International Journal of Pharmaceutics, 37 (1987) 87–95
Elsevier

IJP 01243

Prodrug forms for the sulfonamide group. I. Evaluation of *N*-acyl derivatives, *N*-sulfonylamidines, *N*-sulfonylsulfilimines and sulfonylureas as possible prodrug derivatives *

Jørn Drustrup Larsen and Hans Bundgaard

The Royal Danish School of Pharmacy, Department of Pharmaceutical Chemistry AD, Copenhagen (Denmark)

(Received 17 November 1986)
(Accepted 19 December 1986)

Key words: Prodrug; Sulfonamide; Stability; Enzymatic hydrolysis

Summary

Several derivatives of model sulfonamides were prepared and evaluated as potential prodrug forms for the sulfonamide group occurring in several drugs such as diuretics and carbonic anhydrase inhibitors. The derivatives studied included *N*-acyl and *N*-alkoxycarbonyl derivatives, *N*-sulfonylamidines, sulfonylureas, an *N*-sulfonyl sulfilimine and an *N*-sulfonyl sulfoximine. The stability characteristics of the derivatives was examined in aqueous solution at various pH values as well as in the presence of human plasma and rat liver homogenate. The results obtained showed that *N*-sulfonylamidines and sulfonylureas are too stable to be considered as potentially useful prodrug forms. *N*-Acyl and *N*-alkoxycarbonyl derivatives of primary sulfonamides also proved very resistant to undergo chemical or enzymatic hydrolysis whereas *N*-acyl derivatives of secondary sulfonamides are easily hydrolyzed enzymatically. Since *N*-alkylated sulfonamides are known to undergo dealkylation in vivo a promising prodrug approach for a primary sulfonamide involving both *N*-alkylation and *N*-acylation was suggested. *N*-Sulfonyl sulfilimes may also represent a potentially useful prodrug type for the sulfonamide group as assessed on the basis of the hydrolytic and enzymatic lability observed for *N*-*p*-toluenesulfonyl dimethylsulfilimine.

Introduction

A promising approach to improve drug delivery is chemical transformation of the active drug substances into per se inactive derivatives (prodrugs) which convert to the parent compounds by virtue of enzymic or chemical lability within the body system (Bundgaard, 1985b). A basal requisite for this prodrug approach is the ready availability of chemical derivative types satisfying the prodrug requirements, the most prominent of these being reconversion of the prodrug to the parent drug in vivo. Although several types of bioreversible derivatives have been exploited for utilization in designing prodrugs of various functional groups or entities occurring in a variety of drug molecules (for a recent review, see Bundgaard, 1985a), surprisingly few bioreversible derivatives for the sulfonamide group have been explored. In fact, the only described prodrug derivatives appear to

* This paper is part 64 of the series: Prodrugs as drug delivery systems (see Bundgaard and Nielsen, 1987).

Correspondence: H. Bundgaard, The Royal Danish School of Pharmacy, Department of Pharmaceutical Chemistry AD, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

be *N*-Mannich bases (Bundgaard and Johansen, 1980a–c) which, however, are highly unstable in aqueous solution.

Examples of drugs containing a sulfonamide group are numerous and include e.g. antibacterial agents, diuretics like furosemide (frusemide) and chlorothiazide, and carbonic anhydrase inhibitors such as acetazolamide, ethoxzolamide, methazolamide and dichlorphenamide. Several of these drugs exhibit delivery problems which may be solved by the prodrug approach. This is especially apparent for the carbonic anhydrase inhibitors. These compounds are useful for the treatment of glaucoma but due to unfavourable aqueous solubility and lipophilicity characteristics they are not active when given topically and must be given orally or parenterally (Maren et al., 1983; Friedland and Maren, 1984). Systemic side effects severely limit this mode of therapy (Lichter et al., 1978; Friedland and Maren, 1984) and consequently, great activities are presently going on to find a new carbonic anhydrase inhibitor that would penetrate the cornea and be active in lowering intraocular pressure when topically administered to the eye (Schoenwald et al., 1984; Eller et al., 1985a and b; Stein et al., 1983; Maren et al., 1983; Lewis et al., 1984, 1986; Sugrue et al., 1985; Maren and Jankowska, 1985; Duffel et al., 1986).

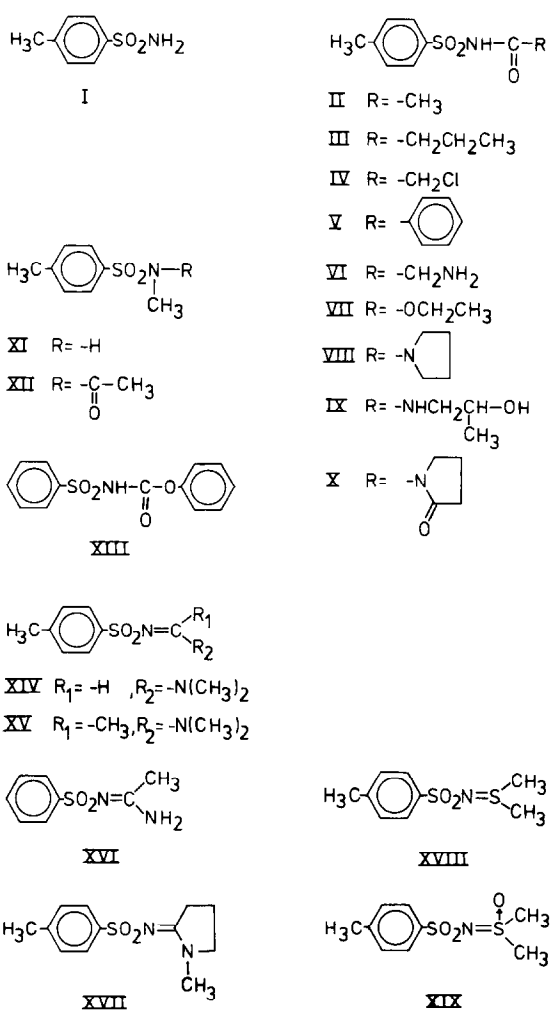

Fig. 1. Derivatives of benzenesulfonamide and *p*-toluenesulphonamide (see text).

An alternative approach to solve the delivery problems with these drugs may be the development of prodrug derivatives possessing enhanced corneal permeability characteristics and the ability to be reconverted to the parent active drug following the corneal passage. The major difficulty in using this approach is to find truly bioreversible derivatives and therefore, studies aiming to identify prodrug forms for the sulfonamide group have been initiated in our laboratories.

To this end, various derivatives of sulfonamide model substances such as *p*-toluenesulfonamide (Fig. 1, I) have been prepared and their capability to undergo conversion to the parent sulfonamide was examined. In the present paper the stability of a number of *N*-acyl derivatives (Fig. 1, II–VII, XII, XIII), sulfonylureas (VIII–X), *N*-sulfonylamidines (XIV–XVII), an *N*-sulfonyl sulfilimine (XVIII) and an *N*-sulfonyl sulfoximine (XIX) in aqueous solution and biological media is described.

Materials and Methods

Apparatus

Ultraviolet spectral measurements were performed with a Shimadzu UV-190 spectrophotometer equipped with a thermostatically controlled cell compartment, using 1-cm quartz cells. 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. 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 Chromosphere C18 (5-μm particles). Microanalyses were performed at the Microanalytical Department, University of Copenhagen.

Chemicals

p-Toluenesulfonamide and benzenesulfonamide were obtained from E. Merck, Darmstadt. *N*-Methyl-*p*-toluenesulfonamide was purchased from Aldrich. Chemicals and solvents used in the kinetic studies were of reagent grade.

Synthesis of sulfonamide derivatives

The derivatives investigated (Fig. 1, II–XIX have all previously been described in the literature. Table 1 lists the references to the procedures which were used in the preparation of the compounds. The melting points observed were in good agreement with those reported.

TABLE 1

Melting points and references to procedures used in the preparation of various sulfonamide derivatives

Compound	Melting point (°C)	Reference
II	136–137	Fowkes and McClelland (1945)
III	81– 82	Kemp and Stephen (1948)
IV	97– 98 (98–99) [a]	Abderhalden and Riesz (1931)
V	147–147.5	Kemp and Stephen (1948)
VI	212–213	Abderhalden and Riesz (1931)
VII	81– 82 (80–82) [b]	Billeter (1904)
VIII	214–215	Reppe (1955)
IX	134–135	Nagasawa et al. (1985)
X	153–154	Reppe (1955)
XII	57– 58	Chaplin and Hunter (1937)
XIII	125–126	Billeter (1904)
XIV	133–134	Logemann and Artini (1957)
XV	122–123	Logemann and Artini (1957)
XVI	120–121	Chua et al. (1974)
XVII	163–164	King (1960)
XVIII	157–158	King (1960)
XIX	169–170	Ohashi et al. (1971)

[a] Wieland and Hennig (1960).
[b] Gensler et al. (1971).

Kinetic studies

The degradation of the sulfonamide derivatives was studied in aqueous buffer solutions at 37 or 60 °C. Hydrochloric acid, acetate, phosphate, borate, carbonate and sodium hydroxide buffers were used; the total buffer concentration was generally 0.02 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 degradation were followed by using a reversed-phase HPLC procedure. Mobile phase systems of 20–45% v/v methanol in 0.01 M acetate buffer of pH 4.0 were generally used. For compound XVI a solvent system consisting of methanol–acetonitrile–0.02 M KH_2PO_4 solution (9.5 : 9.5 : 81 v/v) was used and for compound XVIII a system consisting of methanol–acetonitrile–0.02 M KH_2PO_4 solution (2 : 1 : 17 v/v) was used. The flow rate was 0.3–1.2 ml/min and the column effluent was monitored at 215 nm. All the systems used enabled separation of the derivatives from their parent sulfonamides and other degradation products. The compounds were quantified by measuring the peak heights in relation to those of standards chromatographed under the same conditions. In the kinetic runs, the reactions were initiated by adding 100 μl of a stock solution of the compounds in ethanol or acetonitrile to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentration of the compounds being $5 \cdot 10^{-4}$–$5 \cdot 10^{-5}$ M. The solutions were kept in a water bath at 37 or 60 °C and at appropriate intervals samples were taken and chromatographed. Pseudo-first-order rate constants for the degradation were determined from the slopes of linear plots of the logarithm of residual derivative against time.

The degradation of the *N*-sulfonylamidines XIV–XVII (Fig. 1) in sodium hydroxide solutions at 37 °C were also followed spectrophotometrically by monitoring the absorbance decrease at 230–240 nm. The reactions were performed in 2.5 ml aliquot portions of sodium hydroxide solutions

in a thermostated quartz cuvette and were initiated by adding 25 μl of stock solutions of the derivatives in acetonitrile to give a final concentration of about 4×10^{-5} M. Pseudo-first-order rate constants were calculated from the slopes of linear plots of log $(A_t - A_\infty)$ against time where A_t and A_∞ are the absorbance readings at times t and infinity, respectively.

Stability studies in biological media were performed in 0.01 M phosphate buffer (pH 7.4) containing either 80% human plasma or 20–30% rat liver homogenate (at 37 °C). Preparation of the liver homogenate was done as previously described (Buur and Bundgaard, 1985). The reactions were initiated by adding 50 μl of stock solutions of the derivatives to the preheated (37 °C) solutions, the initial concentration being about 5×10^{-4} M. At appropriate times samples of 250 μl were withdrawn and added to 1000 μl of methanol (for the plasma samples) or a mixture of 300 μl of 0.1 M $ZnSO_4$ solution and 50 μl of 70% perchloric acid (for the liver homogenate samples). After mixing and centrifugation for 2 min, 20 μl of the clear supernatant was subjected to HPLC analysis as described above.

Results and Discussion

Hydrolysis of N-acyl derivatives

The *N*-acyl derivatives of *p*-toluenesulfonamide or benzenesulfonamide (Fig. 1, II–VII, XIII) proved to be highly resistant to undergo hydrolysis in aqueous solution. Only by prolonged heating in 1 M sodium hydroxide or hydrochloric acid could a hydrolytic cleavage yielding the parent sulfonamide be detected. Some rate data are shown in Table 2. A slight enzymatic hydrolysis by human plasma was only observed in the case of *N*-butyryl-*p*-toluenesulfonamide (III) and the alkoxycarbonyl derivative (VII). When incubated at 37 °C in 0.05 M phosphate buffer solutions of pH 7.4 for 3 days no sign of degradation was observed for any of the *N*-acyl and *N*-alkoxycarbonyl derivatives. The observed greater enzymatic lability of the *N*-butyryl derivative relative to the *N*-acetyl derivative can be paralleled to previous findings on the metabolism of N^1-acylsulfanilamides in dogs (Robinson and Crossley, 1943). Whereas the N^1-acetyl derivative was excreted unchanged in the urine following peroral administration the N^1-butyryl derivative was hydrolyzed to about 85%. Similarly, Maren (1956) has reported that the *N*-butyryl derivative of acetazolamide is converted to acetazolamide in the dog whereas the corresponding *N*-acetyl derivative is not.

TABLE 2

Rate data for the hydrolysis of various sulfonamide derivatives at 37 °C

Compound	Half-lives		% Degradation in 80% human plasma after 24 h
	1 M HCl	1 M NaOH	
II	2.3 h	48 h	<1
III	7.1 h	> 50 h	40
IV	–	> 50 h	<1
V	160 h	> 100 h	<1
VI	–	> 100 h	<1
VII	148 h	> 100 h	10
VIII	–	–	<1

The *N*-acetyl derivative (XII) of *N*-methyl-*p*-toluenesulfonamide (XI) was found to be much more labile than the corresponding derivative of unsubstituted *p*-toluenesulfonamide (II). It was readily hydrolyzed in neutral and alkaline aqueous solution at 37 °C. HPLC analysis of the reaction solutions as well as of plasma solutions revealed a 100% conversion to the parent *N*-methyl-*p*-toluenesulfonamide. As seen from the pH-rate profile in Fig. 2 the hydrolysis is subject to specific base catalysis. At 37 °C and $\mu = 0.5$ a value of 185 M^{-1} min^{-1} was determined for the specific base catalytic rate constant k_{OH} by means of the following rate equation:

$$k_{obs} = k_{OH} a_{OH} \quad (1)$$

where a_{OH} is the hydroxide ion activity. This was calculated from the measured pH as described by Harned and Hamer (1933).

The hydrolysis of compound XII (Fig. 1) was markedly catalyzed by human plasma enzymes. Thus, in 80% human plasma solution of pH 7.4 and at 37 °C the compound disappeared rapidly

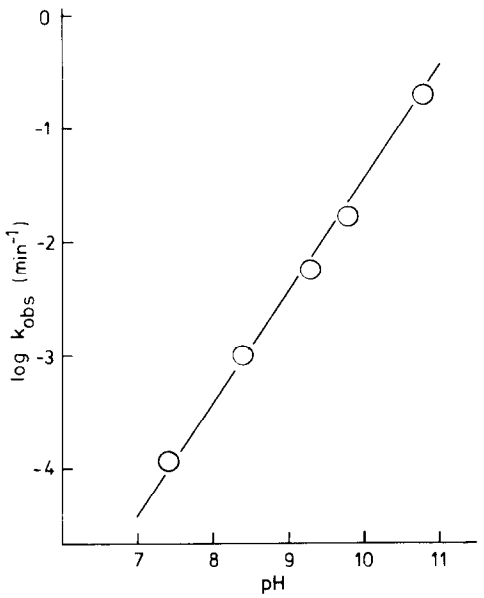

Fig. 2. The pH-rate profile for the hydrolysis of *N*-acetyl-*N*-methyl-*p*-toluenesulfonamide (XII) in aqueous solution at 37 °C.

according to first-order kinetics (Fig. 3), the half-life being 29 min. In pure buffer solution of pH 7.4 and at 37 °C the half-life of hydrolysis was found to be 102 h.

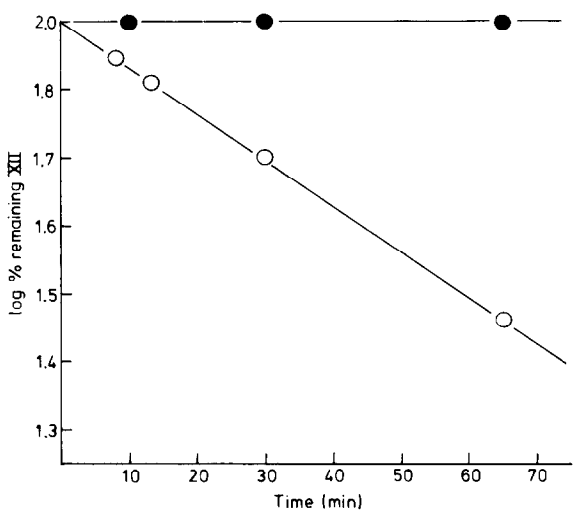

Fig. 3. Plots showing the rate of hydrolysis of *N*-acetyl-*N*-methyl-*p*-toluenesulfonamide (XII) in 0.05 M phosphate buffer solution of pH 7.4 (●) and in 80% human plasma solution (○) at 37 °C.

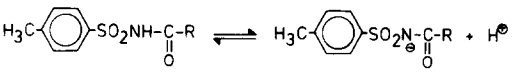

Fig. 4. Dissociation of *N*-acetylsulfonamides.

This difference in both chemical and enzymatic lability of *N*-acyl derivatives of unsubstituted sulfonamide and *N*-methylsulfonamide can be ascribed to the difference in acidic character of the derivatives. Whereas *N*-acyl derivatives of unsubstituted sulfonamides like II (Fig. 4) are weak acids with a pK_a value of 4–5 (Openshaw and Spring, 1945) those of *N*-alkylsulfonamides like XII are neutral compounds. Thus, the former derivatives are fully ionized in neutral and basic solutions, thereby rendering them more resistant to undergo hydroxide ion- or enzyme-catalyzed hydrolysis.

Hydrolysis of tolylsulfonylureas (Fig. 1, VIII–X)

Not unexpectedly the sulfonylurea derivative VIII proved quite resistant to undergo hydrolysis in 1 M hydrochloric acid or 1 M sodium hydroxide solutions at 37 °C. Incubation for 24 h at 37 °C in plasma solution revealed likewise no sign of decomposition. The cyclic acylated sulfonylurea derivative X was, on the other hand, hydrolyzed in aqueous solution. In 0.1 M sodium hydroxide it showed a half-life of 35 min and in 1 M hydrochloric acid a half-life of 65 h (at 37 °C). In 80% human plasma at 37 °C a half-life of hydrolysis of about 200 h was observed. However, HPLC analysis of the reaction solutions revealed no formation of *p*-toluenesulfonamide but instead showed the appearance of an unknown product. Most likely this product is a carboxylic acid arising from hydrolysis of the pyrrolidone moiety in compound X (Fig. 5).

Compound IX was studied in view of the state-

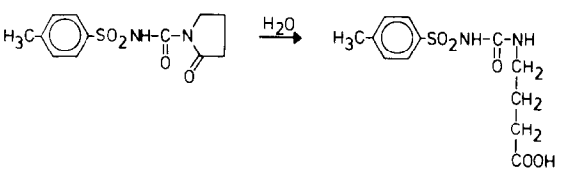

Fig. 5. Conversion of substance X.

ment (Thomas and Judy, 1972) that the corresponding derivative 1-(*p*-chlorophenylsulfonyl)-3-(2-hydroxypropyl)urea, a metabolite of chlorpropamide, is unstable in acidic solution (below pH 4). No data were given, however, except for hydrolysis in 6 M hydrochloric acid at 120 °C. In our experiments compound IX turned out to be highly stable. No degradation was observed following treatment with 1 M sodium hydroxide or 1 M hydrochloric acid at 37 °C for 2 days or by incubation in 80% human plasma or 30% rat liver homogenate for 24 h.

Hydrolysis of N-p-toluenesulfonyl dimethylsulfilimine (Fig. 1, XVIII)

The derivative XVIII was found to hydrolyze relatively easily in aqueous solution even at neutral pH. Therefore, the hydrolysis was studied in detail in the pH range 0–13 at 60 °C. At constant pH the disappearance of the derivative followed strict first-order kinetics over several half-lives. As determined by HPLC the compound was quantitatively hydrolyzed to yield *p*-toluenesulfonamide, the other degradation product being dimethylsulfoxide (Fig. 6).

The influence of pH on the observed pseudo-first-order rate constants, k_{obs}, is shown in Fig. 7 where log k_{obs} is plotted against pH. As seen from Fig. 7 the pH-rate profile is U-shaped, indicating the occurrence of specific acid and base catalysis as well as a spontaneous or water-catalyzed reaction according to the following expression:

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

where a_H and a_{OH} refer to the hydrogen ion and hydroxide ion activity, respectively. Values of the second-order rate constants for the specific acid- (k_H) and specific base- (k_{OH}) -catalyzed hydrolysis were determined from the straight-line portions of the pH-rate profile at low and high pH values, respectively, whereas the value of the first-order

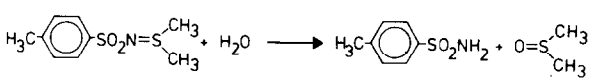

Fig. 6. Conversion of substance XVIII.

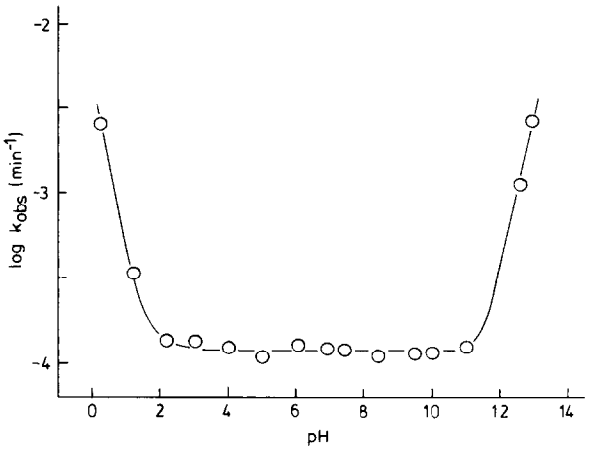

Fig. 7. The pH-rate profile for the hydrolysis of *N-p*-toluenesulfonyl dimethylsulfilimine (XVIII) in aqueous solution at 60 °C.

rate constant for spontaneous hydrolysis (k_0) was obtained from the rate data in the pH range 3–10. The following values were obtained (at 60 °C):

$$k_H = 7.2 \times 10^{-3} M^{-1} \text{ min}^{-1}$$

$$k_{OH} = 5.0 \times 10^{-3} M^{-1} \text{ min}^{-1}$$

$$k_0 = 2.1 \times 10^{-4} \text{ min}^{-1}$$

At 37 °C and pH 7.4 the half-life for the hydrolysis of compound XVIII was found to be 86 h. The hydrolysis was not catalyzed significantly by plasma enzymes since in 80% human plasma solutions at 37 °C a half-life of 80 h was observed. The hydrolysis was, however, markedly catalyzed by liver enzymes. Thus, in 20 and 30% rat liver homogenates at 37 °C half-lives of 9.4 h and 4.0 h, respectively, were found. This catalysis does not involve oxidation of the sulfur atom to give the corresponding sulfoximine XIX (Fig. 1) since this compound was found to be more stable than the sulfilimine XVIII. Thus, less than 1% decomposition of XIX was observed following incubation in 1 M hydrochloric acid, 1 M sodium hydroxide and 0.05 M phosphate buffer (pH 7.4) solutions for 24 h at 60 °C. The greater stability of the sulfoximine relative to the sulfilimine may most likely be ascribed to resonance stabilization of the N–S bond through the oxygen atom.

TABLE 3

Rate data for the hydrolysis of various N-sulfonylamidines at 37 °C

Compound	Half-lives		% Degradation in 80% human plasma after 24 h
	1 M HCl	0.1 M NaOH	
XIV	631 min	2.1 min	<1
XV	818 min	50 min	<1
XVI	24 min	16 min	<1
XVII	>100 h	400 min	<1

Hydrolysis of N-sulfonylamidines

The N-sulfonylamidines XIV–XVII (Fig. 1) were found to undergo specific acid- and base-catalyzed hydrolysis in aqueous solution. Rate data for the hydrolysis in strong acid and alkaline solutions are given in Table 3. At physiological pH the compounds were only slowly hydrolyzed. Thus, the half-life of hydrolysis of the most reactive derivative, XIV, at pH 7.4 and 60 °C was 184 h. As seen from Table 3 no appreciable hydrolysis took place in human plasma solutions in 24 h. Likewise, incubation in 30% rat liver homogenate for 24 h revealed no degradation of the compounds.

The degradation of the *N*-sulfonylamidines was found to result in the formation of both the parent sulfonamide and *N*-acyl sulfonamide, the relative amounts being dependent on pH. HPLC analysis was used to identify the compounds. To illustrate the degradation behaviour the time courses for compound XV and its degradation products in acidic and alkaline solutions are shown in Fig. 8. The pathway leading to the *N*-acyl derivative is dominating. In acidic solution the initially formed *N*-acetyl derivative (II) is subsequently hydrolyzed to yield *p*-toluenesulfonamide as seen from Fig. 8A. The first step of the *N*-sulfonylamidine hydrolysis is most likely hydration (Chen et al., 1986). The hydrated species are then degraded by two routes as shown in Fig. 9 for compound XV.

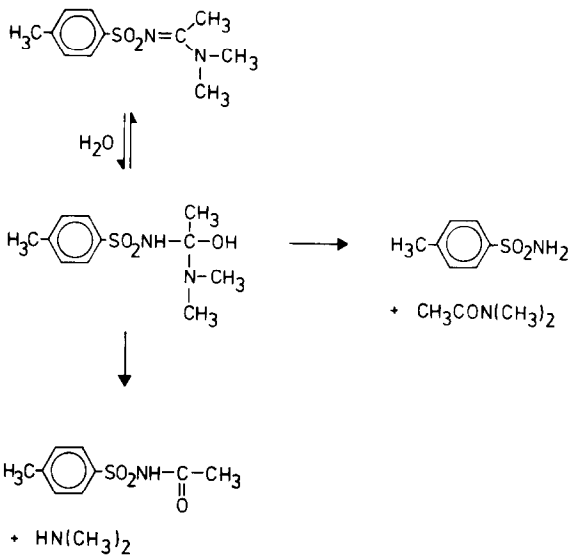

Fig. 9. Degradation pathways of an *N*-sulfonylamidine.

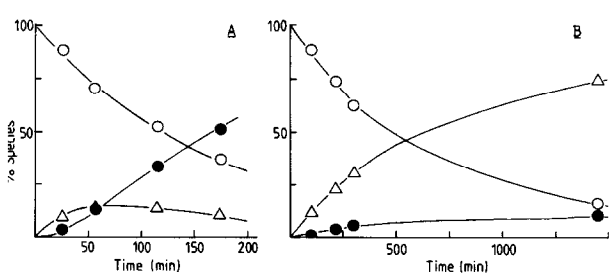

Fig. 8. Time courses for compound XV (○), compound I (●) and compound II (△) during hydrolysis of the *N*-sulfonylacetamidine (XV) in 1.0 M hydrochloric acid (A) and 0.02 M carbonate buffer of pH 10.3 (B) at 60 °C.

Conclusions

In assessing the potential utility of the derivatives examined as prodrug forms for the sulfonamide group the principal requirement to be considered is the ability of the derivatives to be reconverted to the parent sulfonamide in vivo. From the results obtained the following conclusions can be made regarding the various derivative types studied:

N-Sulfonylamidines and sulfonylureas are too stable, both chemically and enzymatically, to be considered as potentially useful prodrug forms. In addition, the *N*-sulfonylamidines are not cleaved quantitatively to the parent sulfonamide.

N-Sulfonyl sulfilimines are hydrolyzed quantitatively to yield the parent sulfonamide in aqueous solution but at a rather slow rate at physiological conditions of pH and temperature. The hydrolysis is not accelerated by plasma enzymes but the observed marked catalysis by liver enzymes indicates that this derivative type deserves further consideration as a possible prodrug form.

N-Acyl and *N*-alkoxycarbonyl derivatives of primary sulfonamides are very stable in aqueous solutions. Although the hydrolysis of some derivatives, especially the N-butyryl derivative, is catalyzed by plasma enzymes the derivatives appear to be too stable to be considered as promising prodrug forms. *N*-Acyl derivatives of secondary sulfonamides, on the other hand, show highly favourable hydrolysis characteristics. As demonstrated for the *N*-acetyl derivative of *N*-methyl-*p*-toluenesulfonamide, a rapid and quantitative hydrolysis takes place in the presence of human plasma at pH 7.4 and 37 °C. Based on this finding *N*-acyl derivatives show great promise as prodrug forms for compounds containing a secondary sulfonamide group. However, since *N*-alkylated sulfonamides may undergo dealkylation in vivo (Maren, 1956; Duffel et al., 1986) *N*-acylation may also become a useful approach for primary sulfonamides when combined with *N*-alkylation. Enzymatic reactions involving deacylation followed by dealkylation should thus lead to the parent primary sulfonamide as illustrated in Fig. 10. Considering the possibility of improving ocular delivery characteristics of carbonic anhydrase inhibitors by such a prodrug approach a recent report by Duffel et al. (1986) is of great interest in that it was found that ocular tissues are capable of metabolizing *N*-methylacetazolamide to acetacolamide. Accordingly, by appropriate acylation of *N*-methylacetazolamide it should be feasible to obtain prodrug forms of acetazolamide with varying physicochemical properties of primary importance for drug delivery such as water-solubility and lipophilicity. Other possibilities of obtaining bioreversible derivatives of sulfonamides are presently being studied in our laboratory and the results will be communicated in a later paper.

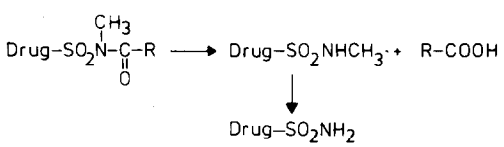

Fig. 10. Deacylation and dealkylation of *N*-methyl-*N*-acylsulfonamides.

References

Abderhalden, E. and Riesz, E., Vergleichende Untersuchungen über die Spaltbarheit der CO-NH-Bindung in Polypeptiden und verwandten Verbindungen, deren NH_2-bzw. COOH-gruppe mit verschiedenen Substituented besetzt ist, durch verdünntes Alkali, Erepsin und Trypsin-Kinase. *Z. Fermentforsch.*, 12 (1931) 180–222.

Billeter, O.C., Ueber die Einwirkung von cyansaurem Silber auf Säurechloride. *Chem. Ber.*, 37 (1904) 690–696.

Bundgaard, H. (Ed.), *Design of Prodrugs*, Elsevier, Amsterdam, 1985a.

Bundgaard, H., Design of prodrugs: bioreversible derivatives for various functional groups and chemical entities. In Bundgaard, H. (Ed.), *Design of Prodrugs*, Elsevier, Amsterdam, 1985b, pp 1–92.

Bundgaard, H. and Johansen, M., Prodrugs as drug delivery systems. IV. N-Mannich bases as potential novel prodrugs for amides, ureides, amines and other NH-acidic compounds. *J. Pharm. Sci.*, 69 (1980a) 44–46.

Bundgaard, H. and Johansen, M., Prodrugs as drug delivery systems. X. N-Mannich bases as novel prodrug candidates for amides, imides, urea derivatives, amides and other NH-acidic compounds. Kinetics and mechanism of decomposition and structure–reactivity relationships. *Arch. Pharm. Chem. Sci. Ed.*, 8 (1980b) 29–52.

Bundgaard, H. and Johansen, M., Prodrugs as drug delivery systems. XV. Bioreversible derivatization of phenytoin, acetazolamide, chlorzoxazone and various other NH-acidic compounds by N-aminomethylation to effect enhanced dissolution rates. *Int. J. Pharm.*, 7 (1980c) 129–136.

Bundgaard, H. and Nielsen, N.M., Esters of *N*,*N*-disubstituted 2-hydroxy-acetamides as a novel highly biolabile prodrug type for carboxylic acid agents. *J. Med. Chem.*, 30 (1987) 451–454.

Buur, A. and Bundgaard, H., Prodrugs of 5-fluorouracil. III. Hydrolysis kinetics in aqueous solution and biological media, lipophilicity and solubility of various 1-carbamoyl derivatives of 5-fluorouracil. *Int. J. Pharm.*, 23 (1985) 209–222.

Chaplin, H.O. and Hunter, L., The associating effect of the hydrogen atom. Part I. Amides and sulphonamides. *J. Chem. Soc.*, 1937, 1114–1118.

Chen, C.-M., Coppola, W.P., Johns W.H., Bogardus, J.B. and Lipper, R.A., Degradation kinetics and mechanism of N^6-[(dimethylamino)methylene] mitomycin C in aqueous solutions. *J. Pharm. Sci.*, 75 (1986) 208–210.

Chua, S.-O., Cook, M.J. and Katritzky, A.R., Substituent effects in tautomerism. Part I. Acyl- and sulphonylamidines. *J. Chem. Soc., Perkin Trans.*, II (1974) 546–552.

Duffel, M.W., Ing, I.S., Segarra, T.M., Dixson, J.A., Barfknecht, C.F. and Schoenwald, R.D., N-Substituted sulfonamide carbonic anhydrase inhibitors with topical effects on intraocular pressure, *J. Med. Chem.*, 29 (1986) 1488–1494.

Eller, M.G., Schoenwald, R.D., Dixson, J.A., Segarra, T. and Barfknecht, C.F., Topical carbonic anhydrase inhibitors III: optimization model for corneal penetration of ethoxzolamide analogues. *J. Pharm. Sci.*, 74 (1985a) 155–160.

Eller, M.G., Schoenwald, R.D., Dixson, J.A., Segarra, T., and Barfknecht, C.F. Topical carbonic anhydrase inhibitors IV: Relationship between excised corneal permeability and pharmacokinetic factors. *J. Pharm. Sci.*, 74 (1985b) 525–529.

Fowkes, F.S. and McClelland, E.W., The reaction of some arylsulphonylbenzisothiazolones with acetic anhydride and potassium acetate. *J. Chem. Soc.*, (1945) 405–407.

Friedland, B.R. and Maren, T.H., Carbonic anhydrase: Pharmacology of inhibitors and treatment of glaucoma. In Sears, M.L. (Ed.), *Handbook of Experimental Pharmacology, Vol. 69, Pharmacology of the Eye*, Springer, Heidelberg, 1984, pp. 279–310.

Gensler, W.J., Frank, F.J., Dheer, S.K. and Lauher, J.W., *N*-Monoalkylation of sulfonamides. *J. Org. Chem.*, 36 (1971) 4102–4105.

Harned, H.S. and Hamer, W.J., The ionization constant of water and the dissociation of water in potassium chloride solution from electromotive forces of cells without liquid junctions. *J. Am. Chem. Soc.*, 55 (1933) 2194–2206.

Kemp, A.D. and Stephen, H., The preparation of some *N*-substituted derivatives of *p*-toluenesulphonamide. *J. Chem. Soc.*, (1948) 110–112.

King, C., Some reactions of *p*-toluenesulfonyl isocyanate. *J. Org. Chem.*, 25 (1960) 352–356.

Lewis, R.A., Schoenwald, R.D., Eller, M.G., Barfknecht, C.F. and Phelps, C.D., Ethoxzolamide analogue gel. A topical carbonic anhydrase inhibitor. *Arch. Ophthalmol.*, 102 (1984) 1821–1824.

Lewis, R.A., Schoenwald, R.D., Barfknecht, C.F. and Phelps, C.D., Aminozolamide gel. A trial of a topical carbonic anhydrase inhibitor in ocular hypertension. *Arch. Ophthalmol.*, 104 (1986) 842–844.

Lichter, P.R., Newman, L.P., Wheeler, N.C. and Beall, O.V., Patient tolerance to carbonic anhydrase inhibitors. *Am. J. Ophthalmol.*, 85 (1978) 495–502.

Logemann, W. and Artini, D., Über die Einwirkung von *N*-Substituierten Säureamiden auf Isocyanate, I. *Chem. Ber.*, 90 (1957) 2527–2531.

Maren, T.H. Carbonic anhydrase inhibition. V. N^5-substituted 2-acetylamino-1,3,4-thiadiazole-5-sulfonamides: Metabolic conversion and use as control substances. *J. Pharmacol. Exp. Ther.*, 117 (1956) 385–401.

Maren, T.H., Jankowska, L., Sanyal, G. and Edelhauser, H.F., The transcorneal permeability of sulfonamide carbonic anhydrase inhibitors and their effect on aqueous humor secretion. *Exp. Eye Res.*, 36 (1983) 457–480.

Maren, T.H. and Jankowska, L., Ocular pharmacology of sulfonamides: the cornea as barrier and depot. *Curr. Eye Research*, 4 (1985) 399–408.

Nagasawa, H.T., Smith, W.E. and Kwon, C.-H., Acetylative cleavage of (arylsulfonyl)ureas to N-acetylarenesulfonamides and isocyanates. *J. Org. Chem.*, 50 (1985) 4993–4996.

Ohashi, T., Matsunaga, K., Okahara, M. and Komori, S., Novel synthesis of N-sulfonylsulfoximines and N-sulfonylsulfimines. *Synthesis*, (1971) 96.

Openshaw, H.T. and Spring, F.S., Preparation and properties of sulphonacetamides: a method for the separation of sulphonamides from N-alkylsulphonamides. *J. Chem. Soc.*, (1945) 234–236.

Reppe, W., Äthinylierung VI. *Liebigs Ann. Chem.*, 596 (1955) 158–224.

Robinson, E.J. and Crossley, M.L., The metabolism of N^1 – acylsulfanilamides in the dog. *Arch. Biochem.*, 1 (1943) 415–423.

Schoenwald, R.D., Eller, M.G., Dixson, J.A. and Barfknecht, C.F., Topical carbonic anhydrase inhibitors, *J. Med. Chem.*, 27 (1984) 810–812.

Stein, A., Pinke, R., Krupin, T., Glabb, E., Podos, S.M., Serle, J. and Maren, T.H., The effect of topically administered carbonic anhydrase inhibitors on aqueous humor dynamics in rabbits. *Am. J. Ophthalmol.*, 95 (1983) 222–228.

Sugrue, M.F., Gautheron, P., Schmitt, C., Viader, M.P., Conquet, P., Smith, R.L., Share, N.N. and Stone, C.A., On the pharmacology of 2-646,151: a topically effective ocular hypotensive carbonic anhydrase inhibitor. *J. Pharmacol. Exp. Ther.*, 232 (1985) 534–540.

Thomas, R.C. and Judy, R.W., Metabolic fate of chlorpropamide in man and in the rat. *J. Med. Chem.*, 15 (1972) 964–968.

Wieland, T. and Hennig, H.J., Aminosäure-sulfimide. *Chem. Ber.*, 93 (1960) 1236–1246.