Acta Poloniae Pharmaceutica – Drug Research, Vol. 60 No. 4 pp. 253–256, 2003

ISSN 0001-6837
Polish Pharmaceutical Society

HYDROLYSIS OF N,N– AND N,S–DIMETHYL DERIVATIVES OF 2–THIOPHENOBARBITAL

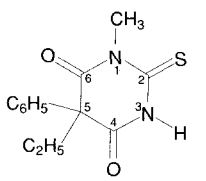
MONIKA TARSA, GRZEGORZ ŻUCHOWSKI and JACEK BOJARSKI

Department of Organic Chemistry, Medical College, Jagiellonian University, 9 Medyczna Str., 30–688 Kraków, Poland

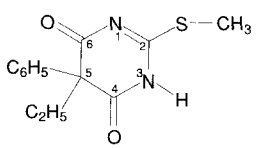
Abstract: Kinetics of hydrolysis of N,N– and N,S–dimethyl–2–thiophenobarbital and products of this reaction were investigated. The UV spectroscopy served as a tool for kinetic investigations and chromatography was used to separate and isolate the main products of hydrolysis. These products were identified by spectroscopic methods and the course of hydrolysis of both isomers was compared.

Keywords: N,N– and N,S–dimethyl–2–thiophenobarbital, hydrolysis, kinetic parameters, hydrolysis products, stability.

In previous papers we reported investigations on kinetics of hydrolysis of N–methyl–2–thiophenobarbital (1) and its S–methyl isomer (2). We were interested to compare these results with those for N,N–dimethyl– (compound **I**) and N,S–dimethyl (compound **II**) derivatives of 2–thiophenobarbital. Besides, N,N–dimethyl–2–thiophenobarbital has no possibility to ionize and thus may serve as model compound for hydrolysis of undissociated species of 2–thiobarbiturates. The separation of hydrolysis products could contribute to elucidation of hydrolysis course of this type of compounds.



I



II

EXPERIMENTAL

N,N– and N,S–dimethyl derivatives of 2–thiophenobarbital (**I** and **II**, respectively) were obtained according to (3). Other experimental details, apparatuses and procedures were the same as described in the preceeding paper. The solvent systems for TLC investigations were: a) chloroform, b) chloroform : toluene : acetone (2:1:1, v/v/v) and c) cyclohexane : ethyl acetate (4:1, v/v) for **I** and d) n–hexane : ethanol : triethylamine (7:1:1, v/v/v) and e) n–hexane : acetone (2:1, v/v) for **II**.

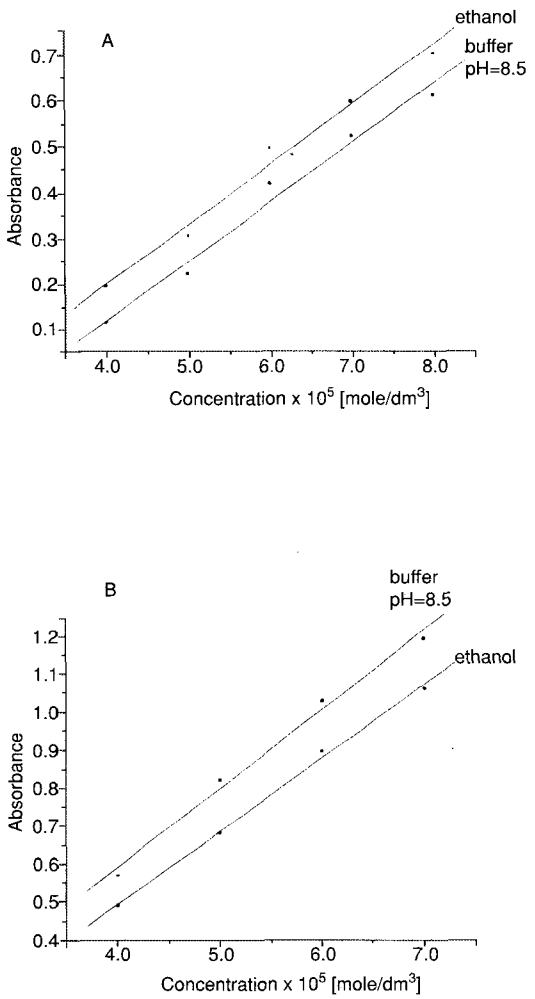


Figure 1. Absorbance–concentration relationships for compound **I** (A) and **II** (B)

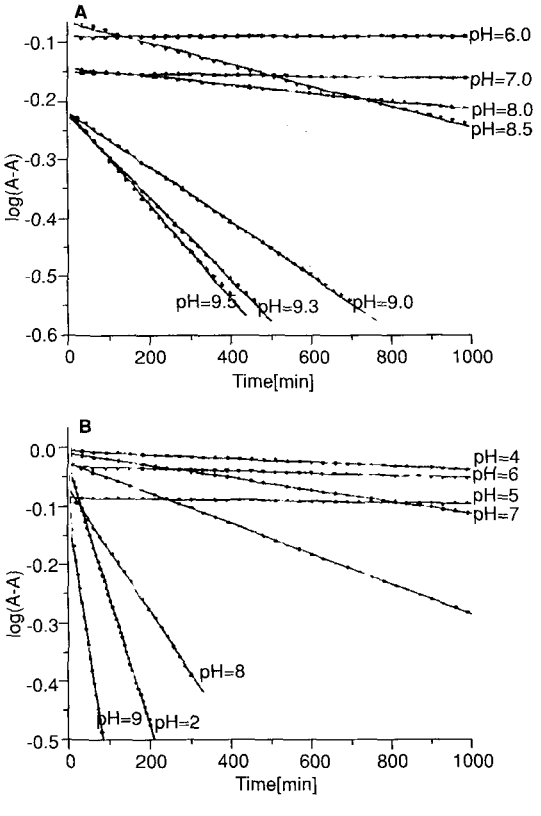


Figure 2. Pseudo–first order plots for hydrolysis of **I** (A) and **II** (B) at different pH values at 25°C

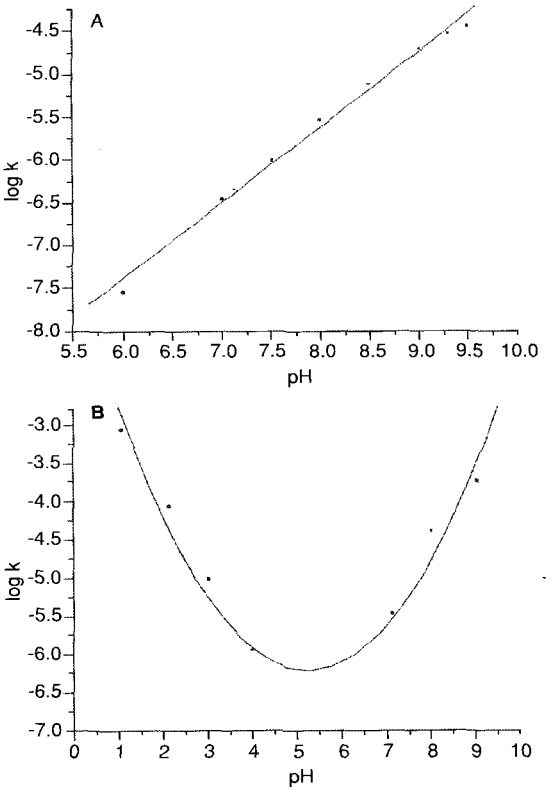


Figure 3. The log k/pH profiles for hydrolysis of **I** (A) and **II** (B) at 25°C

Table 1. Vaules of experimental rate constants (k) for hydrolysis of **I** and **II** at different pH* values

Compound I		
pH**	k × 10^{-5} [s^{-1}]	log k
6.0	0.0699	–6.156
7.0	0.0340	–6.469
7.12	0.0441	–6.356
7.52	0.0951	–6.022
8.0	0.2823	–5.549
8.5	0.7363	–5.133
9.0	1.8470	–4.734
9.3	2.8130	–4.551
9.5	3.3270	–4.478

Compound II		
pH**	k × 10^{-5} [s^{-1}]	log k
1.01	90.3800	–3.047
2.1	8.8910	–4.051
3.0	0.9950	–5.002
4.0	0.1158	–5.936
5.02	0.0271	–6.567
6.0	0.0498	–6.303
7.1	0.3568	–5.454
8.0	4.4210	–4.360
9.3	19.2200	–3.716

* buffers the same as in [2]

** experimental pH measured at 25°C

RESULTS

Linear UV absorbance–concentration relationship was checked in the 4.0 × 10^{-5} – 8.0 × 10^{-5} M range for buffer (pH = 8.5) and ethanol solutions of **I** and **II** (Figure 1). Typical absorbance changes during degradations of **I** and **II** are shown in Figure 2. Plots of log ($A - A\infty$) *vs.* time were linear indicating the pseudo–first order reaction. The rate constants (k) (Table 1) were calculated from the expression:

$$\log (A - A\infty) = \log (A_o - A\infty) - kt/2.303$$

where A_o is the absorbance at time t = 0; $A\infty$ is the final (residual) absorbance and A is the absorbance at time = t.

The calculated rate constants served for construction of log *k/pH* profiles for hydrolysis of both compounds (Figure 3).

The rate constants at different temperatures (between 20 and 45°C) and in various buffers are listed in

Table 2. Values of experimental rate constants (k) for hydrolysis of **I** and **II** at different temperatures

		Compound I (pH = 9.8)		Compound II (pH = 8.5)		Compound II (pH = 3.0)	
Temp. [K]	1/T [$^1/_K$]	$k \times 10^{-4}$	log k	$k \times 10^{-4}$	log k	$k \times 10^{-4}$	log k
293	3.413×10^{-3}	2.3523	–3.639	0.5195	–4.282	0.0302	–5.521
303	3.3×10^{-3}	4.4875	–3.348	1.6220	–3.789	0.0831	–5.080
308	3.25×10^{-3}	6.2374	–3.205	2.3598	–3.627	0.1273	–4.895
318	3.15×10^{-3}	11.7689	–2.929	4.4450	–3.352	0.2172	–4.633
		E_a = 53.01 kJ/mol		E_a = 67.96 kJ/mol		E_a = 61.96 kJ/mol	

Table 3. Spectroscopic data for degradation products of compound **I** and **II**

	H^1 NMR ($CDCl_3$) [ppm]	MS (%)	IR (KBr) [cm^{-1}]
Compound III	0.972 (t, 3H, J = 7.5, CH_3–CH_2–)	250 (20) M^+	
	1.681–1.781 (m, 1H, CH_3–CH_2–)	249 (100) $[C_{13}H_{17}N_2OS]^+$	
	2.044–2.114 (m, 1H, CH_3–CH_2–)	178 (32) $[C_{11}H_{16}NO]^+$	
	3.180 (s, 3H, CH_3–NH–)	117 (8) $[C_8H_5O]^+$	
	3.672 (s, 3H, CH_3–N=)	91 (5) $[C_7H_7]^+$	
	3.810 (t, 1H, J = 7.5, –CH_2–CH–C_6H_5)		
	7.297–7.378 (m, 5H, –C_6H_5)		
	11.592 (s, 1H, –NH–)		
Compound IV	0.962 (t, 3H, J = 7.5, CH_3–CH_2–)	246 (12) M^+	3199 N–H
	2.172 (s, 1H, HO–)	231 (5) $[C_{12}H_{11}N_2O_3]^+$	3092 C–H aromat.
	2.470 (q, 2H, J=7.5, CH_3–CH_2–)	128 (100) $[C_{12}H_{14}N_2O_2]^+$	3067
	3.340 (s, 3H, CH_3–N=)	175 (6) $[C_{11}H_{13}NO]^+$	2979 C–H aliph.
	7.253–7.381 (m, 5H, C_6H_5)	16 (7) $[C_{10}H_{11}NO]^+$	2885
	8.447 (s, 1H, –NH–)	146 (16) $[C_{10}H_{10}O]^+$	1575
		117 (19) $[C_8H_5O]$+	1715 C=O
		91 (7) $[C_7H_7]$+	1689
		77 (5) $[C_6H_5]$+	1435 N–H
Compound V	0.895 (t, 3H, J = 7.5, CH_3–CH_2–)	251 (2) $[C_{13}H_{19}N_2OS]^+$	3212 N–H
	1.753–1.857 (m, 1H, CH_3–CH_2–)	235 (2) $[C_{12}H_{15}N_2OS]^+$	3080 C–H romat.
	2.172–2.274 (m, 1H, CH_3–CH_2–)	220 (2) $[C_{11}H_{12}N_2OS]^+$	3023
	2.436 (s, 3H, CH_3–S–)	203 (2) $[C_{12}H_{15}N_2O]^+$	2967 C–H aliph.
	2.915 (s, 3H, CH_3–N=)	174 (2) $[C_{10}H_{10}N_2O]^+$	1591 C=O
	3.496 (t, 1H, J = 7.5, –CH=)	159 (2) $[C_9H_7N_2O]^+$	1559 N–H
	7.171–7.385 (m, 5H, –C_6H_5)	146 (2) $[C_{10}H_{10}O]$+	1354 C–N
	10.780 (s, 1H, NH=C=)	131 (100) $[C_9H_{11}]^+$	
		119 (2) $[C_4H_7N_2OS]^+$	

Table 2. The Arrhenius equation was used for calculation of activation energies from these data (Table 2).

The results of TLC monitoring of hydrolysis course for **I** and **II** are shown in Figure 4. The structures of the main products of hydrolysis of **I** (compound **III**) and **II** (compound **IV** and **V**) separated by column and circular chromatography and identified by spectroscopic methods are shown in Figure 5. Their spectroscopic data are presented in Table 3.

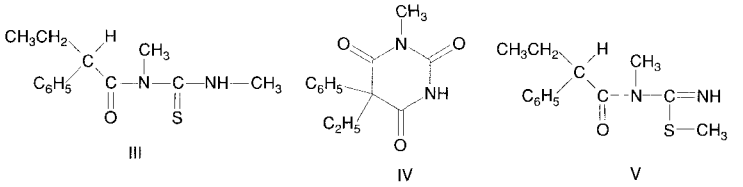


Figure 5. Structures of main hydrolysis products of **I** and **II** in alkaline (**III, V**) and acid (**IV**) medium, respectively.

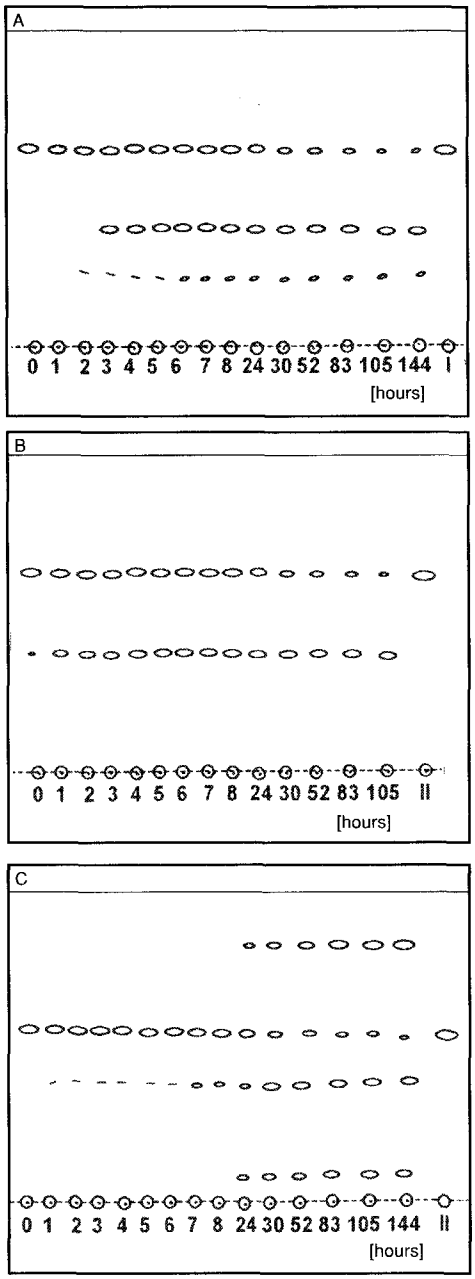


Figure 4. TLC monitoring of hydrolysis of **I** (A – pH = 9.5, at 40°C, mobile phase: chloroform) and **II** (B – pH = 2.5, C – pH = 8.5, at 40°C; mobile phase: n–hexane : ethanol : triethylamine (7:1:1, v/v/v)).

DISCUSSION

The results presented above indicate that hydrolysis of N,N– and N,S–dimethyl derivatives of 2–thiophenobarbital (**I** and **II**, respectively) is a pseudo–first order process. For both compounds the specific hydroxyl ion catalysis was observed in the alkaline region but only for **II** the specific acid catalysis was found. These results are in full agreement with those previously found for N– and S–methyl derivatives of 2–thiophenobarbital (see preceeding paper), but contrary to previous findings the rates of hydrolysis of **I** and **II** in the alkaline region were within the same order of magnitude and the N,S–dimethyl derivative was hydrolyzed even faster than the N,N isomer.

In the alkaline region the hydrolytic pyramidine ring opening is characteristic of both compounds but in the acidic region only desulfuration of **II** was observed and the pyrimidine ring remained intact. Desulfuration was also observed for hydrolysis of S–methyl–2–thiophenobarbital (see preceeding paper) but the product of ring opening and the structure of isourea derivative was also identified.

Since compound **I** cannot ionize and its hydrolysis is still catalyzed by hydroxyl ions, it is quite possible that the hydrolysis of undissociated species of other 2–thiobarbiturates and their oxo analogs follow the same pattern and not the kinetically equivalent attack of water on monoionized species, suggested by their log *k/pH* profiles. The mechanistic pathways of hydrolysis of N–methyl and N,N–dimethyl derivatives are quite similar to those of other barbiturates and 2–thiobarbiturates but those for S–methyl substituted isomers seem more complicated and their full elucidation requires further studies.

Acknowledgment

The work was supported by the Grant No. 4P05F02915 from the Polish State Committee for Scientific Research (KBN), Warszawa, Poland. The authors are indebted to Dr. hab. M. Kłys, from the Department of Toxicology, Institute of Forensic Medicine, Medical College of the Jagiellonian University for enabling LC/MS measurements.

REFERENCES

1. Tarsa M., Bojarski J.: Bull. Acad. Pol. Sci. Chemistry 45, 63 (1997).
2. Tarsa M., Żuchowski G., Bojarski J.: Acta Polon. Pharm. – Drug Res., preceeding paper.
3. Kubaszek M., Paluchowska M., Chmiel E., Bojarski J.: Pol. J. Chem. 68, 117 (1994).

Received: 10.02.2003