8-Substituted 7-(Oxoalkyl)theophyllines

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8-Substituted 7-(oxoalkyl)theophyllines were synthesized by alkylation of the respective theophyllines with chloroacetone or 6-chloro-2-hexanone, and alternatively, by addition of 8-substituted theophylline to methyl vinyl ketone. The effect of final compounds on aggregation of blood platelets and red blood cells was tested.
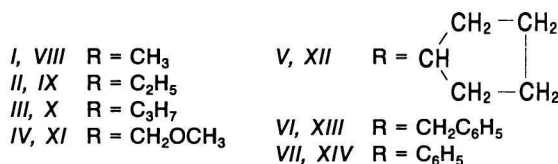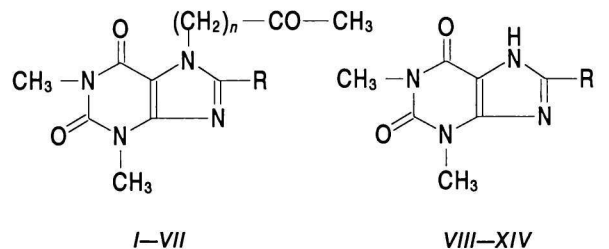
Several oxoalkylxanthines as *e.g.* pentoxifylline [1-(5-oxohexyl)theobromine], propentofylline [1-(5-oxohexyl)-7-propyl-3-methylxanthine], and lomifylline [7-(5-oxohexyl)theophylline] are drugs improving blood circulation in cerebrum and peripheral regions of the body. Improvement of blood circulation in this case is due not only to vasodilatation but preferentially to platelet aggregabilities [1]. All the three above-mentioned medicament molecules have hydrogen in position 8 of their purine skeleton. It was of interest whether the hitherto not reported oxoalkylxanthines with a hydrocarbon residue in position 8 of the purine ring system would change the platelet aggregation. This paper is a continuation of our previous study [2] on analogous 1-oxoalkyl-3,7,8-trialkylxanthines.

The 7-oxoalkyl-8-alkyltheophyllines *I—VII* chosen for these pharmacological experiments were synthesized from the corresponding 8-alkyltheophyllines *VIII—XIV* prepared according to known procedures [3—5]. The starting 8-alkyltheophyllines *VIII—XIV* were alkylated with functionalized methyl ketones (chloroacetone, methyl vinyl ketone, 6-chloro-2-hexanone). A 5—20 mole % excess of the alkylating reagent, the presence of potassium carbonate and a 3 h heating in dimethylformamide at 120—125 °C were needed to complete the reaction of chloroacetone with the starting compounds *VIII—XIV*. A greater excess of the reagent and higher temperatures were applied with reactants bearing bulkier substituents in position 8 of the purine ring (cyclopentyl, phenyl, benzyl). Reactants with unsaturated substituents (vinyl, styryl) gave products greatly contaminated with polymeric tars preventing thus to isolate them in the pure form and reasonable yields (more than 10 %).

Of 7-oxoalkyl derivatives with a longer oxoalkyl chain the following representatives were prepared: 7-(3-oxobutyl)-8-methyltheophylline (*Ib*), 7-(5-oxohexyl)-8-methyltheophylline (*Ic*), and 7-(5-oxohexyl)-8-propyltheophylline (*IIIc*). The first one, *Ib*, was ob-

tained by a base-catalyzed nucleophilic addition of 8-methyltheophylline (*VIII*) to methyl vinyl ketone in dioxane; sodium methoxide and trimethylbenzylammonium hydroxide (Triton B) were found to be convenient catalysts. It is worth noting that only a 50 mole % excess of methyl vinyl ketone (against a 1000 mole % excess required with 1-oxobutyl derivatives) was sufficient for a complete reaction of the starting *VIII* to furnish compound *Ib* in contrast with preparation of 1-(3-oxobutyl)xanthine reported in our previous paper [2]. This finding might be rationalized by a greater acidity of the proton in position 7 than of that in position 1 and consequently, by an easier course of the nucleophilic addition. Further compounds with a longer oxoalkyl group, *Ic* and *IIIc*, were obtained by alkylation of xanthine with 6-chloro-2-hexanone in a 10 mole % excess under analogous conditions as with oxopropylxanthines *Ia—VIIa* excepting the reaction time, which was doubled. Yields and other specific data of the final 7-oxoalkyl derivatives *I—VII* are listed in Table 1.

The structure of xanthines *I—VII* was proved by elemental analyses, mass, ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{13}C NMR shifts are presented in Tables 2 and 3. The respective signals were as-

I—VII   VIII—XIV

I, VIII   R = CH₃   V, XII   R = CH⟨CH₂—CH₂ / CH₂—CH₂⟩
II, IX   R = C₂H₅
III, X   R = C₃H₇
IV, XI   R = CH₂OCH₃   VI, XIII   R = CH₂C₆H₅
                                      VII, XIV   R = C₆H₅

In formulae I—VII: a n = 1, b n = 2, c n = 4.

Table 1. Characteristic Data of 8-Substituted 7-(Oxoalkyl)theophyllines *I—VII*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C (Solvent)	M⁺ m/z
		C	H	N			
Ia	$C_{11}H_{14}N_4O_3$ 250.3	52.79 52.86	5.64 5.96	22.39 22.67	57	227—228 (Ethanol)	250
Ib	$C_{12}H_{16}N_4O_3$ 264.3	54.53 54.31	6.10 6.19	21.20 21.45	55	151—153 (Tetrahydrofuran— *tert*-butyl methyl ether)	264
Ic	$C_{14}H_{20}N_4O_3$ 292.3	57.52 57.38	6.90 7.01	19.17 19.17	44	125—128 (Methyl ethyl ketone)	292
IIa	$C_{12}H_{16}N_4O_3$ 264.3	54.53 54.64	6.10 6.34	21.20 21.28	56	203—204 (Methanol)	264
IIIa	$C_{13}H_{18}N_4O_3$ 278.3	56.10 56.14	6.52 6.68	20.13 20.24	90	142—144 (Ethanol)	278
IIIc	$C_{16}H_{24}N_4O_3$ 320.4	59.98 60.14	7.55 7.82	17.49 17.64	58	85—88 (Ethanol)	320
IVa	$C_{12}H_{16}N_4O_3$ 280.3	51.42 51.44	5.75 5.87	19.99 20.08	85	158—159 (Methanol)	280
Va	$C_{15}H_{20}N_4O_3$ 304.3	59.19 59.21	6.62 6.83	18.41 18.67	67	185—186 (Methanol)	304
VIa	$C_{17}H_{18}N_4O_3$ 326.3	62.56 62.64	5.56 5.71	17.17 17.33	86	186—187 (Ethanol)	326
VIIa	$C_{16}H_{16}N_4O_3$ 312.3	61.53 61.60	5.16 5.38	17.94 18.01	69	224—226 (Ethanol)	312

signed according to their multiplicities, DEPT and selective decoupling techniques were employed for assignment of the ^{13}C NMR signals in the more complex structures.

Compounds *I—VII* were tested both for aggregation of blood platelets and red blood cells in the whole blood as well as for aggregation of blood platelets in the platelet-rich plasma. Platelet aggregation in the

Table 2. ^{1}H NMR Spectra of Compounds *I, III—VII*

Compound	Chemical shift, δ				
	N-1—CH$_3$	N-3—CH$_3$	CH$_3$CO	N-7—CH$_2$	C-8—R
Ia	3.26	3.49	2.29	5.08	2.24 (CH$_3$)
IIIa	3.27	3.50	2.25	5.07	0.91 (CH$_3$), 1.69 (CH$_2$), 2.50 (C-8—CH$_2$)
*IIIc**	3.38	3.57	2.17	4.25	1.02 (CH$_3$), 1.65 (CH$_2$), 2.57(C-8—CH$_2$)
IVa	3.33	3.60	2.32	5.30	3.58 (CH$_3$O), 4.57 (C-8—CH$_2$)
Va	3.33	3.58	2.33	5.30	1.65—2.00 (CH$_2$), 2.88 (CH)
VIa	3.37	3.62	2.13	5.03	4.10 (C-8—CH$_2$), 7.15—7.35 (C$_6$H$_5$)
VIIa	3.39	3.64	2.33	5.13	7.40—7.60 (C$_6$H$_5$)

*δ = 1.82 (CO—CH$_2$CH$_2$CH$_2$), 2.72 (CO—CH$_2$CH$_2$CH$_2$).

Table 3. ^{13}C NMR Spectra of Compounds *I, III—VII*

Compound	Chemical shift, δ					
	N-1—CH$_3$	N-3—CH$_3$	CH$_3$CO	N-7—CH$_2$	CH$_3$CO	C-8—R
Ia	27.5	29.5	26.9	53.5	199.4	12.7 (CH$_3$)
IIIa	27.5	29.5	26.9	53.4	199.6	13.6 (CH$_3$), 20.9 (CH$_2$), 28.3 (C-8—CH$_2$)
*IIIc**	29.5	30.0	27.4	42.2	207.4	13.6 (CH$_3$), 19.9 (CH$_2$), 28.2 (C-8—CH$_2$)
IVa	27.7	29.7	26.8	53.8	199.6	58.5 (C-8—CH$_2$), 66.6 (CH$_3$O)
Va	27.6	29.6	27.0	53.4	199.9	25.5 (CH—CH$_2$—CH$_2$), 32.0 (CH—CH$_2$—CH$_2$), 36.4 (CH—CH—CH$_2$)
VIa	27.7	29.8	26.8	53.8	199.3	33.7 (C-8—CH$_2$), 127.4, 128.2, 129.0, 134.8 (C$_6$H$_5$)
VIIa	27.8	29.8	27.1	54.9	200.2	127.8, 128.9, 129.0, 130.6 (C$_6$H$_5$)

*δ = 21.0, 29.2 (CO—CH$_2$—CH$_2$—CH$_2$), 44.4 (CO—CH$_2$—CH$_2$—CH$_2$).

whole blood was quantified by means of electronic aggregometer [2]. The aggregometer recorded the impedance increase between electrodes as a result of blood platelet aggregation. For monitoring of blood platelet aggregation in the platelet-rich plasma optical aggregometer based on the turbidimetric method was used. The instrument transferred transmittance changes associated with blood platelet aggregation into voltage changes and recorded them as time-variable. The effect in both tests was evaluated by means of the amplitude of aggregation curves. The third test was carried out with red blood cell aggregometer recording the time dependence of optical changes of flowing blood due to the presence or absence of red blood cell aggregates. The aggregation response was quantified on the basis of rate constants taken at the tenth second.

Results listed in Table 4 are the percentual quotients of the native to the lowered aggregations. In contrast with other 1-oxoalkylxanthines described in our previous paper [2] none of the 7-oxoalkylxanthines under investigation revealed activity of the propentofylline reference. This result is associated evidently with the shift of the oxoalkyl grouping from position 1 to position 7 of the heterocyclic ring system.

Table 4. Pharmacological Evaluation of Compounds *I, III—VII*[a]

| Compound | Aggregation of blood platelets[b] | | Aggregation of red blood cells k^c/% |
	in the whole blood A_1/%	in the platelet-rich plasma A_2/%	
Ia	98.9 ± 18.8	104.0 ± 10.3	115.5 ± 35.4
Ic	104.7 ± 22.0	104.1 ± 17.4	108.8 ± 24.6
IIIa	87.5 ± 23.9	107.3 ± 17.4	103.6 ± 8.9
IIIc	102.4 ± 26.3	106.8 ± 8.6	100.7 ± 32.2
IVa	95.8 ± 23.4	105.6 ± 10.4	106.4 ± 14.6
Va	97.1 ± 14.2	102.5 ± 10.2	109.8 ± 22.0
VIa	111.3 ± 17.2	105.1 ± 9.3	110.1 ± 10.1
VIIa	93.2 ± 12.2	104.9 ± 17.1	119.1 ± 27.4

a) A_1, A_2 — amplitude of the aggregation curve; k — rate constant of aggregation at the 10th second; A_1, A_2 and k — value of native aggregation (as control) = 100 %. b) A_1 for propentofylline = 78 %; c) k for propentofylline = 83 %.

EXPERIMENTAL

The melting points are uncorrected. Samples for analyses were dried over phosphorus pentaoxide at temperatures in the 40—100 °C interval at 65 Pa pressure for 10 h to 8 h, depending on the melting points of the individual compounds. The mass spectra were measured with a Jeol 100-D spectrometer at ionization energy 70 eV. The ^1H and ^{13}C NMR spectra of deuterochloroform solutions containing tetramethylsilane as an internal reference were recorded with a Bruker AM-300 apparatus operating at 300 MHz and 75 MHz, respectively. The reaction course was monitored by TLC on Silufol$_{254}$ sheets (Kavalier, Czech Republic) in chloroform—methanol (φ_r = 9 : 1). Purity of the final compounds *I—VII* was verified by HPLC (Laboratorní přístroje, Prague, Czech Republic) on a 15 cm × 0.3 cm column packed with Separon SGX RPS (Tessek, Czech Republic) using the mobile phase water—acetonitrile (φ_r = 7 : 3); flow rate 0.3 cm^3 min^{-1}, UV detector (278 nm). Purity of compounds for pharmacological tests was found to be at least 99.9 mass %. The blood platelet aggregation experiments were run with an electronic aggregometer Chrono-log, model 530 and the red blood cell aggregations were measured with red blood cell aggregometer assembled according to Ref. [6].

8-Substituted 7-(2-Oxopropyl)theophyllines *Ia—VIIa*

Method A. The respective compound *VIII—XI* (20 mmol), potassium carbonate (2.90 g; 21 mmol), dimethylformamide (30 cm^3) and chloroacetone (2.04 g, 1.75 cm^3, 21 mmol) were heated at 120 °C for 3 h (compound *Ia* for 2 h). The volatile portions were distilled off under reduced pressure; chloroform (30 cm^3) was added to the distillation residue, the inorganic salts and the unreacted starting material were extracted with 1 M sodium hydroxide (20 cm^3), the organic layer was washed with water (3 × 10 cm^3), dried (Na$_2$SO$_4$) and purified through a short silica-gel packed column (100—160 μm, 11 g, eluent chloroform). Chloroform was removed from the purified solution under diminished pressure and the product was crystallized from an appropriate solvent.

Method B. The procedure was analogous to that described in method *A* with the difference that only 24 mmol of potassium carbonate (3.32 g), 24 mmol of 95 mass % chloroacetone (2.22 g, 2.02 cm^3) and more dimethylformamide (60 cm^3) were reacted with 20 mmol of the respective compound *XII—XIV* at 125 °C.

7-(3-Oxobutyl)-8-methyltheophylline (*Ib*)

Methyl vinyl ketone (1.05 g, 1.29 cm^3, 15 mmol) and a catalytic amount of trimethylbenzylammonium hydroxide (0.1 cm^3 of methanolic solution, 400 g dm^{-3}) were added to compound *VIII* (1.95 g; 10 mmol) dissolved under reflux in dioxane and cooled to room temperature. The mixture was heated at 100 °C with stirring for 1 h, cooled to ambient temperature, basicity of the catalyst was neutralized with acetic acid and the solvent was distilled off under diminished pressure. The residue was dissolved in

chloroform (30 cm³), the unreacted starting compound was extracted with 1 M-NaOH (2 × 10 cm³), the organic layer was washed with water (2 × 10 cm³), dried with Na_2SO_4 and purified through a short silica-gel packed column (100—160 µm, 6 g, eluent chloroform). The product obtained after removal of chloroform *in vacuo* was crystallized from tetrahydrofuran—*tert*-butyl methyl ether.

7-(5-Oxohexyl)-8-propyltheophylline (*IIIc*)

Method A was applied for preparation of the title compound; the starting compound *X* (20 mmol) was treated with 22 mmol of potassium carbonate (3.04 g), chloroacetone was replaced for 6-chloro-2-hexanone [7] (2.96 g, 2.86 cm³, 21 mmol) and the temperature 120 °C was kept for 6 h.

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Influence of Structure on Antimicrobial Activity of Some Heterocycles
III. 1-Substituted 2-Methyl-5-nitroimidazoles

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Several 1-(3-alkyl- resp. 3-arylthio-2-hydroxypropyl)-2-methyl-5-nitroimidazoles were prepared starting from ornidazole. Some sulfones as well as sulfoxides were obtained by oxidation of corresponding sulfides by hydrogen peroxide. The structure of the prepared compounds was confirmed on the basis of IR, mass, NMR spectral data and elemental analysis. Antimicrobial activity of these compounds was also determined. No significant results were found in this respect.

5-Nitroimidazoles are chemotherapeutically important as antiprotozoal and antibacterial agents [1—4]. Many of them are good amebicides [5] and trichomonacides [6—8]. Some other compounds of this group are very effective against a variety of protozoan infections [1, 8—11] or exhibit antibiotic properties [12].

In our previous papers [13, 14] we have found that some nitrogen heterocycles substituted with a longer alkyl chain exhibit remarkable antimicrobial activity especially against gram-positive bacteria. This finding promoted us to study in this respect also some 5-nitroimidazoles having various alkyl chain at N-1

atom. For comparison, aryl substitution was also studied. As a starting material we chose ornidazole — 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*I*) and 1-(2,3-epoxypropyl)-2-methyl-5-nitroimidazole (*II*) prepared from *I* by alkaline dehydrohalogenation [15].

Displacement of chlorine atom in *I* as well as the ring-opening displacement reaction of *II* with sulfur nucleophiles proceeded smoothly under formation of corresponding sulfides (*III—XV*) in good yields (Scheme 1). When the above sulfides were treated with hydrogen peroxide in acetic acid, corresponding sulfones were produced. In the case of com-