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Drug-delivery by ion-exchange. Hydrolysis and rearrangement of ester pro-drugs of propranolol

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Summary

The stability of a series of *O-n*-acyl propranolol derivatives, prepared as potential pro-drugs of propranolol suitable for complexation with cationic exchange resins, has been investigated. All *O-n*-acyl compounds undergo competitive hydrolysis, to propranolol, and rearrangement, to the *N-n*-acyl analogue. The relative importance of these degradation routes, as measured by the k_1/k_2 ratio, is influenced by both the structure of the ester and the reaction conditions. With increasing chain length of the *O-n*-acyl residue the rearrangement is progressively inhibited until only very low amounts are observed with *O-n*-hexanoyl and longer esters. The degradation rate is also dependent upon the presence of cosolvents but some (propylene glycol) also influence the k_1/k_2 ratio whereas others (DMF) do not. The extent of rearrangement is also controlled by the pH and the temperature of the medium. In contrast, the *O*-pivaloyl derivative was found to be a true precursor of propranolol and did not yield detectable amounts of amide.

Introduction

Ion-exchange systems have found many medicinal applications (Calmon and Kressman, 1957; Schacht, 1983). The delivery of drugs by such methods has advantages in the design of controlled-release liquid products, in the enhancement of stability profiles and in overcoming taste problems (Amsel, 1980; Raghunathan, 1981; Motyka et al., 1985; Burke et al., 1986). As a controlled-release system, ion-exchange resins offer the benefit that release of a complexed drug is initiated by an influx of competing ions from the gastrointestinal tract. This makes possible a sustained release oral suspension which, in a low ionic strength vehicle, does not leach out drug during storage. In general, release rates from unmodified resins are too great for adequate control of delivery and coating with a diffusional barrier to delay drug egress is employed in commercial products (Pennwalt, 1980). To provide further information on the influence of physicochemical properties of the drug on its release from resinates within a homologous series we have prepared a series of *O-n*-acyl propranolol pro-drugs (Irwin and Belaid, 1987a and b) and reported on the loading and release profiles on complexation with cationic ion-exchange resins (Irwin et al., 1987c, 1988). In this paper we report on the hydrolytic

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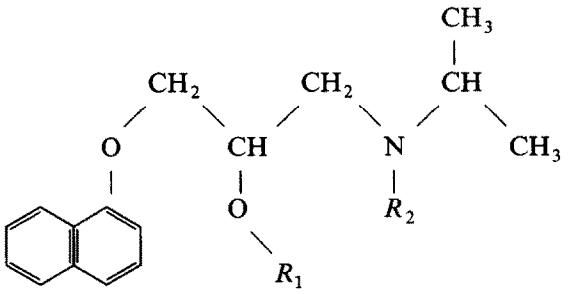
properties of these derivatives (**1–10**) as precursors of propranolol (**11**).



	R_1	R_2
1,	$CO\text{-}CH_3$	H
2,	$CO\text{-}C_2H_5$	H
3,	$CO\text{-}C_3H_7$	H
4,	$CO\text{-}C_4H_9$	H
5,	$CO\text{-}C_5H_{11}$	H
6,	$CO\text{-}C_7H_{15}$	H
7,	$CO\text{-}C_9H_{19}$	H
8,	$CO\text{-}C(CH_3)_3$	H
9,	$CO\text{-}CH_3$	$CO\text{-}CH_3$
10,	$CO\text{-}CH_3$	$CO\text{-}OC_2H_5$
11,	H	H

Experimental

Apparatus

HPLC analyses were undertaken using a system constructed from an Altex 100A dual-piston reciprocating solvent-metering pump and a reversed-phase stainless steel Shandon-type column (10 cm × 4.6 mm i.d.) packed with Hypersil-ODS (5 μm). Samples were introduced by means of a Rheodyne 7125 injection valve, fitted with a 20 μl loop, and detection was accomplished with a Pye LC3 variable wavelength UV detector, fitted with an 8 μl flow cell, and operated at a wavelength of 290 nm with a sensitivity usually of 0.08 AUFS. The mobile phases consisted of aqueous acetonitrile, adjusted to pH 2.8 with phosphoric acid, containing diethylamine as moderator and were delivered at 1 $ml \cdot min^{-1}$.

Materials and Methods

Solutions of *O-n*-acyl propranolols (Irwin and Belaid, 1987a) were prepared in 50% aqueous dimethyl formamide (DMF) prepared by mixing equal volumes of Britton-Robinson buffer, adjusted to an ionic strength of 0.25–0.5 M (Mongay and Cerda, 1974). This system was necessary to ensure complete dissolution of the esters and the degradation products during reaction. pH values, measured with a Radiometer PHM64 instrument, were re-adjusted after mixing with phosphoric acid and the values quoted are final values after the addition of DMF at the experimental temperature. Standard solutions were prepared to give ester concentrations equivalent to those of the experimental solution in the range 0.1–1 mM with the pH lowered to 3.5 to avoid degradation. There was no chromatographic effect due to the changing pH of the reaction medium (Williams et al., 1980). Standard solutions were diluted using the same solvent to provide a concentration range of 10–100% of that in the kinetic experiment. The standard solution (2 ml) was mixed with the internal standard (2 ml), containing 7 mg of ethyl paraben in 100 ml of 0.1 M HCl, and 20 μl aliquots were injected onto the HPLC column and the components were eluted with mobile phases comprising:

I $CH_3CN/Et_2NH/88\%\ H_3PO_4 : H_2O$ (65 : 0.15 : 0.1 : 34.75; pH 2.8) for propranolol, *O*-acetyl ester, ethyl paraben, *N*,*O*-diacetylpropranolol, *N*-ethoxycarbonyl-*O*-acetylpropranolol.

II $CH_3CN/Et_2NH/88\%\ H_3PO_4/H_2O$ (65 : 0.2 : 0.1 : 34.7; pH 2.8) for propranolol, *O-n*-propanoyl- to *O-n*-hexanoyl esters, *O*-pivaloylpropranolol and Et-paraben.

III $CH_3CN/Et_2NH/88\%\ H_3PO_4/H_2O$ (85 : 0.4 : 0.15 : 14.45; pH 2.8) for *O-n*-octanoyl and *O-n*-decanoyl esters.

Degradation of O-n-acyl propranolols

Stock solutions of *O*-acetyl, *O-n*-propanoyl, *O-n*-butanoyl, *O-n*-valeroyl, *O-n*-hexanoyl, *O-n*-octanoyl and *O-n*-decanoyl propranolols (Irwin and Belaid, 1987a), each of 50 mM, were prepared separately in 100 ml of DMF. Each stock solution (1 ml) was separately measured into a 3-necked

reaction vessel and the volume was adjusted to 100 ml by the addition of 50% buffered DMF solution at the required pH and pre-heated to the appropriate temperature. The final pH of the mixture was measured immediately at that temperature. The mixture was maintained in a constant temperature bath with continuous stirring. A sample was withdrawn immediately after mixing and further aliquots were withdrawn at appropriate intervals (5–60 min) by means of a glass syringe fitted with a teflon needle. The sample (1 ml) and the internal standard (1 ml) were mixed and 20 μl were injected onto the HPLC column. Alternatively, acidified samples were immediately stored at $-10\,^{\circ}$C in a dry-ice bath for later analysis. These conditions were shown to inhibit further reaction.

The effect of pH, in the range 2–9.45, in buffered DMF at 80 °C and of temperature, in the range 40–80 °C, in 50% buffered DMF at pH 9.45 (*O*-acetyl), 9.6 (*O*-pivaloyl), or 10.7 (*O*-*n*-hexanoyl), on the degradation of *O*-acetyl, *O*-pivaloyl and *O*-*n*-hexanoyl propranolol were studied similarly. To evaluate the effect of buffer concentration on the stability of *O*-acetylpropranolol at pH 7.4 at 37 °C, a constant ionic strength of 0.5 M was maintained while the concentration of buffer salts was varied over the range 25–100% of the initial concentration of 0.0258 M in each of CH_3COOH, H_3PO_4 and H_3BO_3 with 0.071 M NaOH.

The effects of cosolvents on the stability of *O*-acetylpropranolol in pH 7.4 at 37 °C were monitored using DMF (0–50%), propylene glycol (PG, 0–40%) and polyethylene glycol (PEG, 0–3%; M, 1000, 4000, 6000, 20,000). Aliquots of the stock solution of *O*-acetylpropranolol in acetonitrile (1 ml, 50 mM) were delivered initially to the reaction vessels containing the various concentrations of buffer-additive (99 ml). A similar study was undertaken with polyvinylpyrrolidone (PVP, 2%; M, 10,000, 40,000, 360,000 and 700,000) using *O*-acetylpropranolol at pH 7.4 and 37 °C.

Non-isothermal degradation of O-pivaloylpropranolol

The reaction medium consisting of 50% DMF (199 ml, pH 9.6) at 25 °C in a thermostatic water bath in which the heater was capable of increasing the temperature to 80 °C in about 2 h. Neutralised DMF (1 ml), containing *O*-pivaloylpropranolol (38 mg) was delivered to the reaction vessel and immediately the heater was turned on. Both reaction solution and water bath temperatures were monitored during the run. The solution was stirred continuously and aliquots were withdrawn immediately and at intervals of 2–5 min over a period of about 2 h. Samples were stored in a dry-ice bath ($-10\,^{\circ}$C) and the test solution (1 ml) was diluted with the internal standard (1 ml of ethyl paraben solution containing 8 mg in 100 ml of 0.1 M HCl) and 20 μl aliquots were analysed by HPLC. Isothermal degradation was also conducted using the same reaction mixture but at fixed temperatures of 40, 50, 60, 70 and 80 °C.

Synthesis of N-ethoxycarbonyl-O-acetylpropranolol

O-Acetylpropranolol hydrochloride (2 g, 5.9 mmol) was added slowly to a cold mixture of ethyl chloroformate (0.65 g, 5.9 mmol) and triethylamine (2 g, 19.7 mmol) dissolved in methylene dichloride (40 cm^3) over a period of 30 min. The mixture was heated at 45 °C for 2 h and was then washed with water, aqueous hydrochloric acid (0.2 M) to remove triethylamine, aqueous sodium carbonate (5%) to neutralise residual acid, and finally with water again. The organic phase was dried over anhydrous sodium sulphate and evaporated to yield the amide as a non-crystallisable yellow oil (1.2 g, 54%) which was shown to be homogeneous by HPLC and the structure was confirmed by spectroscopic analysis and by subsequent chemical conversions.

Synthesis of 1-isopropyl-4-naphthyloxymethyloxazolidin-2-one

Propranolol hydrochloride (1.5 g, 5.08 mmol) was heated together under reflux with ethyl chloroformate (3.26 g, 30 mmol) and triethylamine (8.1 g, 80 mmol), dissolved in chloroform (40 cm^3), for 1 h. The mixture was washed as described to yield a dark oil which, on trituration with dry ether yielded the oxazolidine as colourless crystals (0.72 g, 50%) melting at 127–129 °C. The product was shown to be homogeneous by HPLC and the structure was confirmed by spec-

troscopic analysis and by subsequent chemical conversions.

Additionally, *O*-acetyl-*N*-ethoxycarbonylpropranolol and the cyclic oxazolidinone derivative were also obtained from *O*-acetylpropranolol or the unsubstituted parent compound with ethyl chloroformate in the presence of triethylamine.

Degradation of N,O-diacyl propranolols

N,O-Diacetylpropranolol (Irwin and Belaid, 1987a; 34.3 mg) and *N*-ethoxycarbonyl-*O*-acetylpropranolol (37.3 mg) were delivered separately to reaction vessels and dissolved in preheated 50% DMF-0.5M NaOH (pH 13) mixture (200 ml) at 37 °C to provide 0.5 mM solutions. Aliquots were withdrawn immediately and at various intervals (0.25–50 h) and the degradation processes were instantly quenched by the addition of an equal volume of internal standard with storage in an ice bath. For *N,O*-diacetylpropranolol, standard solutions containing *N,O*-diacetylpropranolol with *N*-acetylpropranolol and propranolol (0.5 mM) as the degradation products were prepared together in 50% DMF–0.5 M HCl. For *N*-ethoxycarbonyl-*O*-acetylpropranolol standard solutions of *N*-ethoxycarbonyl-*O*-acetylpropranolol with 1-isopropyl-4-naphthoxymethyloxazolidin-2-one (0.5 mM) as the degradation product were prepared together in 50% DMF–0.5 M HCl. Standard solutions were then diluted with the same solvent over the concentration range of 0.05–0.5 mM (10–100% of the analyte concentration).

Results and Discussion

Fig. 1 records the fate of *O*-acetylpropranolol in buffered DMF solution, pH 9.45, at 80 °C. The initial ester is seen after 30 min to degrade to the expected product propranolol. A small trace of a third product is also observed. During the next 2–3 h this product becomes more intense and was identified as *N*-acetylpropranolol formed by a competitive intramolecular rearrangement. The intra-molecular rearrangement was confirmed by high-field ^{1}H-NMR and mass spectrometric studies (Irwin and Belaid, 1987a) and parallels the

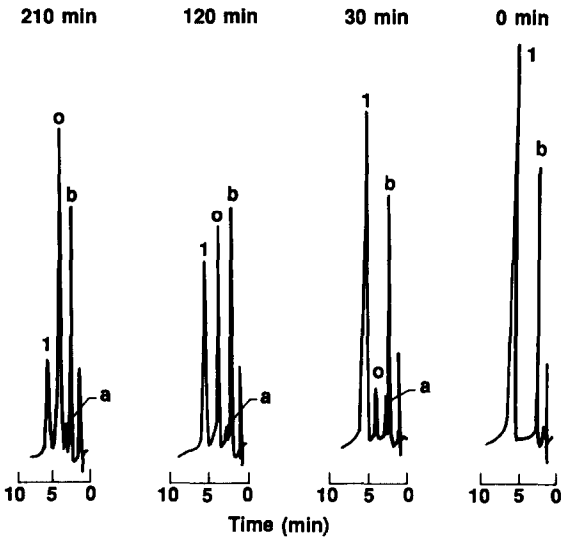


Fig. 1. HPLC analysis of *O*-acetylpropranolol showing the appearance of propranolol and *N*-acetylpropranolol in 50% buffered DMF at pH 9.45 and 80 °C. (Components are: a = *N*-acetylpropranolol; b = ethyl paraben; 1 = *O*-acetylpropranolol; 0 = propranolol.)

formation of amides under more forcing preparative conditions (Crowther and Smith, 1968; Nelson and Walker, 1978). The *N*-acetyl product was found to be stable under the conditions of the reaction and the degradation profile (Fig. 2) followed that of a competitive first order degradation

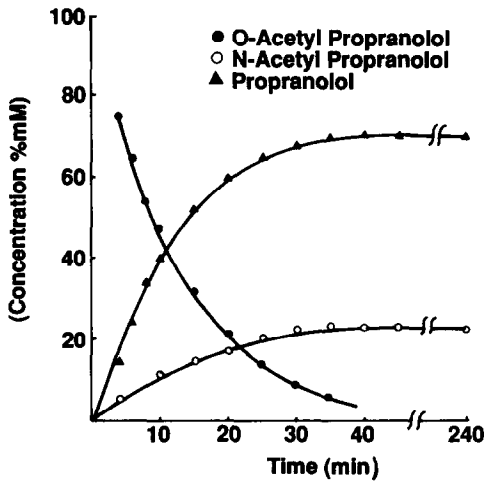


Fig. 2. Concentration–time profile for the competitive hydrolysis and rearrangement of *O-n*-acetylpropranolol in 50% buffered DMF at pH 9.45 and 80 °C.

TABLE 1

Effect of cosolvent concentration on the degradation of O-acetylpropranolol at pH 7.4 and 37 °C

Cosolvent	% (m/v)	$k_1 + k_2$ ($min^{-1} \times 10^4$)	k_1 ($min^{-1} \times 10^4$)	k_2 ($min^{-1} \times 10^4$)	$\frac{k_1}{k_2}$
Dimethyl formamide	0	73.20	67.10	6.10	11.0
	5	67.75	61.96	5.79	10.7
	10	61.48	56.40	5.08	11.1
	15	53.17	48.68	4.49	10.8
	20	44.96	41.25	3.71	11.1
	30	29.30	26.94	2.36	11.4
	40	16.26	14.87	1.39	10.7
Propylene glycol	0	76.28	69.65	6.63	10.5
	5	89.21	81.96	7.25	11.3
	10	102.20	95.30	6.90	13.8
	15	108.99	102.32	6.67	15.3
	20	112.84	107.03	5.81	18.4
	30	113.44	108.54	4.90	22.1
	40	113.29	109.25	4.04	27.0

which may be represented by the following kinetic model:

$$A \begin{matrix} \xrightarrow{k_1} & B \\ \xrightarrow{k_2} & C \end{matrix}$$

where A represents the ester, B propranolol, C *N*-acetylpropranolol and k_1 and k_2 are the hydrolysis and rearrangement rate constants, respectively.

The integrated rate equations for this model, giving species concentrations at time t, may be usefully expressed as:

$$A_t = A_0 \cdot \exp[-(k_1 + k_2)t] \quad (1)$$

$$B_t = \frac{A_0 \cdot k_1}{k_1 + k_2} - \frac{A_0 \cdot k_1 \cdot \exp[-(k_1 + k_2)t]}{k_1 + k_2} \quad (2)$$

$$C_t = \frac{A_0 \cdot k_2}{k_1 + k_2} - \frac{A_0 \cdot k_2 \cdot \exp[-(k_1 + k_2)t]}{k_1 + k_2} \quad (3)$$

This form allows an internal data check to be made as both slope and intercept should provide the same estimate when the exponential term versus species concentration are plotted. This model has been used to derive the rate constants k_1 and k_2 in order to assess the relevant importance of the hydrolysis and rearrangement reactions. Changes in concentration over the range 0.1–1 mM had no effect on estimates of the rate constants derived from this model and confirms the first-order nature of the degradation.

To overcome solubility problems, particularly with the longer chain esters, the addition of a cosolvent was necessary for comparison between analogues. The influence of DMF and propylene glycol (PG) concentration on the degradation of *O*-acetylpropranolol at pH 7.4 and 37 °C is displayed in Table 1. A rather different pattern of involvement is revealed for these two additives. With DMF a linear fall in the degradation rate

TABLE 2

Degradation rate constants of O-n-acyl propranolols in 50% buffered DMF solution at pH 10, μ = 0.5 M, at 37 °C

Ester	$k_1 + k_2$ ($min^{-1} \times 10^3$)	k_1 ($min^{-1} \times 10^3$)	k_2 ($min^{-1} \times 10^3$)	$\frac{k_1}{k_2}$
Acetyl	11.755	6.552	5.100	1.28
Propanoyl	7.547	6.242	1.306	4.78
Butanoyl	5.132	4.661	0.471	9.90
Valeroyl	3.601	3.389	0.212	15.99
Hexanoyl	3.097	2.948	0.148	19.92
Octanoyl	2.199	2.938	0.010	293.80
Decanoyl	2.463	2.463		

TABLE 3

Effect of pH on the degradation rate constants of O-acetyl and O-n-hexanoyl propranolol in 50% buffered DMF solutions at 80 °C

Ester	pH	$k_1 + k_2$ ($h^{-1} \times 10^2$)	k_1 ($h^{-1} \times 10^2$)	k_2 ($h^{-1} \times 10^2$)	$\frac{k_1}{k_2}$
O-Acetyl	2.00	1.654	1.530	0.124	12.8
	2.50	0.996	0.924	0.072	12.8
	3.2	0.764	0.698	0.966	10.6
	4.28	2.690	2.397	0.293	8.2
	5.3	7.820	6.960	0.860	8.1
	6.54	29.69	25.42	4.720	5.9
	7.80	76.20			
	9.45	482.30	376.90	105.40	3.6
O-n-Hexanoyl	2.5	0.0136			
	3.6	0.0084			
	5.10	0.0423	0.0410	0.0002	186.1
	6.20	0.4256	0.4200	0.0057	73.3
	7.40	4.4704	4.3316	0.0139	31.2
	7.70	4.8884	5.6854	0.2300	24.6
	8.30	13.2860	12.5520	0.7340	17.1
	8.80	25.4300	23.6390	1.7910	13.2

was observed ($k_1 + k_2 = 74.65 \times 10^{-4}$–$1.47 \times 10^{-4}$[DMF], $r = 0.999$), with a 4–5-fold reduction being observed over the concentration range examined. The individual processes, however, are affected to a similar degree and the k_1/k_2 ratio shows no systematic variation. Such a result might be expected of a falling dielectric constant of the medium due to the increasing DMF proportion (Noyes, 1956; Irwin et al., 1984, 1985). In contrast, propylene glycol shows a significant enhancement of the overall reaction rate, a change which is entirely due to acceleration of the hydrolytic component (k_1). The rearrangement rate constant (k_2) continues to fall although it is less affected than in the DMF systems. Indeed, the k_1/k_2 ratio increases linearly with PG proportion ($k_1/k_2 = 0.417$[PG] + 9.856, $r = 0.996$) although the overall degradation rate appears maximal from 20% PG onwards. The influence of propylene glycol is probably 2-fold. At low levels, a catalysis involving the alcoholic residues may accelerate the production of propranolol but the effect of this is limited as the dielectric constant of the medium falls at higher glycol concentrations and reduces reaction rates. The effect of lower amounts of viscosity-modifying agents (PEG, PVP) had no effect upon reaction rates. Pooled results for the hydrolysis of *O*-acetylpropranolol at pH 7.4 at 37 °C changing concentration (PEG 1000, 0–3.0% m/v), or PEG (1000–20,000) or PVP (10,000–700,000) molecular weight give a mean rate of 74.16×10^{-4} min^{-1} ($\sigma = 0.578 \times 10^{-4}$, CV = 0.780%, $n = 14$). DMF was chosen as the cosolvent for further experiments as this closely reflected the true aqueous k_1/k_2 ratio.

The rearrangement reaction involves an intramolecular *O*-to-*N* acyl migration and the transition state for this is rather crowded. It might be expected that when larger substituents are present the rearrangement process may become less favoured. This was indeed found to be true. When esters other than acetyl are employed the rearrangement is still observed and the effect of alkyl chain length on the extent of rearrangement is shown in Table 2. This reveals that as the size of the ester side chain increases, a dramatic decrease in the rearrangement potential is observed. When *O-n*-propanoylpropanolol was monitored, the rearrangement rate falls significantly compared to that of the *O*-acetyl compound. This substituent also reduced the hydrolysis rate but overall, at pH 10, the propanoyl compound is a significantly better precursor of propranolol than the acetyl derivative with the hydrolysis pathway being

TABLE 4

Effect of buffer concentration on the degradation of O-acetylpropranolol in 50% buffered DMF at pH 7.4 at 37°C

Buffer concentration (M) [a]	pH	$k_1 + k_2$ ($min^{-1} \times 10^4$)	k_1 ($min^{-1} \times 10^4$)	k_2 ($min^{-1} \times 10^4$)	$\frac{k_1}{k_2}$
0.0065	7.37	70.67	63.99	6.67	9.59
0.0129	7.39	73.26	67.16	6.10	11.00
0.0194	7.40	75.90	69.98	5.92	11.82
0.0258	7.41	77.23	71.38	5.85	12.20

[a] Individual concentrations of acetic, phosphoric and boric acids.

TABLE 5

Effect of temperature on the competitive hydrolysis and rearrangement of O-acetyl (pH 9.45) and O-n-hexanoyl (pH 10.7) propranolol in buffered 50% DMF, $\mu = 0.5$ M

Ester	Temp. (°C)	$k_1 + k_2$ ($min^{-1} \times 10^2$)	k_1 ($min^{-1} \times 10^2$)	k_2 ($min^{-1} \times 10^2$)	$\frac{k_1}{k_2}$
O-Acetyl	40	40.395	3.868	0.477	8.10
	50	10.210	8.850	1.360	6.50
	60	22.188	18.670	3.520	5.30
	70	44.055	36.050	8.065	4.51
	80	80.350	62.816	17.570	3.60
O-*n*-Hexanoyl	40	4.112	3.538	0.574	6.20
	50	8.135	6.845	1.290	5.30
	60	50.100	12.278	2.822	4.35
	70	26.820	20.989	5.830	3.60
	80	44.775	32.854	11.920	2.760

favoured by a factor of about 5. Higher chain analogues continue this trend and showed a somewhat reduced hydrolysis rate coupled with further suppression of the rearrangement reaction. Maximum effects were observed with the *O*-*n*-hexanoyl derivative and further increases in chain length had little effect upon purely chemical degradation processes. These results are in favorable agreement with literature findings on the reactivity of ester functions (Tablot, 1976).

In order to study the pH dependence of the degradation of *O*-acetylpropranolols the acetyl ester was chosen as an example of the short chain esters and the *n*-hexanoyl derivative for the longer chain compounds. Calculated values of the degradation rate constants and k_1/k_2 ratios for these compounds at various pH values are summarised in Table 3. These data indicate that the reactions were first-order with respect to the two esters and the optimum pH for maximum stability

TABLE 6

Arrhenius parameters for the hydrolysis and rearrangement reactions of O-acetyl (pH 9.45) and O-n-hexanoyl (pH 10.7) propranolol in 50% buffered DMF, $\mu = 0.5$ M

Ester	E_a (kJ · mol^{-1})			A ($min^{-1} \times 10^{12}$)		
	$k_1 + k_2$	k_1	k_2	$k_1 + k_2$	k_1	k_2
O-Acetyl	67.11	64.23	82.61	7.06	2.10	30.1
O-*n*-Hexanoyl	54.53	50.97	69.15	0.05	0.01	0.12

TABLE 7

The effect of pH on the hydrolysis rate constant of O-pivaloylpropranolol in 50% buffered DMF at 80 °C

pH	2.83	3.80	4.80	5.85	7.80	8.82	9.60
k ($h^{-1} \times 10^2$)	1.556	1.454	3.061	6.084	24.67	49.31	69.12

was found to be in the region 3–3.5 for both compounds. As the pH increases from this value the overall degradation rate constant $k_1 + k_2$ and the hydrolysis rate constant k_1 increase. The plot of a log(k) versus pH is linear but does not yield a value of unity. An observation which is possibly due to specific buffer catalysis and the involvement of both free base and protonated pro-drug in competing reactions at higher pH. The influence of buffer salts is illustrated in Table 4 which indicates a small enhancement in the hydrolysis rate, with increasing buffer concentration, at the expense of the rearrangement reaction. The rate of formation of the *N*-acyl products is also pH dependent. As the pH increases the rate of the amide formation increased as indicated by a decrease in the k_1/k_2 ratio. This is probably the result of an increasing proportion of non-protonated base being available for anchimeric attack of the *O-n*-acyl group. In the physiological range of pH values direct hydrolysis of the hexanoyl ester to yield propranolol was found to be some 30 times faster than the formation of the corresponding amide while with the *O*-acetyl derivative a 5-fold difference was observed.

The effect of temperature on the rate constants for the degradation of *O*-acetyl and *O-n*-hexanoyl propranolols was also studied and data are re-

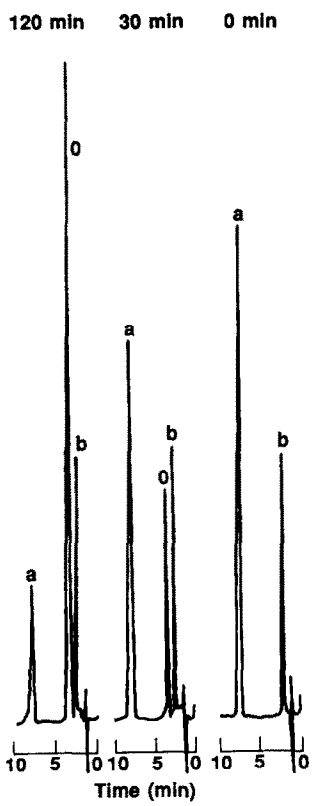


Fig. 3. HPLC analysis of the degradation of *O*-pivaloylpropranolol in 50% buffered DMF at pH 9.6 at 80 °C. (Components are: a, *O*-pivaloylpropranolol; b, ethyl paraben; 0, propranolol.)

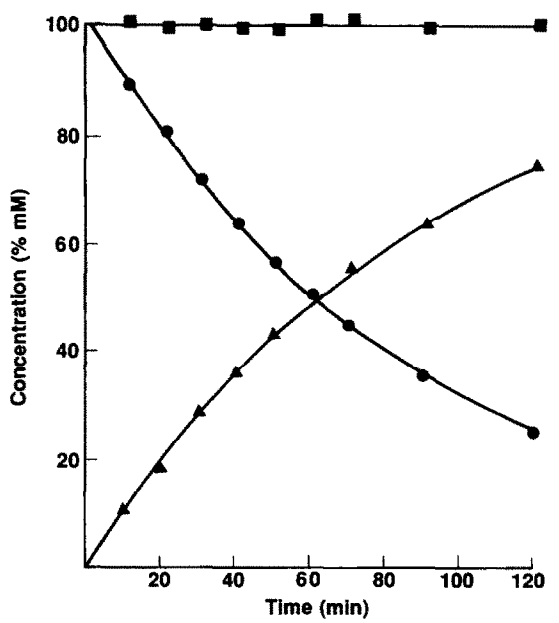


Fig. 4. Concentration–time profile for the hydrolysis of *O*-pivaloylpropranolol in 50% buffered DMF at pH 9.6 and 80 °C. (Components are: ●, *O*-pivaloylpropranolol; ▲, propranolol; ■, mass balance.)

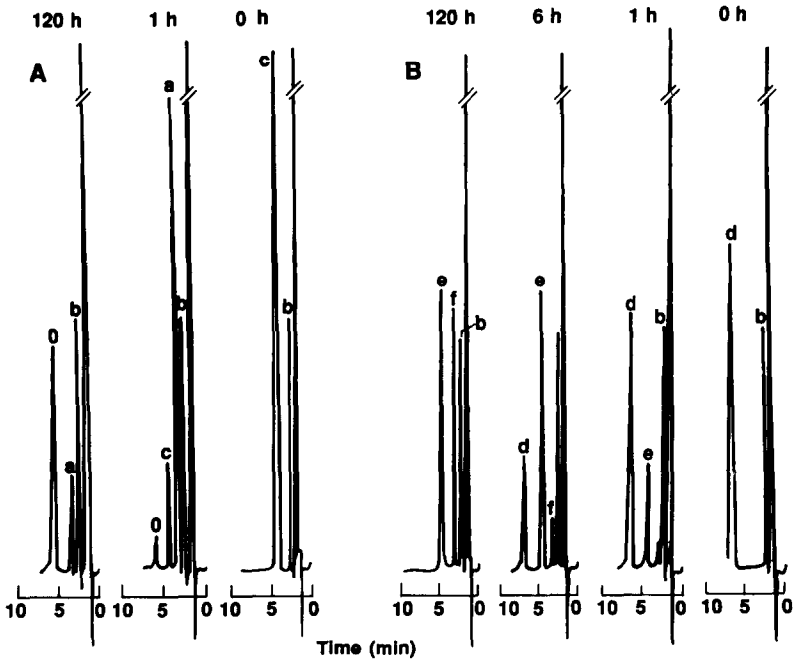


Fig. 5. HPLC analysis of the degradation of (A) *N,O*-diacetylpropranolol and (B) 1-isopropyl-4-naphthyloxymethyloxazolidin-2-one in 50% buffered DMF with 0.25 M NaOH at 37 °C. (Components are: a, *N*-acetylpropranolol; b, ethyl paraben; c, *N,O*-diacetylpropranolol; d, *N*-ethoxycarbonyl-*O*-acetylpropranolol; e, *N*-ethoxycarbonylpropranolol; f, 1-isopropyl-4-naphthyloxymethyloxazolidin-2-one; 0, propranolol.)

corded in Table 5. Increasing temperature caused an acceleration of the overall degradation rates of both esters but the rearrangement was more influenced as indicated by a decrease in the k_1/k_2 ratio with increasing temperature. Arrhenius parameters are recorded in Table 6.

Although only small amounts of amide were formed with the longer alkyl chain compounds, a derivative was sought which did not yield any of the rearrangement product. In contrast to the *O*-*n*-acyl esters, *O*-pivaloylpropranolol undergoes a simple hydrolysis to the parent compound (Eqn. 4) without the involvement of competing intramolecular rearrangement as shown in Figs. 3 and 4. This is probably due to the steric hindrance involving the bulky *tert*-butyl group in the ester side chain which prevents the close interaction between the carbonyl group and the amino residue in the side chain. The effect of pH and temperature on reaction rates are recorded in Tables 7 and 8. Arrhenius parameters were calculated to be E_a, 53.97 kJ · mol^{-1} and A, 9.65×10^9 min^{-1} from the isothermal study and E_a, 51.75 kJ · mol^{-1} and A, 4.82×10^9 min^{-1} from non-isothermal analyses (Hempenstall et al., 1983; Li Wan Po et al., 1983). This derivative also has a maximum stability at pH 3–3.5 and although it is considerably more stable ($t_{1/2} = 30$ h) than the *O*-acetyl analogue ($t_{1/2} = 9.5$ h), as calculated from the Arrhenius data for 25 °C, it has a stability profile similar to the longer chain esters but with no detectable amide by-product during hydrolysis.

The degradation of *N,O*-diacetylpropranolol and *N*-ethoxycarbonyl-*O*-acetylpropranolol in alkaline DMF may be represented by a sequential degradation scheme of the type:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

where A, B and C represent the di-acylpropranolol, the mono-acyl derivative and the final product, respectively. The equations for individual

TABLE 8

Effect of temperature on the hydrolysis rate constant of O-pivaloylpropranolol in 50% buffered DMF, pH 9.6

Temperature (°C)	35.7	50.0	60.0	70.0	80.0
k ($min^{-1} \times 10^3$)	1.100	2.026	3.740	6.627	11.52

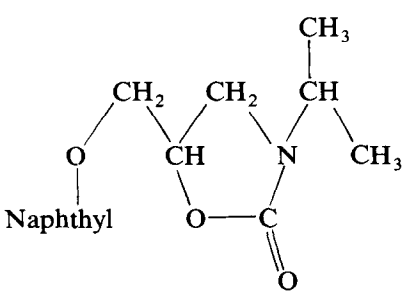
species concentration at time t derived from this model are:

$$A_t = A_0 \cdot \exp(-k_1 t) \quad (4)$$

$$B_t = \frac{A_0 \cdot k_1}{(k_2 - k_1)} \cdot \{\exp(-k_1 t) - \exp(-k_2 t)\} \quad (5)$$

$$C_t = A_0 \cdot \left\{1 - \exp(-k_1 t) - \left[\frac{k_1}{(k_2 - k_1)} \cdot \{\exp(-k_1 t) - \exp(-k_2 t)\}\right]\right\} \quad (6)$$

Rate constants k_1 and k_2 were calculated using this model by means of linear and non-linear regression analysis. HPLC traces following the degradation of both compounds are shown in Fig. 5. The initial ($t = 0$) trace indicates the presence of the starting compound and the internal standard. Over a period of time the degradation results in the formation of the *N*-acyl intermediate, *N*-acetylpropranolol or *N*-ethoxycarbonylpropranolol, and these in turn break down to the final product propranolol or 1-isopropyl-4-naphthyloxymethyloxazolidin-2-one (**12**), respectively.



(11)

Neither compound is a useful precursor of propranolol. The *N*-acetyl intermediate generates this drug only under very forcing conditions while the *N*-ethoxycarbonyl analogue undergoes cyclisation to the oxazolidinone which is totally resistant to further hydrolysis under these experimental conditions. The reaction profiles showing the fate of *N,O*-diacetylpropranolol, intermediate *N*-acetylpropranolol and the final product are shown in Fig. 6. These data yield values for k_1 of 2.25 h^{-1} and k_2 of 43.0×10^{-4} h^{-1}, with maximum levels of *O*-acetylpropranolol found at 2.8 h given by: $t_{B_{max}} = (\ln[k_1/k_2])/(k_1 - k_2)$. *N*-ethoxycarbonylpropranolol shows a similar profile and yields values for k_1 of 0.16 h^{-1} and k_2 of 6.02 $\times 10^{-4}$ h^{-1} with maximum levels of the intermediate being found at 34.8 h. The maximum concentrations of both intermediates may be calculated from:

$$B_{max} = A_0 \cdot \left[\frac{k_2}{k_1}\right]^{\frac{k_2}{k_2 - k_1}}$$

Both show maximum concentrations close to 100% of the initial level as $k_1 \gg k_2$. It is interesting to note the great difference in the rates of

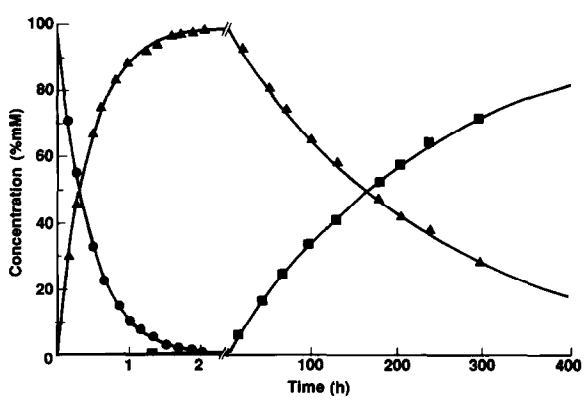


Fig. 6. Concentration–time profile for the degradation of *N,O*-diacetylpropranolol in 50% buffered DMF with 0.25 M NaOH at 37 °C. (Components are: ▲, *N*-acetylpropranolol; ●, *N,O*-diacetylpropranolol; ■, propranolol.)

hydrolysis of the *O*-acetyl functions in these two analogues. The slower rate of disappearance of the *N*-ethoxycarbonyl compound may be explained by the presence of the more bulky ethoxy group inhibiting the formation of the tetrahedral transition state during hydrolysis.

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