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Evaluation of phenyl carbamates of ethyl diamines as cyclization-activated prodrug forms for protecting phenols against first-pass metabolism

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Abstract

A series of phenyl *N*-(2-aminoethyl)carbamates derived from various substituted ethyl diamines and phenol was prepared and evaluated as prodrug forms with the aim of protecting phenolic drugs against first-pass metabolism. The stability of the compounds was studied in aqueous buffer solutions and in various biological media. The compounds showed a high stability at lower pH but degraded by a cyclization process at higher pH values with a quantitative release of the parent phenol. The rate of cyclization was not affected by plasma, liver or gut enzymes but depended on the pH value of the medium and on the steric properties of the various substituents. By appropriate selection of the substituents, it is readily feasible to obtain prodrug derivatives having useful rates of cyclization, and hence release of the parent phenolic drug at pH 7.4 and 37°C, corresponding to half-lives of 10–60 min. The results suggest that this prodrug principle involving a non-enzymatic but pH-dependent conversion may be a potentially useful approach to reduce the extent of first-pass metabolism of the vulnerable phenol group.

Keywords: Prodrug; First-pass metabolism; Phenol; Carbamate; Cyclization; Non-enzymatic conversion; pH dependence; Stability

1. Introduction

Several drugs containing a phenolic group show low and variable bioavailability after peroral administration. This is often due to pronounced first-pass metabolism and not limited absorption from the gastrointestinal tract. First-pass metabolism of phenolic drugs occurs in the gut mucosa and/or the liver by sulphation, methylation or glucuronidation of the phenolic moieties (George, 1981; Mulder, 1982; Pond and Tozer, 1984; Ilett et al., 1990). The prodrug principle may be a useful approach to protect the vulnerable phenol group against first-pass metabolism. However, traditional esterification of the phenol group has

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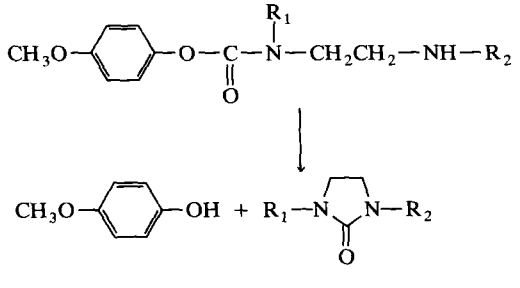
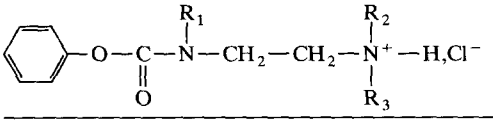
only met with limited success at preventing first-pass metabolism (Svensson and Tunek, 1988; Lokind et al., 1991; Bundgaard, 1992). The reason for this is most likely that enzymatic hydrolysis of the ester group occurs in the intestinal tract and/or the liver during first-pass. As a consequence, the phenolic drug will thereby be released within organs with high enzymatic activity and, therefore, no protection of the phenolic group will be achieved. A more promising approach to prevent or depress the first-pass metabolism of phenolic drugs may be the use of prodrug derivatives where the prodrug-to-drug conversion mainly occurs at the target organ or in the blood stream after passage of the intestinal wall and the liver. Derivatives where the conversion to the parent phenol occurs by non-enzymatic means, e.g., via chemical hydrolysis or an intramolecular reaction occurring with an appropriate rate at physiological pH (7.4) and at 37°C might be useful. To ensure passage of the prodrug in largely intact form through the stomach and the upper intestine, suitable prodrug forms should preferably be more stable at lower pH values. Studies to exploit this new prodrug approach have been initiated in our laboratory (Hansen et al., 1992; Thomsen and Bundgaard, 1993) as well as by others (Saari et al., 1990; Patel et al., 1991; Getz et al., 1992). In a previous paper (Thomsen and Bundgaard, 1993), we have found that phenyl carbamates of *N*-substituted 2-aminobenzamides, that release the parent phenol by a pH-dependent ring-closure reaction, possess properties close to the ideals mentioned above. In 1990, Saari et al. reported that *N*-(2-aminoethyl)carbamates of 4-hydroxyanisole may act as possible prodrugs for this melanocytotoxic drug. They showed that 4-hydroxyanisole and an



Scheme 1.

Table 1
Structure and melting point of various phenyl N-(2-aminoethyl)carbamates (Hydrochlorides)



Compound	R_1	R_2	R_3	M.p. (°C)
1	CH_3	CH_3	CH_3	129–131
2	CH_2CH_3	CH_2CH_3	CH_2CH_3	oil
3	CH_3	CH_2CH_3	CH_2CH_3	oil
4	CH_2CH_3	CH_3	CH_3	143–144
5	CH_3	CH_3	H	oil
6	CH_2CH_3	CH_2CH_3	H	125–126
7	H	CH_3	CH_3	124–126
8	H	CH_3	H	167–169
9	H	H	H	169–171

imidazolidione were released from these derivatives by an intramolecular ring-closure reaction (Scheme 1) and suggested that a nonprotonated amine function was critical for the reaction to occur. For one of the derivatives, it was also shown that plasma enzymes had no influence on the rate of degradation.

In our laboratory, we have investigated this prodrug type further using phenol as a model compound for phenolic drugs. A number of *N*-(2-aminoethyl)carbamates of phenol with various substituents at the nitrogen atoms were prepared (Table 1). The stability of the derivatives has been studied in aqueous solutions as a function of pH and the kinetics and mechanism of the degradation have been described. The degradation of the derivatives in various biological media (human plasma, pig and rat liver homogenate and rat gut homogenate) has also been studied.

2. Materials and methods

2.1. Apparatus

High-performance liquid chromatography (HPLC) was performed with a Merck-Hitachi apparatus consisting of an L-6000 pump, an L-4000 UV variable-wavelength UV detector, and a Rheodyne 7125 injection valve with a 20 μl loop. A deactivated Supelcosil LC-8-DB reversed-phase

column (33 × 4.6 mm i.d.) (3 μm particles) from Supelco Inc., U.S.A., was used in conjunction with a Supelguard precolumn. Readings of pH were carried out on a Radiometer PHM Autocal instrument at the temperature of study.

2.2. Chemicals

Phenyl chloroformate, di-*tert*-butyl dicarbonate, 1-amino-3-methylbutane and the various diamines used were purchased from Aldrich Chemie, Germany. Buffer substances and solvents used were of reagent grade.

2.3. Synthesis of the phenyl N-(2-aminoethyl)carbamates 1–9

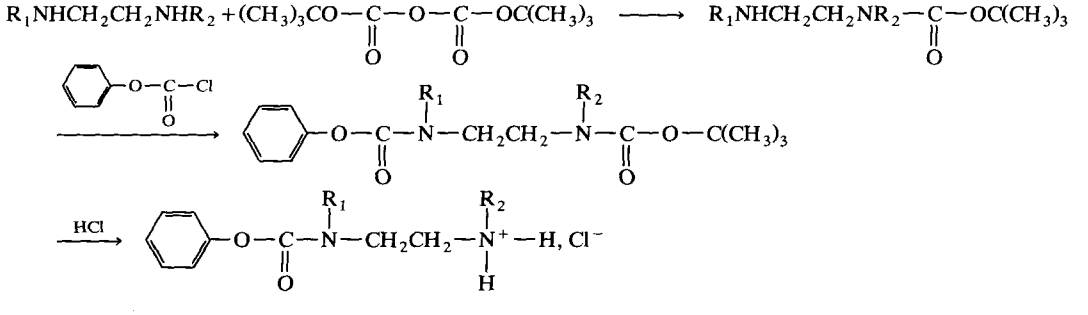
The phenyl carbamates **1–9** (Table 1) were prepared by reacting phenyl chloroformate with the appropriate diamine or the appropriate mono-*tert*-butoxycarbonyl-protected diamine (BOC-protected) according to the method described by Saari et al. (1990). Removal of the BOC group with HCl in ethanol allowed isolation of the carbamates as the stable HCl salts (Scheme 2).

2.3.1. Compounds 1–4 and 7

The preparation of compound **4** represents a general method for the preparation of the carbamates by reaction between an amine and phenyl chloroformate. A solution of *N,N*-dimethyl-*N'*-ethylethylenediamine (1.16 g, 10 mmol) and *N,N*-diisopropylethylamine (1.29 g, 10 mmol) in 20 ml tetrahydrofuran (THF) was added over 30 min with stirring and cooling in an ice-bath to a solution of phenyl chloroformate (1.57 g, 10 mmol) in 30 ml THF. After stirring at 0°C for 1 h and then 2 h at room temperature, the solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and water. The ethyl acetate phase was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulphate, filtered and evaporated in vacuo. Flash chromatography of the residue on silica gel (type 60) using elution with ethyl acetate to remove non-polar impurities and then elution with methanol gave 0.54 g of the product as an oil. The hydrochloride was prepared by adding the oil to 1.1 equivalent of HCl (from acetylchloride) in ethanol. After 30 min, ethyl acetate, ether and petroleum ether were added and after cooling for 1 h the precipitate was filtered off.

2.3.2. Compounds 5, 6, 8 and 9

The preparation of compound **6** represents a typical procedure for the preparation of carbamates, where protection with *tert*-butoxycarbonyl is necessary. A solution of di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) in 20 ml THF was added at 0°C to a stirred solution of *N,N'*-diethylethylenediamine (3.83 g, 33 mmol) in 65 ml THF over 30 min. The reaction mixture was allowed to stand for 24 h. The solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated aqueous sodium chloride. The ethyl acetate phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated in vacuo. The oil (1.5 g) was used without further purification for the reaction with phenyl chloroformate according to the general method described above with the difference that the reaction mixture was allowed to stand at the ice-bath for 30 min and then at room temperature for 24 h. The residue obtained after evaporation was partitioned between ethyl acetate and saturated aqueous sodium chloride.



Scheme 2.

The crude product was flash chromatographed on silica gel (type 60) eluting with ethyl acetate-petroleum ether (15:85) to give 1.07 g of the product as an oil. The BOC-protected carbamate (0.84 g) was dissolved in 7.5 ml ice-cold ether and 2.5 ml of 2.5 M HCl in ethanol was added. After stirring for 30 min at 0°C the reaction mixture was allowed to stand for 3 h at room temperature. Additional ether was added and the mixture was placed in a freezer. The precipitate formed was filtered off and dried.

In the case of the unsymmetrical *N*-methylethylenediamine, BOC protection would be expected to occur at each nitrogen as described by Saari et al. (1990). After flash chromatography only one BOC-protected *N*-methylethylenediamine was isolated. After reaction with phenyl chloroformate and deprotection of the BOC group the ^{1}H-NMR spectrum of the carbamate HCl salt was consistent with structure **8**.

^{1}H-NMR spectra of the carbamates **1–9**, recorded on a Bruker (200 MHz) instrument in $CDCl_3$ or D_2O, were all consistent with the assigned structures.

*2.3.3. Synthesis of phenyl N-(3-methyl)butyl carbamate **10***

Compound **10** was prepared according to the general method described above. After evaporation the solidified residue was recrystallized from ethanol-water, to give m.p. 66–68°C (reported m.p. 66–69°C (Patonay et al., 1990)).

2.4. Kinetic measurements

2.4.1. Degradation in aqueous solutions

The rates of degradation of the compounds **1–9** were determined by using reversed-phase HPLC procedures capable of separating the compounds from their degradation products. Mobile phase systems of 5–20% (v/v) acetonitrile in 0.1% (v/v) phosphoric acid were used with triethylamine added at a concentratiom of 10^{-3} M to improve peak shapes. The concentration of acetonitrile was adjusted for each compound to give a retention time of 2–10 min. The column effluent was monitored at 215 nm.

The degradation reactions in buffer solutions were initiated by adding 100 μl of a stock solution of the compounds in acetonitrile or methanol to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentration being about 5×10^{-5}–10^{-4} M. The buffers used were hydrochloric acid (pH 1–2), acetate (pH 4–5), phosphate (pH 3, 6–7.4), borate (pH 8.5–10) and carbonate (pH 11) solutions at a total buffer concentration of 0.02 M. A constant ionic strength (μ) of 0.5 was maintained by adding a calculated amount of potassium chloride. The solutions were kept in a water-bath at constant temperature and, at appropriate intervals, samples were withdrawn and chromatographed immediately. Pseudo-first-order rate constants for the degradation were determined from the slopes of linear plots of the logarithm of residual compound against time.

2.4.2. Degradation in biological media

The degradation of the compounds was studied at 37°C in 40% human plasma, 20% pig liver homogenate and 20% rat liver homogenate. Compounds **1** and **5** were also studied in 20% rat gut homogenate. The homogenates were prepared by homogenizing the tissue in ice-cold 0.05 M phosphate buffer. The homogenates (50%) were frozen in samples of 2 ml until use, where the final homogenates (20%) were prepared by diluting with 0.05 M phosphate buffer. The initial concentrations of the compounds were 1×10^{-4}–2×10^{-4} M. The reaction mixtures were kept in a water-bath at 37°C and at appropriate intervals samples of 250 μl were withdrawn and added to 500 μl of a 2% zinc sulphate solution in methanol-water (1:1, v/v) in order to stop the reactions and deproteinize the samples. After mixing and centrifugation for 3 min at 13000 rpm, 20 μl of the supernatant was analyzed by HPLC as described above.

3. Results and discussion

3.1. Kinetics of degradation

All the phenyl carbamates studied underwent quantitative degradation to phenol in aqueous buffer solutions as revealed by HPLC analysis of

the reaction solutions. At constant pH and temperature, the degradation followed strict first-order kinetics for several half-lives.

In Fig. 1. pH profiles are shown for selected compounds at 37°C. For the *N,N*-disubstituted carbamates (R_1 = alkyl), the rate of degradation is directly proportional to the fraction present as free base and may therefore be accounted for by a spontaneous decomposition of the free base species according to the following expression:

$$k_{obs} = k_1 \frac{K_a}{a_H + K_a} \quad (1)$$

where k_{obs} is the observed first-order rate constant, K_a denotes the apparent ionization constant for the protonated carbamate and k_1 is the first-order rate constant for the spontaneous degradation of the unprotonated carbamate.

For the *N*-monosubstituted carbamates (R_1 = H) an additional term corresponding to an apparent base-catalyzed degradation of the unprotonated carbamate is needed to account for the observed pH profile. The following rate expression is thereby obtained:

$$k_{obs} = k_1 \frac{K_a}{a_H + K_a} + k_{OH} a_{OH} \frac{K_a}{a_H + K_a} \quad (2)$$

where a_{OH} is the hydroxide ion activity and k_{OH} a second-order rate constant for the apparent base-catalyzed degradation of the unprotonated carbamate. The obtained rate constants for all the carbamates are listed in Table 2 together with the observed half-lives of degradation at pH 7.4 and the pK_a values. The pK_a values were estimated by fitting the above equation to the experimental data.

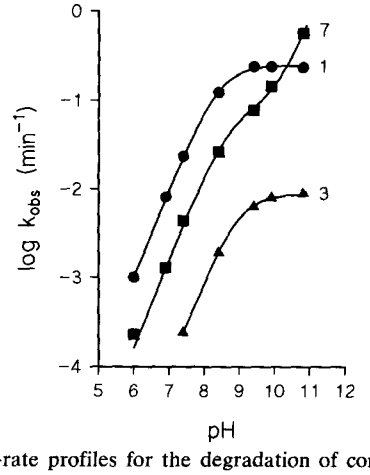


Fig. 1. pH-rate profiles for the degradation of compounds **1** (●), **3** (▲) and **7** (■) in aqueous solutions at 37°C.

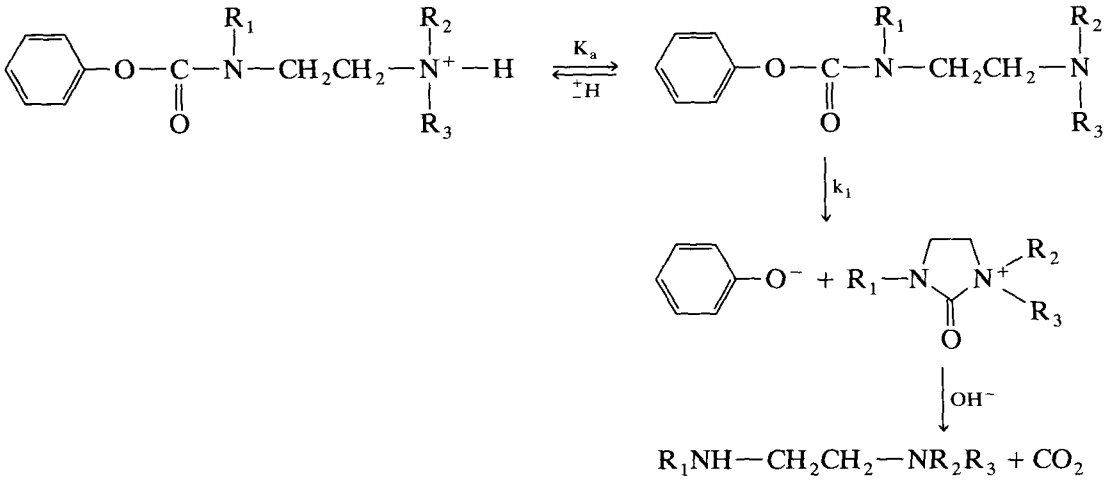
Table 2
Half-lives of degradation of compounds **1–9** at pH 7.4 and 37°C, their rate constants and their kinetically determined pK_a values

Compound	$t_{\frac{1}{2}}$ (min) pH 7.4 buffer	k_1 (min^{-1})	k_{OH} (M^{-1} min^{-1})	pK_a
1	30	0.25	–	8.4
2	2.8×10^3	0.0074	–	8.9
3	2.9×10^3	0.0088	–	8.95
4	30	0.24	–	8.4
5	24	1.8	–	9.2
6	121	0.47	–	9.3
7	160	0.08	325	8.7
8	167	0.35	350	9.3
9	273	0.15	350	9.2

In order to examine the stability of the compounds in acidic solutions the degradation of compounds **1**, **5** and **7** were also studied at lower pH values at 60°C. The compounds were very stable at pH 1–4 with half-lives of more than 35 h at pH 4 and half-lives in the range of weeks at pH 1 and 2.

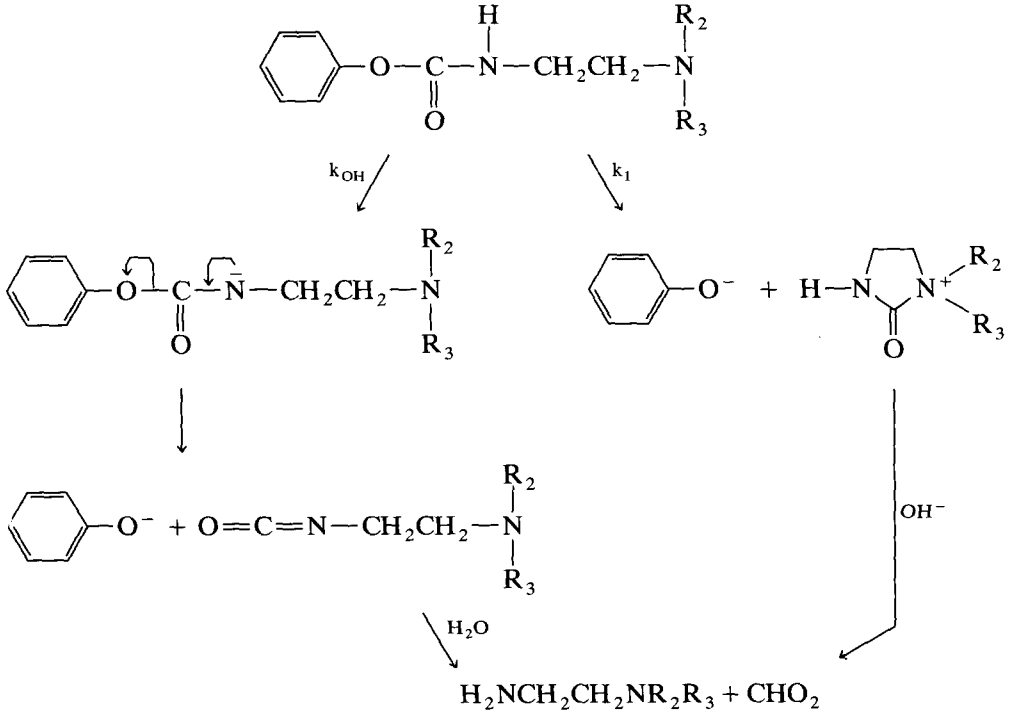
3.2. Mechanism of degradation

N,N-disubstituted phenyl carbamates are generally highly chemically stable (Dittert and Higuchi, 1963; Christenson, 1964; Hansen et al., 1991). The high reactivity of the studied *N,N*-disubstituted phenyl carbamates can be ascribed to an intramolecular ring-closure reaction. Saari et al. (1990) studied the degradation of 4-methoxyphenyl *N*-methyl-*N*-[2-(methylamino)ethyl] carbamate at pH 7.4 and showed that this compound degraded via a ring-closure reaction resulting in the formation of 4-methoxyphenol and *N,N'*-dimethylimidazolidinone. In the present study the influence of pH on the degradation of these compounds has been further examined and this makes it possible to propose a mechanism of



Scheme 3.

degradation. The initial step in the degradation is most likely an intramolecular ring-closure reaction with an attack of the amine nitrogen lone-pair on the carbamate carbonyl group (Scheme 3). This reaction results in the formation of phenolate ion and a positively charged cyclization product. Such an intramolecular nucleophilic addition to a carbonyl group has previously been described (Bruice and Benkovic, 1963; Hutchins and Fife, 1973; Hegarty et al., 1974; Fife et al., 1975). The proposed reaction mechanism is in accordance with the observed reaction kinetics. As pH in-



Scheme 4.

creases, the fraction of the carbamate on the reactive base form increases effecting an increased rate of cyclization. Saari et al. (1990) have isolated the cyclization product *N,N'*-dimethylimidazolidinone from the degradation of 4-methoxyphenyl *N*-methyl-*N*-[2-(methylamino) ethyl]carbamate ($R_1 = R_2 = CH_3$ in Scheme 1) in aqueous solution, showing that the cyclization products are stable for compounds where R_2 and/or R_3 are hydrogen. For compounds in which R_2 and R_3 are alkyl, the cyclization products are unstable cyclic quaternary imides which will decompose to CO_2 and the diamines (Scheme 3).

It has previously been established that hydrolysis of monosubstituted carbamates in neutral and alkaline solutions proceeds by an elimination-addition (E1cB) mechanism involving the formation of an intermediate unstable isocyanate (Dittert and Higuchi, 1963; Williams 1972; Hegarty and Frost, 1973). For the studied monosubstituted carbamates (compounds **7–9**) one could envisage two different ways of degradation, namely hydrolysis via an unstable isocyanate or the cyclization reaction mentioned above (Scheme 4). The pH-rate profiles obtained for these monosubstituted carbamates show that the cyclization reaction clearly dominates at pH 6–9, whereas the isocyanate reaction is the dominating one at the highest pH values studied. This shift in degradation mechanism has previously been described for other monosubstituted carbamate derivatives. For phenyl *N*-(*o*-carboxyphenyl)carbamate an intramolecular ring-closure reaction involving the *ortho* carboxylate group is dominating at lower pH values whereas the isocyanate route takes over at higher pH values (Frost and Hegarty, 1973). The same phenomenon has been described for phenyl *N*-(*o*-hydroxyphenyl)carbamate where the ring-closure reaction at lower pH values involves the *ortho* phenolate group (Hutchins and Fife, 1973).

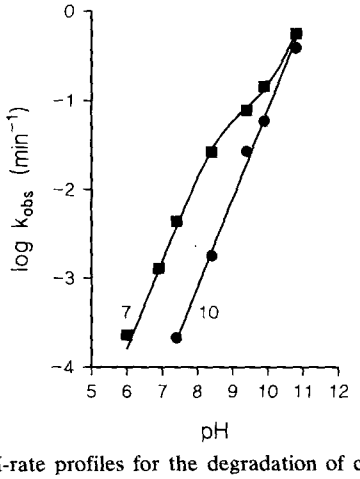


Fig. 2. pH-rate profiles for the degradation of compounds **7** (■) and **10** (●) in aqueous solutions at 37°C.

Comparing the pH-rate profiles for compounds **7** and **10** (phenyl *N*-(3-methyl)butyl carbamate) shown in Fig. 2 provides further evidence that the studied monosubstituted carbamates are degraded by the cyclization reaction. Compound **10** can only be degraded via an isocyanate and compound **10** is 20 times more stable than compound **7** at pH 7.4. The higher reactivity of compound **7** can be explained by the existence of a much faster cyclization reaction for this compound.

3.3. Structural effects on the rate of cyclization

The reactivity of the phenyl carbamates varies widely as can be seen from Table 2 with first-order rate constants ranging from 0.0074 to 1.8 min^{-1}. The steric properties of the R_2 and R_3 substituents have a great influence on the rate of cyclization. Thus, the reactivity of the phenyl carbamates decreases very markedly with increasing steric effects of these substituents. Compound **2** ($R_2 = R_3$ = ethyl) is 64 times more stable than compound **6** (R_2 = ethyl, R_3 = H) whereas changing from two methyl groups to one only reduces the reactivity 4–7 times (**1** → **5**, **7** → **8**). This decrease in reactivity with increasing steric effects is readily understandable from the cyclization mechanism. The attack on the carbamate carbonyl by the lone-pair on the amine nitrogen is more difficult if the amine nitrogen is sterically hindered. As mentioned above, *N,N*-disubstituted phenyl carbamates are more stable towards hydrolysis than the corresponding monosubstituted carbamates. The increased reactivity of the disubstituted carbamates observed in this study

and that of Saari et al. (1990) is due to an activation of the cyclization process by the extra substituent on the carbamate nitrogen. Cyclization of the carbamates involves a transition state in which the amino group is close to the carbamate carbonyl group. A possible explanation for the increased cyclization rate of the disubstituted carbamates is that the substituent at the amide nitrogen forces the dimethylene amino group to the position in which cyclization can take place. The obtained k_{OH} values (325–350 M^{-1} min^{-1}) for the base-catalyzed degradation of the monosubstituted carbamates (compounds **7–9**) are very similar, indicating that the proposed base-catalyzed hydrolysis via an isocyanate intermediate is less dependent on the structure of the side chain. The values obtained are consistent with that reported by Dittert and Higuchi (1963) for the base-catalyzed hydrolysis of phenyl *N*-methylcarbamate (190 M^{-1} min^{-1}, at 34°C).

3.4. Stability in biological media

To examine the possible influence of various biological media on the degradation of some of the phenyl carbamates, their stability was studied at 37°C in 40% human plasma, 20% pig liver homogenate and 20% rat liver homogenate. The degradation was, in all cases, found to conform closely with first-order kinetics and for all the compounds phenol was released in quantitative amounts as shown in Fig. 3. The obtained half-lives for the cyclization in the biological media are listed in Table 3 together with the half-lives determined in buffer solutions at pH 7.4.

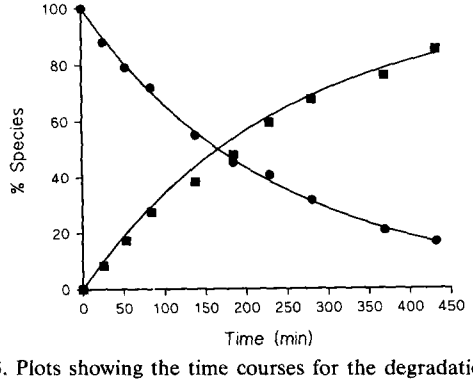


Fig. 3. Plots showing the time courses for the degradation of compound **8** (●) and formation of phenol (■) in 40% human plasma at 37°C.

Table 3
Half-lives of degradation of various phenyl *N*-(2-aminoethyl) carbamates in aqueous buffer solutions (pH 7.4) and biological media at 37°C

Compound	$t_{\frac{1}{2}}$ (min)			
	pH 7.4 buffer	40% human plasma	20% pig liver homogenate	20% rat liver homogenate
1	30	28	46	66
4	30	28	63	91
5	24	22	57	67
6	121	95	249	414
7	160	170	255	235
8	167	166	294	277
9	273	374	364	369

The data in Table 3 show that neither plasma nor liver enzymes have any catalytic influence on the degradation of the compounds. The obtained half-lives in liver homogenates are approx. 2 times longer than those in buffer solutions at pH 7.4. The liver homogenate reaction mixtures had pH values in the range 7.10–7.25. The difference in pH between liver homogenate and buffer solution corresponds to a 1.5–2 times decrease in hydroxide ion activity for the liver homogenates. This decreased activity of hydroxide ion means that a smaller fraction of the compound will be on the reactive base form, i.e., the lower pH value of liver homogenates can explain the longer half-lives obtained in these biological media. Compounds **1** and **5** were also studied in 20% rat gut homogenate (pH 7.4, 37°C) and again no catalytic effect was observed. Lack of in vitro enzymatic catalysis against *N,N*-disubstituted carbamates has been described previously (Digenis and Swintosky, 1975; Hansen et al., 1991; Thomsen and Bundgaard, 1993). In the case of *N*-monosubstituted carbamates of phenol or phenolic drugs different results regarding enzymatic catalysis have been reported (Hansen et al., 1991, 1992; Huang et al., 1993). The lack of evident enzymatic catalysis for the studied monosubstituted carbamates (compounds **7–9**) may be due to the great facility of the intramolecular cyclization reaction.

4. Conclusions

The results obtained in this study suggest that derivatization of the phenolic group as carbamates of various ethyl diamines may be a useful prodrug approach to reduce the extent of first-pass metabolism of phenolic drugs in the gut and/or liver. The studied carbamates are very stable in acidic solutions and are expected to survive the passage through the stomach and upper intestine and a large fraction of the carbamate may pass the liver in an intact form. In contrast, the carbamates are easily degraded by an intramolecular cyclization process at pH 7.4 with quantitative release of the parent phenol. The rate of cyclization is not affected by plasma, liver or gut enzymes. The rate of cyclization is greatly influenced by the various substituents and increasing steric effects at the amine nitrogen decrease the reactivity significantly. In the present study, phenol was used as a model compound and the usefulness of the studied prodrug type for other phenolic drugs can only be fully evaluated by studying such derivatives of each individual drug. Thus, it can be envisaged that the pK_a value of the phenolic group and the bulkiness of the drug will exert a great influence on the rate of cyclization. By careful selection of substituents, both at the carbamate nitrogen and at the amine nitrogen, it seems feasible to obtain prodrug derivatives with appropriate rates of conversion to the parent phenols at pH 7.4 and 37°C, i.e., the half-lives in the order of 10–60 min. Further studies for this prodrug type are planned including preparation of these derivatives of a phenolic drug and bioavailability studies to demonstrate whether the prodrug approach is useful in reducing first-pass metabolism.

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