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Prodrugs of propranolol: hydrolysis and intramolecular aminolysis of various propranolol esters and an oxazolidin-2-one derivative

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Summary

As part of a series of studies to develop prodrug derivatives of β-blockers, the *O*-acetyl, propionyl, butyryl and pivaloyl esters of propranolol as well as its 2-oxazolidone derivative were synthesized and their kinetics of conversion studied in aqueous solution and in 80% human plasma. The propranolol esters were all hydrolyzed to yield propranolol in solutions of pH < 7 whereas in neutral and alkaline solutions they underwent simultaneous hydrolysis and intramolecular aminolysis to produce *N*-acylated propranolol. The relative importance of the hydrolysis and aminolysis reactions was shown to depend on pH and on the steric properties of the acyl moiety of the esters. At pH 7.4 and 37 °C, the half-lives of degradation of the esters to yield largely (> 90%) propranolol ranged from 85 min for the *O*-acetyl ester to 780 min for the *O*-pivaloyl ester. Human plasma catalyzed the degradation of the esters except for the *O*-pivaloyl ester in which case a rate-retarding effect by plasma was observed. In contrast to the esters, the oxazolidin-2-one derivative of propranolol was highly stable in aqueous solution as well as in the presence of human plasma, thus rendering it unsuitable as a prodrug form.

Introduction

In previous studies various aliphatic esters of timolol, a non-selective β-adrenergic receptor blocker, have been developed as prodrugs to potentially diminish the systemic absorption and therefore side-effects of topically applied timolol through increased corneal absorption (Bundgaard et al., 1986; Chang et al., 1987). In comparison to timolol the esters indeed showed enhanced corneal permeability characteristics and at the same time unaltered or slightly reduced systemic absorption. As such, they are promising timolol prodrugs for ocular delivery. Unfortunately, they suffer from instability in aqueous solutions.

To further examine the basis of this instability a similar series of esters (II–V) of the structurally related β-blocker propranolol (I) have been examined. Moreover, the present study, which elucidates the kinetics of degradation of the pro-

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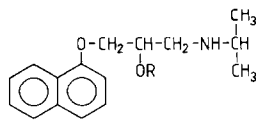
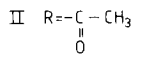
pranolol esters II–V in aqueous solution and in human plasma solutions, may be of interest in the consideration of prodrugs of propranolol itself. Due to extensive first-pass metabolism the peroral bioavailability of propranolol is low and highly variable (Shand and Rangno, 1972; Johnsson and Regårdh, 1976; Frishman, 1979; Routledge and Shand, 1979; Prichard and Owens, 1980; Roscoe et al., 1982; Cid et al., 1986). The prodrug approach may be a potentially useful means to reduce first-pass metabolism as has already been demonstrated with a hemisuccinate ester of propranolol on the basis of experiments in dogs (Garceau et al., 1978). Furthermore, *O*-acetyl and *O*-pivaloyl esters of propranolol have recently been encapsulated into rat erythrocytes in an attempt to obtain a slow release carrier system for the drug (Alpar et al., 1986). Despite these studies on various propranolol prodrug esters basic information on the kinetics of their chemical and enzymic degradation is non-existing.

In the present study, a cyclic oxazolidin-2-one derivative of propranolol (VII) has also been studied along with the esters to assess its potential suitability as a novel prodrug form.



I R=H



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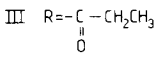

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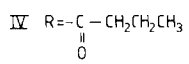

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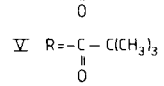

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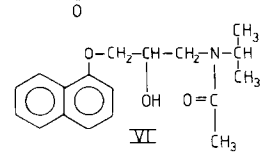

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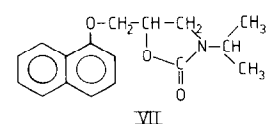


VII

Materials and Methods

Apparatus

Ultraviolet spectral measurements were performed with a Shimadzu UV-190 spectrophotometer equipped with a thermostatically controlled cell compartment, using 1-cm quartz cells. ^{1}H-NMR spectra were run on a Varian 360 L instrument using tetramethylsilane as internal reference. Melting points were taken on a capillary melting-point apparatus and are uncorrected. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. High-performance liquid chromatography (HPLC) was done with a system consisting of a Waters pump model 6000A, a variable-wavelength UV-detector Waters type 480 and a 20-μl loop injection valve. A column, 100 × 3 mm, packed with CP SPHER C-8 (7 μm particles) was used. Microanalyses were performed at the Microanalytical Laboratory, Leo Pharmaceutical Products, Ballerup, Denmark.

Chemicals

Propranolol hydrochloride was kindly provided by DAK Laboratories AS, Copenhagen. Buffer substances and all other chemicals or solvents used were of reagent grade.

Preparation of propranolol esters

The propranolol esters II–V were prepared by reacting propranolol hydrochloride with the corresponding acid chloride. A mixture of propranolol hydrochloride (3.4 mmol, 1.0 g) and the appropriate acid chloride (10 mmol) was refluxed with stirring for 2 h. After cooling, the mixture was evaporated under reduced pressure. Benzene (10 ml) was added and the mixture evaporated again. The residue was slurried in ether, heated on a steam bath and ethanol was added to give a clear solution. Upon cooling the hydrochloride salts of the propranolol esters precipitated. The compounds were filtered off, washed with ether and recrystallized from ethanol–ether. Physical and analytical data for the compounds are given in Table 1. The NMR and IR spectra of the compounds were consistent with their structures. Crowther and Smith (1968) have previously pre-

pared the acetyl ester of propranolol hydrochloride under similar conditions.

Preparation of N-acetylpropranolol (VI)

This compound was prepared by reacting propranolol hydrochloride with acetyl chloride in the presence of an excess of triethylamine as reported by Nelson and Walker (1978).

Preparation of 3-isopropyl-5-[(naphthyloxy)methyl] oxazolidin-2-one (VII)

The oxazolidin-2-one derivative of propranolol (VII) was prepared by refluxing a solution of propranolol hydrochloride (2.95 g, 10 mmol) and *N,N'*-carbonyldiimidazole (1.8 g, 11 mmol) in 50 ml of tetrahydrofuran for 2 h. The reaction mixture was evaporated in vacuo and the residue taken up in 50 ml of water and ethyl acetate. The ethyl acetate layer was separated, washed with 1 M hydrochloric acid and water, dried over anhydrous sodium sulphate and evaporated in vacuo to leave an oil which crystallized from ethanol–ether–petroleum ether. The crystalline title compound was finally recrystallized from ethanol–ether, m.p. 124–125 °C, rep. m.p. 124 °C (Cardillo et al., 1986). The synthetic procedure utilizing *N,N'*-carbonyldiimidazole was adopted from the method described by Wright (1965).

Kinetic measurements

The decomposition of the propranolol esters II–V was studied in aqueous buffer solutions at 37.0 ± 0.2 °C. Hydrochloric acid, acetate, phosphate, borate, carbonate and sodium hydroxide were used as buffers; the total buffer concentration was generally 0.02 M and a constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride.

The degradation of *O*-acetylpropranolol (II) at pH values higher than 9 was followed spectrophotometrically by recording the increase in absorption at 240 nm accompanying its degradation. The reactions were performed in 2.5 ml aliquot portions of buffer solutions in a thermostated quartz cuvette and were initiated by adding 10 μl of a stock solution of II to give a final concentration of about 10^{-4} M. Pseudo-first-order rate constants were determined from linear plots of $\log(A_\infty - A_t)$ vs time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively.

All other rate constants were determined by means of a reversed-phase HPLC procedure capable of separating the derivatives from the parent propranolol and the corresponding *N*-acyl derivatives. Solvent systems of 45–70% v/v methanol in 0.01 M acetate buffer of pH 4.5 were used. The

TABLE 1

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

Compound	Yield (%)	M.p. (°C)	Formula	Analysis (%)	
				Calculated	Found
O-Acetyl (II)	89	171–172 [a]	$C_{18}H_{24}ClNO_3$	*C* 63.99	64.07
				H 7.16	7.17
				N 4.15	4.18
O-Propionyl (III)	85	119–120	$C_{19}H_{26}ClNO_3$	*C* 64.85	64.80
				H 7.45	7.49
				N 3.98	3.96
O-Butyryl (IV)	90	108–109	$C_{20}H_{28}ClNO_3$	*C* 65.64	65.60
				H 7.71	7.70
				N 3.83	3.85
O-Pivaloyl (V)	82	145–146	$C_{21}H_{30}ClNO_3$	*C* 66.39	66.38
				H 7.96	7.98
				N 3.69	3.65

[a] Reported m.p.: 170–171 °C (Crowther and Smith, 1968); 170–171 °C (Nelson and Walker, 1978).

flow rate was 1.0 ml/min and the column effluent was monitored at 290 nm. Quantitation of the compounds was done by measuring the peak heights in relation to those of standards chromatographed under the same conditions.

The reactions were initiated by adding 50 μl of a stock solution of the derivatives (1–2 mg/ml water or methanol) to 10.0 ml of buffer solution, pre-heated at 37 °C, in screw-capped test tubes. The solutions were kept in a water-bath at 37.0 ± 0.2 °C and at appropriate intervals samples were taken and immediately chromatographed. Pseudo-first-order rate constants for the overall degradation were determined from the slopes of linear plots of the logarithm of residual propranolol derivative against time.

The susceptibility of the derivatives to undergo conversion to the parent propranolol was also studied in 0.01 M phosphate buffer of pH 7.4 containing 80% human plasma (at 37 °C). The initial concentration of the compounds was about 0.01 mg/ml. At appropriate times 250 μl samples were withdrawn and added to 1000 μl of ethanol in order to deproteinize the plasma. After mixing and centrifugation at 12,000 rpm for 2 min, 20 μl of the clear supernatant were analyzed by HPLC as described above.

Results and discussion

Kinetics of degradation of propranolol esters (II–V)

The degradation of the 4 propranolol esters II–V was studied in aqueous solution at 37 °C over a wide range of pH. At constant pH and temperature the disappearance of propranolol ester displayed strict first-order kinetics for several half-lives. Typical first-order plots are shown in Fig. 1. At buffer concentrations of 0.02 M or less no significant catalysis by the buffer substances used to maintain pH constant was observed. This is in agreement with a similar finding for various esters of timolol (Bundgaard et al., 1986).

The influence of pH on the rates of degradation at 37 °C is shown in Fig. 2 in which the logarithm of the observed pseudo-first-order rate constants (k_{obs}) is plotted against pH. The shape of the pH–rate profiles indicates that the overall degradation process 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 the following rate expression:

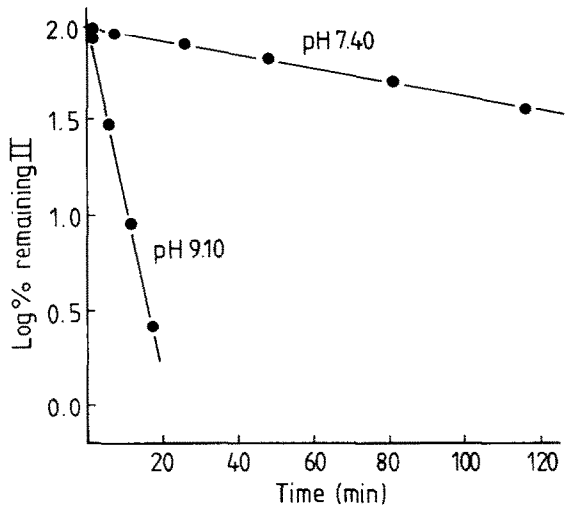
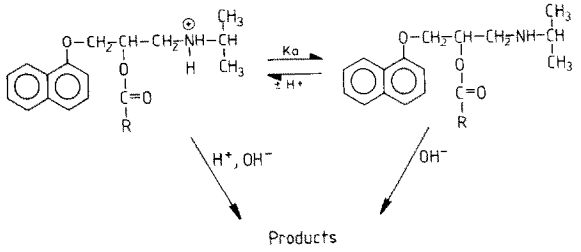


Fig. 1. First-order plots for the degradation of *O*-acetylpropranolol at pH 7.40 and 9.10 at 37 °C.

$$k_{obs} = k_H a_H \frac{a_H}{a_H + K_a} + k_{OH} a_{OH} \frac{a_H}{a_H + K_a} + k'_{OH} a_{OH} \frac{K_a}{a_H + K_a} \quad (1)$$

where a_H and a_{OH} refer to the hydrogen ion and hydroxide ion activities, respectively, $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ are the fractions of total ester in protonated and free base forms, respectively, and K_a is the apparent ionization constant of the protonated NH-group in the esters. The rate constant k_H refers to the specific acid-catalyzed reaction of the protonated ester, and k_{OH} and k'_{OH} are the second-order rate constants for the apparent specific base-catalyzed reactions of the protonated and neutral species respectively (Scheme 1).

Only the *O*-acetyl ester (II) was studied over a broad pH range. The V-shaped pH–rate profile observed for this compound indicates that a possible spontaneous (or water-catalyzed) reaction of



Scheme 1.

the protonated species is insignificant to the overall reaction. Such lack of a water-catalyzed reaction is in contrast to previous findings for the acetate ester of timolol (Bundgaard et al., 1986). For this compound a water-catalyzed hydrolysis was the major decomposition route at pH 3–4.

The various rate and ionization constants derived from the pH–rate profiles are listed in Table 2. In Fig. 2 the solid curves drawn were constructed from these constants and Eqn. 1 and a good agreement between calculated and experimental data is observed.

The kinetically determined pK_a values for the esters (8.3) are similar to those of analogous esters of timolol (8.4) (Bundgaard et al., 1986). The esters are considerably less basic than the parent propranolol, which has a pK_a of 9.2 at 35 °C (Schoenwald and Huang, 1983). The difference may be ascribed to the greater polar effect of the ester moiety relative to a hydroxyl group.

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. This difference in reactivity becomes more pronounced by increased steric hindrance within the acyl groups. This is shown in Fig. 3, where log k_{OH} and log k'_{OH} have been plotted against the steric substituent parameter ν (Charton, 1977). Besides steric factors polar effects also influence the reactivity of esters, but for compounds II–V the polar effects of the acyl groups are almost identical.

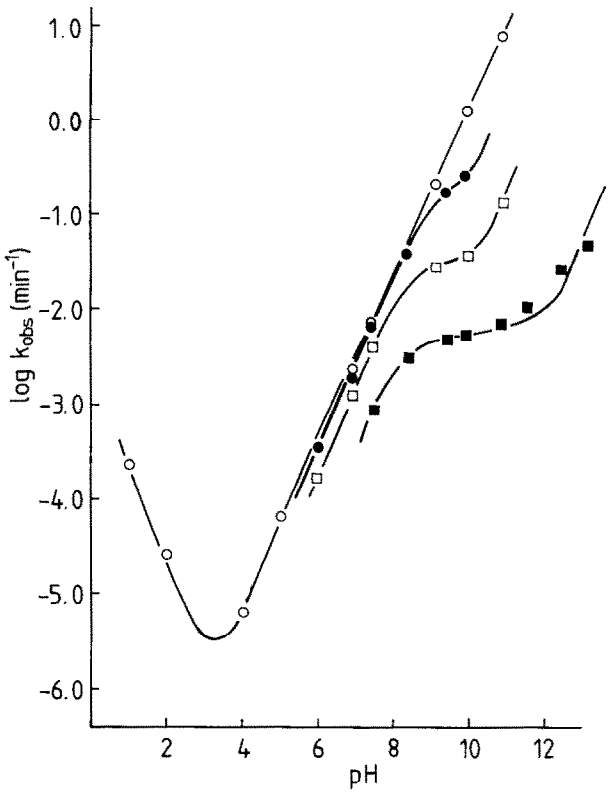


Fig. 2. The pH–rate profiles for the degradation of various propranolol esters in aqueous solution ($\mu = 0.5$) at 37 °C. Key: ○, *O*-acetylpropranolol (II); ●, *O*-propionylpropranolol (III); □, *O*-butyrylpropranolol (IV); ■, *O*-pivaloylpropranolol (V).

TABLE 2

Ionization constants and rate data for the degradation of various propranolol esters in aqueous solution ($\mu = 0.5$; 37 °C)

Compound	k_H ($M^{-1}\cdot min^{-1}$)	k_{OH} ($M^{-1}\cdot min^{-1}$)	k'_{OH} ($M^{-1}\cdot min^{-1}$)	pK_a
II	2.4×10^{-3}	2.6×10^{4}	6.0×10^{3}	8.3
III	2.4×10^{-3}	1.3×10^{4}	9.1×10^{2}	8.3
IV		7.4×10^{3}	75	8.3
V		1.3×10^{3}	0.4	8.3

Mechanism of degradation

There are 3 possible kinetically indistinguishable mechanisms which might account for the shape of the pH–rate profiles in the alkaline pH region (Scheme 2): (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 pro-

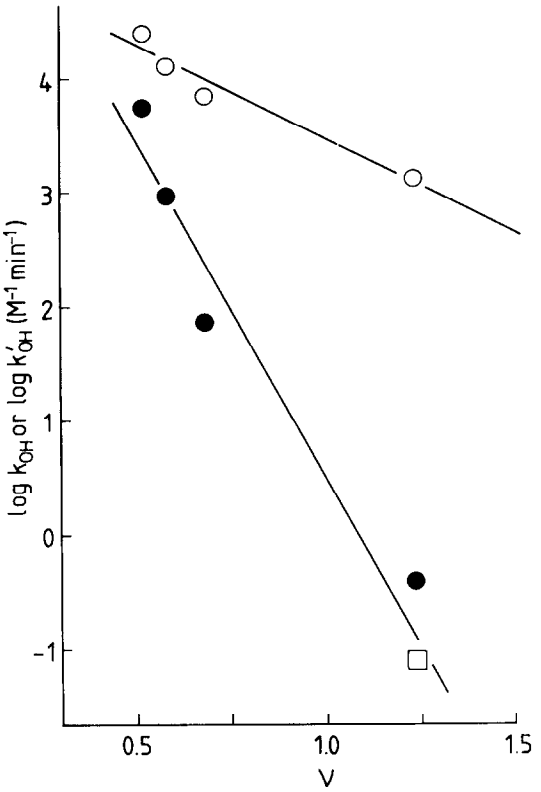
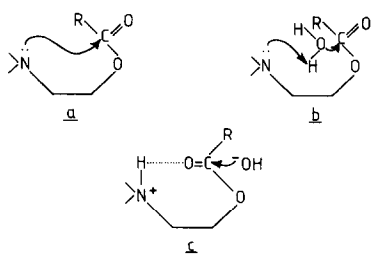


Fig. 3. Plots of log k_{OH} (○) and log k'_{OH} (●) vs the steric parameter (ν) for various propranolol esters. The ν values refer to the alkyl moiety in the acyl groups. The symbol, □, represents the log k'_{OH} value for the *O*-pivaloyl ester due to intramolecular aminolysis.

tonated amino group of the attack of hydroxide ion. In Eqn. 1 the latter reaction has been used although it is kinetically equivalent to the two other reactions. Whereas both mechanisms (b) and (c) are hydrolytic reactions resulting in the formation of propranolol, mechanism (a) represents an



Scheme 2.

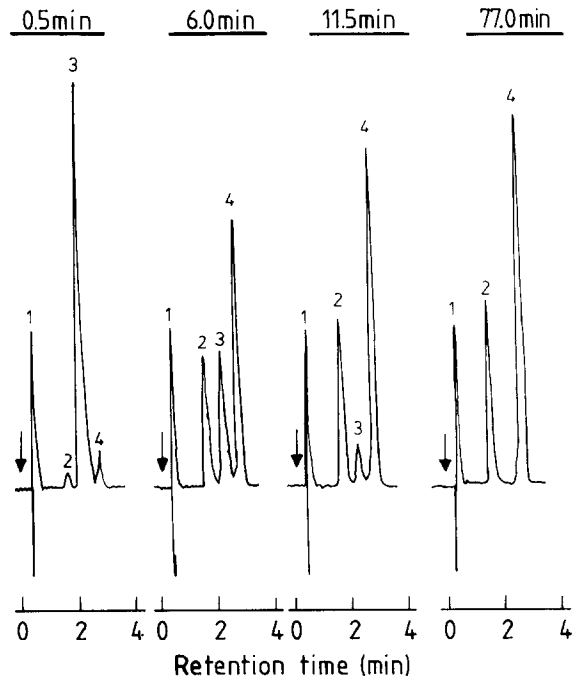


Fig. 4. Chromatographic tracings of a reaction solution of *O*-acetylpropranolol in 0.02 M borate buffer solution of pH 9.10 (at 37 °C) assayed at the times indicated. Key: Peak 1, solvent front; peak 2, propranolol; peak 3, *O*-acetylpropranolol; peak 4, *N*-acetylpropranolol.

intramolecular aminolysis giving rise to the formation of stable *N*-acylated propranolol derivatives like VI.

Evidence for the occurrence of intramolecular aminolysis was obtained by product analysis studies. As revealed by HPLC the disappearance of the acetyl ester II in alkaline solutions was accompanied by the progressive appearance of a peak with the same retention time as an authentic sample of *N*-acetylpropranolol (VI). Besides, a peak corresponding to propranolol appeared during the degradation (Fig. 4). Fig. 5 shows the time courses of disappearance of *O*-acetylpropranolol and the concurrent appearance of propranolol and *N*-acetylpropranolol in a 0.02 M borate buffer solution (pH 9.10) of the acetyl ester at 37 °C. As can be seen the *N*-acetyl derivative is stable under these conditions. This was also confirmed in separate experiments with the authentic sample of VI.

The relative importance of the two degradation routes of the propranolol esters, hydrolysis to

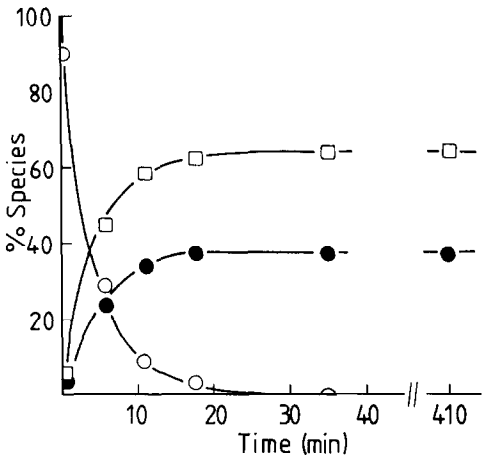


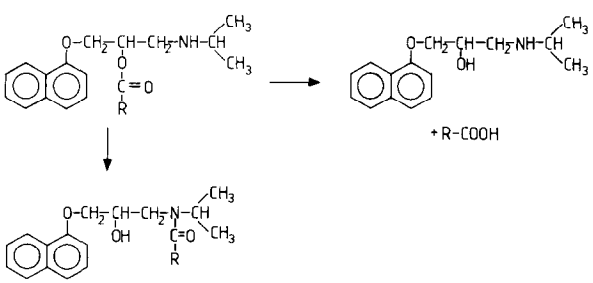
Fig. 5. Time-course of disappearance of *O*-acetylpropranolol (○) and appearance of propranolol (●) and *N*-acetylpropranolol (□) in a 0.02 M borate buffer solution (pH 9.10) of *O*-acetylpropranolol at 37 °C.

yield propranolol and intramolecular aminolysis resulting in the formation of *N*-acyl propranolol (an amide derivative) (Scheme 3) was assessed as a function of pH. Calculation of the amount of amide derivative formed was done from measurement of the amounts of propranolol formed at the end of each reaction according to Eqn. 2:

$$\% \text{ amide} = 100 - \% \text{ propranolol formed} \qquad (2)$$

In the case of compound II this indirect determination agreed well (within ±5%) with the direct determination based on the use of authentic *N*-acetylpropranolol.

The results obtained showed that in solutions of pH < 6 ester hydrolysis to yield propranolol



Scheme 3.

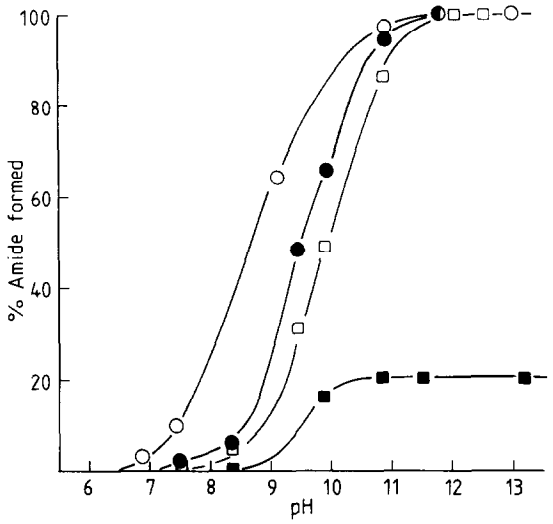
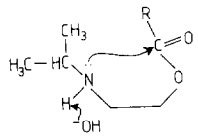


Fig. 6. Plots showing the yield of *N*-acylated propranolol formed upon degradation of propranolol esters in aqueous solution at 37 °C. Key: ○, *O*-acetylpropranolol; ●, *O*-propionylpropranolol; □, *O*-butyrylpropranolol; ■, *O*-pivaloylpropranolol.

was the only reaction taking place. With increasing pH at pH > 7 the aminolysis becomes increasingly more significant (Fig. 6). Thus, at pH > 11 the overall degradation of the esters II–IV consists of aminolysis to an extent of more than 90%. For the pivaloyl ester derivative (V), however, only about 20% amide is formed even at pH 13. This different behaviour of the pivaloyl ester may certainly be due to the steric hindrance exhibited by the bulky tertiary butyl group, making the nucleophilic $O \rightarrow N$ acyl transfer reaction more difficult compared to hydrolysis of the ester moiety.

At pH > 11.5 the sole reaction taking place for the esters II–IV is intramolecular aminolysis (cf. Fig. 6). From Fig. 2 is seen that in this pH-range the predominant kinetic reaction is specific base-catalyzed degradation of the free base forms of the esters. These findings taken together show that the intramolecular aminolysis is subject to catalysis by hydroxide ions. Most probably hydroxide ions are acting as a general base catalyst for the nucleophilic addition as depicted in Scheme 4. Hydroxide ion catalysis of intramolecular aminolysis is well known in other reactions such as

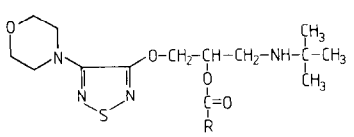


Scheme 4.

piperazinedione formation from various amino acid esters and dipeptide esters (Martin et al., 1964b; Meresaar and Ågren, 1968; Purdie and Benoiton, 1973) as well as amino-cephalosporins (Bundgaard, 1976).

Intramolecular $O \rightarrow N$ acyl transfer reactions have previously been observed in esters of various β-aminoalcohols, including *O*-acetylethanolamine (Martin and Parcell, 1961; Hansen, 1963; Martin et al., 1964a; Schmir, 1968), *O*-acetylserine (Caswell et al., 1981), *O*-acetylephedrine (Welsch, 1947; Fodor et al., 1949) and *O*-nicotinoylethanolamine (Nagai et al., 1984). For these compounds intramolecular aminolysis predominates over hydrolysis in neutral and alkaline solutions. For example, *N*-acetylserine was formed in a yield of 92% from decomposition of *O*-acetylserine at pH 7.2 and 30 °C (Caswell et al., 1981). At the same pH the $O \rightarrow N$ acyl transfer reaction of the propranolol esters constituted less than 7% of the overall reaction (cf. Fig. 6).

On the other hand, similar alkyl esters of timolol (VIII) have recently been shown to be entirely hydrolyzed in aqueous solution (Bundgaard et al., 1986). Even at basic pH values of 12–13 no intramolecular aminolysis was observed. This inability of timolol esters to undergo intramolecular aminolysis can most likely be ascribed to steric hindrance exhibited by the bulky tertiary butylamino group in the compounds. Compared to *O*-acyl derivatives of ethanolamine and serine, which both contain a primary amino group, the propranolol esters show a greater tendency to



VIII

hydrolyze than to undergo intramolecular aminolysis at pH 7–10. Thus, the behaviour of the propranolol esters containing a secondary isopropylamino group occupies an intermediate position between the primary β-aminoalcohols and timolol with its bulky secondary amino group. Therefore, the steric properties of the amino group in esters of β-aminoalcohols appear to be the predominant factor determining the relative importance of hydrolysis and intramolecular aminolysis. Considering the structural effects within the acyl moiety of such esters steric properties do also appear to determine the relative importance of hydrolysis and aminolysis, cf. the decreased propensity of the *O*-pivaloyl ester (V) to undergo aminolysis relative to the alkyl esters II–IV.

Comparison of chemical reactivity of propranolol and timolol esters

Despite the fact that the propranolol esters undergo intramolecular aminolysis in addition to hydrolysis in neutral and alkaline solutions, these esters show a somewhat higher stability than similar timolol esters (VIII) which are only degraded by hydrolysis. Thus, whereas k_{OH} for *O*-acetyltimolol is 5.2×10^4 $M^{-1} \cdot min^{-1}$ at 37 °C (Bundgaard et al., 1986) *O*-acetylpropranolol shows a k_{OH} value of 2.6×10^4 $M^{-1} \cdot min^{-1}$. Similarly, the k'_{OH} value for *O*-pivaloyltimolol is 1.3 $M^{-1} \cdot min^{-1}$ while that for *O*-pivaloylpropranolol is 0.4 $M^{-1} \cdot min^{-1}$. Correcting for the contribution of aminolysis (22%) the k'_{OH} parameter representing only hydrolysis of the *O*-pivaloylpropranolol becomes even less (0.31 $M^{-1} \cdot min^{-1}$). In acidic solutions *O*-acetylpropranolol is slightly more unstable than *O*-acetyltimolol, the k_H values being 2.4×10^{-3} and 1.8×10^{-3} $M^{-1} \cdot min^{-1}$, respectively. At pH 3–4, however, the propranolol esters show about a 10-fold greater stability than esters of timolol. In contrast to propranolol esters, the timolol esters showed a pronounced spontaneous or water-catalyzed hydrolysis which is the dominating reaction in this pH-range (Bundgaard et al., 1986). A study of the kinetics of degradation of esters of other structurally related β-blockers of the β-aminoalcohol type is planned in an effort to elucidate more fully the relationships between chemical structure and reac-

TABLE 3

Half-lives of degradation of various propranolol esters in 0.02 M phosphate buffer solutions (pH 7.4) and 80% human plasma solutions (pH 7.4) at 37°C and yields of propranolol formed in the solutions

Compound	Buffer		Plasma	
	$t_{1/2}$ (min)	Propranolol formed (%)	$t_{1/2}$ (min)	Propranolol formed (%)
II	85	90	52	80
III	91	98	55	90
IV	162	98	71	90
V	780	100	1400	100

tivity. In any case, it can be concluded from the previous timolol study and the present work that structural inability to undergo intramolecular aminolysis does not necessarily ensure a higher stability of β-aminoalcohol esters in aqueous solution including neutral and basic solutions.

Hydrolysis in human plasma

The rates of degradation of the propranolol esters were determined in 80% human plasma at 37°C in order to obtain information on the susceptibility of these esters to enzymatic catalysis. As shown in Table 3, the degradation of the esters II–IV is accelerated in the presence of plasma. The *O*-pivaloyl ester, on the other hand, was more stable in the plasma solution compared to a buffer solution of the same pH and temperature. Such rate-retarding effect by plasma has previously been observed for esters of timolol (Bundgaard et al., 1986). It is of interest to note that the plasma-catalyzed degradation of the esters II–IV involves not only ester hydrolysis but apparently also intramolecular aminolysis. This is seen from the fact that the percentage amounts of propranolol formed in the plasma solutions are less than those formed in the buffer solutions. For *O*-acetyl propranolol this was directly confirmed by the observation of the formation of 20% *N*-acetylpropranolol in the presence of plasma as compared to 10% in the pH 7.4 buffer solution. Since the *N*-acetyl propranolol was found to be highly stable in human plasma solutions (no degradation was observed after incubation at 37°C for 24 h) this finding may be of relevance in considering propranolol esters as prodrugs as well as of similar esters as prodrugs for structurally related β-blockers.

Stability of the oxazolidin-2-one derivative VII

The oxazolidin-2-one VII was included in the study with the purpose of examining its potential as a prodrug form of propranolol and, by extension, of other β-blockers. As expected from its tertiary carbamate structure the compound turned out to be highly stable in aqueous solution. No degradation was observed in 0.1 M hydrochloric acid at 37°C after 8 h. In strongly alkaline solution degradation to propranolol was observed. At pH 13.2 and 37°C a half-life of hydrolysis of 11 h was observed whereas at pH 13.5 a half-life of 6.3 h was found, thus indicating a high stability in aqueous solution which parallels the behaviour of other oxazolidin-2-ones [Brånstad, 1969; Brånstad and Ekberg, 1972). This high stability was, however, maintained in human plasma solutions in that no degradation of VII or any formation of trace amounts of propranolol could be detected using HPLC after incubation of the compound in 80% human plasma solution for 4 h at 37°C. Thus, oxazolidin-2-ones are considered to be too stable under conditions simulating those prevailing in vivo to have any potential as prodrug forms of β-blockers or other β-aminoalcohols.

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