A Study of the Relationship between the Structure and Physicochemical Parameters of a Homologous Series of Oxprenolol Esters at Various pH Values and Temperatures

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Abstract □ A number of β-adrenergic blockers, including timolol and propranolol, are administered in eyedrops for the treatment of glaucoma, but their therapeutic value is limited by a relatively high incidence of cardiovascular and respiratory side effects. Because of poor ocular bioavailability, many ocular drugs are applied in high concentrations, which give rise to both ocular and systemic side effects. Methods to increase ocular bioavailability include (a) the development of drug delivery devices designed to release drugs at controlled rates, (b) the use of various vehicles that retard precorneal drug loss, and (c) the conversion of drugs to biologically reversible derivatives (prodrugs) with increased corneal penetration properties, from which the active drugs are released by enzymatic hydrolysis. A homologous series of aliphatic esters of oxprenolol were synthesized and investigated as potential prodrugs for ocular use. The stability of each *O*-acyl derivative was investigated in aqueous solutions over the pH range 2.2–9.0 at 37 °C. The observed rate constants (k_{obs}), shelf-lives (t_{90}), lipophilicities, and Arrhenius parameters were determined for each ester. A study of the relationship between the structure and physicochemical parameters of the homologous series of oxprenolol esters at various pH values and temperatures was made.

Introduction

Several β-adrenergic blocking agents, notably propranolol and timolol, are used in glaucoma therapy. The corneal penetration behavior of a number of β-blockers has been investigated.[1−3] Several of these compounds, including propranolol,[4] have been shown to lower intraocular pressure. The hydrophobic properties of these drugs are apparently the primary determinants of their pharmacokinetic and corneal penetration behavior. The development of prodrugs with improved corneal absorption characteristics has been used successfully to enhance the ocular bioavailability of a number of drugs,[5,6] including adrenaline and pilocarpine.

Considerable attention has been focused on the use of bioreversible derivatives (prodrugs) to improve the delivery characteristics of various drugs.[7] A fundamental requisite for the usefulness of the prodrug approach is the ready availability of chemical derivative types satisfying the prodrug requirements, principally reconversion of the prodrug to the parent drug *in vivo*. Esters are the best known prodrugs because of the predominance of carboxylic and hydroxyl substituents in drug molecules and the availability of enzymes in living systems that are capable of hydrolyzing these substituents.

In previous studies,[8−10] esters of timolol were developed to potentially diminish the systemic absorption of topically added timolol by increased corneal absorption, and the cardiovascular and respiratory side effects were thereby reduced. However, these esters are unstable in aqueous solutions, so a series of esters of both propranolol[11−13] and timolol[14,15] were synthesized and the kinetics of degradation of the prodrugs in aqueous solution were studied. Also, the relationship between the structures and physicochemical parameters of the prodrugs was determined.

To further examine the basis of this instability and structure−activity relationships, hydrolytic studies of a homologous series of aliphatic esters of the structurally related β-adrenergic blocker oxprenolol {1-[(1-methylethyl)amino-3-[2(-propenyloxy)phenoxy]-2-propanol} are presented here. Oxprenolol is an important β-adrenergic blocking agent of the 3-aryloxy-1-(alkylamino)-2-propanol type. The overall conformation of the side chain in oxprenolol and its orientation relative to the aromatic ring is virtually identical to that in propranolol hydrochloride. Because of thermal agitation, the bonds of the allyl group are unusually long.[16] Oxprenolol is effective in reducing blood pressure, particularly systolic levels in cats.[17] The feasibility of substituting oxprenolol for adrenergic blockers in the treatment of essential hypertension with relatively minor side effects has been shown[18] in a trial comprising almost 900 patients. The configuration of the biologically more active (−)-isomer is *S*.[19]

Materials and Methods

Apparatus—The homologous series of oxprenolol esters was characterized by a variety of analytical techniques. The ^{1}H NMR spectra were recorded in $CDCL_3$ solution with tetramethylsilane (TMS) as internal standard at 80 MHz with a Bruker Specrospin spectrometer. Mass spectra were obtained with a Kratos M5902 instrument. Spectra were run in an electron impact mode with an ionization energy of 70 eV. The scan was taken over the range 720−30 amu, with perfluorokerosene as the reference compound. Data were processed with a computer system based on an Arcom Stebus computer (80188 processor). The ultraviolet (UV) spectral data were obtained with a Pye Unicam SP-8−100 double-beam spectrometer equipped with a thermostatically controlled cell compartment using 1-cm quartz cells. The infrared (IR) spectral data were recorded with a Pye Unicam SP-3−300 spectrometer with polystyrene as reference. A differential scanning calorimetry (DSC) analysis of each compound was carried out with a Perkin Elmer DSC-20 instrument and a Thermal Analysis Data Station (TADS) for data collection, handling, and presentation. Melting points that were determined from DSC analysis compared favorably with those obtained with a Gallenkamp melting point apparatus.

High-performance liquid chromatography (HPLC) was carried out with a system consisting of a Waters 501 HPLC pump, a variable-wavelength UV detector attached to a Houston omniscribe recorder, and a 20-μL Rheodyne loop injection valve. The column used (100 × 4.6 mm) was packed with Spherisorb C-8 (5-μm particles). A precolumn (50 × 4.6 mm) was similarly packed. A sample of 10 μL was introduced with a Hamilton syringe.

The pH value of each solution was determined with a Radiometer M-26 pH meter fitted with a glass electrode (Radiometer G-202B) and a calomel reference electrode (Radiometer K-401). Reference buffers were Radiometer standard solutions (pH 4.00/22 °C, pH 6.97/22 °C, and pH 8.86/22 °C). A Heto thermostat water bath with a Heto contact thermometer attached was used in all experiments.

Potentiometric titrations were carried out with a Mettler DL 25 automatic titrator fitted with an interchangeable burette and rod

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stirrer with a variable speed adjuster. Results were obtained in tabular form with a GA 44 printer, and a dot matrix graphics printer was used to plot the curve of the titration profile on a GA 14 recorder.

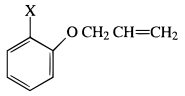
Chemicals—Samples of oxprenolol hydrochloride were obtained from both Ciba-Geigy Ltd. and Sigma Chemical Company (U. K.). The acid chlorides were obtained from Aldrich Chemical Company (U. K.). All solvents used were either HPLC grade or distilled before use. Solid reagents were analytical or reagent grade and were used as supplied or were recrystallized before use.

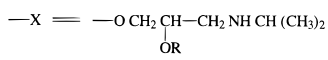
All solvents used in HPLC (i.e., acetonitrile, methanol, acetone, and tetrahydrofuran) were HPLC grade. All buffer substances used were of reagent or analytical grade. The ionic strength of each buffer solution was adjusted to 0.5 by adding a specific quantity of analytical grade potassium chloride. Commercial grade *n*-octanol was used in the partitioning experiments.

Synthesis of Oxprenolol Esters—The homologous series of aliphatic oxprenolol esters was synthesised according to a previously described method.[20]

Stability Studies in Solution—The decomposition of the aliphatic oxprenolol esters was studied in aqueous buffer solutions over the pH range 2.2−9.0 at 37 ± 0.2 °C. Phosphate and citrate buffers were used in the pH range 2.5−5.0, and borate buffers were used in the pH range 8.0−12.0. The total buffer concentration was 0.05 M, and a constant ionic strength (μ) of 0.5 was maintained for each buffer.

The rates of hydrolysis were measured by a reversed-phase HPLC procedure capable of separating the esters from the parent compounds. A mobile phase system consisting of acetonitrile:methanol: 0.02 M phosphate buffer of pH 4.5 (65:5.0:30, v/v) was used. All solvents were deaerated in an ultrasonic bath for 15 min before use. The phosphate buffer was filtered through a Millipore filter and was deaerated. A flow rate of 1.0 mL min^{-1} achieved satisfactory results. The column efluent was monitored at 275 nm.





Compound	R
Oxprenolol (V)	H
O-Acetyl (VI)	-CO CH_3
O-Propionyl (VII)	-CO CH_2CH_3
O-Butyryl (VIII)	-CO $(CH_2)_2CH_3$
O-Valeryl (IX)	-CO $(CH_2)_3CH_3$
O-Pivaloyl (X)	-CO $C(CH_3)_3$

The retention times for the compounds were in the range of 2.65 min (*O*-acetyl) to 9.91 min (*O*-pivaloyl). In the case of the *O*-acetyl derivative, a mobile phase consisting of acetonitrile:methanol:0.02 M phosphate buffer of pH 4.5 (55:5.0:40, v/v) was used to ensure separation. Hydrolysis was initiated by adding 7 mL of the stock solution (20 mg% of each compound in methanol) to 3 mL of buffer solution (pre-equilibrated at the appropriate temperature). At 20-min intervals, 10-μL samples were chromatographed. Quantitation of the compounds was carried out by measuring the peak heights in relation to those of standard solutions that were chromatographed under the same conditions.

Pseudo-first-order rate constants for the hydrolysis were determined from the slopes of linear plots of the logarithm of residual oxprenolol ester versus time.

Determination of Partition Coefficients—The apparent partition (distribution) coefficients (P_{app}) of the oxprenolol esters were determined in the *n*-octanol:buffer system (pH 7.40) at 22 °C by potentiometric titration with a multiparametric curve-fitting technique.[21,22] The method involves the potentiometric titration of the compound both in water and in a rapidly stirred mixture of water and *n*-octanol. The method is rapid and accurate for compounds with ionization constant (pK_a) values between 4 and 10. Distribution coefficients calculated over a range of pH values may be presented graphically as distribution profiles. Subtraction of the titration curve of solvent alone from that of the compound in the solvent allows the calculation of pKa values.

In the cited method,[23] the pK_a and the apparent pK_a [$(pK_a)_{app}$] are obtained, respectively, from the results of potentiometric titrations without and with *n*-octanol present. The log *P* value is calculated from the difference between the pK_a and $(pK_a)_{app}$ values and the volume of water and *n*-octanol.

For the titration of a salt of a weak base with a strong base in the presence of *n*-octanol, the following equations have been derived for the calculation of *P* and P_{app}:

$$P = \frac{V_w}{V_o[10^{pK_a - (pK_a)_{app}} - 1]} \quad (1)$$

$$P_{app} = P(1 - \alpha) = P[10^{pK_a - pH} + 1] \quad (2)$$

$$\alpha = [10^{pH - pK_a} + 1] \quad (3)$$

where *P* is the partition coefficient, P_{app} denotes the distribution coefficient (apparent partition coefficient) at a specific pH, V_w is the aqueous volume, and V_o represents the volume of *n*-octanol.

The value of log P_{app}, in terms of log *P*, is therefore given by the following equation

$$\log P_{app} = \log P - \log (10^{pK_a - pH} + 1) \quad (4)$$

The apparent ionization constant $(K_a)_{app}$ is defined in terms of K_a by 5:

$$K_a = f^{-1}(K_a)_{app} \quad (5)$$

where *f* is a partition factor, which is given by eq 6:

$$f = \left(\frac{V_o P}{V_w} + 1\right) \quad (6)$$

Corresponding expressions may be derived for the titration of the salt of a weak acid with a strong acid. The value of K_a is given by eq 7:

$$K_a = f(K_a)_{app} \quad (7)$$

where *f* is defined by eq 5. The partition coefficient is given by eq 8:

$$P = \frac{V_w}{V_o[10^{(pK_a)_{app} - pK_a} - 1]} \quad (8)$$

and the apparent partition coefficient, P_{app}, is given by eq 9:

$$P_{app} = P\,[10^{pH - pK_a} + 1] \quad (9)$$

The value of log P_{app}, in terms of log *P*, is given by the following equation:

$$\log P_{app} = \log P - \log (10^{pH - pK_a} + 1) \quad (10)$$

Results and Discussion

Kinetics of Degradation of Oxprenolol—The degradation of all the aliphatic oxprenolol esters was studied in aqueous solution at 37 °C over the pH range 2.2−9.0. The decomposition of the esters displayed strict first-order kinetics for several half-lives at constant pH and temperature. Typical first-order plots for the degradation of *O*-acetyloxprenolol are shown in Figure 1. Pseudo-first-order rate constants (k_{obs}) were determined from plots of log (100[*A*]/[A_o]) versus time, where $[A]_o$ and [*A*] are the concentrations at time $t = 0$ and $t = t$, respectively. The value of the rate constant is equal to -2.3026 (slope). The values of the observed pseudo-first-order rate constant (k_{obs}) at each value are given in Table 1.

The rates of degradation for the straight-chain aliphatic derivatives decrease with increasing chain length, the most stable compound being the *O*-pivaloyl derivative and the least

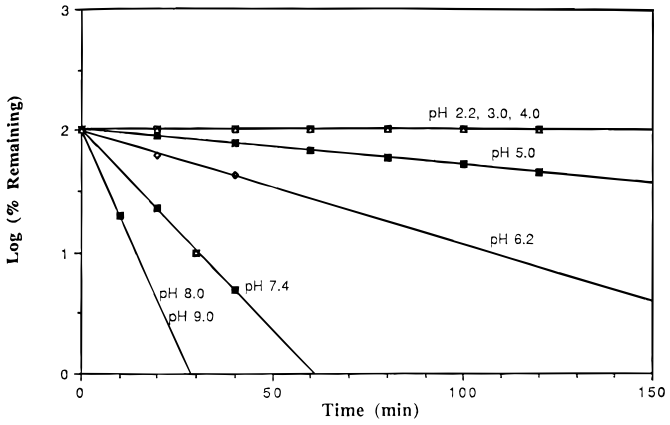


Figure 1—First-order plots for the degradation of *O*-acetyloxprenolol over the pH range 2.2–9.0 at 37 °C.

Table 1—Observed Pseudo-First-Order Rate Constants (k_{obs}) for the Degradation of Oxprenolol Esters in Aqueous Solution at Different pH Values and at 37 °C (μ = 0.5)

	k_{obs} ($\times 10^3$) (min^{-1})							
Ester	pH 2.2	pH 3.0	pH 4.0	pH 5.0	pH 6.2	pH 7.4	pH 8.0	pH 9.0
O-Acetyl	—	—	—	6.7	21.4	75.4	161.8	160.9
O-Propionyl	—	—	—	3.8	18.1	66.2	86.3	91.5
O-Butyryl	—	—	—	—	15.6	36.1	43.8	48.0
O-Valeryl	—	—	—	—	12.7	32.8	40.6	40.9
O-Pivaloyl	—	—	—	—	—	0.3	0.4	0.4

[a] No degradation.

Table 2—Predicted Values of the Shelf-Life (t_{90}) for Various Oxprenolol Esters in Aqueous Solution at Different pH Values and at 37 °C (μ = 0.5)

	t_{90} (min)							
Ester	pH 2.2	pH 3.0	pH 4.0	pH 5.0	pH 6.2	pH 7.4	pH 8.0	pH 9.0
O-Acetyl	—	—	—	15.7	4.9	1.4	0.7	0.7
O-Propionyl	—	—	—	27.7	5.8	1.6	1.2	1.2
O-Butyryl	—	—	—	—	6.8	2.9	2.4	2.2
O-Valeryl	—	—	—	—	8.3	3.2	2.6	2.6
O-Pivaloyl	—	—	—	—	—	309.9	257.0	266.7

[a] No degradation.

stable compound being the *O*-acetyl derivative. Their shelf-lives (t_{90}) of degradation (times for 10% degradation) decrease as the temperature increases. These values are determined with eq 11 and are listed in Table 2:

$$t_{90} = \frac{\ln(1.11)}{k_{obs}} \qquad (11)$$

The results show that the shelf-lives at 37 °C are greatly dependent on the ester structure; the shelf-lives increase as the chain length of the ester increases (Table 2). At pH 5.0 (37 °C), most esters studied do not degrade, indicating a very high stability. The shelf-lives at this temperature are of the order of minutes at pH values >5.0. The influence of pH on the rate of hydrolysis of the esters at 37 °C is shown in Figure 2.

The shape of the pH−rate profiles indicates that (a) the free base and the protonated forms of the esters undergo hydrolysis at different rates and (b) the hydrolysis can be described in terms of specific base-catalyzed reactions involving both species as well as a specific acid-catalyzed reaction involving the protonated ester (Scheme 1). All esters studied are quite stable at pH values <5.0. Consequently, rate constants were

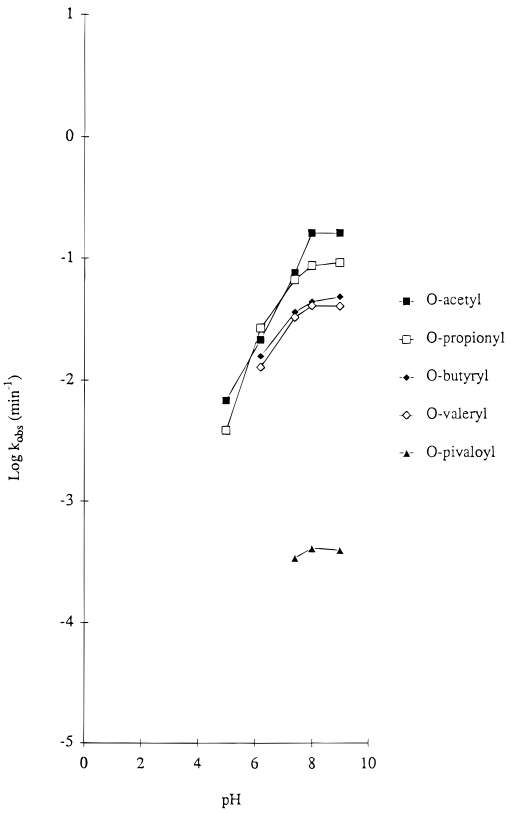
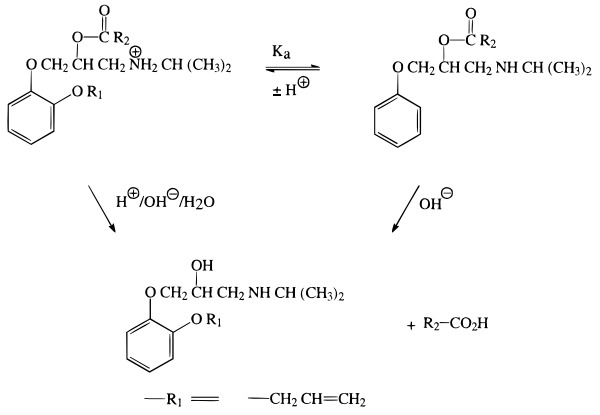


Figure 2—pH–rate profiles for the degradation of aliphatic oxprenolol esters (μ = 0.5) at 37 °C.



Scheme 1

not determined in this pH range. Oxprenolol esters are generally more stable than the corresponding propranolol because of the overriding steric effects (shielding) of the *ortho* substituent on the benzene ring.

The reactivity of the esters is a function of steric and polar factors. Because 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. It was shown[24] that the rates of acid-catalyzed esterification are solely a function of steric effects. The relationship between the steric substituent parameter, ν,[24−26] and the logarithm of the shelf-life was investigated. The literature values of this parameter are listed in Table 3. One would expect a linear relationship for a plot of log t_{90} versus ν for the aliphatic oxprenolol esters at pH 7.4 and 37 °C and that is what was obtained (Figure 3).

As demonstrated by HPLC, the disappearance of almost all the esters studied was accompanied by the progressive ap-

Table 3—Literature Values for the Steric Substituent Constant (ν) of Various Alkyl Groups

Compound	R_2	ν[2]
O-Acetyl	$-CH_3$	0.52[a]
O-Propionyl	$-CH_2CH_3$	0.56[a]
O-Butyryl	$-(CH_2)_2CH_3$	0.68[a]
O-Valeryl	$-(CH_2)_3CH_3$	0.68[a]
O-Pivaloyl	$-C(CH_3)_3$	1.24[a]

[a] Data from ref 24.

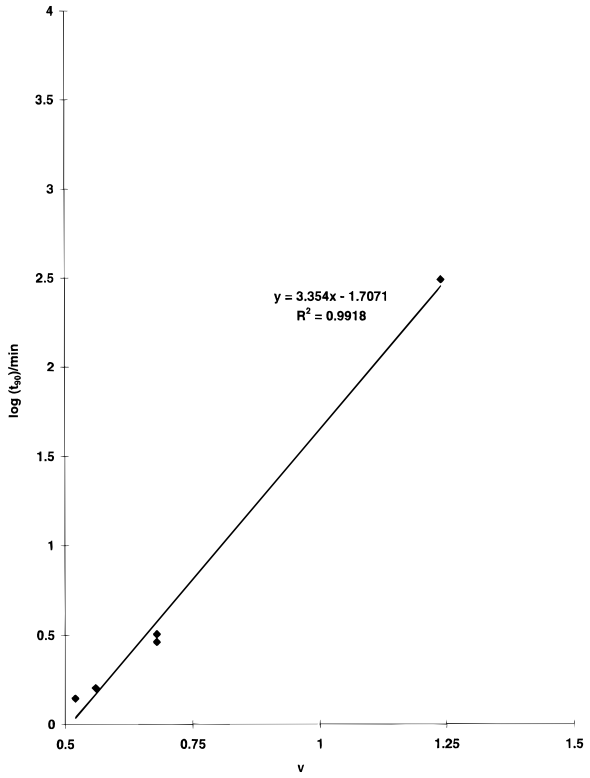


Figure 3—Plot of log t_{90} (at pH 7.4 and 37 °C) versus the steric parameter (ν) for aliphatic oxprenolol esters (the ν values refer to the alkyl moiety in the acyl groups; Table 3.

pearance of free oxprenolol, and a very small trace of a third product was also observed in all esters except the *O*-pivaloyl derivative. This unknown product was observed at higher pH values (pH > 6), was very stable, and had a short retention time.

The shape of the pH−rate profiles can be described in terms of specific acid- and base-catalyzed reactions of the protonated species along with a specific base-catalyzed reaction of the free base form of the esters according to eq 12:

$$k_{obs} = k_H a_H\left(\frac{a_H}{a_H + K_a}\right) + k_o a_H\left(\frac{a_H}{a_H + K_a}\right) + k_{OH} a_{OH}\left(\frac{a_H}{a_H + K_a}\right) + k_{OH} a_{OH}\left(\frac{K_a}{a_H + K_a}\right) \quad (12)$$

where a_H and a_{OH} refer to the hydrogen ion and hydroxide ion activities, respectively, $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ represent the fractions of total ester in the protonated and free base forms, respectively, and K_a is the ionization constant of the protonated NH group in the esters. Thus, the degree of ionization α may be identified with the term $a_H/(a_H + K_a)$, and $(1 - \alpha)$ is equal to $K_a/(a_H + K_a)$. The rate constant k_o refers to the spontaneous or water-catalyzed hydrolysis of the protonated form of the ester, k_H is the specific acid-catalyzed rate constant for the protonated ester form, and k_{OH} and k^1_{OH} denote the second-order rate constants for the apparent hydroxide ion-catalyzed hydrolysis of the protonated and unprotonated species, respectively.

Table 4—Ionization Constants (pK_a) and Apparent Ionization Constants ($pK_a)_{app}$ of Oxprenolol and Its Aliphatic Esters at 22 °C

Compound	pK_a	$(pK_a)_{app}$
Oxprenolol	9.48; 9.50;[a] 9.60;[b] 9.32[c]	7.18
O-Acetyl	8.70	5.06
O-Propionyl	8.58	4.99
O-Butyryl	8.06	4.29
O-Valeryl	7.83	4.00
O-Pivaloyl	8.07	4.71

[a] Reference 32. [b] Potentiometric titration (20 °C); ref 33. [c] Potentiometric titration (35 °C); ref 3.

Table 5—Second-Order Rate Constants (k_{OH}) for the Hydroxide Ion-Catalyzed Hydrolysis of the Protonated Species (Values are Quoted at two pH values: 6.2 and 7.4)

	k_{OH} ($\times 10^{-5}$) (M^{-1} min^{-1})	
Compound	pH 6.2	pH 7.4
O-Acetyl	6.34	1.48
O-Propionyl	7.95	1.33
O-Butyryl	4.68	0.81
O-Valeryl	3.87	0.86
O-Pivaloyl	—	0.0008

The processes described by eq 12 may be represented schematically (Scheme 1). In this scheme, the R_2CO group corresponds to the R group defined previously; for example, $R_2 = CH_3$ for the *O*-acetyl ester.

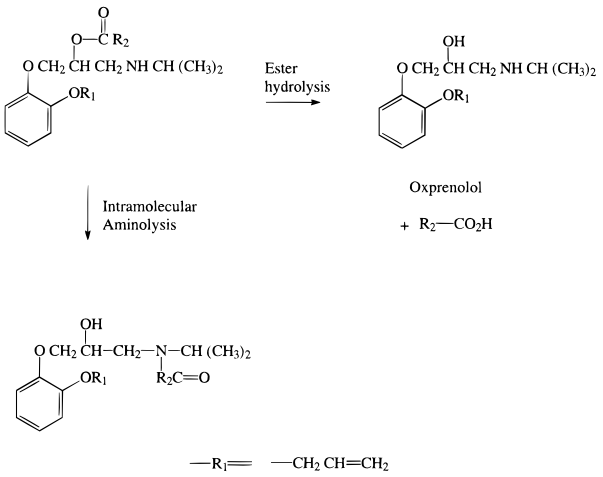
The pK_a values of the esters (Table 4) were lower than that of the parent compound (**V**), indicating that they are less basic than oxprenolol. The difference may be ascribed to the greater polar effect of the ester moiety relative to a hydroxyl group. The electron-withdrawing effect of the ester moiety decreases the basicity of the oxprenolol esters relative to the parent oxprenolol.

In their studies of propranolol esters, Bundgaard and coworkers[11] concluded that the possible spontaneous (water-catalyzed) reaction of the protonated species (described by the second term on the right-hand side of eq 12) is insignificant to the overall reaction. This result is in contrast to the findings for the timolol esters.[14] Previous studies on both propranolol[11] and timolol[14] esters have indicated that the values of k_{OH} are much greater than those of k_H. These values are of the order 10^7-10^8 greater than k_H. Because values of k_{obs} at pH values <5.00 have not been determined, the data as presented would not provide reliable values of k_H. Thus, the first term (on the right-hand side) in eq 12 cannot be isolated. For example, in the case of *O*-acetyloxprenolol, the value of the degree of ionization $[a_H/(a_H + K_a]$ at pH 5.00 is ~0.9998. The difference between this value and unity is large by comparison with the ratio k_H/k_{OH}. This term would not be the predominant term under these conditions, because the value of k_{OH} a_{OH} would not be negligible by comparison with k_H a_H. Only at very low pH values can the value of k_H be assigned unambiguously.

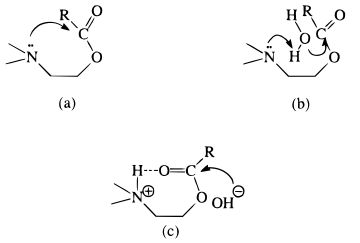
The values of k_{OH}, listed in Table 5, were estimated at the pH values 6.2 and 7.4. These values are much more reliable because the third term in eq 12 under these conditions is the predominant term; thus:

$$k_{obs} \cong k_{OH} a_{OH}\left(\frac{a_H}{a_H + K_a}\right) \quad (13)$$

At pH 6.2, the value of k_{OH} determined with eq 13 is 6.39



Scheme 2



Scheme 3

$\times 10^5$ for the *O*-acetyl ester. The corresponding value at pH 7.4 is 1.48×10^5.

The observed differences in the stability of the esters in weakly acidic and slightly alkaline aqueous solution can be ascribed to differences in the steric properties of the acyl groups, expressed in terms of the steric substituent parameter (ν). The k^1_{OH} term may not be estimated accurately because sufficiently high pH values were not studied. This term becomes increasingly important as the pK_a value is lowered.

Mechanism of Degradation—From the HPLC data, it is clear that at pH < 6, ester hydrolysis to yield oxprenolol was the only reaction taking place.

At pH values >7, ester hydrolysis is accompanied by a competitive intramolecular rearrangement reaction (Scheme 2). The disappearance of all esters was accompanied by the appearance of a trace amount of product along with free oxprenolol. This result was confirmed by ^{1}H NMR and mass spectroscopic data for the corresponding *N*-acyloxprenolol. These compounds were stable under the conditions of the reaction. It was shown[12] that the formation of *N*-acetylpropranolol from the *O*-acetyl compound indicated competitive first-order degradation. In contrast to the hydrolysis of propranolol esters, the amount of the *N*-acyloxprenolol derivative formed during neutral and alkaline hydrolysis is very small (1%).

There are three possible kinetically indistinguishable mechanisms that may account for the shape of the pH−rate profiles in the alkaline region (Scheme 3); these are (a) intramolecular nucleophilic attack by the unprotonated amino group on the ester moiety; (b) intramolecular general base catalysis by the unprotonated amino group of the attack of a water molecule on the ester group; and (c) intramolecular general acid catalysis by the protonated amino group of the attack of hydroxide ion.[11] The rearrangement reaction involves an intramolecular *O*−*N* migration (Scheme 3a), the transition state of which is rather susceptible to steric interactions. When larger substituents (R) are present, it may be expected that the rearrangement process is less favoured; this expectation was found to be the case. Approximately 5% of the *N*-acetyl derivative is formed, whereas only ~1% of the *N*-valeryl derivative is produced. The percentage recovery of the *N*-propionyl derivative is 2%.

In the case of the *O*-pivaloyl ester, a simple hydrolysis to the parent compound, without the involvement of a competing intramolecular rearrangement, is observed. Hydrolytic reactions (Scheme 3b and c) result in the formation of oxprenolol alone. The inability of this compound to undergo intramolecular aminolysis is undoubtedly due to the presence of the bulky *tert*-butyl substituent in the ester side chain. This group prevents the close interaction between the carbonyl group and the amino residue in the side chain.

While studying timolol ester hydrolysis,[14] Bundgaard et al. argued that the ester with the protonated amino group is much more reactive than the free base form. These authors found that $k_{OH} \gg k^1_{OH}$. Such reactivity is most likely ascribed to mechanism c that was just described. The enhanced reactivity of protonated esters compared with that of the unprotonated form of other β-aminoalcohols has been observed.[27,28] It is noteworthy that even at high pH values, no intramolecular aminolysis was observed for timolol esters.[14] This result can be ascribed to steric hindrance exhibited by the tertiary butylamino group. The behavior of the oxprenolol esters would be more comparable with that of the propranolol esters[11] in this regard as both sets of derivatives contain a secondary isopropylamino group. These compounds are, therefore, more susceptible to intramolecular aminolysis than the timolol derivatives. The relative importance of hydrolysis and aminolysis is also determined by steric effects within the acyl moiety.

The shape of the pH−rate profiles indicates that ester hydrolysis accompanied by intramolecular aminolysis are the dominant reactions taking place in the neutral and alkaline regions. A base-catalyzed hydrolytic reaction occurs in this region of the profile. All esters exhibit highest stability at pH < 5.0. In the case of the *O*-pivaloyl derivative, stability is also displayed at higher pH values. As the pH increased, the rate of amide formation increased slightly as indicated by the HPLC data. This parallel change is presumably the result of an increasing proportion of unprotonated base being available for anchimeric attack on the *O*-acyl group (Scheme 3a).

In the physiological range of pH values, direct hydrolysis of the *O*-valeryl derivative to yield oxprenolol was much faster than the formation of the corresponding amide, whereas in the case of the *O*-acetyl derivative, the amide was formed almost as rapidly as the parent compound. This difference in the rate of amide formation is due to the larger size of the *O*-acyl group in the *O*-valeryl ester.

Prediction of Shelf-Lives—Oxprenolol esters, because of their weak basicity, are readily soluble in aqueous solutions at pH 5.0. To predict the stability of these compounds under conditions similar to those for storage, the rate of hydrolysis was measured at pH 5.0 over the temperature range 37−70 °C. Under these conditions, the predominant mechanism of hydrolysis is the hydroxide ion-catalyzed hydrolysis of the protonated form of the esters (Scheme 1). Intramolecular aminolysis did not usually occur at this pH value. However, with increasing temperature there was a significant increase in the rate of formation of the amide derivative.

The Arrhenius parameters, defined in eq 14, are given in Table 6:

$$\ln(k_{obs}) = \ln A - \frac{E_a}{RT} \qquad (14)$$

where A is the pre-exponential frequency factor and E_a denotes the activation energy of decomposition. The values quoted are those degradation rates at pH 5.0. In Figure 4

Table 6—Arrhenius Parameters for the Hydrolysis of Various Oxprenolol Esters at pH 5.0 (μ = 0.5)

Compound	ln A	E_a (kJ mol^{-1})	r^a	n^b
O-Acetyl	26.06	80.26	0.997	4
O-Propionyl	25.63	80.23	0.996	4
O-Butyryl	22.84	73.04	0.995	3
O-Valeryl	25.86	81.76	0.990	3

[a] Correlation coefficient. [b] Number of temperature values.

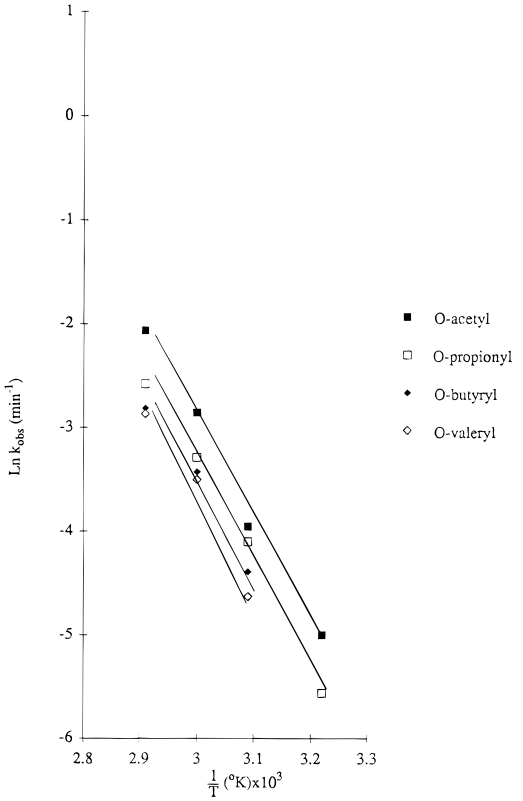


Figure 4—Arrhenius plots of the rates of hydrolysis of aliphatic oxprenolol esters (μ = 0.5) at pH 5.0.

Table 7—Predicted Values of the Shelf-Life (t_{90}) for Aliphatic Oxprenolol Esters in Aqueous Solution at pH 5.0 (μ = 0.5)

Ester	t_{90} (h) 10 °C	t_{90} (h) 25 °C
O-Acetyl	5.4	1.0
O-Propionyl	8.2	1.5
O-Butyryl	6.3	1.3
O-Valeryl	12.5	2.2
O-Pivaloyl	—	—

the rate data obtained for all esters are plotted according to eq 14. The rate of degradation for the *O*-pivaloyl derivative was determined at 70 °C only and, hence, the Arrhenius parameters could not be determined. The activation energy of hydrolysis of the *O*-*n*-esters is of the order of 80 kJ mol^{-1}, which is typical of many reported values for drug decompositions.[29]

On the basis of these values, it is possible to predict the shelf-life of aqueous solutions of the esters at lower temperatures (e.g., 10 or 25 °C). At lower temperatures, the stability is much improved (Table 7), with the most stable ester being the *O*-pivaloyl derivative.

Lipophilicity of the Oxprenolol Esters—The potentiometric titration method for the determination of partition

Table 8—Partition Coefficients (log *P*), Apparent Partition Coefficients (log $P)_{app}$ and Capacity Factors (log k^1) of Oxprenolol and Its Aliphatic Esters at 22 °C

Compound	log *P*	log P_{app}[a]	log k^1 [b]
Oxprenolol	2.40; 2.62;[c] 2.18;[d] 2.29;[e] 1.62;[f] 2.37[g]	0.32; 0.09;[e] 2.28[h]	0.22
O-Acetyl	3.82	2.52	0.43
O-Propionyl	3.76	2.58	0.58
O-Butyryl	3.95	3.29	0.74
O-Valeryl	4.00	3.57	0.90
O-Pivaloyl	3.54	2.78	0.95

[a] pH 7.40 - calculated from log *P* with eq 4. [b] pH 7.4. [c] Molal partition coefficient; ref 32. [d] Reference 30. [e] 20 °C; ref 33. [f] Calculated value using MedChem Software; ref 34. [g] 35 °C; ref 3. [h] 35 °C; ref 31.

coefficients provides for the accurate measurement of the ionization constant in aqueous solution (pK_a) and the apparent ionization constant [(pK_a)$_{app}$] in the presence of *n*-octanol (Table 4). The partition coefficients are determined with eq 1, and the distribution coefficients are calculated from these data with eq 2.

The lipophilicities of a number of adrenoceptor blocking agents have been determined by several investigators.[3,30–33] These values have been compared with theoretical estimates of log *P*.[33,34] These compounds may be classified in terms of their lipophilicities, and three categories have been recognized;[3] namely, highly lipophilic (e.g., propranolol), lipophilic (timolol and oxprenolol), and hydrophilic (e.g., atenolol). The thermodynamics of partitioning of these compounds in the *n*-octanol—water system have been studied.[32,35]

Partition coefficients (log *P*) for the oxprenolol esters between *n*-octanol and water at 22 °C are listed in Table 8. The results indicate that the esters are all more lipophilic than the parent compound. A similar trend was found in the case of propranolol[36] and timolol[14] esters. Distribution coefficients (log P_{app}) and capacity factors (log k^1) determined at pH 7.4 are also included in Table 8. The capacity factor, k^1, of a solute is defined by the following equation:

$$k^1 = \frac{t_r - t_o}{t_o} \qquad (15)$$

where t_r is the retention time of the solute and represents the elution time of the solvent.

The increase in lipophilicity on esterification is partly due to the replacement of the hydroxyl group by an ester group. An important contribution to the observed change in lipophilicity is the observed decrease in the pK_a value on esterification (Table 4). Thus, a higher proportion of the lipophilic free base form is present at any given pH value.

The relationship between both the partition (log *P*) and distribution coefficients (log P_{app}) and log^1 is shown in Figure 5. The relationship is not as linear as has been observed previously.[14,37]

Conclusion—We conclude that there is a relationship between the structure and physicochemical parameters of the homologous series of oxprenolol esters studied. The most stable ester is the *O*-pivaloyl derivative and the least stable is the *O*-acetyl ester. This ranking is, of course, to the size of the ester moiety, with the *O*-pivaloyl being the most bulky. The lipophilicity increases as the ester chain length increases, which indicates the speed at which a prodrug would reach the target organ. It could be suggested that the best prodrugs are the *O*-propionyl and the *O*-butyryl derivatives because they break down at an average rate to release the active drug at physiological pH.

Another paper is currently being prepared on how the stability of a homologous series of oxprenolol esters is affected by an increase in the carbon chain length of the ester moiety in the presence of biological enzymes.

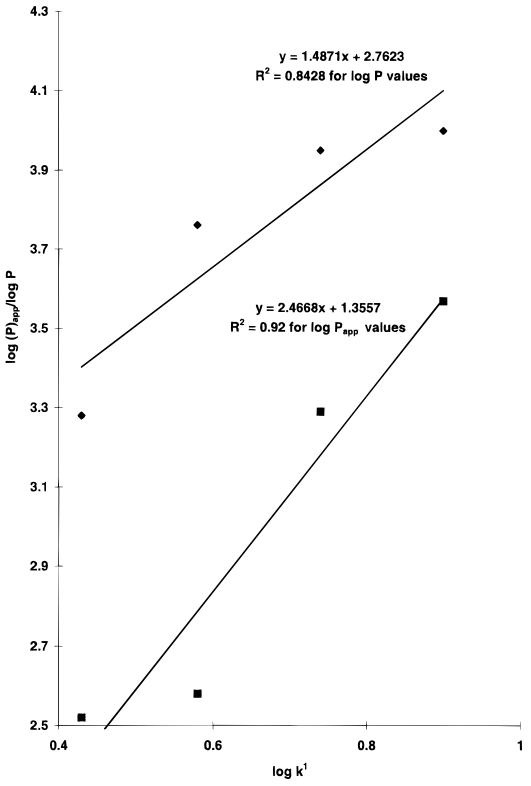


Figure 5—Plot of both log *P* and log P_{app} (pH 7.4 and 22 °C) against log k^1 for the aliphatic oxprenolol esters. The values are taken from Table 8.

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