2.5. 3-(4-Nitrobenzyl)-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3e**)

Yield: 52.0%, m.p: 287 °C. IR (KBr) cm^{-1}: 1644 (C=O, γ-pyron), 1683, 1738 (C=O, thiazolidinedione ring). ^1H NMR (DMSO-d_6): δ = 5.10 (s, 2 H, CH_2), 6.97 (s, 1 H, 3-H), 7.46 (ddd, 1 H, 6-H), 7.57–8.17 (m, 10 H, 7,8,2′,3′,5′,6′,a,a′,b,b′-H)), 8.18 (s, 1 H, =CH), 8.22 (d, 1 H, 5-H). MS (EI): m/z (%) = 484 (5.00) $[M]^{+\cdot}$, 278 (100), 221 (12.34), 136 (10.53), 120 (27.80), 102 (5.63), 101 (5.55), 92 (83.55), 63 (88.82).
$C_{26}H_{16}N_2O_4S$ (484)

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The kinetics of alkaline hydrolysis of 1-methyl-2-piperidinoethyl esters of alkyloxyphenylcarbamic acid

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The 1-methyl-2-piperidinoethyl esters of phenylcarbamic acid, substituted at the positions 2, 3 or 4 of the benzene ring by an alkyloxy substituent – 2-hexyloxy- (**1**), 2-heptyloxy- (**2**), 3-heptyloxy (**3**), and 4-heptyloxy (**4**) have been prepared by Pokorná et al. [1]. These substances possess high local anaesthetic activity, comparable with that of heptacaine (*N*-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-piperidine chloride, (**5**) and carbisocaine (*N*-[2-methyl-2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-diethylamonium chloride, (**6**) [2, 3]. The aim of this work was to determine the rate constants of alkaline hydrolysis of the new potential local anaesthetic drugs **1–4** at increased temperature and to compare these values with the rate constants of hydrolysis of **5** and **6** [4], as well as the study of hydrolysis of **2** in buffer solutions. In alkaline media, these substances decompose to final products – substituted aniline, basic alcohol, and carbon dioxide. The studied substances possess the branched connecting chain between the carbamate functional group and the basic part of the molecule. This is the difference to piperidinoethyl esters of phenylcarbamic acid. Substance **2** differs from **6** in the basic part of the molecule. In the Table the values for second order rate constants at 60, 65, 70 and 75 °C and values of activation parameters E_A, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are presented. It follows from the results that the rate constants decrease depends on the size of the alkyloxy substituent. The 4-substituted derivative shows the slowest rate of hydrolysis. The influence of the position of the substituent on the benzene ring on the rate of hydrolysis is more distinct at higher temperature. The values of rate constants of hydrolysis of the studied substances at 60 °C are significantly higher than those of the piperidinoethyl esters [4, 5]. The rate of hydrolysis of **1** is approximately six times slower than that of its analogue. The rate of hydrolysis of **2** is approximately five times slower than that of **5**. The branching in the connecting chain – the methyl in α-position is advantageous in view of stability, because the methyl group protects the carbamate functional group sterically. In contrary, the rate of hydrolysis of **2** is approximately two times higher than that of **6**. These substances differ in the basic part of the molecule.

The values of activation parameters of the compounds are in accordance with values of other derivatives of phenylcarbamic acid esters [4].

Hydrolysis of compound **2** was also studied in media of different pH values at equal ionic strength of the reaction medium ($\mu = 0.1\ mol \cdot l^{-1}$). As reaction media for stability testing [6], buffers were chosen with different concentrations of sodium hydroxide, where the presence of ethanol was required because of the low basic solubility of compounds. In all cases the ethanol concentration was equal to 50% (v/v). The dependence of log k on sodium hydroxide concentration at 70 °C is shown in the Fig. It follows from the results that **2** is stable in aqueous-ethano-

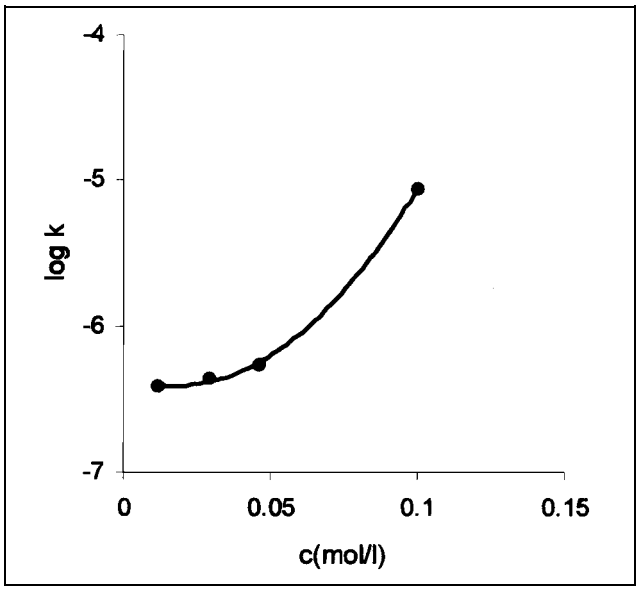
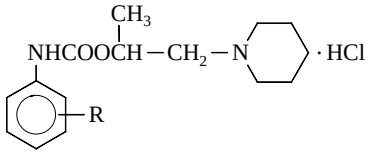


Fig.: Dependence of log k(s^{-1}) of compound **2** on sodium hydroxide concentration at 70 °C. Ionic strength μ = 0.1 mol/l

Table: Studied substances, their rate constants of alkaline hydrolysis and activation parameters



1: 2-OC_6H_{13}
2: 2-OC_7H_{15}
3: 3-OC_7H_{15}
4: 4-OC_7H_{15}

Compd.	Temp. (°C)	$k \cdot 10^5$ ($s^{-1} \cdot l \cdot mol^{-1}$)	$t_{1/2}$ (h)	n	r	F	s	a	b
1	60	3.297 ± 0.135	59	11	0.990	462.8	0.00488	0.0029	0.00504
	65	5.890 ± 0.244	33	11	0.992	581.6	0.00819	−0.0110	0.00898
	70	9.612 ± 0.282	20	10	0.997	1163	0.00780	−0.0104	0.01465
	75	14.21 ± 0.401	14	10	0.997	1254	0.01111	−0.0160	0.02165
2	60	3.118 ± 0.141	63	7	0.995	488.7	0.00227	−0.0016	0.00475
	65	5.651 ± 0.115	35	10	0.998	2420	0.00318	−0.0026	0.00861
	70	8.948 ± 0.275	22	6	0.998	1060	0.00350	−0.0036	0.01364
	75	12.53 ± 0.502	16	7	0.996	623.8	0.01708	−0.0086	0.01910
3	60	4.509 ± 0.089	44	12	0.998	2649	0.00685	−0.0108	0.00675
	65	7.691 ± 0.283	26	16	0.991	735.4	0.01658	−0.0187	0.01134
	70	11.06 ± 0.433	18	13	0.992	653.0	0.01114	−0.0124	0.01632
	75	15.73 ± 0.806	13	11	0.988	380.4	0.02388	−0.0241	0.02330
4	60	3.179 ± 0.121	64	16	0.990	694.0	0.01055	−0.0096	0.00467
	65	3.820 ± 0.185	53	12	0.987	383.1	0.01091	0.0053	0.00561
	70	5.136 ± 0.214	38	14	0.990	572.9	0.01297	−0.0124	0.00795
	75	6.369 ± 0.296	32	8	0.994	462.7	0.00851	−0.0022	0.00944

	E_A ($kJ \cdot mol^{-1}$)	ΔH^+ ($kJ \cdot mol^{-1}$)	ΔS^+ ($J \cdot K^{-1} \cdot mol^{-1}$)
1	94.0 ± 4.9	91.7 ± 4.6	−56.1 ± 13.6
2	89.4 ± 7.0	86.6 ± 7.1	−71.7 ± 20.7
3	74.4 ± 2.5	71.6 ± 2.5	−113.4 ± 7.3
4	45.9 ± 3.0	43.1 ± 3.0	−202.9 ± 8.7

lic buffers at pH 7; basic media have an infavourable influence on its stability in solution.

Experimental

The alkaline hydrolysis of the studied substances was carried out in aqueous-ethanolic NaOH (0.1 $mol \cdot l^{-1}$) in closed flasks tempered in an ultrathermostat at 60.0, 65.0, 70.0 and 75.0 ± 0.2 °C. The buffer solutions at pH 7.0, 8.0 and 9.0 possessed an amount of NaOH in the concentration of 0.0115 $mol \cdot l^{-1}$, 0.0291 $mol \cdot l^{-1}$ and 0.0461 $mol \cdot l^{-1}$, respectively. The ionic strength of buffers was 0.1 $mol \cdot l^{-1}$. Hydrolysis was carried out at 70.0 ± 0.2 °C. The C_2H_5OH concentration was 50% (v/v). The concentration of the studied substances was 0.001 $mol \cdot l^{-1}$. The concentration of the corresponding alkyloxyaniline, produced by the reaction, was determined spectrophotometrically [7], (spectrophotometer Specol 11, Carl Zeiss Jena, Germany). Rate constants of alkaline hydrolysis were calculated using the kinetic equation of the second order. Values of E_A were determined by the Arrhenius equation. Values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were determined by the Eyring equation [8].

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Effect of curing and storage on fluid-bed granules

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Aqueous colloidal polymer dispersions (latexes or pseudolatexes) have been developed as an alternative to organic polymer solutions for the coating of solid dosage forms [1–3]. So films or coatings of water-insoluble polymers can be prepared without toxic organic solvents.

During coating of solid dosage forms with an aqueous polymer dispersion, coalescence of the colloidal polymer particles into a homogeneous film is often incomplete. To overcome this problem, it is recommended to expose the product to elevated temperatures (curing) [4, 5].

The objective of this work was to study the influence of storage time and temperature on granules, coated with a commercial ethylcellulose pseudolatex, Aquacoat®.

Oven-curing of new coated theophylline granules at 70 °C decreased the released amount of drug of about a quarter