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Prodrug forms for the sulfonamide group. II. Water-soluble amino acid derivatives of *N*-methylsulfonamides as possible prodrugs

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Summary

Various *N*-acyl derivatives (acetyl, benzoyl, *N*,*N*-diethylaminoacetyl and morpholinoacetyl) of the model sulfonamide *N*-methyl-*p*-toluenesulfonamide were synthesized and evaluated as potential prodrug forms for the sulfonamide group occurring in e.g. carbonic anhydrase inhibitors. The kinetics of hydrolysis of the derivatives were determined at 37 °C in the pH range 0–12 and in the presence of human plasma. Maximal stability was achieved at pH around 4. The *N*-acyl compounds were readily hydrolyzed enzymatically to yield the parent sulfonamide in quantitative amounts. The derivatives with an ionizable amino function in the acyl moiety possess a high water-solubility as well as adequate lipophilicity at physiological pH. Since various *N*-methylsulfonamides are known to undergo demethylation in vivo a promising prodrug approach for a primary sulfonamide may be *N*-acylation of the corresponding *N*-methylsulfonamide.

Introduction

Carbonic anhydrase inhibitors such as acetazolamide, ethoxzolamide and methazolamide are useful for the treatment of glaucoma. However, due to limited aqueous solubility and unfavourable lipophilicity they are not active when given topically and must be given orally or parenterally (Maren et al., 1983; Friedland and Maren, 1984; Maren, 1987). Systemic side effects severely limit this mode of therapy (Friedland and Maren, 1984) and consequently, great activities are presently going on to find a new carbonic anhydrase inhibitor that would readily penetrate the cornea and be active in lowering intraocular pressure when topically administered to the eye (Maren et al., 1983, 1987; Maren, 1987; Schoenwald et al., 1984; Lewis et al., 1986; Sugrue et al., 1985; Maren and Jankowska, 1985; Duffel et al., 1986; Bar-Ilan et al., 1986; Katritzky et al., 1987; Putnam et al., 1987).

An alternative approach to solve the delivery problems with these drugs, which all contain a primary sulfonamide group as the most prominent functional moiety, may be the development of prodrug derivatives possessing adequate water solubility and lipophilicity characteristics combined with the ability to be reconverted to the parent active sulfonamide following corneal passage.

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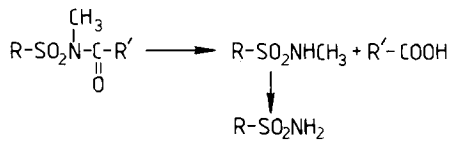
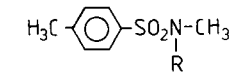
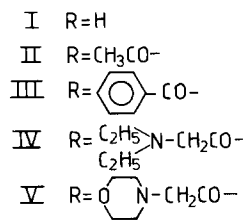
In a previous paper (Larsen and Bundgaard, 1987), various derivatives of sulfonamide model substances such as *p*-toluenesulfonamide were evaluated as potential prodrug forms for the sulfonamide group. Whereas *N*-acyl derivatives of primary sulfonamides proved very resistant to undergo chemical or enzymatic hydrolysis due to sulfonamide ionization the *N*-acetyl derivative of the secondary sulfonamide *N*-methyl-*p*-toluenesulfonamide was found to be easily hydrolyzed enzymatically. Since *N*-alkylated sulfonamides may undergo dealkylation in vivo (Maren, 1956; Duffel et al., 1986) this finding suggested that *N*-acylation may be a useful prodrug approach for primary sulfonamides when combined with *N*-alkylation (Larsen and Bundgaard, 1987). Enzymatic reactions involving deacylation followed by dealkylation should thus lead to the parent primary sulfonamide as depicted in Scheme 1. Considering the possibility of improving the ocular delivery characteristics of carbonic anhydrase inhibitors by such a double prodrug approach it is of particular interest to note that ocular tissues have been shown to be capable of metabolizing *N*-methylacetazolamide to acetazolamide (Duffel et al., 1986).



Scheme 1.

To further explore this possible prodrug approach, we have now prepared and studied various *N*-acylated derivatives (**II**–**V**) of the model compound *N*-methyl-*p*-toluenesulfonamide (**I**). In the derivatives **IV** and **V** an amino function was introduced in the acyl moiety with the aim of obtaining derivatives with a good water solubility, but at the same time an adequate lipophilicity at pH 7.4. In the present paper the chemical and enzymatic hydrolysis of the derivatives **II**–**V** is described along with their physicochemical characteristics in terms of solubility and lipophilicity. The corneal transport and metabolic characteristics of these derivatives will be reported in a future paper.





Materials and Methods

Apparatus

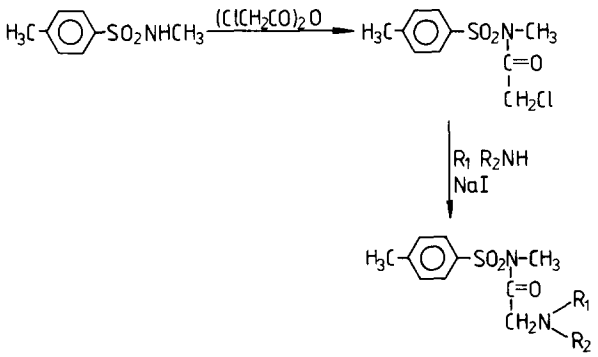
High-performance liquid chromatography (HPLC) was done with a Kontron apparatus consisting of an LC Pump T-414, a Uvikon 740 LC UV detector, a 20 μl loop injection valve and a Chrompack column (100 × 3 mm) packed with Chromsphere C 18 (5 μm particles). UV spectral measurements were performed with a Shimadzu UV-190 spectrophotometer equipped with a thermostatically controlled cell compartment, using 1-cm quartz cells. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. Melting points were taken on a capillary melting point apparatus and are uncorrected. Microanalyses were performed at Leo Pharmaceuticals, Ballerup, Denmark.

Chemicals

N-Methyl-*p*-toluenesulfonamide was obtained from Aldrich. Chemicals and solvents used in the kinetic studies were of reagent grade.

Synthesis of sulfonamide derivatives

N-Acetyl-*N*-methyl-*p*-toluenesulfonamide (**II**) was prepared by reacting **I** with acetic anhydride as described by Chaplin and Hunter (1937) (Scheme 2). The *N*-benzoyl derivative **III** was obtained according to the method of Kemp and Stephen (1948) by stirring a mixture of *N*-methyl-*p*-toluenesulfonamide (3.70 g, 0.02 mol), benzoyl chloride (2.81 g, 0.02 mol) and pyridine (3.2 ml,



Scheme 2.

0.04 mol) for 4 h at 110 °C. Upon cooling, the mixture was poured into 1 M hydrochloric acid and stirred at 4 °C for 3 h. The precipitate formed was filtered off, washed with water and recrystallized from ethanol–water.

The amino acid derivatives **IV** and **V** were prepared as outlined in Scheme 2. A mixture of *N*-methyl-*p*-toluenesulfonamide (4.5 g) and chloroacetic anhydride (10 g) was heated to 140 °C for 5 h. Upon cooling 50 ml of water was added. The mixture was stirred at room temperature for 1 h and the precipitate formed was filtered off,washed with a 5% solution of sodium bicarbonate and finally recrystallized from ethanol–water to give 3.5 g of *N*-chloroacetyl-*N*-methyl-*p*-toluenesulfonamide, m.p. 71–72 °C.

Anal.: Calc. for $C_{10}H_{12}ClNO_3S$: C, 45.89; H, 4.62; N, 5.35. Found: C, 46.05; H, 4.67; N, 5.32.

A solution of *N*-chloroacetyl-*N*-methyl-*p*-toluenesulfonamide (4 mmol, 990 mg), sodium iodide (1 mmol, 150 mg) and diethylamine (12 mmol, 1.25 ml) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 h. TLC (silica gel; acetic acid-ethyl acetate-toluene (1 : 20 : 80)) showed that the reaction was complete after this time. The reaction mixture was evaporated under reduced pressure and the residue was taken up in ethyl acetate (40 ml) and water (30 ml). After separation of the phases the ethyl acetate layer was washed with a 5% sodium bicarbonate solution, water and subsequently dried with anhydrous sodium sulphate and evaporated in vacuo to give compound **IV** as an oil. It was dissolved in ether (50 ml) and a solution of fumaric acid (4 mmol, 460 mg) in 2-propanol (4 ml) was added. After standing for 1 h at 4 °C the precipitate formed was filtered off yielding 850 mg of compound **IV** as monofumarate. The compound was recrystallized from ethanol–ether.

Compound V was prepared by the same procedure using morpholine instead of diethylamine. Physical and analytical data for the compounds are given in Table 1.

TABLE 1

Physical and analytical data of various N-acyl derivatives of N-methyl-p-toluenesulfonamide

Compound	Melting point (C °)	Formula	Analysis (%)	
			Calculated	Found
II	57– 58 [a]	$C_{10}H_{13}NO_3S$		
III	59– 60	$C_{15}H_{15}NO_3S$	C 62.26	62.19
			H 5.23	5.29
			N 4.84	4.82
IV [b]	115–116	$C_{18}H_{26}N_2O_7S$	C 52.16	51.99
			H 6.32	6.29
			N 6.76	6.61
			S 7.74	7.65
V [b]	167–168	$C_{18}H_{24}N_2O_8S$	C 50.46	50.29
			H 5.65	5.61
			N 6.54	6.49
			S 7.48	7.26

[a] Reported m.p.: 57–58 °C (Chaplin and Hunter, 1937).
[b] Isolated as salts with 1 equivalent fumaric acid.

Kinetic measurements

The degradation of the sulfonamide derivatives was studied in aqueous buffer solutions at 37.0 ± 0.2 °C. Hydrochloric acid, acetate, phosphate, borate, carbonate and sodium hydroxide buffers were used; the total buffer concentration was generally 0.01 M and a constant ionic strength (μ) of 0.5 was maintained, when possible, for each buffer by adding a calculated amount of potassium chloride.

The rates of hydrolysis were in some cases (at basic pH) followed by recording the absorbance decrease accompanying the hydrolysis at 240 nm where the decrease was maximal. The reactions were performed in 2.5 ml aliquot portions of buffer solutions in a thermostated quartz cuvette and were initiated by adding 25 μl of stock solutions of the derivatives in acetonitrile (**II** and **III**)

or water (**IV** and **V**) to give a final concentration of $0.5–1 \times 10^{-4}$ M. Pseudo-first-order rate constants were determined from the slopes of linear plots of $\log(A_t - A_\infty)$ against time where A_t and A_∞ are the absorbance readings at time t and infinity, respectively.

Most reactions were followed by using a reversed-phase HPLC procedure. A mobile phase system of 55% v/v methanol in a 0.01 M acetate buffer of pH 4.0 was used for the compounds **II** and **III** whereas a solvent system of methanol–0.01 M phosphate buffer of pH 7.0 (55 : 45 v/v) containing 1% of triethylamine was used for the compounds **IV** and **V**. The flow rate was 0.7–1.0 ml/min and the column effluent was monitored at 215 nm. Under these conditions the *N*-acyl derivatives were well separated from compound **I**. 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 100 µl of a stock solution of the compounds in acetonitrile (**II** and **III**) or water (**IV** and **V**) to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentrations of the compounds being about 5×10^{-4} M. The solutions were kept in a water bath at 37 °C and at appropriate intervals samples were taken and chromatographed. Pseudo-first-order rate constants for the hydrolysis were determined from the slopes of linear plots of the logarithm of residual derivative against time.

In cases of slow reactions the rates of hydrolysis were determined by the initial rate method. In this method the progressive appearance of the product of hydrolysis, compound **I**, was followed using the HPLC methods described above. The reactions were followed up to 3–5% formation of compound **I**. The pseudo-first-order rate constants were determined by dividing the slopes of linear plots of amount of **I** formed vs time by the initial concentration of sulfonamide derivative.

Hydrolysis in human plasma solutions

The hydrolysis of the derivatives **II–V** was studied in 0.01 M phosphate buffer (pH 7.4) containing 80% human plasma at 37 °C. At appropriate times, samples of 250 µl of the plasma solutions with an initial concentration of the derivatives of about 10^{-4} M were withdrawn and deproteinized by mixing with 500 µl of methanol. After centrifugation for 2 min at 13,000 rpm, 20 µl of the clear supernatant was analyzed by HPLC as described above.

Determination of aqueous solubility and partition coefficients

The aqueous solubility of the derivatives were determined at 22 °C by adding excess amounts of the compounds to water or a 0.05 M acetate buffer solution (pH 5.0). The mixtures were placed in an ultrasonic water bath for 10 min and then rotated on a mechanical spindle for about 18 h. Upon filtration an aliquot of the filtrate was diluted with an appropriate amount of water and the mixture analyzed by HPLC.

The apparent partition coefficients were determined in octanol–0.02 M phosphate buffer (pH 7.40) at 22 °C. The buffer and octanol were mutually saturated at 22 °C before use. The compounds were dissolved in the aqueous phase and the octanol–buffer mixtures were shaken for 5–10 min to reach a distribution equilibrium. The volumes of each phase were chosen so that the solute concentration in the aqueous phase, before (C_i) and after (C_w) distribution, could readily be determined using the aforementioned HPLC methods. Centrifugation was used to separate the two phases. The partition coefficients (P) were calculated from Eqn. 1:

$$P = \frac{C_i - C_w}{C_w} \times \frac{V_w}{V_0} \quad (1)$$

where V_w and V_0 represent the volume of the aqueous and octanol phase, respectively.

Results and Discussion

Kinetics of hydrolysis

The kinetics of hydrolysis of the *N*-acyl derivatives (**II–V**) of *N*-methyl-*p*-toluenesulfonamide (**I**) was studied at 37 °C in aqueous buffer solutions over the pH-range 0–12. Under the experimental conditions the compounds **II–V** hydrolyzed to yield *N*-methyl-*p*-toluenesulfonamide quantita-

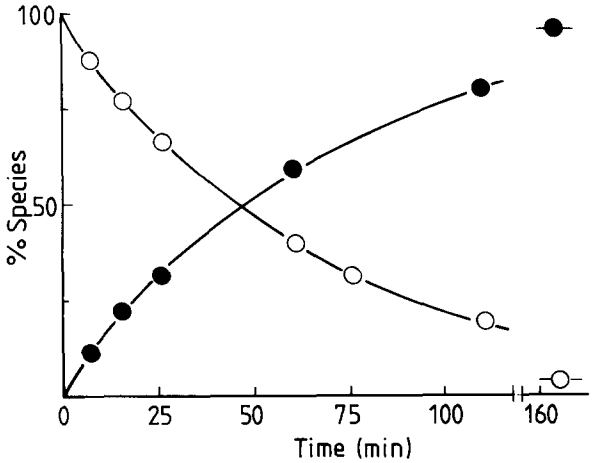


Fig. 1. Time-courses of disappearance of compound **III** (○) and appearance of compound **I** (●) in a 0.01 M borate buffer solution (pH 9.9) of compound **III** at 37 °C.

tively as evidenced by HPLC analysis. An example is shown in Fig. 1.

At constant pH and temperature the reactions displayed strict first-order kinetics. In cases where the hydrolysis was followed both by direct UV-spectrophotometry and HPLC the rate constants obtained therefrom agreed within 5%. At the buffer concentrations used (0.01 M) no significant buffer catalytic effect was observed. The effect of pH on the rates of hydrolysis is shown in Fig. 2 in which the logarithm of the observed pseudo-first-order rate constants (k_{obs}) has been plotted against pH.

The shapes of the pH-rate profiles for the neutral *N*-acyl derivatives **II** and **III** (Fig. 2) indicate that the hydrolysis of these compounds can be described in terms of specific acid-catalyzed (k_H), spontaneous (k_0) and specific base-catalyzed

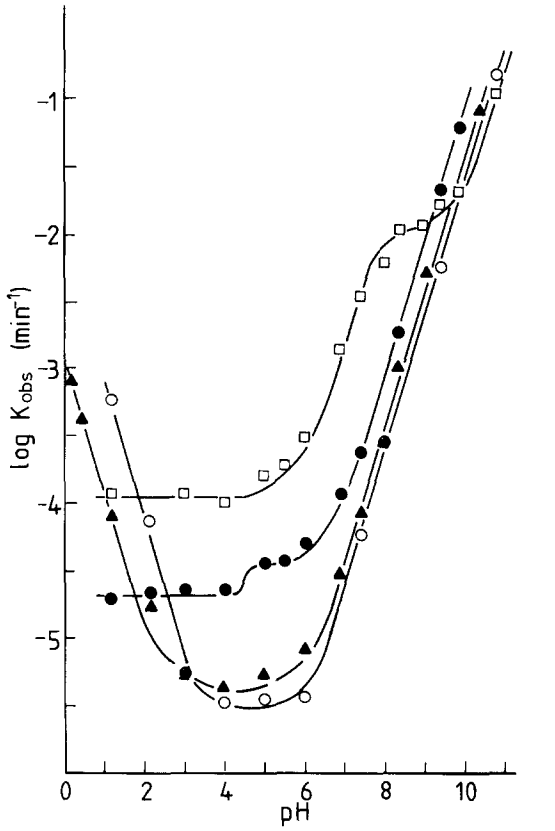


Fig. 2. The pH-rate profiles for the hydrolysis of compound **II** (○), compound **III** (▲), compound **IV** (□) and compound **V** (●) in aqueous solution ($\mu = 0.5$) at 37 °C.

(k_{OH}) reactions according to the following equation:

$$k_{obs} = k_H a_H + k_0 + k_{OH} a_{OH} \quad (2)$$

where a_H and a_{OH} are the hydrogen ion and hydroxide ion activity, respectively. The latter was

TABLE 2

Ionization constants and rate data for the hydrolysis of various N-acyl N-methyl-p-toluenesulfonamide derivatives ($\mu = 0.5$; 37 °C)

Compound	k_H (M^{-1} min^{-1})	k_0 (min^{-1})	k_{OH} (M^{-1} min^{-1})	k^I_{OH} (M^{-1} min^{-1})	pK_a
II	9.3×10^{-3}	3.1×10^{-6}	99.5		
III	1.1×10^{-3}	4.0×10^{-6}	156		
IV		1.2×10^{-4}	5.5×10^{3}	66	8.0
V		2.2×10^{-5}	1.0×10^{4}	330	5.0

calculated from the measured pH according to Eqn. 3 (Harned and Hamer, 1933):

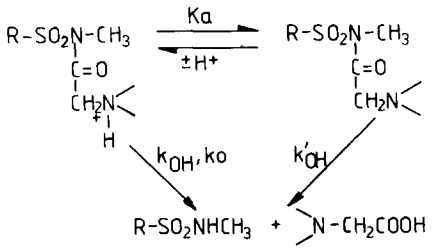
$$\log a_{OH} = pH - 13.62 \quad (3)$$

The values of the rate parameters k_H, k_{OH} and k_0 are listed in Table 2.

The pH-rate profiles (Fig. 2) obtained for the *N*-acyl derivatives containing an amino function (**IV** and **V**) show that the hydrolysis of these compounds can be described in terms of specific base-catalyzed degradation of the free base and protonated forms along with a spontaneous or water-catalyzed reaction of the protonated species (Scheme 3):

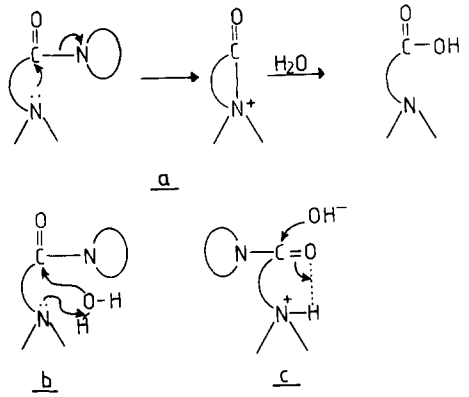
$$k_{obs} = k_0 \frac{a_H}{a_H + K_a} + k_{OH} a_{OH} \frac{a_H}{a_H + K_a} + k'_{OH} a_H \frac{K_a}{a_H + K_a} \quad (4)$$

where $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ are the fractions of the derivatives in the protonated and free base form, respectively, and K_a is the apparent ionization constant of the amino function in the derivatives. The rate constant k_o refers to the pH-independent hydrolysis of the protonated form (equal to k_{obs} at pHs < 4) while k_{OH} and k'_{OH} are the second-order rate constants for the apparent attack of hydroxide ion on the protonated and unprotonated species, respectively. Values of the latter constants were determined from the straight line portions of the pH-rate profiles. The lines drawn in Fig. 2 were constructed from Eqn. 4 and the rate and ionization constants were listed in Table 2.



Scheme 3.

The results obtained show that the introduction of an α-amino group in the acyl moiety results in a markedly increased lability in weakly acid and neutral solutions which can be ascribed to intramolecular catalysis by the amino group. By comparing the k_{OH} and k'_{OH} values for the *N*-acyl derivatives **IV** and **V** it is seen that the derivatives with a protonated amino group possess 30–80 fold greater susceptibility to undergo hydrolysis as compared to the free base forms. Such rate differences have previously been observed for various amino acid esters of alcohols or phenols (Hay and Morris, 1972; Kirby and Lloyd, 1976; Caswell et al., 1981) or for amides formed with various amino acids (Bundgaard and Falch, 1985). Several forms of catalysis by the amino group may occur (Scheme 4): intramolecular nucleophilic catalysis (a), intramolecular general base catalysis (b), and intramolecular general acid-specific base catalysis (c). These mechanisms are kinetically indistinguishable and the present kinetic data make it impossible to prefer one mechanism from another.



Scheme 4.

Hydrolysis in human plasma

The susceptibility of the *N*-acyl sulfonamides to undergo a possible enzymatic hydrolysis was investigated in human plasma diluted to 80% with phosphate buffer of pH 7.40. Under the given reaction conditions strict first-order kinetics was observed and the reactions proceeded to give the parent compound **I** in stoichiometric amounts as evidenced by HPLC analysis. As appears from the rate data obtained (Table 3), plasma accelerates the rate of hydrolysis markedly, the rate of en-

TABLE 3

Rate data for the hydrolysis of N-acyl derivatives of N-methyl-p-toluenesulfonamide in aqueous solution and in 80% human plasma at 37°C

Compound	Half-lives		
	pH 4.0 (days)	pH 7.4 (h)	80% plasma (h)
II	139	192	0.5
III	115	123	1.8
IV	4.3	3.2	1.0
V	24	49	6.8

zymatic hydrolysis being greatest for the *N*-acetyl derivative.

Lipophilicity and water solubility of the derivatives

Apparent partition coefficients (P) for the *N*-acyl derivatives and the parent sulfonamide as determined using the octanol-pH 7.4 buffer system are listed in Table 4 along with data for the water solubility. Compound **I** has a pK_a value of 10.1 so the data for this compound are for the unionized form. As expected, *N*-acylation of I to give the neutral compounds **II** and **III** results in increased lipophilicity and decreased water solubility. By introduction of an ionizable amino function in the acyl moiety as in compounds **IV** and **V** derivatives with greatly increased solubility in weakly acidic solutions are obtained. The fumarate salts of **IV** and **V** showed solubilities in water greater than 5%. The log P value given for compound **V** is for the free base form since the compound ($pK_a \sim 5.0$) is totally unionized at pH 7.4.

TABLE 4

Partition coefficients (P) and water solubilities (S) of N-methyl-p-toluenesulfonamide and its N-acyl derivatives

Compound	log P [a]	S (mg/ml)
I	1.28	2.2
II	1.73	1.0
III	2.95	0.02
IV (fumarate)	0.79	> 50
V (fumarate)	1.16	> 50

[a] Partition coefficients between octanol and phosphate buffer pH 7.4 at 22°C.

In contrast, compound **IV** having a pK_a value of about 8.0 is partly ionized at pH 7.4.

Conclusions

The results obtained show that *N*-acylation of *N*-methylsulfonamides may be a potentially useful approach to obtain prodrug forms of primary sulfonamides with the premise that *N*-demethylation is taking place in vivo following deacylation as outlined in Scheme 1. By introducing an ionizable amino function in the acyl moiety derivatives with a high water solubility and a ready capability to undergo enzymatic hydrolysis can be obtained. By appropriate selection of the amino functionality it is further possible to achieve an adequate lipophilicity at physiological pH. Thus, the α-amino acid derivatives **IV** and **V** possess pK_a values that allow the derivatives to be only partly (**IV**) or almost not (**V**) ionized at pH 7.4. A potential drawback of the derivatives is their limited chemical stability in aqueous solution. The compounds are most stable at pH 4 but even at this pH stability is so limited, in particular for the amino acid derivatives, that ready-to-use solutions with practical shelf-lives cannot be made (cf. Table 3). Formulation into polymeric matrices or the use of ophthalmic rods (Gwon et al., 1986) may be approaches to overcome the solution instability problem.

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