International Journal of Pharmaceutics, 101 (1994) 145–163
Elsevier Science Publishers B.V.

IJP 03352

The synthesis, hydrolysis kinetics and lipophilicity of *O*-acyl esters of propranolol

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(Received 7 May 1993)
(Accepted 14 June 1993)

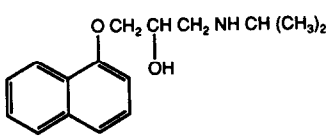
Key words: Propranolol; Propranolol ester; Partition coefficient; Distribution coefficient; Hydrolysis; Stability; Intramolecular aminolysis

Summary

The stability of a series of *O*-acyl esters of propranolol, prepared as potential prodrugs, is investigated over the pH range 2.2–9.0 at 37°C. All compounds were hydrolyzed to yield propranolol. In solutions of pH ≥ 7, an alternative degradation route must be taken into consideration, namely a rearrangement reaction to the *N*-acyl analogue. The relative importance of the hydrolysis and intramolecular aminolysis reactions depends on both the pH of the solution and the steric properties of the acyl moiety of the esters. The relationship between the Charton steric parameter (ν) and the rate of hydrolysis is investigated. From Arrhenius-type plots, the activation energy (E_a) and frequency factor (A) were obtained and on the basis of these data, the shelf-lives of the esters were determined at both 10°C and 25°C. All the esters were more lipophilic than propranolol in terms of octanol-buffer partition coefficients.

Introduction

Propranolol {1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol} (**I**),



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a non-selective, highly liposoluble, β-adrenergic antagonist of β_1- and β_2- receptors (Hansson and Werkö, 1977), has been used mainly to treat systemic hypertension (Prichard and Gillam, 1964, 1969). β-Adrenergic antagonists have also been used in liver diseases to control portal hypertension (Kulcsár-Gergely and Kulcsár, 1992). Features that are important for adrenergic activity include (a) an extended π aromatic system, (b) a four-atom chain separating the aromatic system from a terminal amine, (c) a terminal amine that is a secondary amine, (d) amine substituents that are bulky or branched and (e) a hydroxyl group on the side chain (Comer et al., 1981). Removal of the side-chain hydroxyl group of propranolol and conversion of its secondary amine to a tertiary amine reduced affinity for β-adrenergic sites

(Pierson et al., 1989). The crystal structure of this compound was elucidated by Ammon et al. (1977).

Glaucoma is a serious eye disease in which intra-ocular pressure is elevated. It was found that systemic propranolol lowered the pressure (Phillips et al., 1967; Vale et al., 1972; Pandolfi and Orhström, 1974; Williamson et al., 1985). However, the drug is too irritant when applied topically to be used in this way, and ophthalmologists are, understandably, reluctant to use potent cardiac drugs orally. β-Blockers are absorbed into the systemic circulation remarkably well after installation into the eye, and, though plasma levels are far below the normal cardiovascular therapeutic range, bradycardia, hypotension, and bronchospasm have been reported on occasion (Himber et al., 1987). The actions of β-antagonists in the treatment of glaucoma have been reviewed (Hitchings, 1982). The corneal penetration behaviour of a number of β-blockers has been investigated (Huang et al., 1983a,b; Schoenwald and Huang, 1983). More recently, the influence of formulation composition on conjunctival drug penetration of four β-blockers (including timolol) has been reported (Ashton et al., 1991). An investigation of the transdermal permeation of β-blockers revealed a direct correlation between permeability coefficients and distribution coefficients (Ghosh et al., 1993). Unlike corneal permeation, no optimum value of distribution coefficient for transdermal permeation was found.

The development of prodrugs with improved corneal absorption characteristics has been used successfully to enhance the ocular bioavailability of a number of drugs (Bodor and Visor, 1984; Bundgaard et al., 1986). Active drug species containing hydroxyl or carboxyl groups can often be converted to prodrug esters from which the active forms are regenerated by esterases within the body (Bundgaard, 1985).

A structurally similar compound, timolol, has been used in glaucoma therapy. Many other β-blockers, both cardioselective and non-selective, will lower intra-ocular pressure but timolol is by far the most widely used, as it is potent and non-irritant (LeBlanc et al., 1985). Timolol esters have been developed as prodrugs (Bundgaard et al., 1986, 1988; Chang et al., 1987) to diminish the systemic absorption and side-effects (Munroe et al., 1985; Nelson et al., 1986) of topically administered timolol. In addition to lipophilicity, susceptibility to hydrolysis may influence the extent of prodrug absorption (Chien et al., 1991). Ketoxime analogues of β-adrenergic antagonists, e.g. propranolol (Bodor et al., 1988; El-Koussi and Bodor, 1989), timolol (Bodor et al., 1988) and alprenolol (Bodor and El-Koussi, 1991), have been investigated as potential antiglaucoma agents. A hydrolysis-reduction sequence could produce the active amino-alcohol at the iris-ciliary body, the site of action.

Timolol esters are rather unstable in aqueous solutions. To further examine the basis of this instability, hydrolytic studies of a series of esters of the structurally similar β-blocking agent, oxprenolol, have been presented (Jordan et al., 1992). Stability studies of propranolol esters have been reported (Buur et al., 1988; Irwin and Belaid, 1988a,b). The present study extends the range of propranolol esters which have been examined.

Materials and Methods

Apparatus

The propranolol esters were characterised by a variety of analytical techniques. ^{1}H-NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard at 80 MHz by means of a Bruker Spectrospin spectrometer. Mass spectra were obtained using a Kratos M5902 instrument. Spectra were run in an electron impact mode using an ionization energy of 70 eV. The scan was taken over the range 720–30 amu using perfluorokerosene as the reference compound. Data were processed by a computer system based on an Arcom Stebus computer (80188 processor). UV spectral data were obtained using a Pye Unicam double beam spectrometer equipped with a thermostatically controlled cell compartment using 1 cm quartz cells. IR spectral data were obtained using a Pye Unicam SP-3-300 spectrometer with polystyrene as reference. A DSC analysis of each compound was carried out using a Perkin Elmer DSC-20 instrument with the Thermal Analysis

Data Station (TADS) being employed for data collection, handling and presentation. Melting points determined from DSC analysis compared favourably with those obtained using a Gallenkamp melting point apparatus.

High-performance liquid chromatography (HPLC) was carried out using 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 pre-column, 50 × 4.6 mm, was similarly packed. A 10 μl sample was introduced by means of a Hamilton syringe.

The pH value of each solution was determined using 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 using a Mettler DL 25 automatic titrator fitted with an interchangeable burette and rod stirrer with a variable speed adjuster. Results were obtained in tabular form using 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 propranolol hydrochloride were obtained from Orsynetics Ltd (U.K.), while the acid chlorides were obtained from Aldrich Chemical Co. (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 recrystallised before use.

All solvents used (i.e., acetonitrile, methanol, tetrahydrofuran and acetone) were HPLC grade. All buffer substances used were of reagent or analytical grade and they were degassed in an ultrasonic bath for 15 min before use. The 0.02 M phosphate buffer was filtered through a Millipore filter as well as being degassed.

The ionic strength of each buffer solution was adjusted to 0.5 by adding a specific quantity of analytical grade potassium chloride. Commercial

TABLE 1

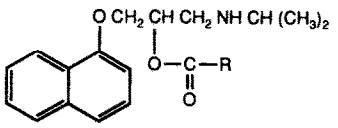
Physical and analytical data of various esters (hydrochloride salts) of propranolol

Ester	Yield (%)	Melting point (°C)	Formula	Analysis (%)	
				Calculated	Found
II	79	171–172	$C_{18}H_{24}ClNO_3$	C 64.00	64.27
				H 7.11	7.37
				N 4.15	3.97
III	70	146–147	$C_{21}H_{30}ClNO_3$	C 66.40	66.16
				H 7.90	7.99
				N 3.68	3.57
IV	64	131–132	$C_{20}H_{28}ClNO_3$	C 65.66	64.98
				H 7.66	7.65
				N 3.83	3.84
V	78	155–156	$C_{20}H_{26}ClNO_3$	C 66.20	65.63
				H 7.15	7.18
				N 3.85	3.72
VI	67	151–152	$C_{20}H_{26}ClNO_3$	C 66.20	66.92
				H 7.15	7.25
				N 3.85	3.83
VII	65	240–241	$C_{23}H_{25}ClN_2O_5$	C 62.09	62.15
				H 5.62	6.08
				N 6.29	6.01

grade *n*-octanol was used in the partitioning experiments.

Synthesis of propranolol esters

The esters were prepared by heating propranolol hydrochloride (1 g) under reflux for a specified length of time with the appropriate acid chloride. Excess acid chloride was removed under vacuum. A solid product was obtained with the *O*-acetyl derivative. An oily residue, obtained in all other cases, was crystallised by adding 5 ml acetone followed by 30 ml petroleum ether. Continuous removal of the acetone and petroleum ether under vacuum and repetition of the process resulted in the formation of a milky precipitate which was recrystallised from isopropanol. Physical and analytical data for the compounds are given in Table 1. The NMR, mass spectral and IR data were consistent with their structures. Elemental analyses were consistent with the molecular formulae.



Propranolol Ester	—R
O-Acetyl (II)	—CH_3
O-Pivaloyl (III)	—$C(CH_3)_3$
O-Isobutyryl (IV)	—$CH(CH_3)_2$
O-Cyclopropanoyl (V)	—CH—CH_2—CH_2
O-Crotonyl (VI)	—CH=CH CH_3
O-*p*-Nitrobenzoyl (VII)	—NO_2

Hydrolysis kinetics in aqueous solution

The decomposition of the propranolol esters (**II–VII**) was studied in aqueous buffer solutions over the pH 2.2–9.0 range at 37.0 ± 0.2°C. Phosphate and citrate buffers were used in the pH 2.0–8.0 range, while borate buffers were used in the pH 8.0–12.0 range. 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 means of 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 previously degassed in an ultrasonic bath for 15 min. Before commencing an experiment it was necessary to allow the mobile phase flow through the column until a steady base line was achieved. A flow rate of 1.0 ml/min achieved satisfactory results and the sensitivity was maintained at 0.32 AUFS. The column effluent was monitored at 288 nm (Irwin and Belaid, 1987a).

The retention times (t_r) for the compounds were in the range 3.65 min [propranolol (**I**)] to 8.24 min [*O*-pivaloylpropranolol (**III**)]. In the case of the *O*-acetyl derivative (compound **II**), 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 done by measuring the peak heights in relation to those of standard solutions 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 propranolol ester vs time.

Determination of partition coefficients

The apparent partition (distribution) coefficients, P_{app}, of the propranolol esters were determined in the *n*-octanol/buffer system (pH 7.40) at 22°C by potentiometric titration using a multiparametric curve-fitting technique (Clarke, 1984; Clarke and Cahoon, 1987). The method, involving

the potentiometric titration of the compound both in water and in a rapidly stirred mixture of water and *n*-octanol, is rapid and accurate for compounds with 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 pK_a values.

In the method of Kaufman et al. (1975), the ionization constant (pK_a) and the apparent ionization constant, $(pK_a)_{app}$, are first obtained from the results of two potentiometric titrations, one without and one with the presence of *n*-octanol, respectively. 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}:

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

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

since

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

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 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 the equation:

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

where *f* is a partition factor given by

$$f = [(V_o P/V_w) + 1] \quad (6)$$

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:

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

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

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

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

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

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

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

Results and Discussion

Kinetics of degradation of propranolol esters

The degradation of all propranolol esters (**II–VII**), 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 according to the rate equation:

$$[A] = [A]_0 e^{-k_{obs}t} \quad (11)$$

for several half-lives at constant pH and temperature. For each ester, the log(% remaining) was plotted as a function of time. $[A]_0$ and [A] are the concentrations at time, $t = 0$ and time, $t = t$, respectively and thus, the % remaining may be expressed as $100([A]/[A]_0)$. These plots are shown for the *O*-acetylpropranolol ester (**II**) in Fig. 1. Rate constants (k_{obs}) are estimated from the slopes of these graphs, values of which are listed in Table 2. These data {$\log(k_{obs})$/pH} are illustrated in Fig. 2.

The rate of degradation of each ester increases with increasing pH. The most stable compound is the *O*-pivaloyl (**III**) derivative, the shelf-life of

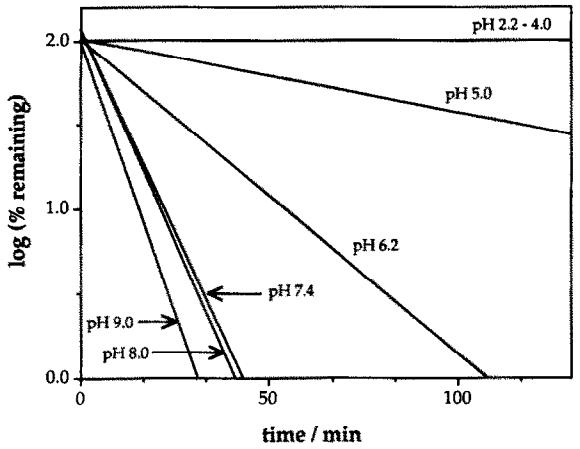


Fig. 1. First-order plots for the degradation of *O*-acetylpropranolol (**II**) over the pH range 2.2–9.0 at 37°C.

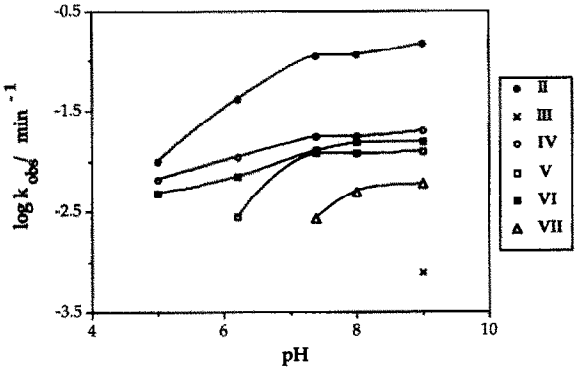


Fig. 2. The kinetic pH profiles for the degradation of *O*-acyl esters (**II–VII**) of propranolol ($\mu = 0.5$) at 37°C.

which is only measurable at pH 9.0, while the least stable compound is the *O*-acetyl (**II**) derivative. The same trend is observed in the oxprenolol esters (Jordan et al., 1992). The shelf-lives (t_{90}) of the ester series at 37°C, defined as the time taken for 10% decomposition to occur and determined using Eqn 12, are listed in Table 3 for each pH value.

$$t_{90} = \ln(1.11)/k_{obs} \qquad (12)$$

The results show that the shelf-lives are greatly dependent on the ester structure. No significant

TABLE 2

Observed pseudo first-order rate constants (k_{obs}) for the degradation of various propranolol esters in aqueous solution at different pH values and at 37°C ($\mu = 0.5$)

Ester	k_{obs} ($\times 10^3$) (min^{-1}) at pH							
	2.2	3.0	4.0	5.0	6.2	7.4	8.0	9.0
II	–	–	–	9.91	41.3	111.08	115.55	145.69
III	–	–	–	–	–	–	–	0.76
IV	–	–	–	6.58	10.84	17.43	17.42	19.76
V	–	–	–	–	2.72	11.85	11.90	12.27
VI	–	–	–	4.74	6.87	12.51	15.13	15.29
VII	–	–	–	–	–	2.68	4.93	5.83

TABLE 3

Predicted values of the shelf-life (t_{90}) for various propranolol esters in aqueous solution at different pH values and at 37°C ($\mu = 0.5$)

Ester	t_{90} (min) at pH							
	2.2	3.0	4.0	5.0	6.2	7.4	8.0	9.0
II	–	–	–	10.63	2.55	0.95	0.91	0.72
III	–	–	–	–	–	–	–	138.50
IV	–	–	–	16.01	9.72	6.04	6.05	5.33
V	–	–	–	–	38.74	8.89	9.37	8.59
VI	–	–	–	22.23	15.34	8.42	6.89	6.96
VII	–	–	–	–	–	39.34	21.36	18.08

degradation was observed at pH values less than 5.0. The stability of the esters increases with increasing bulk or length of the *O*-acyl substituent. Those substituents which are particularly bulky (e.g., pivaloyl and *p*-nitrobenzoyl) confer enhanced stability on the *O*-acyl ester. The *O*-pivaloyl derivative has a shelf-life of 2 h 18 min 30 s at pH 9.0, while the *O*-acetyl compound has a shelf-life of 43 s at the same pH (Table 3).

The pH/kinetic profiles of the esters may be analysed in terms of specific acid and base-catalysed reactions of the protonated species along with a specific base-catalysed reaction involving the free base form of the esters according to the following rate equation:

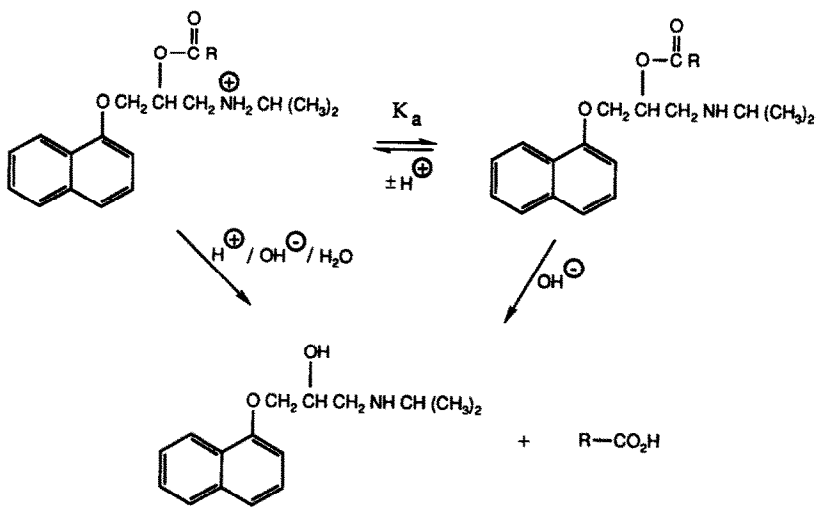
$$k_{obs} = k_H a_H[(a_H/(a_H + K_a)] + k_0 a_H[a_H/(a_H + K_a)] + k_{OH} a_{OH}[a_H/(a_H + K_a)] + k'_{OH} a_{OH}[K_a/(a_H + K_a)] \quad (13)$$

where a_H and a_{OH} refer to the hydrogen ion and hydroxide ion activities, respectively, $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ denote 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, α, the degree of ionization, may be identified with the term $a_H/(a_H + K_a)$ while $(1 - \alpha)$ is equal to $K_a/(a_H + K_a)$. The rate constant k_0 refers to the spontaneous or water-catalysed hydrolysis of the protonated form of the ester, k_H is the specific acid-catalysed rate constant for the protonated ester form and k_{OH} and k'_{OH} are the second-order rate constants for the apparent hydroxide ion-catalysed hydrolysis of the protonated and unprotonated species, respectively. It is quite informative to express the above equation in terms of α, i.e.

$$k_{obs} = \{(k_H + k_0)a_H + k_{OH} a_{OH}\}(\alpha) + k'_{OH} a_{OH}(1 - \alpha) \quad (14)$$

The above processes may be represented schematically (Scheme 1).

The hydrolysis kinetics of the *O*-acetyl and *O*-pivaloyl derivatives are comparable with earlier studies of Buur et al. (1988). They found that the propranolol esters were all hydrolysed to give propranolol in solutions of pH < 7, but in neutral and alkaline solutions they underwent simultaneous hydrolysis and intramolecular aminolysis to



Scheme 1

produce the *N*-acylated propranolol. The occurrence of intramolecular aminolysis at pH values above 7 was also observed for each of the esters in our studies. For example, as revealed by HPLC, the disappearance of the *O*-isobutyryl ester in alkaline solutions was accompanied by the progressive appearance of a peak with the same retention time as *N*-isobutyrylpropranolol. A peak corresponding to propranolol also appeared during the degradation. The degradation profile followed that of a competitive first order degradation which may be represented by Scheme 2 (Irwin and Belaid, 1988a; Irwin, 1990).

Representing the *O*-acyl ester, propranolol and the *N*-acyl ester by A, B and C, respectively, the rates of change in concentration of the three species are:

$$-\mathrm{d[A]}/\mathrm{d}t = (k_1 + k_2)[\mathrm{A}] = k_{\mathrm{obs}}[\mathrm{A}] \quad (15)$$

$$\mathrm{d[B]}/\mathrm{d}t = k_1[\mathrm{A}] \quad (16)$$

$$\mathrm{d[C]}/\mathrm{d}t = k_2[\mathrm{A}] \quad (17)$$

The respective concentrations of species A–C (at time t) are given by [A]–[C].

Integration of these equations, between the limits of time zero ($[\mathrm{A}] = [\mathrm{A}]_0$; $[\mathrm{B}]_0 = [\mathrm{C}]_0 = 0$) to time t leads to the rate equations which describe the time concentration profile of each species.

From Eqn 15,

$$\ln\{[\mathrm{A}]_0/[\mathrm{A}]\} = (k_1 + k_2)t = k_{\mathrm{obs}}t \quad (18)$$

The values of [B] and [C] may be derived from Eqn 18 subject to the following conditions:
(i) $[\mathrm{A}] = [\mathrm{A}]_0 - \{[\mathrm{B}] + [\mathrm{C}]\}$ and
(ii) $[\mathrm{B}]/[\mathrm{C}] = k_1/k_2$.

Expressing [C] in terms of [B] {condition (ii)} and substituting the expression for [A] {condition (i)} into Eqn 18 yields:

$$\ln([\mathrm{A}]_0/\{[\mathrm{A}]_0 - [\mathrm{B}] - (k_2/k_1)[\mathrm{B}]\}) = (k_1 + k_2)t \quad (19)$$

Rearranging the above equation yields:

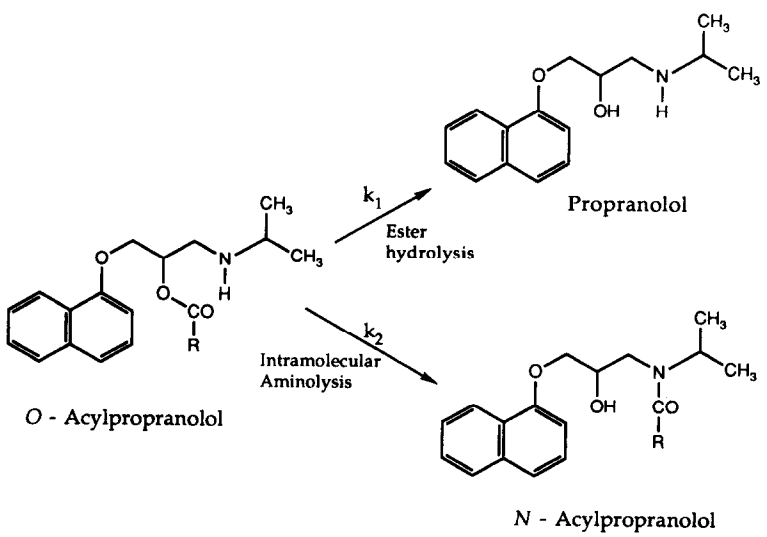
$$\ln\{[\mathrm{A}]_0 - [\mathrm{B}] - (k_2/k_1)[\mathrm{B}]\} = \ln [\mathrm{A}]_0 - (k_1 + k_2)t \quad (20)$$

Hence,

$$[\mathrm{A}]_0 - [\mathrm{B}]\{1 + (k_2/k_1)\} = [\mathrm{A}]_0 e^{-(k_1+k_2)t} \quad (21)$$

Thus,

$$[\mathrm{A}]_0 - [\mathrm{B}]\{(k_1 + k_2)/k_1\} = [\mathrm{A}]_0 e^{-(k_1+k_2)t} \quad (22)$$



Scheme 2

and, on rearranging Eqn 22,

$$[B]\{(k_1+k_2)/k_1\} = [A]_0\{1 - e^{-(k_1+k_2)t}\} \quad (23)$$

The expression for the concentration of species B (propranolol) at time t, [B], may thus be expressed in terms of the initial concentration of species A (*O*-acyl ester) and the rate constants for hydrolysis and rearrangement by means of the following equation:

$$[B] = \{[A]_0 k_1/(k_1 + k_2)\}[1 - e^{-(k_1+k_2)t}] \quad (24)$$

Similarly, the value of [C] (the concentration of the *N*-acyl ester at time t) may be derived to give:

$$[C] = \{[A]_0 k_2/(k_1 + k_2)\}[1 - e^{-(k_1+k_2)t}]$$

Since there is always a constant ratio between the two products, given by condition (ii) above, the values of k_1 and k_2 may be determined more conveniently by calculating the ratio of the concentrations formed by each reaction at any time (t):

$$k_{obs} = k_1 + k_2, k_{obs} = k_2([B]/[C]) + k_2$$

$$= k_2\{([B]/[C]) + 1\}$$

Propranolol esters are generally more stable than the corresponding timolol esters above pH 3 (Buur et al., 1988). The reactivity of the esters is a function of steric and polar factors. 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 (1975) showed that the rates of acid-catalysed esterification are solely a function of steric effects. The relationship between the steric substituent parameter, ν (Charton, 1975, 1976, 1977), and the logarithm of the shelf-life, log t_{90}, was investigated. The literature values of this parameter are listed in Table 4. The relationship (Fig. 3) was shown to be linear ($r = 0.999$). However, due to the particular range of esters under study, only three points are plotted. A wider range of esters would be desirable in order to establish definitively whether such a relationship exists.

TABLE 4

Literature values for the steric substituent constant (ν) of various alkyl groups

Compound	R	ν [a]
II	$-CH_3$	0.52
III	$-C(CH_3)_3$	1.24
IV	$-CH(CH_3)_2$	0.98
V	$-c\text{-}C_3H_5$	1.06 [b]

The alkyl moiety R refers to that shown in the structural formulae.
[a] Charton (1975).
[b] Charton (1976).

The pK_a values of the esters (Table 5) were lower than that of the parent compound (**I**) which has a value of 9.43 at 22°C, indicating that they are less basic than propranolol. This decrease in basicity is due to the greater polar (electron-withdrawing) effect of the ester moiety with respect to the hydroxyl group. Table 5 compares the values obtained in this work with previously published results. The ionization constants of propranolol hydrochloride and the *O*-*n*-acyl esters prepared by Irwin and Belaid (1987b) were determined by potentiometric titration in methanol/aqueous mixtures using 0.1 M NaOH

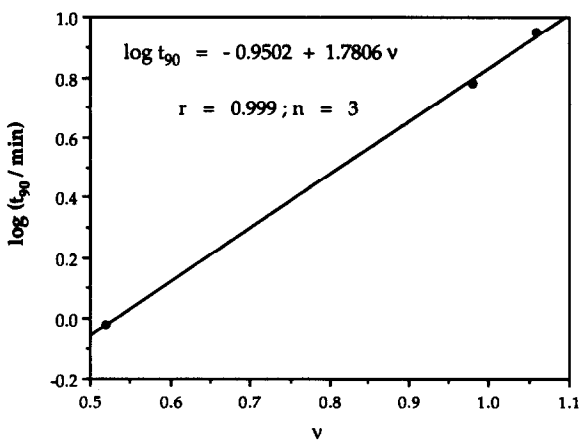


Fig. 3. Plot of log t_{90} (at pH 7.40 and 37°C) vs the steric parameter (ν) for various propranolol esters. The ν values refer to the alkyl or cycloalkyl moiety in the acyl groups (Table 4).

at 25°C. Rapid addition of the titrant was employed in order to minimise degradation. Extrapolation of the plots to zero concentration of methanol provided the estimated pK_a values. With the exception of the *O*-pivaloyl derivative there is reasonable agreement between the respective sets of results (Table 5). Indeed, the values for the esters listed in Table 5 exhibit slightly wider variation than has been observed for oxprenolol esters (Jordan et al., 1992). The pK_a value of the *O*-*p*-nitrobenzoyl ester is particularly low, presumably due to the strong electron-withdrawing effect of the *p*-NO_2 substituent.

The effect of changing the pK_a value upon esterification is shown in Fig. 4. The variation of α, the degree of ionization, with pH exhibits sigmoidal behaviour. The curve for the *O*-isobutyryl ester (**IV**), is displaced to lower pH values relative to that for propranolol (**I**) itself, reflecting the decrease in the pK_a value. Thus, at any pH value the degree of ionization (α) of propranolol is greater than that of the ester. This is particularly evident in the pH range 7.0–11.0.

In their studies of propranolol esters, Buur et al. (1988) concluded that the possible spontaneous (water-catalyzed) reaction of the protonated species (described by the second term on the right-hand side of Eqn 13) is insignificant to the overall reaction. This is in contrast to the findings for the timolol esters (Bundgaard et al., 1986, 1988). These studies reveal that the values of k_{OH} are much greater than k_H by a factor of the order 10^7–10^8. Since values of k_{obs} below pH 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 Eqn 13 cannot be isolated. For example, in the case of *O*-acetyl propranolol the value of the degree of ionization $[a_H/(a_H + K_a)]$ at pH 5.0 is approximately equal to 0.9996. 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 since the value of $k_{OH}a_{OH}$ would not be negligible by comparison with k_Ha_H. Only at very low pH values can the value of k_H be assigned unambiguously.

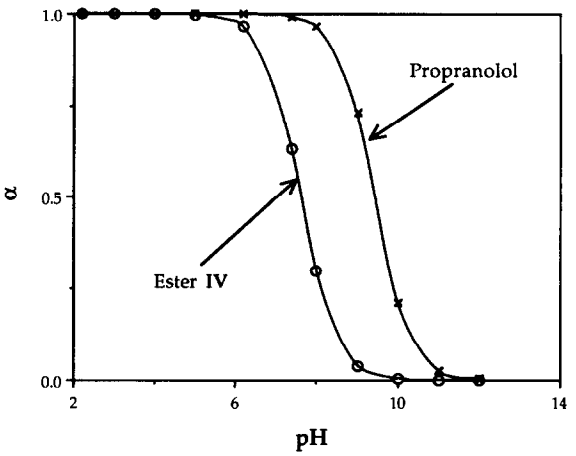


Fig. 4. Variation of the degree of ionization (α) with pH at 37°C. The curve for propranolol is compared with that for the *O*-isobutyryl ester (**IV**).

TABLE 5

The ionisation constants (pK_a) and apparent ionisation constants $(pK_a)_{app}$ of propranolol and its esters at 22°C

Compound	pK_a	$(pK_a)_{app}$
I	9.43; 9.51 [a]; 9.45 [b]; 9.40 [c]; 9.23 [d]; 9.32 [e]	6.42
II	8.39; 8.52 [a]; 8.30 [f]	4.23
III	6.94; 8.71 [a]; 8.30 [f]	3.96
IV	7.63	4.29
V	7.66	4.15
VI	8.44	6.67
VII	4.31	10.10

[a] Irwin and Belaid (1987b) – potentiometric titration (25°C).
[b] Betageri and Rogers (1987).
[c] Mannhold et al. (1990) – potentiometric titration (20°C).
[d] Schoenwald and Huang (1983) – potentiometric titration (35°C).
[e] Zaagsma and Nauta (1974).
[f] Buur et al. (1988) – (37°C).

Fig. 5 provides a graphical representation of the variation of the terms in Eqn 13 with pH for the *O*-isobutyryl ester (**IV**). The term associated with k_H decreases dramatically from a value of 6.31×10^{-3} at pH 2.2 to values $< 1.0 \times 10^{-4}$ above pH 4.0. The term associated with k_{OH} shows a sigmoidal relationship with pH. At high pH, this term approximates K_w/K_a. Setting $pK_w = 13.62$ (Harned and Hamer, 1933) and $pK_a =$

7.63, the curve approaches 1.023×10^{-6} asymptotically. The curve shows a point of inflection when $pH = pK_a$, since at this value $\alpha = 0.5$ and hence the term is equal to $0.5a_{OH}$ ($= 5.12 \times 10^{-7}$). The term associated with k'_{OH} increases markedly with increasing pH.

The values of k_{OH}, listed in Table 6, were estimated at the pH values 6.2 and 7.4. These values are much more reliable since the third term in Eqn 13 under these conditions is the predominant term. Thus,

$$k_{obs} \cong k_{OH} a_{OH} \{a_H/(a_H + K_a)\} \quad (25)$$

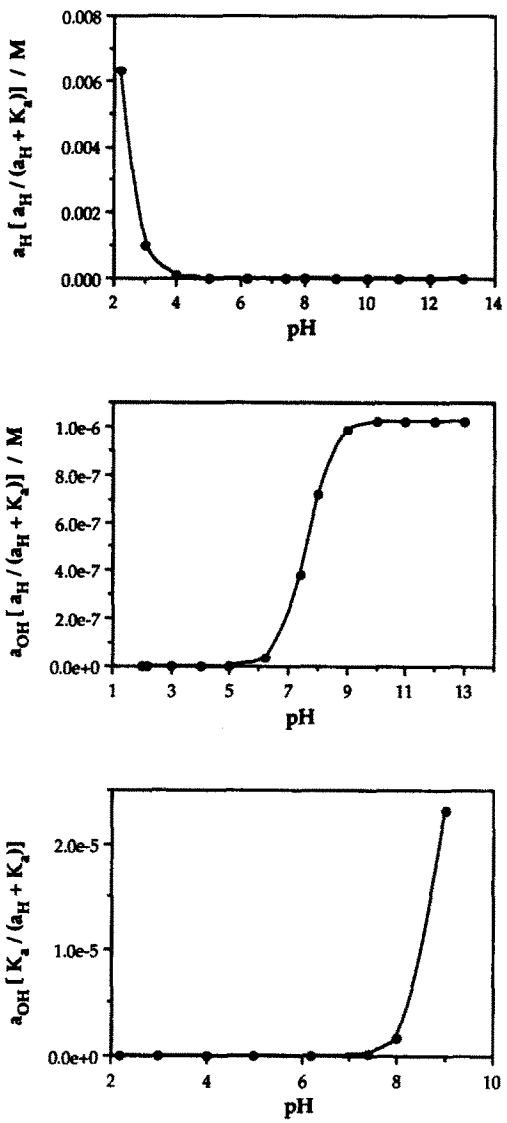


Fig. 5. The variation of the individual terms in Eqn 13 with pH for the *O*-isobutyryl ester (**IV**).

TABLE 6

Second-order rate constants (k_{OH}) for the specific base-catalyzed hydrolysis of the protonated species

Compound	k_{OH} ($\times 10^{-5}$) (M^{-1} min^{-1})	
	pH 6.2	pH 7.4
II	10.9	2.03
III	–	–
IV	2.96	0.46
V	0.74	0.31
VI	1.82	0.23

Values are quoted at two pH values (6.2 and 7.4).

At pH 6.2, the value of k_{OH} determined using Eqn 25 is 1.09×10^6 M^{-1} min^{-1} for the *O*-acetyl ester. The corresponding value at pH 7.4 is 2.03×10^5 M^{-1} min^{-1}. No values are quoted for the *p*-nitrobenzoyl ester (**VII**) as at these pH values the values of α are exceedingly small (due to the low measured value of the pK_a). It is obviously desirable to estimate k_{OH} at high pH where the value of α is also reasonably high (i.e., the rate of hydrolysis of the ionized species is being measured). However, as the pH increases, the degree of ionization (α) decreases and the k'_{OH} term becomes more important. For example, the *O*-acetyl ester (**II**) is 19.7% ionized at pH 9.0, while the *O*-isobutyryl ester (**IV**) is 4.1% ionized at the same pH. At pH 8.0, the value of k_{OH} for the *O*-acetyl ester (71% ionized) is 6.78×10^4 M^{-1} min^{-1} which is in reasonable agreement with the value quoted by Buur et al. (1988), i.e., 2.6×10^4 M^{-1} min^{-1}.

Since $k'_{OH} < k_{OH}$ (Buur et al., 1988), k'_{OH} can only be reasonably estimated at high pH. From Fig. 5, the data for pH 9.0 provide a fair approximation of this parameter. At sufficiently high pH, the rate constant is approximated by:

$$k_{obs} \cong k'_{OH} a_{OH} \{K_a/(a_H + K_a)\} = k'_{OH} a_{OH} (1 - \alpha) \quad (26)$$

For example, the term $a_{OH}\ \{K_a/(a_H + K_a)\}$ increases by a factor of about 164 from pH 6.2 to 7.4 for ester **IV** while the increase from pH 7.4 to 9.0 is 100-fold for the same ester (Fig. 5). The value for α in all cases is less than 22% (Table 7). The above term becomes increasingly important as the pK_a value is lowered. At a particular pH value, the proportion of the unprotonated form increases as the pK_a is lowered. The estimated values of k'_{OH} are given in Table 7, along with the degree of ionization. The value obtained in this way for the *O*-acetyl ester $[k'_{OH}(\mathbf{II}) = 7.6 \times 10^3\ M^{-1}\ min^{-1}]$ is in good agreement with that obtained by Buur et al. (1988), i.e., $6.0 \times 10^3\ M^{-1}\ min^{-1}$, while the value for the *O*-pivaloyl ester (**III**) is higher than that quoted by these authors.

As shown in Fig. 6, 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).

Mechanism of degradation

From the HPLC data, it is clear that at pH < 6, ester hydrolysis to yield propranolol was the only reaction taking place. At pH values greater than 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 a product along with free propranolol. This was confirmed by ^{1}H-NMR and mass spectroscopic data to be the corresponding *N*-acylpropranolol. These compounds were stable under the conditions of the reaction. Irwin and Belaid (1988a) showed that the formation of *N*-acetylpropranolol from the *O*-acetyl compound indicated competitive first-order degradation. Evidence for the occurrence of intramolecular aminolysis was obtained by product analysis studies (Buur et al., 1988). As revealed by HPLC, the disappearance of any propranolol ester in alkaline solutions was accompanied by the progressive appearance of an extra peak which had a short retention time. In the case of *O*-acetylpropranolol and *O*-isobutyrylpropranolol, authentic samples of their *N*-acyl derivatives were synthesised. The physicochemical properties were different from their corresponding *O*-acyl derivatives (i.e., shorter retention times, higher stability, lower melting points and lower solubility in many organic solvents). From retention time measurements, the unknown peaks which appear during the hydrolysis of the *O*-acyl derivatives were the corresponding *N*-acyl esters. This peak appeared in all cases with the exception of the *O*-pivaloyl ester. This is probably due to steric hindrance exhibited by the bulky *tert*-butyl group, making the nucleophilic O → N acyl transfer more difficult as compared to hydrolysis of the ester moiety.

At high pH values, the degradation of the *O*-acyl esters involved parallel hydrolysis (rate

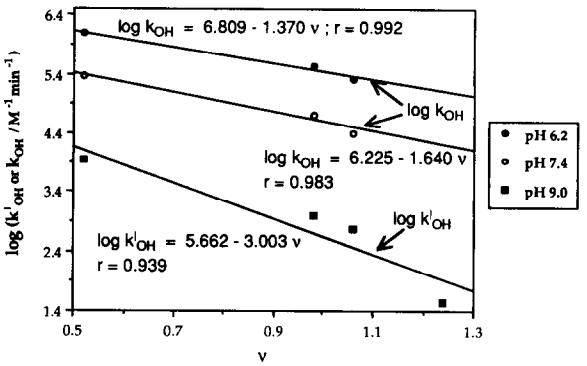


Fig. 6. Plot of log k_{OH} (at pH 6.2 and 7.4) and log k'_{OH} (at pH 9.0) vs the steric parameter (ν) for various propranolol esters. The ν values refer to the alkyl or cycloalkyl moiety in the acyl groups.

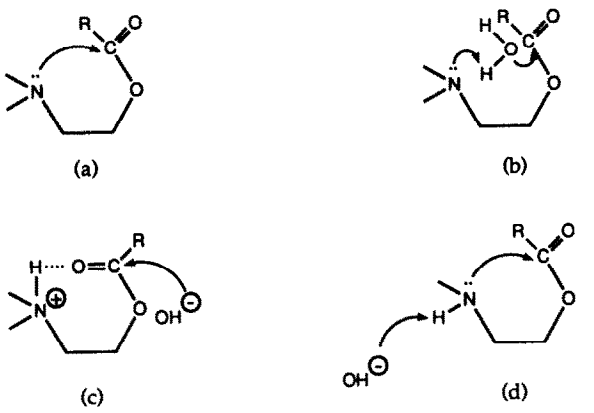
TABLE 7

Second-order rate constants (k'_{OH}) for the hydroxide ion-catalyzed hydrolysis of the neutral species

Compound	k'_{OH} (M^{-1} min^{-1})	100α
II	7.57×10^3; 6.00×10^3 [a]	19.7
III	32.0; 0.4 [a]	0.9
IV	859.3	4.1
V	534.4	4.3
VI	804.7	21.6
VII	243.2	1.9×10^{-5}

Values are estimated at pH 9.0 and the degree of ionization (100α) is also listed.

[a] Buur et al. (1988).



Scheme 3

constant k_1), to yield propranolol, and *O*-to-*N* rearrangement (rate constant k_2), to give the *N*-acyl analogue. In the case of the *O*-cyclopropanoyl ester, the ratio [B]/[C] = 104/6 [condition (ii) above] and since $k_{obs} = 12.27 \times 10^{-3}$ min^{-1}, $k_1 = 11.6 \times 10^{-3}$ min^{-1} $\{= k_{obs}[B]/([B] + [C])\}$ and hence $k_2 = 6.693 \times 10^{-4}$ min^{-1}. The ratio $k_1/k_2 = 17.3$.

There are three possible kinetically indistinguishable mechanisms which 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 (Buur et al., 1988). 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 is found to be the case.

The aminolysis reaction becomes increasingly significant at elevated pH values. Above pH 11.0, Buur et al. (1988) concluded that the overall degradation of propranolol esters consists of aminolysis to an extent of more than 90%.

At yet higher pH values, (pH > 11.5), the predominant kinetic reaction is specific base-catalysed degradation of the free base forms of the esters. These findings taken together show that the intramolecular aminolysis is subject to general base catalysis by hydroxide ions (Buur et al., 1988). It is probable that hydroxide ions are acting as a general base catalyst for the nucleophilic addition as shown in Scheme 3d. Hydroxide ion catalysis of intramolecular aminolysis is well known in other systems (Bundgaard, 1976).

The inability of the *O*-pivaloyl ester (**III**) 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. Irwin and Belaid (1988a) found that as the size of the ester side chain increases, a decrease in the rearrangement potential is observed.

Bundgaard et al. (1986, 1988), in studying timolol ester hydrolysis, argue that the ester with the protonated amino group is much more reactive than the free base form, i.e., $k_{OH} \gg k'_{OH}$. Such enhanced reactivity, also observed for other esters of β-aminoalcohols (Zaslowsky and Fisher, 1963; Bruice and Mautner, 1973), is most likely ascribed to either intramolecular general base catalysis by the unprotonated amino group of water attack on the ester group (mechanism b in Scheme 3) or to intramolecular general acid-catalyzed hydroxide ion nucleophilic attack (mechanism c in Scheme 3). Our results are consistent with this observation. A comparison of the values of k_{OH} and k'_{OH} shows that the protonated form of the esters is more susceptible to degradation than the free base form (Tables 6 and 7). This difference in reactivity becomes more pronounced by increased steric hindrance within the acyl groups and corroborates earlier observations (Buur et al., 1988).

Propranolol esters (containing a secondary isopropylamino group) are more susceptible to intramolecular aminolysis than the corresponding timolol derivatives (Bundgaard et al., 1986) as the steric properties of the amino group in β-aminoalcohols appear to be the predominant factor determining the relative importance of hydrolysis and intramolecular aminolysis (Buur et al., 1988).

The shape of the pH-rate profiles indicate that ester hydrolysis accompanied by intramolecular aminolysis are the dominant reactions taking place in the neutral and alkaline regions. A base-catalysed hydrolytic reaction occurs in this region of the profile. As the pH increased, the rate of amide formation increased slightly as indicated by the HPLC data. This is presumably the result of an increasing proportion of non-protonated base being available for anchimeric attack on the *O*-acyl group (Scheme 3a).

Prediction of shelf-lives

The shelf-life, defined by Eqn 12, indicates the period of storage to which a product may be subjected without serious loss of potency. In order to predict the stability of the propranolol esters under conditions similar for storage, temperature-accelerated stability studies were performed over the temperature range 37–70°C at pH 5.0. This reaction is facilitated by the strongly electron withdrawing effect of the protonated amino group which activates the ester linkage towards nucleophilic attack.

Although intramolecular aminolysis did not usually occur at this pH, the esters were more susceptible to *N*-acylation at elevated temperatures. At 70°C the formation of the *N*-acetyl derivative constituted approx. 5% of the overall reaction.

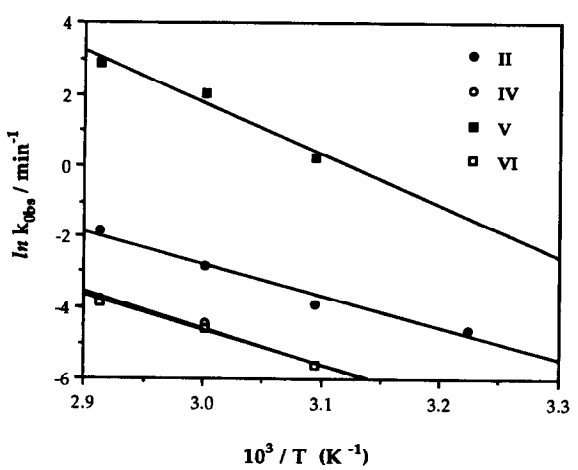


Fig. 7. Arrhenius plots of the rates of hydrolysis of *O*-acyl esters of propranolol ($\mu = 0.5$) at pH 5.0.

TABLE 8

Arrhenius parameters for the hydrolysis of various propranolol esters at pH 5.0 ($\mu = 0.5$)

Compound	ln A	E_a (kJ mol^{-1})	r [a]	n [b]
II	24.18	74.73	0.984	4
IV	26.04	84.82	0.991	3
V	45.25	120.50	0.983	3
VI	24.51	80.79	0.997	3

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

In Fig. 7 the rate data obtained for esters **II**, **IV**, **V** and **VI** are plotted according to the Arrhenius equation:

$$\ln k_{obs} = \ln A - E_a/RT \quad (27)$$

A is the pre-exponential frequency factor while E_a denotes the activation energy of decomposition. The Arrhenius parameters (A, E_a) are listed in Table 8. In the case of esters **III** and **VII** these parameters could not be determined as the degradation rates were measurable at only one temperature, i.e., 70°C. The activation energy of hydrolysis is of the order of 80 kJ mol^{-1} in the case of three of the esters, which is typical of many reported values for drug decompositions (Kennon, 1964). The value for the *O*-cyclopropranoyl ester is somewhat higher, in line with that found for the corresponding oxprenolol ester (Jordan et al., 1992).

The Arrhenius parameters allow extrapolation of the rate constant and hence, the shelf-life of aqueous solutions at lower temperatures, e.g., 10

TABLE 9

Predicted values of the shelf-life (t_{90}) for various propranolol esters in aqueous solution at pH 5.0 ($\mu = 0.5$)

Ester	t_{90} (h)	
	10°C	25°C
II	3.38	0.68
IV	38.27	6.25
V	0.66	0.05
VI	31.91	5.68

or 25°C (Table 9). The *O*-isobutyryl ester (**IV**), which is branched, is reasonably stable.

The half-life, $t_{1/2}$, quoted by Buur et al. (1988) for the *O*-acetyl ester is 85 min in 0.02 M phosphate buffer solution (pH 7.4 at 37°C). Since for a first-order reaction:

$$t_{1/2} = \{\ln 2/\ln(10/9)\}t_{90} \qquad (28)$$

the above value represents a shelf-life (t_{90}) of 12.9 min. Using the parameters for the same ester (**II**), the value which is obtained upon extrapolation to 37°C is 12.8 min. However, the latter value is observed at pH 5.0 and our results predict a higher lability of the esters.

Lipophilicity of the propranolol esters

The potentiometric titration method for the determination of partition 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 5). These physicochemical parameters, along with distribution coefficients, have been estimated using Eqns 1–4.

The lipophilicities of a number of β-adrenoceptor blocking agents have been determined by several investigators (Hellenbrecht et al., 1973; Zaagsma and Nauta, 1974; Cruickshank, 1980; Woods and Robinson, 1981; Schoenwald and Huang, 1983; Betageri and Rogers, 1987; Reca-

TABLE 10

Partition coefficients (log P), apparent partition coefficients (log $P)_{app}$ and capacity factors (log k') of propranolol and its esters at 22°C

Compound	log *P*	log P_{app} [a]	log *k'* [b]
I	3.1; 3.26 [c]; 3.37 [e,f]; 2.75 [g,i]; 3.66 [j]; 3.17 [h]; 3.65 [k]; 3.21 [l]; 3.1 [n]	1.07; 1.18 [d]; 1.17 [h,m]; 1.31 [o]; 0.73 [p]; 0.93 [q]; 0.73 [r]; 1.72 [s]; 1.40 [t]	0.22
II	4.34; 4.51 [c]	3.31	0.43
III	3.16; 6.44 [c]	3.03	0.58
IV	3.52	3.09	0.74
V	3.68	3.23	
VI	3.78	2.70	0.83
VII	5.97	2.88	

[a] pH 7.40 – calculated from log *P* using Eqn 4 except for **VII** (Eqn 10).
[b] pH 7.40.
[c] Irwin and Belaid (1987b).
[d] Irwin and Belaid (1987b) – pH 7.29.
[e] Betageri and Rogers (1987) – molal partition coefficient (30°C).
[f] Recanatini (1989) – measured value.
[g] Recanatini (1989) – calculated value using the CLOGP program.
[h] Mannhold et al. (1990) – measured value at pH 7.40 and 20°C.
[i] Mannhold et al. (1990) – calculated value using the CLOGP program.
[j] Mannhold et al. (1990) – calculated value using hydrophobic fragmental constants (Σf).
[k] Cruickshank (1980).
[l] Schoenwald and Huang (1983) – 35°C.
[m] Zaagsma and Nauta (1974) – pH 7.40 and 20°C.
[n] Zaagsma and Nauta (1974) – calculated from P_{app} and pK_a (9.32) using Eqn 4.
[o] Woods and Robinson (1981) – pH 7.40 and 37°C.
[p] Woods and Robinson (1981) – pH 7.00 and 20°C.
[q] Woods and Robinson (1981) – pH 7.00 and 37°C.
[r] Hellenbrecht et al. (1973) – pH 7.00 and room temperature.
[s] Hellenbrecht et al. (1973) – pH 8.00 and room temperature.
[t] Ghosh et al. (1993) – pH 7.40 – calculated from log *P* (reference 1 above).

natini, 1989; Mannhold et al., 1990) and these values have been compared with theoretical estimates of log P (Recanatini, 1989; Mannhold et al., 1990). These compounds show a wide range of lipophilic character and may therefore be classified in terms of their lipophilicities. Schoenwald and Huang (1983) classified them in three groups, namely highly lipophilic (e.g., propranolol), lipophilic (e.g., timolol) and hydrophilic (e.g., atenolol). Absorption of the hydrophilic compounds is slow and incomplete while that of the lipophilic compounds is rapid and complete (Taylor et al., 1985). The liposolubility of a drug is a major determinant of it's pharmacokinetic profile (Kubinyi, 1979). Highly liposoluble β-blockers undergo a high degree of first-pass metabolism in the liver (Pirttiaho et al., 1980), are highly bound to plasma proteins (Appelgren et al., 1974) and concentrate in the central nervous system. The highly lipophilic compounds in the series (e.g., propranolol) are almost completely metabolised, while the lipophobic compounds (e.g., atenolol and nadolol) are little affected by liver metabolism (Woods and Robinson, 1981). The thermodynamics of partitioning of these compounds in the *n*-octanol-water system have been studied (Betageri and Rogers, 1987; Burgot et al., 1990).

Partition coefficients (log P) for the propranolol esters between *n*-octanol and water at 22°C are listed in Table 10 and are compared with the literature data. The results indicate that the esters are all more lipophilic than the parent compound, in agreement with previous studies of propranolol (Irwin and Belaid, 1987b) and timolol (Bundgaard et al., 1986, 1988). The value of log P obtained for propranolol (**I**), i.e., 3.1, is in close agreement with literature values (Table 10). The value calculated from the distribution coefficient, using Eqn 4, measured by Zaagsma and Nauta (1974) yields precisely the same result. The value of log P for the *O*-acetyl ester (**II**) is in reasonable agreement with that quoted by Irwin and Belaid (1987b), while the value obtained for the *O*-pivaloyl ester (**III**) is substantially lower than their value. The discrepancy could well be due to our rather low value for the pK_a in the latter case. Distribution coefficients (log P_{app})

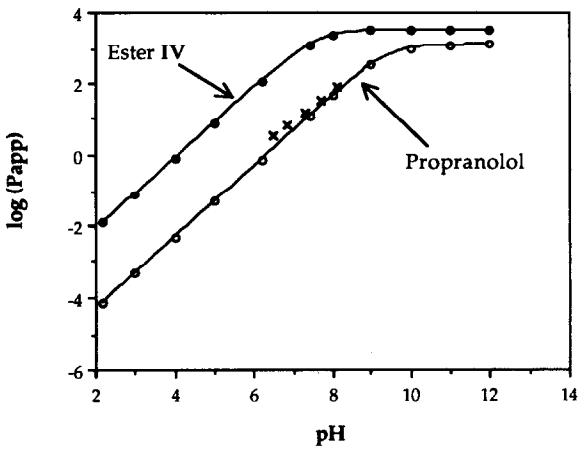


Fig. 8. Variation of log P_{app} with pH at 37°C. The curve for propranolol (log $P = 3.1$, $pK_a = 9.43$), is compared with that for the *O*-isobutyryl ester (log $P = 3.52$, $pK_a = 7.63$). The data were calculated using Eqn 4 and the measured P_{app} values of Irwin et al. (1987b) for propranolol (represented by ×) are included for comparison.

and capacity factors (log k') determined at pH 7.4 are also included in Table 10. The variation of log P_{app} with pH, calculated using Eqn 4, is shown in Fig. 8 for both propranolol (log $P = 3.1$) and *O*-isobutyrylpropranolol (log $P = 3.52$). The results obtained by Irwin and Belaid (1987b) for propranolol are included for comparative purposes. Combining the value of log P for propranolol with the pK_a value (Table 5) and substituting in Eqn 4, the value of log P_{app} at pH 7.0 is 0.67, which is in reasonable agreement with that quoted by Woods and Robinson (1981) at the same pH and 20°C.

The capacity factor, k', of a solute is defined by the following equation:

$$k' = (t_r - t_0)/t_0 \qquad (29)$$

where t_r is the retention time of the solute and t_0 denotes the elution time of the solvent.

The increased lipophilicity of the esters as compared with propranolol is reflected in the values for the capacity factors (Table 10) as the log k' values of the esters are invariably higher than that of the parent compound. Linear relationships between log P_{app} and log k' have been observed (Hafkenscheid and Tomlinson, 1983;

Bundgaard et al., 1988). However, the results presented here are inconclusive in this regard.

The increase in lipophilicity on esterification is partly due to the replacement of the hydroxyl group by an ester group. Such a change in lipophilicity is due largely to the observed decrease in the pK_a value on esterification (Table 5). Thus, a higher proportion of the lipophilic free base form is present at any given pH value as is evident from Fig. 8. For example, at pH 7.40, the value of $K_a/[a_H + K_a]\ (= 1 - \alpha)$ for propranolol ($pK_a = 9.43$) is 9.24×10^{-3} (Fig. 4) while the corresponding values for the esters range between 0.084 (**VI**) and 0.743 (**III**). The value for the *O-p*-nitrobenzoyl ester (**VII**) is quite high (0.999), due to the particularly low value of the pK_a. The values of log P_{app} (as calculated from log P) for all esters are substantially higher than the value for propranolol itself. This is also due to the decrease in the pK_a upon esterification.

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