.6 (CH_3CO)
VIa	^{1}H	1.35 t, 3 H (C(8)–CH_2CH_3); 2.24 s, 3 H (CH_3CO); 2.78 q, 2 H (C(8)–CH_2); 3.57 s, 3 H (N(3)–CH_3); 3.84 s, 3 H (N(7)–CH_3); 4.82 s 2 H (N(1)–CH_2)
	^{13}C	11.6 (C(8)–CH_2CH_3); 20.2 (C(8)–CH_2); 27.1 (CH_3CO); 29.6 (N(3)–CH_3); 31.5 (N(7)–CH_3); 49.8 (N(1)–CH_2); 201.2 (CH_3CO)
VIb	^{1}H	1.35 t, 3 H (C(8)–CH_2CH_3); 2.19 s, 3 H (CH_3CO); 2.75 q, 2 H (C(8)–CH_2); 2.80 t, 2 H (N(1)–CH_2); 3.55 s, 3 H (N(3)–CH_3); 3.90 s, 3 H (N(7)–CH_3); 4.28 t, 2 H ($COCH_2$)
	^{13}C	11.7 (C(8)–CH_2CH_3); 20.2 (C(8)–CH_2); 29.6 (N(3)–CH_3); 29.9 (CH_3CO); 31.5 (N(7)–CH_3); 36.4 ($COCH_2$); 41.7 (N(1)–CH_2); 206.6 (CH_3CO)
VIc	^{1}H	1.35 t, 3 H (C(8)–CH_2CH_3); 1.65 m, 4 H (N(1)–$CH_2CH_2CH_2$); 2.14 s, 3 H (CH_3CO); 2.50 t, 2 H (N(1)–CH_2); 2.77 q, 2 H (C(8)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 3.91 s, 3 H (N(7)–CH_3); 4.00 t, 2 H ($COCH_2$)
	^{13}C	11.6 (C(8)–CH_2CH_3); 20.2 (C(8)–CH_2); 20.9 (N(1)–CH_2CH_2); 27.4 (N(1)–$CH_2CH_2CH_2$); 29.5 (CH_3CO); 29.8 (N(3)–CH_2); 31.5 (N(7)–CH_3); 40.5 (N(1)–CH_2); 43.1 ($COCH_2$); 208.6 (CH_3CO)
VIIa	^{1}H	1.03 t, 3 H (C(8)–$CH_2CH_2CH_3$); 1.80 se, 2 H (C(8)–CH_2CH_2); 2.26 s, 3 H (CH_3CO); 2.72 t, 2 H (C(8)–CH_2); 3.56 S, 3 H (N(3)–CH_3); 3.90 s, 3 H (N(7)–CH_3); 4.82 s, 2 H (N(1)–CH_2)

TABLE II
(*Continued*)

Compound	Spectrum	δ, ppm
VIIa	^{13}C	13.8 (C(8)–$CH_2CH_2CH_2$); 21.0 (C(8)–CH_2CH_2); 27.1 (CH_3CO); 28.6 (C(8)–CH_2); 29.7 (N(3)–CH_3); 31.7 (N(7)–CH_3); 49.8 (N(1)–CH_2); 201.2 (CH_3CO)
VIIb	^{1}H	1.02 t, 3 H (C(8)–$CH_2CH_2CH_3$); 1.79 se, 2 H (C(8)–CH_2CH_2); 2.20 s, 3 H (CH_3CO); 2.72 t, 2 H (C(8)–CH_2); 2.81 t, 2 H (N(1)–CH_2); 3.55 s, 3 H (N(3)–CH_3); 3.86 s, 3 H (N(7)–CH_3); 4.24 t, 2 H ($COCH_2$)
	^{13}C	13.7 (C(8)–$CH_2CH_2CH_3$); 20.9 (C(8)–CH_2CH_2); 28.5 (C(8)–CH_2); 29.4 (CH_3CO); 29.7 (N(3)–CH_3); 31.5 (N(7)–CH_3); 36.2 ($COCH_2$); 41.6 (N(1)–CH_2); 206.5 (CH_3CO)
VIIc	^{1}H	1.05 t, 3 H (C(8)–$CH_2CH_2CH_3$); 1.65 m, 4 H (N(1)–$CH_2CH_2CH_2$); 1.80 se, 2 H (C(8)–CH_2CH_2); 2.15 s, 3 H (CH_3CO); 2.50 t, 2 H (N(1)–CH_2); 2.72 t, 2 H (C(8)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 3.92 s, 3 H (N(7)–CH_3); 4.00 t, 2 H ($COCH_2$)
	^{13}C	13.8 (C(8)–$CH_2CH_2CH_3$); 21.0 (C(8)–CH_2CH_2); 21.0 (N(1)–CH_2CH_2); 27.4 (N(1)–$CH_2CH_2CH_2$); 28.6 (C(8)–CH_2); 29.5 (CH_3CO); 29.9 (N(3)–CH_3); 31.6 (N(7)–CH_3); 40.6 (N(1)–CH_2); 43.1 ($COCH_2$); 208.6 (CH_3CO)
VIIIa	^{1}H	0.93 t, 3 H (C(8)–$CH_2CH_2CH_2CH_2CH_3$); 1.38 m, 4 H (C(8)–$CH_2CH_2CH_2$); 1.75 se, 2 H (C(8)–$CH_2CH_2CH_2CH_2$); 2.26 s, 3 H (CH_3CO); 2.73 t, 2 H (C(8)–CH_2); 3.56 s, 3 H (N(3)–CH_3); 3.88 s, 3 H (N(7)–CH_3); 4.82 s, 2 H (N(1)–CH_2)
	^{13}C	13.9 (C(8)–$CH_2CH_2CH_2CH_2CH_3$); 22.3 (C(8)–$CH_2CH_2CH_2CH_2$); 26.7 (C(8)–$CH_2CH_2CH_2$); 27.2 (CH_3CO); 27.3 (C(8)–CH_2CH_2); 29.7 (N(3)–CH_3); 31.4 (C(8)–CH_2); 31.7 (N(7)–CH_3); 49.9 (N(1)–CH_2); 201.2 (CH_3CO)
IXa	^{1}H	1.33 t, 3 H (N(3)–CH_2CH_3); 2.26 s, 3 H (CH_3CO); 2.47 s, 3 H (C(8)–CH_3); 3.88 s, 3 H (N(7)–CH_3); 4.13 q, 2 H (N(3)–CH_2); 4.81 s, 2 H (N(1)–CH_2
	^{13}C	13.0 (N(3)–CH_2CH_3); 13.3 (C(8)–CH_3); 27.1 (CH_3CO); 31.7 (N(7)–CH_3); 38.5 (N(3)–CH_2); 49.7 (N(1)–CH_2); 201.2 (CH_3CO)
IXb	^{1}H	1.33 t, 3 H (N(3)–CH_2CH_3); 2.20 s, 3 H (CH_3CO); 2.44 s, 3 H (C(8)–CH_3); 2.81 t, 2 H (N(1)–CH_2); 3.90 s, 3 H (N(7)–CH_3); 4.12 q, 2 H (N(3)–CH_2); 4.28 t, 2 H ($COCH_2$)
	^{13}C	12.9 (N(3)–CH_2CH_3); 13.2 (C(8)–CH_3); 29.7 (CH_3CO); 31.6 (N(7)–CH_3); 36.2 ($COCH_2$); 38.2 (N(3)–CH_2); 41.6 (N(1)–CH_2); 206.5 (CH_3CO)
IXc	^{1}H	1.33 t, 3 H (N(3)–CH_2CH_3); 1.66 m, 4 H (N(1)–$CH_2CH_2CH_3$); 2.14 s, 3 H (CH_3CO); 2.47 s, 3 H (C(8)–CH_3); 2.51 t, 2 H (N(1)–CH_2); 3.91 s 3 H (N(7)–CH_3); 4.00 t, 2 H ($COCH_2$); 4.13 q, 2 H (N(3)–CH_2)
	^{13}C	13.0 (N(3)–CH_2CH_3); 13.3 (C(8)–CH_3); 20.9 (N(1)–CH_2CH_2); 27.4 ($COCH_2CH_2$); 29.8 (CH_3CO); 31.7 (N(7)–CH_3); 38.3 (N(3)–CH_2); 40.5 (N(1)–CH_2); 43.1 ($COCH_2$); 208.6 (CH_3CO)
Xa	^{1}H	0.96 t, 3 H (N(3)–$CH_2CH_2CH_3$); 1.78 se, 2 H (N(3)–CH_2CH_2); 2.26 s, 3 H CH_3CO); 2.46 s, 3 H (C(8)–CH_3); 3.88 s, 3 H (N(7)–CH_3); 4.02 t, 2 H (N(3)–CH_2); 4.81 s, 2 H (N(1)–CH_2)

TABLE II
(*Continued*)

Compound	Spectrum	δ, ppm
Xa	^{13}C	11.0 (N(3)–$CH_2CH_2CH_3$); 13.0 (C(8)–CH_3); 21.3 (N(3)–CH_2CH_2); 27.1 (CH_3CO); 31.7 (N(7)–CH_3); 44.8 (N(3)–CH_2); 49.8 (N(1)–CH_2); 201.2 (CH_3CO)
Xb	^{1}H	0.88 t, 3 H (N(3)–$CH_2CH_2CH_3$); 1.79 se, 2 H (N(3)–CH_2CH_2); 2.19 s, 3 H (CH_3CO); 2.44 s, 3 H (C(8)–CH_3); 2.81 t, 2 H (N(1)–CH_2); 3.85 s, 3 H (N(7)–CH_3); 4.02 t, 2 H (N(3)–CH_2); 4.29 t, 2 H ($COCH_2$)
	^{13}C	11.0 (N(3)–$CH_2CH_2CH_3$); 13.0 (C(8)–CH_3); 21.2 (N(3)–CH_2CH_2); 29.8 (CH_3CO); 31.7 (N(7)–CH_3); 36.3 ($COCH_2$); 41.6 (N(1)–CH_2); 44.7 (N(3)–CH_2); 206.5 (CH_3CO)
Xc	^{1}H	0.96 t, 3 H (N(3)–$CH_2CH_2CH_3$); 1.65 m, 4 H ($COCH_2CH_2CH_2$); 1.78 se, 2 H (N(3)–CH_2CH_2); 2.14 s, 3 H (CH_3CO); 2.45 s, 3 H (C(8)–CH_3); 2.50 t, 2 H (N(1)–CH_2); 3.90 s, 3 H (N(7)–CH_3); 4.00 t, 2 H (N(3)–CH_2); 4.02 t, 2 H ($COCH_2$)
	^{13}C	11.1 (N(3)–$CH_2CH_2CH_3$); 13.1 (C(8)–CH_3); 21.0 (N(1)–CH_2CH_2); 21.3 (N(3)–CH_2CH_2); 27.4 ($COCH_2CH_2$); 29.9 (CH_3CO); 31.8 (N(7)–CH_3); 40.6 (N(1)–CH_2); 43.2 ($COCH_2$); 44.8 (N(3)–CH_2); 208.7 (CH_3CO)

1-(2-Oxopropyl)-3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *Ia* – *Xa*

Method A. The purinedione *XI* – *XX* (10 mmol) was dissolved under stirring and gentle heating in a mixture of sodium ethoxide (1 mol l^{-1}, 10 ml, 10 mmol) and ethanol (40 ml) and the solvent was evaporated to dryness under diminished pressure. The dry sodium salt was mixed with dimethylformamide (60 ml) and chloroacetone (1.17 g, 1.01 ml, 12 mmol) and heated to 125 °C (bath temperature) for 3 h under stirring. The dimethylformamide was then evaporated under diminished pressure, the remaining syrup was mixed with chloroform (50 ml) and traces of the starting compounds *XI* – *XX* were removed by extraction with dilute sodium hydroxide solution (0.5 mol l^{-1}, 2 × 20 ml). The chloroform solution was dried over sodium sulfate and purified by passing through a short column of silica gel (100 – 160 μm, 12 g, eluent chloroform). After concentration to dryness under diminished pressure, the product was crystallized from an appropriate solvent.

Method B. A stirred mixture of purinedione *XI* or *XIII* (10 mmol), potassium carbonate (1.66 g, 12 mmol), dimethylformamide (16 ml) and chloroacetone (1.17 g, 1.01 ml, 12 mmol) was heated to 125 °C for 3 h. Dimethylformamide was distilled off under diminished pressure, the residue was mixed with chloroform (30 ml), the insoluble salts were filtered off and the filtrate was purified analogously as described for method *A*.

1-(5-Oxohexyl)-3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *Ic* – *Xc*

These compounds were prepared analogously as described for compounds *Ia* – *Xa* (method *A*) except that 6-chloro-2-hexanone[7] (1.56 g, 1.73 ml, 12 mmol) was used instead of chloroacetone. The reaction was performed at 125 °C for 4 h.

1-(3-Oxobutyl)-3,7,8-trialkyl-3,7-dihydro-1*H*-purine-2,6-diones *Ib* – *Xb*

The purinedione *XI* – *XX* (10 mmol) was dissolved in dioxane (50 – 100 ml) at about 70 °C and the solution was cooled to room temperature. Methyl vinyl ketone (3.50 g, 4.1 ml, 50 mmol) and methanolic solution of sodium methoxide (1 mol l^{-1}, 0.4 ml) were added and the mixture was heated to 60 °C (bath) for 1 h in a nitrogen atmosphere. After cooling, another portion of methyl vinyl ketone (50 mmol) and methanolic sodium methoxide (0.4 ml) was added and the mixture was again heated to 60 °C for 1 h. The volatile material was distilled off under diminished pressure, the residue was dissolved in chloroform and traces of the starting compound *XI* – *XX* were extracted with dilute sodium hydroxide solution (0.5 ml l^{-1}, 2 × 20 ml). The further work-up procedure was the same as described in method *A*.

TABLE III
Pharmacological evaluation of compounds *I* – *X*

Compound	Aggregation of platelets[a]		k^d, %
	A_1[b]	A_2[c]	
Ia	100.7 ± 6.8	98.6 ± 12.2	115.5 ± 33.5
Ib	90.4 ± 9.1	100.9 ± 6.5	105.3 ± 5.5
Ic	105.6 ± 47.4	100.1 ± 9.3	95.9 ± 15.7
IIa	82.1 ± 10.4[e]	95.3 ± 12.0	86.6 ± 5.4[e]
IIc	99.9 ± 16.4	101.3 ± 9.8	88.0 ± 15.6
IIIa	87.0 ± 9.4[f]	94.1 ± 8.5	95.4 ± 6.2
IIIb	101.4 ± 8.5	93.9 ± 10.4	89.5 ± 9.7[f]
IVa	88.9 ± 11.7	96.0 ± 14.2	101.1 ± 8.1
IVb	96.8 ± 11.6	103.3 ± 11.4	97.1 ± 18.4
IVc	81.0 ± 21.3	106.6 ± 8.9	94.7 ± 14.6
Vb	99.6 ± 16.6	91.1 ± 9.1	90.9 ± 11.4
VIa	103.7 ± 8.2	95.1 ± 21.5	113.1 ± 19.2
VIc	83.5 ± 25.1	105.1 ± 12.3	98.4 ± 14.4
VIIa	104.2 ± 14.9	93.3 ± 16.9	106.3 ± 22.3
VIIb	89.9 ± 10.4	106.3 ± 3.1	102.1 ± 11.2
VIIc	101.0 ± 16.9	103.7 ± 9.8	92.5 ± 15.0
VIIIa	91.1 ± 20.3	107.8 ± 18.3	115.0 ± 29.6
IXa	90.2 ± 5.4[f]	96.7 ± 17.2	91.7 ± 13.8
IXb	101.0 ± 15.7	98.9 ± 6.0	100.8 ± 11.4
IXc	66.6 ± 23.9[f]	108.9 ± 9.3	100.5 ± 16.4
Xa	84.2 ± 6.4[e]	98.4 ± 8.4	90.7 ± 25.0
Xb	78.8 ± 15.2[f]	103.5 ± 6.9	92.9 ± 11.6
Xc	62.1 ± 27.2[f]	97.3 ± 7.4	99.8 ± 15.4

[a] Measured with a Chrono-log Model 530 electronic aggregometer; [b] amplitude of aggregation curve in whole blood, % of control, A_1 for propentophylline 78% of control; [c] amplitude of aggregation curve in platelet rich plasma, % of control; [d] rate constant of aggregation of erythrocytes at 10 s, measured with a red blood cell aggregometer constructed according to ref.[5], k for propentophylline 83% of control; [e] $p < 0.01$; [f] $p < 0.05$.

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