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Glycolamide esters as a novel biolabile prodrug type for non-steroidal anti-inflammatory carboxylic acid drugs

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Summary

Various glycolamide esters of 13 acidic non-steroidal anti-inflammatory drugs were prepared with the aim of obtaining enzymatically labile ester prodrugs. The glycolamide esters were in general found to be hydrolyzed very rapidly in human plasma solutions, the half-lives of hydrolysis being seconds or a few minutes in 80% plasma for some *N*,*N*-disubstituted glycolamide esters. In contrast, simple methyl or ethyl esters of the carboxylic acid agents were found to be hydrolyzed only very slowly in plasma solutions and thus unsuitable as prodrug forms. Since the esters of *N*,*N*-disubstituted glycolamides combine a high susceptibility to undergo enzymatic hydrolysis in plasma with a high stability in aqueous solution, they are suggested to be a useful prodrug type for several non-steroidal anti-inflammatory acids with the aim of e.g. depressing their gastrotoxicity and improving their delivery characteristics. With respect to the latter aspect it was shown that it is possible to design glycolamide ester derivatives with widely varying water solubilities and lipophilicities and still maintain a high lability of the esters to enzymatic hydrolysis.

Introduction

In recent years much attention has been focused on the development of bioreversible derivatives (prodrugs) of non-steroidal anti-inflammatory (NSAI) drugs in order to depress their gastrointestinal side effects (Jones, 1985) as well as to improve their delivery characteristics, in particular following topical administration (Loftsson and Bodor, 1981; Sloan et al., 1984; Yano et al., 1986). The gastrointestinal lesions produced by the acid NSAI agents are generally believed to be caused by two different mechanisms: a direct contact mechanism on the gastrointestinal mucosa and a generalized systemic action appearing after absorption and which can be demonstrated following intravenous dosing. The relative importance of these mechanisms may vary from drug to drug (Cooke, 1976; Ivey, 1986; Whitehouse and Rainsford, 1977; Cioli et al., 1979; Rainsford, 1978). Acetylsalicylic acid and most newer NSAI drugs are carboxylic acids and temporary masking of the acid function has been proposed as a promising means of reducing or abolishing the gastrointestinal toxicity due to the direct mucosa contact mechanism (Whitehouse and Rainsford, 1977). Thus, esterification of acetylsalicylic acid, salicylic acid, flufenamic acid, tolmetin and various other NSAI acids to produce methyl esters has been shown to greatly suppress the gastric ulcerogenic activity (Whitehouse and Rainsford, 1980). This

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finding has since been followed by the development of a variety of ester derivatives of NSAI drugs (for recent reviews, see Jones (1985) and Büge (1986)).

The usefulness of the principle of esterification of acidic NSAI drugs to reduce gastro-intestinal toxicity depends, however, on various factors. The esters being pharmacologically inactive per se should be readily hydrolyzed following their absorption to release the parent active acid in the blood and furthermore, the esters should possess physicochemical properties (i.e., aqueous solubility and lipophilicity) being favorable for peroral absorption. These requirements do not appear to be fulfilled for several ester types. Thus, simple aliphatic or aromatic esters are often not sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example, the much reduced anti-inflammatory activity observed for the methyl or ethyl esters of naproxen (Harrison et al., 1970), fenbufen (Child et al., 1977) and indomethacin (Boltze et al., 1980) relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo (see below). The double ester types comprising (acyloxy)alkyl and [(alkoxycarbonyl)oxy]alkyl esters show a higher enzymatic lability than simple alkyl esters (Bundgaard, 1985) but the utility of this prodrug ester concept may be limited by the poor water solubility of the double esters. Furthermore, such esters prepared of various NSAI drugs are in many cases oils (Ladkani et al., 1983; Uchida et al., 1983), thus creating pharmaceutical formulation problems.

In attempting to explore new generally applicable ester prodrug types possessing a high enzymatic rate of hydrolysis in plasma or blood, we recently discovered that esters of certain 2-hydroxyacetamides (glycolamides) are cleaved remarkably rapidly in human plasma and at the same time are chemically highly stable (Bundgaard and Nielsen, 1987). A study of a large series of glycolamide esters and structurally related esters of benzoic acid, used as a model of a carboxylic acid drug, showed that the most prominent structural requirement needed for a rapid rate of enzymatic hydrolysis was the glycolamide ester structure combined with the presence of two substituents on the amide nitrogen atom (Nielsen and Bundgaard, 1988). Consequently, such *N,N*-disubstituted glycolamide esters may show promise as a biolabile prodrug type for various acidic drugs including NSAI acid agents.

In the present work, a number of *N,N*-disubstituted glycolamide esters of various NSAI agents containing a carboxylic acid function (Fig. 1) have been prepared and their kinetics of hydrolysis in human plasma were investigated. Water solubilities and octanol-water partition coefficients were also determined for some compounds. A part of the work has previously been described in a preliminary communication (Bundgaard and Nielsen, 1987). A study of a large series of esters of acetylsalicylic acid will be published in a separate paper.

Materials and Methods

Apparatus

Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were run on a Varian 360 L instrument using tetramethylsilane as an internal standard. Measurements of pH were done at the temperature of study using a Radiometer Type PHM 26 instrument. High-performance liquid chromatography (HPLC) was generally carried out using a Spectra-Physics Model 3500 B instrument equipped with a variable wavelength detector, a 10 μl loop injection valve and a LiChrosorb RP-8 (7-μm particles) column (250 × 4 mm) (E. Merck). Microanalyses were performed at the Microanalytical Laboratory, Leo Pharmaceutical Products, Ballerup, Denmark.

Chemicals

The non-steroidal anti-inflammatory drugs were either purchased from Sigma Chemical Co., St. Louis, U.S.A. or provided by various pharmaceutical companies. 2-Chloroacetamide, 2-chloro-*N,N*-dimethylacetamide and 2-chloro-*N,N*-diethylacetamide were purchased from E. Merck, F.R.G. Chemicals and solvents used in the kinetic studies were of reagent grade.

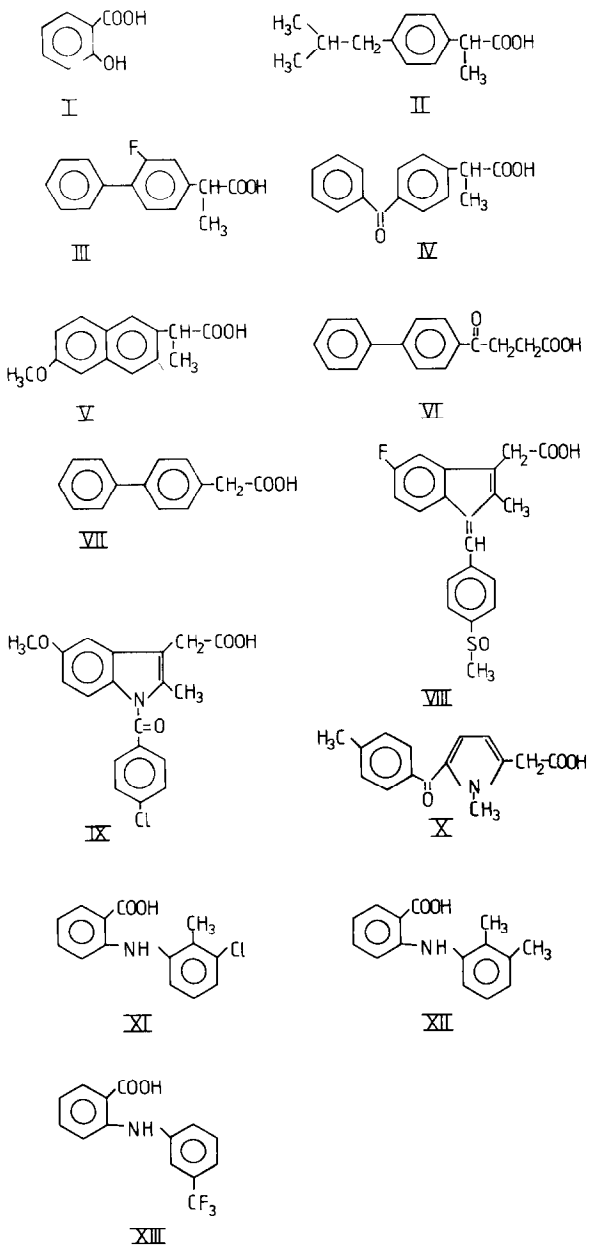


Fig. 1. Chemical structures of various non-steroidal anti-inflammatory drugs investigated in this study. **I**, salicylic acid; **II**, ibuprofen; **III**, flurbiprofen; **IV**, ketoprofen; **V**, naproxen; **VI**, fenbufen; **VII**, 4-biphenylacetic acid; **VIII**, sulindac; **IX**, indomethacin; **X**, tolmetin; **XI**, tolfenamic acid; **XII**, mefenamic acid; **XIII**, flufenamic acid.

Synthesis of glycolamide esters

The glycolamide esters were prepared by reacting the acids with the appropriate 2-chloroacetamide in *N*,*N*-dimethylformamide. To a solution of the acid (0.01 mol) in *N*,*N*-dimethylformamide (10 ml) was added triethylamine (0.011 mol), sodium iodide (0.001 mol) and the appropriate 2-chloroacetamide (0.011 mol). The mixture was stirred at 90 °C for 2 h or, in some cases, stirred at room temperature overnight, poured into water (50 ml) and then extracted with ethyl acetate (2 × 50 ml). The combined extracts were washed with a 2% aqueous solution of sodium thiosulphate, 2% sodium bicarbonate and water. After drying over anhydrous sodium sulphate, the ethyl acetate was removed under reduced pressure to give the glycolamide esters which were purified by recrystallization, usually from ethanol–water, ethyl acetate or ethanol–ether.

Melting points of the glycolamide esters are given in Table 1. Elemental analysis (C, H and N) of the esters were in all cases within ±0.4% of the theoretical values and the ^{1}H NMR spectra of the compounds were consistent with their structures.

The synthetic intermediates 2-chloro-(*N*-methyl-*N*-β-hydroxyethyl)acetamide, 2-chloro-(*N*-ethyl-*N*-β-hydroxyethyl)acetamide and 2-chloro-(*N*,*N*-di-β-hydroxyethyl)acetamide were prepared by reacting methyl chloroacetate with the appropriate ethanolamine as described by Harkins (1965).

α-Chloroacetylsarcosinamide was prepared by adding a solution of chloroacetyl chloride (0.1 mol, 11.3 g) in benzene (40 ml) over 30 min to a mixture of sarcosinamide hydrochloride (0.1 mol, 12.45 g) (obtained as described by Marvel et al. (1946)) and sodium bicarbonate (0.25 mol, 20.0 g) in 40 ml of water. The mixture was vigorously stirred for 3 h at room temperature. The aqueous phase was acidified with 5 M hydrochloric acid to pH 5 and extracted with ethyl acetate (3 × 400 ml). The combined extracts were dried over anhydrous sodium sulphate and evaporated in vacuo. The solid residue obtained was recrystallized from ethanol–ether to give 8.5 g (52%) of α-chloroacetylsarcosinamide, mp 85–86 °C.

Synthesis of the N-Mannich base IId

The *N*-methyl-*N*-carbamoylmethylglycolamide ester of ibuprofen (IIc) (2 mmol, 0.67 g) was dissolved in 2.5 ml of methanol. Morpholine (2

mmol, 0.18 g) and 0.17 ml of 37% aqueous formaldehyde solution were added and the solution heated on a steam bath for 15 min. The oily residue obtained after evaporation of the solution under reduced pressure was dissolved in ether (10 ml) and a 2.5 M methanolic solution of HCl (1 ml) was added followed by petroleum ether. The mixture was kept overnight at −20 °C to allow precipitation of the hydrochloride salt of compound IId which was isolated by filtration, mp 154–155 °C.

Synthesis of methyl or ethyl esters

The methyl or ethyl esters of various acids were prepared by reacting the acids with methyl or ethyl iodide in *N*,*N*-dimethylformamide essentially as described above for the glycolamide esters. The melting points for the esters were as follows: Naproxen ethyl ester, 80–81 °C; ketoprofen methyl ester (oil); tolmetin methyl ester, 121–122 °C; tolfenamic acid methyl ester, 155–157 °C; indomethacin methyl ester, 85–86 °C; fenbufen methyl ester, 99–100 °C. Methyl salicylate was commercially available.

Hydrolysis kinetics in human plasma

The hydrolysis of the esters was studied in human plasma diluted to 80% with 0.05 M phosphate buffer of pH 7.4. The reactions were initiated by adding 50 µl of a stock solution of the compounds in acetonitrile or ethanol–water to 5.00 ml of preheated plasma solution, the final concentrations of the compounds being 3×10^{-4} to 2×10^{-5} M. The solutions were kept in a water bath at 37 °C and at appropriate intervals samples of 250 µl were withdrawn and added to 1000 µl of methanol in order to deproteinize the plasma. After immediate mixing and centrifugation for 3 min at 10000 rpm, 10 µl of the clear supernatant was analyzed by HPLC for remaining ester derivative as well as for the parent acid.

In the HPLC method a reversed-phase C8 column was eluted at ambient temperature with mixtures of methanol or acetonitrile and 0.02 M phosphate (pH 3.5 or pH 4.5). The composition of the eluent was adjusted for each compound in order to provide an appropriate retention time and separation of ester and the corresponding acid. In the case of compound IId a mobile phase system consisting of methanol-acetonitrile–0.02 M phosphate pH 7.0 (5 : 2 : 3 v/v) was used. The flow rate was 1.2 ml/min and the column effluent was monitored spectrophotometrically at an appropriate wavelength. Quantitation of the compounds was done by measurement of the peak heights in relation to those of standards chromatographed under the same conditions.

Stability in aqueous solution

The stability of the esters in aqueous buffer solutions was determined with the use of the same HPLC methods as those used in the plasma hydrolysis studies. Buffer solutions containing the ester derivatives (10^{-5}–10^{-4} M) were kept at constant temperature in a water bath and at appropriate intervals samples were taken and analyzed by HPLC for remaining ester and parent acid.

Determination of aqueous solubility and partition coefficients

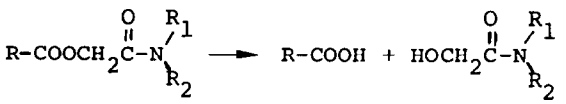
The solubility of some esters in 0.05 M phosphate buffer of pH 7.4 was determined at 22 °C by adding excess amounts of the compounds to the buffer in screw-capped test-tubes. The mixtures were placed in an ultrasonic water bath for about 10 min and then rotated on a mechanical spindle for 20–30 h. It was ensured that saturation equilibrium was established. Upon filtration an aliquot of the filtrate was diluted with water and the mixture analyzed by HPLC.

The partition coefficients of the esters were determined in an octanol–0.05 M phosphate buffer (pH 7.4) system as previously described (Bundgaard et al., 1986).

Bioavailability study

Naproxen and the glycolamide ester derivative Vf were administered orally to the same rabbit in equivalent doses corresponding to 4.8 mg/kg in terms of naproxen. The compounds were given in the form of a suspension in 0.5% aqueous methylcellulose. After administration, blood samples were taken from the marginal ear vein at various times in heparinized test tubes and the plasma fraction immediately deproteinized with ethanol and as-

sayed for naproxen and intact ester using HPLC at the following conditions: column: LiChrosorb RP-8; eluent: methanol-0.02 M KH_2PO_4 (pH 3.5) 65 : 35 v/v; detection: UV at 230 nm.



Scheme 1.

Results and Discussion

The various glycolamide esters of a number of non-steroidal anti-inflammatory carboxylic acid drugs (Table 1) were found to be hydrolyzed quantitatively to the parent acids in 80% human plasma solutions as revealed by HPLC analysis of the reaction solutions (Scheme 1). An example is shown in Fig. 2. At initial concentrations of 2×10^{-4} to 2×10^{-5} M the progress of hydrolysis of all esters except those of salicylic acid followed strict first-order kinetics over several half-lives as illustrated in Fig. 3 for some esters. Pseudo-first-order rate constants (k) for the hydrolysis were calculated from the slopes of linear plots of the logarithm of remaining ester against time and the corresponding half-lives obtained from the iden-

TABLE 1

Physical data and half-lives ($t_{1/2}$) of hydrolysis of glycolamide esters of various non-steroidal anti-inflammatory drugs in 80% human plasma (37°C)

Acid (R-COOH)	Compound No.	R-$COOCH_2CONR_1R_2$		mp (°C)	$t_{1/2}$ (min)
		R_1	R_2		
Salicylic acid	**Ia**	H	H	143 –143.5	80
	Ib	CH_3	CH_3	67.5– 68	0.06
	Ic	C_2H_5	C_2H_5	74 – 75	0.05
	Id	CH_3	CH_2CH_2OH	92 – 93	0.3
Ibuprofen	**IIa**	CH_3	CH_3	~ 5	8.6
	IIb	C_2H_5	C_2H_5	oil	4.0
	IIc	CH_3	CH_2CONH_2	100 –101	9.6
Flurbiprofen	**IIIa**	CH_3	CH_3	74 – 75	10.8
	IIIb	C_2H_5	C_2H_5	60 – 61	4.7
Ketoprofen	**IVa**	CH_3	CH_3	oil	1.1
	IVb	C_2H_5	C_2H_5	oil	0.5
	IVc	CH_3	CH_2CONH_2	83 – 84	2.3
Naproxen	**Va**	H	H	139 –140	148
	Vb	CH_3	CH_3	150 –151	1.1
	Vc	C_2H_5	C_2H_5	89 – 89.5	0.6
	Vd	CH_3	CH_2CONH_2	179 –180	2.1
	Ve	CH_3	CH_2CH_2OH	109 –111	1.0
	Vf	CH_2CH_2OH	CH_2CH_2OH	113 –114	1.4
Fenbufen	**VIa**	CH_3	CH_3	120 –121	9.2
	VIb	C_2H_5	C_2H_5	94 – 95	3.8
4-Biphenylacetic acid	**VIIa**	CH_3	CH_2CONH_2	174 –175	2.1
Sulindac	**VIIIa**	C_2H_5	C_2H_5	100 –101	26
Indomethacin	**IXa**	CH_3	CH_3	149 –150	130
	IXb	C_2H_5	C_2H_5	104 –105	25
	IXc	CH_3	CH_2CH_2OH	138 –139	140
	IXd	CH_2CH_2OH	CH_2CH_2OH	144 –146	88
Tolmetin	**Xa**	CH_3	CH_3	108 –109	14.6
Tolfenamic acid	**XIa**	CH_3	CH_3	106 –107	2.8
	XIb	C_2H_5	C_2H_5	114 –115	5.0
	XIc	C_2H_5	CH_2CH_2OH	85 – 86	3.0
Mefenamic acid	**XIIa**	CH_3	CH_3	85 – 86	2.4
Flufenamic acid	**XIIIa**	CH_3	CH_3	106 –107	2.7

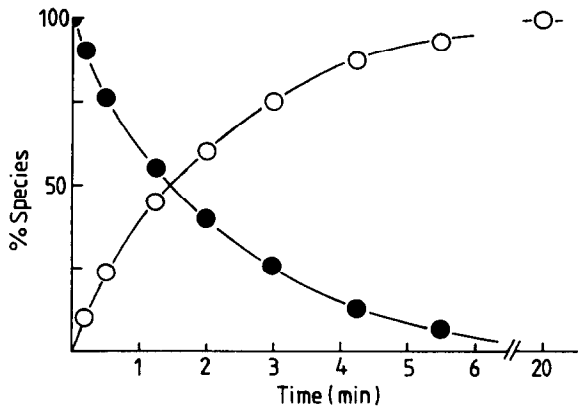


Fig. 2. Time courses for the naproxen *N,N*-dimethylglycolamide ester Vb (●) and naproxen (○) during hydrolysis of the ester in 80% human plasma at 37 °C. The initial ester concentration was 10^{-4} M.

tity: $t_{1/2} = 0.693/k$. The half-lives for the various esters are listed in Table 1.

The rate of hydrolysis of the salicylic acid esters **Ib–d** initially followed zero-order kinetics and as the ester substrate depleted it changed to follow first-order kinetics. A plot of the data from hydrolysis of the *N,N*-dimethylglycolamide ester of salicylic acid (**Ib**) in 80% human plasma is shown in Fig. 4. As described elsewhere for similar benzoate esters (Nielsen and Bundgaard, 1988) such progress curves can be accounted for accord-

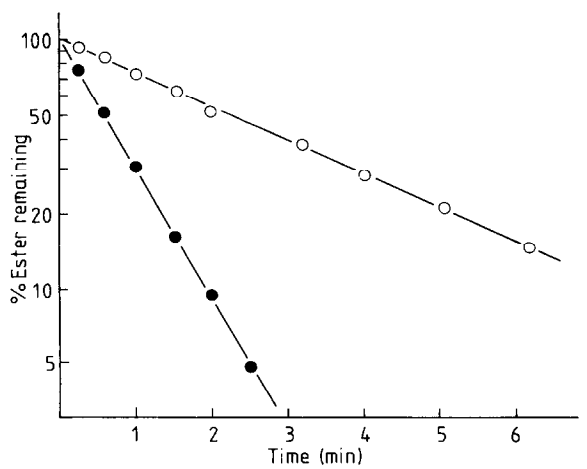


Fig. 3. Plots showing the first-order kinetics of hydrolysis of the esters **IVc** (○) and **Vc** (●) (initial concentration being 10^{-4} M) in 80% human plasma at 37 °C.

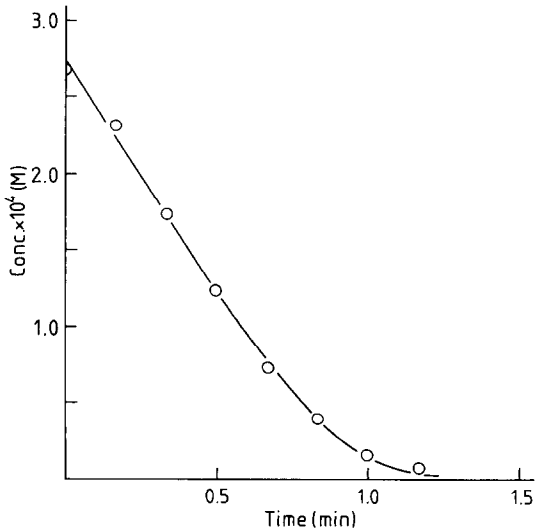


Fig. 4. Plot showing the zero-order followed by first-order rate of hydrolysis of the *N,N*-dimethylglycolamide ester of salicylic acid (**Ib**) in 80% human plasma at 37 °C.

ing to the integrated form of the Michaelis–Menten equation (Robinson and Characklis, 1984) from which the rate parameters K_m and V_{max} can be obtained. Analysis of the curve in Fig. 4 in this way afforded a K_m value of 3.2×10^{-5} M^{-1} and a V_{max} value of 3.6×10^{-4} M^{-1} min^{-1}. At a low substrate concentration, i.e., similar to the conditions prevailing in vivo for prodrug hydrolysis, the enzymatic reaction is first-order with the rate equal to V_{max}/K_m. The half-lives given in Table 1 for the salicylate esters refer to this rate, i.e. $t_{1/2} = 0.693/(V_{max}/K_m)$.

As can be seen from the rate data the *N,N*-disubstituted glycolamide esters of the various acids are hydrolyzed quite rapidly in human plasma although the rate of hydrolysis depends on the structure of the acyl moiety. The esters of indomethacin are the least reactive whereas esters of salicylic acid, naproxen and ketoprofen are quite easily hydrolyzed.

From a study of the plasma-catalyzed hydrolysis of various glycolamide esters of benzoic acid *N,N*-disubstituted glycolamide esters were found to be much more readily hydrolyzed than either monosubstituted or unsubstituted glycolamide esters (Nielsen and Bundgaard, 1988). This structural dependence is also seen in the salicylic acid

and naproxen esters in that the unsubstituted glycolamide esters (**Ia** and **Va**) are hydrolyzed much more slowly than the corresponding *N,N*-disubstituted glycolamide esters (cf. Table 1).

Inspection of the data in Table 1 further shows that the *N,N*-diethylglycolamide esters are hydrolyzed somewhat faster than the corresponding *N,N*-dimethylglycolamide esters, the only exception being the esters of tolfenamic acid. This is also in accordance with the behaviour of the analogous benzoic acid esters. In 50% human plasma the *N,N*-dimethyl- and *N,N*-diethylglycolamide esters of benzoic acid are hydrolyzed with half-lives of 9 and 4.8 s, respectively (Nielsen and Bundgaard, 1988). These rapid rates of hydrolysis were attributed to pseudocholinesterase present in plasma (Nielsen and Bundgaard, 1988) and the relatively slower hydrolysis of the glycolamide esters of the acids studied in the present study may be ascribed to a poorer structural fit to the enzyme as compared with the benzoyl moiety. An exception is the salicylate esters **Ib–d** which are hydrolyzed as rapidly as the corresponding benzoate esters.

The rapid rate of hydrolysis of the glycolamide esters in plasma is readily evident when these rates are compared with those of methyl or ethyl esters of the same acids. As can be seen from Table 2 the simple alkyl esters are hydrolyzed several-fold more slowly than the *N,N*-disubstituted glycolamide esters. The slow rate of hydrolysis of the naproxen, indomethacin and fenbufen alkyl esters may explain the reduced anti-inflammatory activity observed for these esters in comparison to the parent acids (Harrison et al., 1970; Boltze et al., 1980; Child et al., 1977). The slow rate of hydrolysis of methyl salicylate is in agreement with data from a pharmacokinetic study of this compound (Davison et al., 1961) in that appreciable amounts of unhydrolyzed ester were observed in plasma following peroral administration of the ester to humans.

TABLE 2

Half-lives ($t_{1/2}$) of hydrolysis of esters of various drugs in 80% plasma (pH 7.4) at 37°C

Acid	$t_{1/2}$	
	Methyl ester (h)	*N,N*-diethylglycolamide ester (min)
Salicylic acid	17.6	0.05
Ketoprofen	> 20	0.5
Fenbufen	4.7	3.8
Tolmetin	19	13.4 [b]
Tolfenamic acid	100	5.0
Indomethacin	150	25
Naproxen	20.1 [a]	0.6

[a] Value for ethyl ester. [b] Value for the *N,N*-dimethylglycolamide ester.

As has been described for glycolamide esters of benzoic acid (Nielsen and Bundgaard, 1987, 1988) the esters studied herein proved to be highly stable in aqueous solution. At pH 7.4 and 37°C the half-lives of hydrolysis were found to be greater than 300 h. Thus, the specific base catalytic rate constant (k_{OH}) for the hydrolysis of the naproxen ester **Ve** in neutral and alkaline aqueous solution at 60°C was found to be 145 M^{-1} min^{-1}. Maximum stability occurs at pH 3.5–4 and preliminary studies indicated that shelf-lives for the esters of more than 5 years can be achieved at 20°C at these pH values in accordance with the results obtained for the model benzoic acid esters (Nielsen and Bundgaard, 1988).

The most prominent structural requirement for the glycolamide esters to be hydrolyzed rapidly by plasma enzymes is the presence of two substituents on the amide nitrogen but it is, however, readily feasible to select *N,N*-disubstituted esters with greatly varying water solubilities and lipophilicities with retainment of the favorable enzymatic hydrolysis (Bundgaard and Nielsen, 1987; Nielsen and Bundgaard, 1988). This is illustrated by the solubility and partition data for some of the esters given in Table 3. Thus, the naproxen esters show different solubility and lipophilicity characteristics but they are all hydrolyzed with a half-life of less than 2 min in human plasma. It is of interest to note that the ethyl ester has a much poorer water solubility than the glycolamide esters. The same is seen for the salicylic acid esters.

The availability of a free hydroxyl group in esters like compounds **Ve** and **Vf** makes it possible to further modify the physicochemical properties, e.g. by esterification with an amino acid as has been shown for a benzoic acid ester (Nielsen and

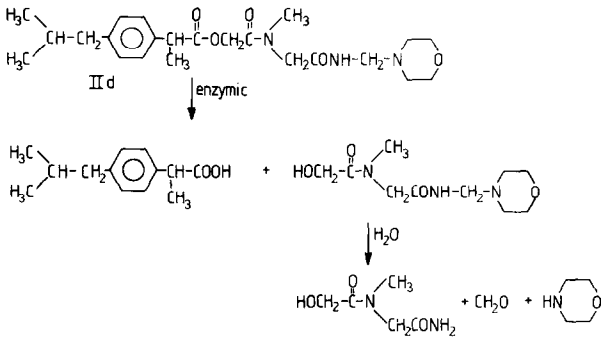
TABLE 3

Aqueous solubility (S) and partition coefficients (P) of various non-steroidal anti-inflammatory acids and their esters

Compound [a]	S (mg·ml^{-1})	log P [b]
Salicylic acid **I**	2.1 [c]	2.21 [d]
ester **Ib**	4.4	1.21
ester **Ic**	0.70	1.99
ester **Id**	6.3	0.86
methyl ester	0.64	2.36
Ketoprofen **IV**	0.23 [c]	
ester **IVc**	1.45	
Ibuprofen **II**	0.064 [c]	
ester **IIc**	0.13	
Naproxen **VI**	0.016 [c]	3.51 [d]
ester **Va**	0.034	2.06
ester **Vb**	0.004	2.05
ester **Vc**	0.012	3.32
ester **Vd**	0.059	1.37
ester **Ve**	0.14	2.01
ester **Vf**	0.41	1.70
ethyl ester	0.0012	3.51

[a] The structure of the esters is given in Table 1.
[b] P is the partition coefficient between octanol and 0.05 M phosphate buffer (pH 7.4).
[c] Solubility in 0.01 M hydrochloric acid at 21° C. The other solubility data refer to solubilities in 0.05 M phosphate buffer (pH 7.4) at 21° C.
[d] Partition coefficients between octanol and 0.01 M hydrochloric acid.

Bundgaard, 1988). Similarly, the terminal amide group in the glycolamide esters derived from sarcosinamide (e.g. compounds **IIc**, **IVc** and **Vd**) can be used as a handle to modify the physicochemical properties with retainment of a high rate of enzymatic hydrolysis. This is demonstrated with compound **IId** which is an *N*-Mannich base derivative of compound **IIc**. Due to the morpholino group compound **IId** is a weak base (pK_a 5.6) which readily forms an acid addition salt. The hydrochloride salt of compound **IId** has a water solubility greater than 10% w/v. It was found to be hydrolyzed to yield the parent ibuprofen in 80% plasma solutions almost as rapidly ($t_{1/2} = 10.8$ min) as the parent ester **IIc** ($t_{1/2} = 9.6$ min) (Scheme 2). According to previous studies on the hydrolysis of *N*-Mannich bases (Bundgaard and Johansen, 1980a and b) the morpholino *N*-Mannich base moiety of compound **IId** is subsequently hydrolyzed non-enzymatically to



Scheme 2.

yield morpholine, formaldehyde and the sarcosineamide derivative as depicted in Scheme 2.

Conclusion

In conclusion, esterification of various non-steroidal anti-inflammatory drugs containing a carboxylic acid function has been shown to be a potentially useful approach to obtain prodrug derivatives of these agents. In contrast to simple alkyl esters, the glycolamide esters described herein have a high capacity to release the parent active drugs under conditions similar to those prevailing in vivo. Furthermore, it is feasible to select glyco-

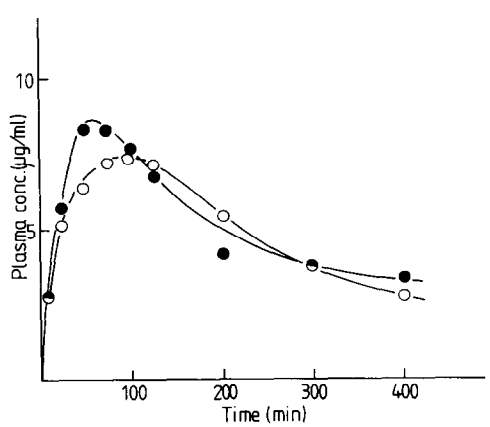


Fig. 5. Plasma concentrations of naproxen in rabbits following peroral administration of naproxen (○) and the naproxen glycolamide ester **Vf** (●) in amounts corresponding to 4.8 mg/kg of naproxen.

lamide esters with physicochemical properties favorable for e.g. peroral or topical absorption with retainment of a high enzymatic/non-enzymatic hydrolysis index. Thus, a limited experiment in rabbits with the naproxen ester **Vf** has shown that this ester is as efficiently absorbed as naproxen itself following oral administration (Fig. 5). No measurable concentrations ($< 0.1\ \mu g\ ml^{-1}$) of intact naproxen ester were observed, indicating very rapid ester hydrolysis in vivo in accordance with the in vitro plasma hydrolysis data.

Studies to reduce the gastrotoxicity of various NSAI drugs with full retainment of their therapeutic effects are certainly wanted. Studies are also in progress to examine the utility of glycolamide ester prodrugs of some NSAI drugs to improve their topical absorption.

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