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A STUDY OF THE RELATIONSHIP BETWEEN THE STRUCTURE OF HOMOLOGOUS SERIES OF OXPRENOLOL AT VARIOUS pH VALUES

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Abstract: Stability of series of O–acyl esters of oxprenolol prepared as potential pro–drugs, is investigated over the pH range 0,4–10 at 37°C. Maximum stability of all esters occurred at pH 3–4. The most stable derivative was found to be pivaloyl ester. The relationship between Charton Steric parameters (v) and the catalytic rate constant of hydrolysis is investigated.

Keywords: Oxprenolol ester, stability, hydrolysis, pro–drug.

Oxprenolol belongs to a group of drugs which are strongly metabolised even before they get into circulation. Despite good absorption of the therapeutic substance, only 30% of the dose gets into general circulation, what indicated low biological availability of the substance. The use of oxprenolol pro–drugs may improve their pharmaco–kinetic parameters. The pro–drugs of the ester character are subjected to a number of factors facilitating their decomposition like: H^+, OH^-, water molecules, temperature or enzymes. The aim of the reported study was to check the influence of H^+, OH^- and water molecules on the decomposition rate of the oxprenolol esters (E–OXP) used as pro–drugs.

EXPERIMENTAL

Materials, reagents and apparatus

Oxprenolol (Coretal, 1–(2–allyloxyphenoxy)–izopropyl–aminopropan–2–ol

All the used chemicals were of analytical–reagent grade.

Apparatus:

Spectrometer „Specord M–40", Carl Zeiss, Jena; pH–meter, N 517 Mera Elwro, Wrocław.

Analytical procedure

The decomposition was traced by spectrometer VIS (M–40). The selective and simple colorimetric method was used for estimation of esters (E–OXP). The method is based on a formation of an iron hydroxamate complex through the ester group. Absorbance was measured at 530 nm. More detailed description of the method was reported in the previous paper (1).

RESULTS AND DISCUSSION

The hydrolysis kinetics of the oxprenolol derivatives is comparable with earlier studies (2). It was found that the β–adrenolitic esters were hydrolysed to give oxprenolol (2), propranolol (3, 4) or timolol (5) in solutions of pH < 7, but in neutral and alkaline solutions they underwent simultaneous hydrolysis and intramolecular aminolysis to produce the N–acylated products (Scheme 1).

The degradation of all oxprenolol esters was studied in aqueous solution at 37°C over the pH range 0,4–10. The following esters were used:

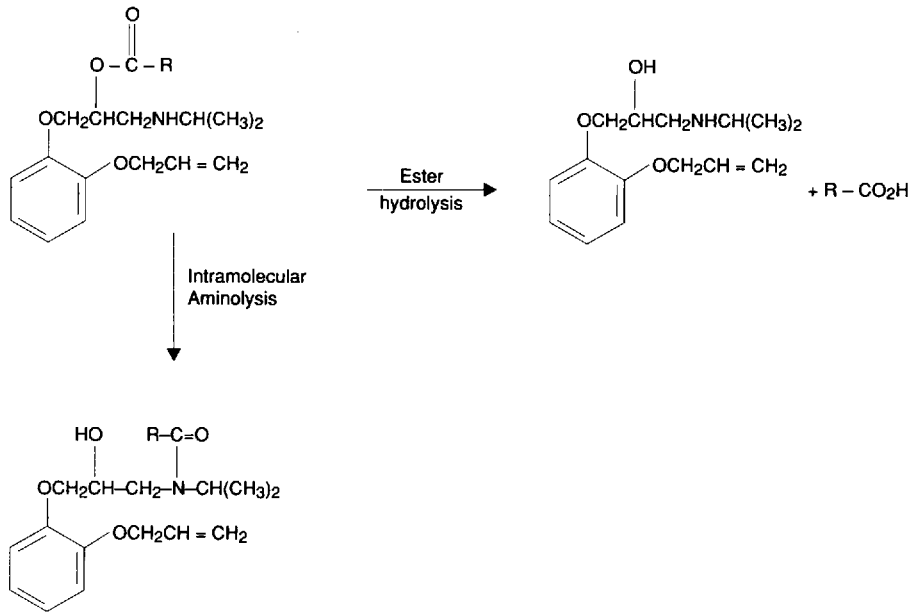
- Acetyl (A–OXP)
- Propanoyl (P–OXP)
- Butyryl (B–OXP)
- Isobutyryl (I–OXP)
- Valeryl (Pent–OXP)
- Capryl (Cap–OXP)
- Pivaloyl (Piv–OXP)
- Caproil (C–OXP)
- Octanoyl (O–OXP)
- Benzoyl (Benz–OXP)
- 2–Cl–benzoyl (Cl–Benz–OXP)

The decomposition of the esters displays strict first–order kinetics according to the rate equation:

$$\ln A_i = \ln A_o - k_{obs} \cdot t \qquad (1)$$

where A_t and A_o are absorbance of E–OXP at time t=i and t=0, respectively. Figure 1 shows the typical first–order plots for the hydrolysis of Benz–OXP. The observed rate constant (k_{obs}) is equal to the slope of the plot $\ln A_i = f(t)$ with opposite sign.

The k_{obs} is equal to the k_{pH} in the hydrochloric acid. The degradation of E–OXP was found to be subject to general acid–base catalysis by some of the buffer substances used in this study. The catalytic effect was examined by measuring the rate of degradation at constant pH, ionic strength and



Scheme 1. Mechanism of the degradation of E-OXP (2).

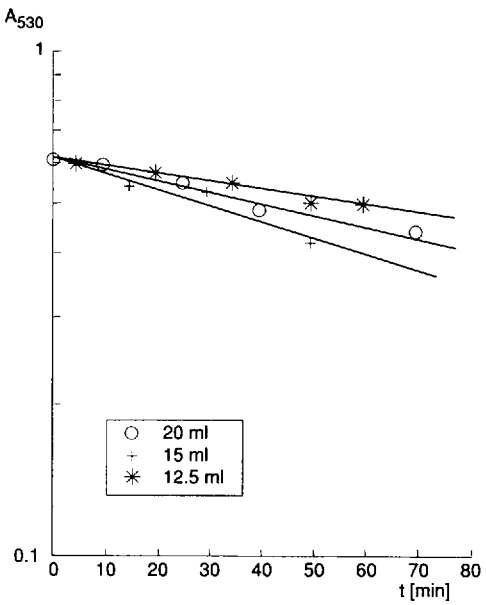


Figure 1. Typical first-order plots for the hydrolysis of Benz-OXP in solutions: a) 20 cm^3 buffer, pH = 9.30; b) 15 cm^3 buffer, pH = 9.30; c) 12.5 cm^3 buffer, pH = 9.30.

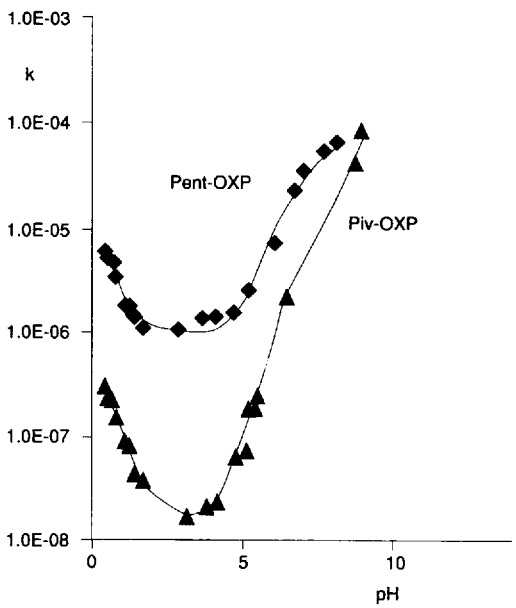


Figure 2. The pH-rate profiles for the degradation of Pent-OXP and of Piv-OXP. The points are the observed apparent first-order rate constants. The lines were calculated from Eq. (3).

temperature, varying only the buffer concentration at a specific pH. The observed rate constant, k_{obs}, in the presence of general acid–base catalysis is described by following equation:

$$k_{obs} = k_{pH} + k_B[B]_T \quad (2)$$

where $[B]_T$ represents the total buffer concentration, k_{pH} is the rate constant at zero buffer concentration, and k_B represents the catalytic effect of buffers. The plots $k_{obs} = f([B]_T)$ are linear with a positive slope equal to k_B. The interval of the ordinate for $B_T = 0$ is equal k_{pH}.

The influence of pH on the rates of hydrolysis of some esters at 37°C was shown in the previous studies (6–10), in which the logarithm of the k_{pH} has been plotted against pH. Figure 2 shows the

typical log k_{pH} = f(pH) profiles for the hydrolysis of Pent–OXP and Piv–OXP.

In the pH–range studied, the E–OXP exist in two different ionic forms:

$$BH^+ \xrightarrow{K'a} B \qquad (3)$$

The values of pK'a were estimated graphically (11) from the profile log k_{pH} = f(pH) (6–10) and are summarized in the previous study (12).
The following scheme has been proposed to account for the observed kinetics:

Reactions		Catalytic rate constants
$BH^+ + H^+$	→ products,	$= k_1$
$BH^+ + H_2O$	→ products,	$= k_2$
$BH^+ + OH^-$	→ products,	$= k_3$
$B + OH^-$	→ products,	$= k_4$

The overall reaction of hydrolysis can be described by following equation:

$$k_{pH} = k_1 \cdot a_{H^+} \cdot f_{BH^+} + k_2 \cdot f_{BH^+} + k_3 \cdot f_{BH^+} \cdot a_{OH^-} + k_4 f_B \cdot a_{OH^-} \qquad (4)$$

where k_1 – is the first–order rate constant for the

Table 1. Rate data for the hydrolysis of various oxprenolol esters in aqueous solution (I = 0,5 mol/l) at 37°C.

E–OXP, HCl	v values (13,14)	k_1 [$mol^{-1} \cdot l \cdot s^{-1}$]	k_2 [s^{-1}]	k_3 [$mol^{-1} \cdot l \cdot s^{-1}$]	k_4 [$mol^{-1} \cdot l \cdot s^{-1}$]
A–OXP (I)	0.52	$3.83 \cdot 10^{-5}$	$5.48 \cdot 10^{-8}$	125	0.359
P–OXP (II)	0.56	$7.61 \cdot 10^{-6}$	$4.80 \cdot 10^{-7}$	40.8	1.35
B–OXP (III)	0.68	$2.19 \cdot 10^{-5}$	$2.84 \cdot 10^{-7}$	109	8.45
Pent–OXP (IV)	0.68	$1.43 \cdot 10^{-5}$	$9.24 \cdot 10^{-7}$	338	14.3
Cap–OXP (V)	0.68	$6.42 \cdot 10^{-6}$	$3.63 \cdot 10^{-8}$	1079	5.13
O–OXP (VI)	0.73	$1.46 \cdot 10^{-6}$	$2.05 \cdot 10^{-7}$	123	7.30
C–OXP (VII)	0.68	$3.50 \cdot 10^{-7}$	$4.20 \cdot 10^{-8}$	2.54	3.94
I–OXP (VIII)	0.76	$6.17 \cdot 10^{-6}$	$8.48 \cdot 10^{-8}$	561	55.8
Piv–OXP (IX)	1.24	$8.94 \cdot 10^{-7}$	$1.51 \cdot 10^{-8}$	30.6	1.72
Benz–OXP (X)	0.57	$6.49 \cdot 10^{-5}$	$1.44 \cdot 10^{-6}$	567	1.56
Cl–Benz–OXP (XI)		$3.68 \cdot 10^{-5}$	$3.68 \cdot 10^{-6}$	7236	0.58

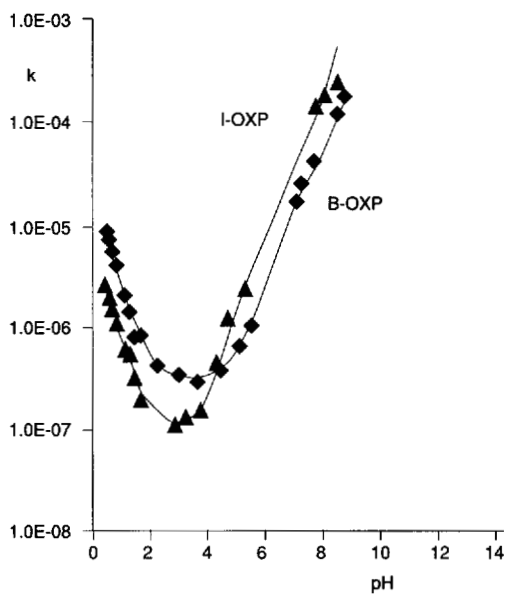


Figure 3. The pH-rate profiles for the degradation of B-OXP and of I-OXP. The points are the observed apparent first-order rate constans. The lines were calculated from Eq. (3).

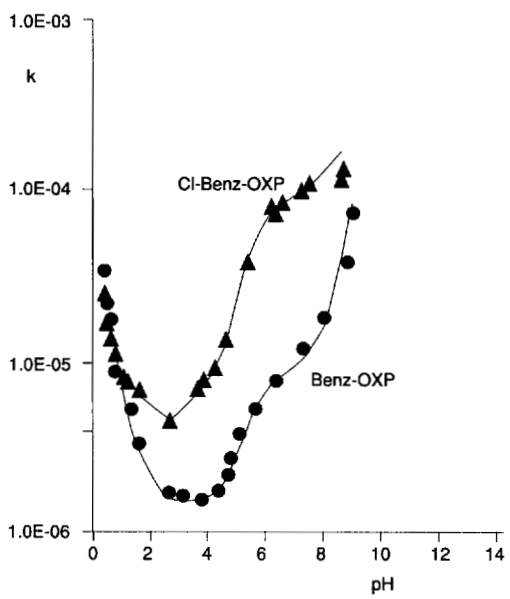


Figure 4. The pH-rate profiles for the degradation of B-OXP and of Cl-Benz-OXP. The points are the observed apparent first-order rate constans. The lines were calculated from Eq. (3).

specific hydrogen ion – catalyzed degradation of the dissociated form of the E–OXP

k_2 – is the first–order rate constant of the dissociated form of the E–OXP for the water – catalyzed degradation

k_3, k_4 – are the rate constants for the hydroxide ion – catalyzed hydrolysis of the dissociated and undissociated forms of the E–OXP, respectively

f_{BH^+}, f_B – are the fractions of the compounds in the dissociated and undissociated forms, respectively.

Figure 2 is the pH–rate profile for the hydrolysis of E–OXP at 37°C and constant ionic strength I = 0,5 mol/l. The line in this figure is defined by Eq. 4, where the points are the rate constants k_{pH}.

Below pH = 1,6 $f_{BH^+} \rightarrow 1$. Plot $k_{obs} = f(a_{H^+})$ is linear and its slope is equal to the catalytic rate constant k_1 (Table 1) which describes the hydrolysis catalyzed by hydrogen ions, while the interval of ordinate for $a_H^+ = 0$ is equal to the catalytic rate constant k_2 (Table 1) which estimates influence of aqueous media. Above pH = 5, the catalysis by hydroxide ions is of the significant importance. It can be assumed, that:

$$k_{pH} = k_3 \cdot a_{OH^-} \cdot f_{BH^+} + k_4 \cdot a_{OH^-} \cdot f_B \qquad (5)$$

The plot $k_{pH}/a_{OH^-} = f(f_B)$ is linear. The values of k_{pH} for $f_B = 1$ is equal to the catalytic rate constant k_4 (Table 1), the interval of the ordinate for $f_B = 0$ is equal to the catalytic rate constant k_3 (Table 1).

The values of catalytic rate constants for the hydrolysis of E–OXP are listed in Table 1.

The optimum pH for maximum stability was found to be in the region 3–4 for compounds. The rate of decomposition depends on the degree of the chain branching, and the esters of much branched chain are characterised by greater stability than those of a straight chain (Figures 2, 3). The most stable compound is the O–pivaloyl derivative. This is probably due to the steric hindrance involving the bulky tert–butyl group in the ester side chain. Cl–Benz–OXP proved to be the most susceptible to hydrolysis among analysed aromatic esters (Figure 4).

The stability of esters is a function of both steric and polar substituent effects.

Since the polar effects of the acyl groups in the aliphatic esters are similar, the observed differences in reactivity in neutral and alkaline solutions may be ascribed to differences in the steric properties. Charton showed, that the rates of acid catalysed esterification are solely a function of steric effects. The relationship between the steric substituent parameter ν (13, 14) and the logarithm of catalytic rate constants for the hydrolysis of E–OXP was investigated.

Hydrolysis under the influence of hydrogen ions is the main reaction of decomposition in low pH solutions. The value log k_1, in terms of value ν (Figure 5), is therefore given by the equation:

$$\log k_1 = -1{,}9237 \cdot \nu - 3{,}7592; \quad (n = 8;\ r = 0{,}7659) \qquad (6)$$

At pH 3–4 the water–catalysed hydrolysis of the esters is the predominant degradation reaction. Also in this case the steric substituent effect is the most important factor determining the relative stability as seen from the plot in Figure 6.

The correlation line is made for the 6 esters. The regression equation between log k_2 (at 37°C) and ν for these esters is given by:

$$\log k_2 = -1{,}9390 \cdot \nu - 5{,}4679;\ (n = 6;\ r = 0{,}8200) \qquad (7)$$

On the base of comparison of the coefficients *a* to ν values in equations 5 and 6, it can be concluded that the similar dependence between k_{pH}

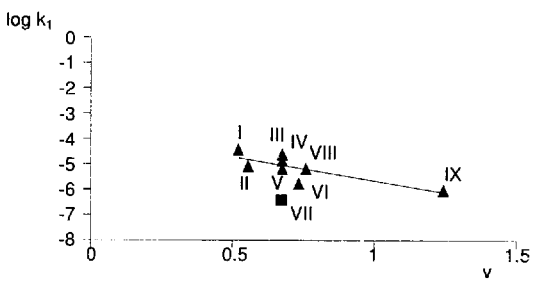


Figure 5. Plot of log k_1 *vs* the steric parameter (*ν*) for various oxprenolol esters.
▲ – the points were used for estimation of the corellation plot
■ – the points were excluded from the correlation plot

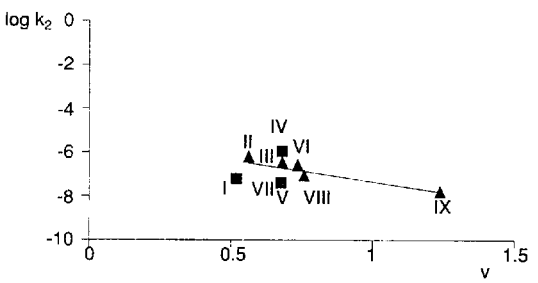


Figure 6. Plot of log k_2 *vs* the steric parameter (*ν*) for various oxprenolol esters.
▲ – the points were used for estimation of the corellation plot
■ – the points were excluded from the correlation plot

and ν exists considering aliphatic oxprenolol esters. Values of *b* in the above equations indicate that esters are more susceptible to hydrolysis in the acid solutions.

In weakly acidic, neutral and basic aqueous solutions, hydrolysis catalysed by hydroxide ions is the main reaction influencing decomposition of ester group. The regression equation between log k_3 (at 37°C) and ν (Figure 7) for these esters is given by:

$$\log k_3 = -1{,}8305 \cdot \nu + 3{,}7756 \; (n = 6; r = 0{,}7214) \quad (8)$$

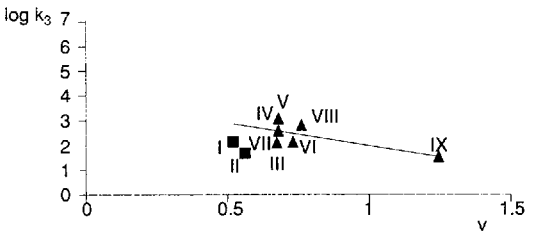


Figure 7. Plot of log k_3 *vs* the steric parameter (ν) for various oxprenolol esters.
▲ – the points were used for estimation of the corellation plot
■ – the points were excluded from the correlation plot

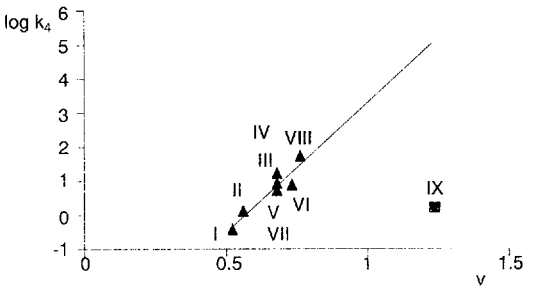


Figure 8. Plot of log k_4 *vs* the steric parameter (ν) for various oxprenolol esters.
▲ – the points were used for estimation of the corellation plot
■ – the points were excluded from the correlation plot

The value log k_4, in terms of value ν (Figure 8), is therefore given by the equation:

$$\log k_4 = 7{,}4863 \cdot \nu - 4{,}2400 \; (n = 8; r = 0{,}9237) \quad (9)$$

The catalytic constant values shows that hydroxide ions, that act on protonised molecules, have the strongest catalytic effect on the decomposition of the all investigated esters. The possible spontaneous (water–catalysed) reaction of the protonated species is the least to the overall reaction.

In the case of the aromatic esters, polar as well as steric effects are important. The most stable ester is Benz–OXP.

REFERENCES

1. Nogowska M.: Chem. Anal. 41, 405 (1996).
2. Jordan C.G.M., Quigley J.M., Timoney R.F.: Int. J. Pharm. 84, 175 (1992).
3. Quigley J.M., Jordan C.G.M., Timoney R.F.: Int. J. Pharm. 101, 145 (1994).
4. Irwin W.J., Belaid K.A.: Int. J. Pharm. 46, 57 (1988).
5. Bundgaard H., Buur A., Chang S.C., Lee V.H.: Int. J. Pharm. 46, 77 (1988).
6. Nogowska M.: Acta Polon. Pharm. 52, 201 (1995).
7. Nogowska M.: Acta Polon. Pharm. 53, 99 (1996).
8. Nogowska M.: Acta Polon. Pharm. 53, 349 (1996).
9. Nogowska M.: Acta Polon. Pharm. 55, 105 (1998).
10. Nogowska M.: Acta Polon. Pharm. 56, 195 (1999).
11. Pawełczyk E., Hermann T.: Podstawy trwałości leków, PZWL, Warszawa 1982.
12. Nogowska M.: Chem. Anal. 44, 97 (1999).
13. Charton M.: J. Am. Chem. Soc. 97, 1552 (1975).
14. Charton M.: J. Org. Chem. 41, 2217 (1976).

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