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Hydrolysis of N-(α-hydroxybenzyl)benzamide and other N-(α-hydroxyalkyl)amide derivatives: implications for the design of N-acyloxyalkyl-type prodrugs

Hans Bundgaard and Marianne Johansen

The Royal Danish School of Pharmacy, Departments of Pharmaceutical Chemistry AD and Pharmaceutics, DK-2100 Copenhagen (Denmark)

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Summary

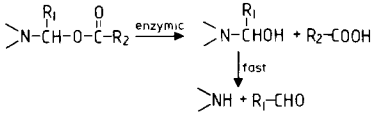
N-Acyloxyalkylation has become a commonly used approach to obtain prodrug forms of various NH-acidic drug substances. The regeneration of the parent drug occurs via a two-step reaction, enzymatic cleavage of the ester grouping followed by spontaneous decomposition of the N-hydroxyalkyl intermediate. The usefulness of this approach depends on the rate of decomposition of the latter intermediate and for several compounds such as amides their N-hydroxymethyl derivatives are too stable to make the approach useful. In this work the kinetics of decomposition of various N-α-hydroxyalkyl compounds derived from benzamide, thiobenzamide and various aldehydes (benzaldehyde, acetaldehyde and chloral) in aqueous solution at 37 °C was determined and compared with that for the corresponding N-hydroxymethyl compounds derived from formaldehyde. All compounds showed apparent specific base catalysis and for N-(α-hydroxybenzyl)benzamide, specific acid catalysis was also observed. The derivatives were much more unstable at physiological conditions of pH and temperature than the N-hydroxymethyl derivatives; thus, whereas the half-life of decomposition of N-(hydroxymethyl)benzamide is 183 h at pH 7.4 and 37 °C the half-life for N-(α-hydroxybenzyl)benzamide is only 6.5 min under the same conditions. The latter compound appears to be the first reported N-alkylol amide derived from an aromatic aldehyde and its synthesis is described. It

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

is concluded that N-acyloxyalkylation may be a useful means of obtaining prodrug forms of also weakly NH-acidic compounds if the (acyloxy)alkyl α-halide normally used for the N-acyloxyalkylation is prepared from other aldehydes than formaldehyde, e.g. benzaldehyde.

Introduction

In recent years N-acyloxyalkylation has become a commonly used approach to obtain bioreversible derivatives (prodrugs) of various amides, imides, hydantoins, uracils, tertiary or N-heterocyclic amines and other NH-acidic compounds (Bodor, 1979, 1981; Pitman, 1981; Bundgaard, 1982). The usefulness of this approach stems from the fact that by varying the acyl portion of the derivatives it is possible to control the rate of regeneration of the parent drug and to obtain prodrugs with varying physicochemical properties such as water-solubility or lipophilicity. Whereas the derivatives show good stability in aqueous solution in vitro, they are in general rapidly cleaved in vivo by virtue of enzyme-mediated hydrolysis. The regeneration of the parent NH-acidic drug takes place via a two-step reaction (Scheme 1). Enzymatic cleavage of the ester grouping results in the formation of an N-hydroxyalkyl derivative which subsequently is assumed to decompose instantaneously into the corresponding aldehyde and the NH-acidic drug. Thus, the rate of drug formation is solely dependent on the rate of the initial ester cleavage, which can be controlled by steric and electronic factors.



Scheme 1

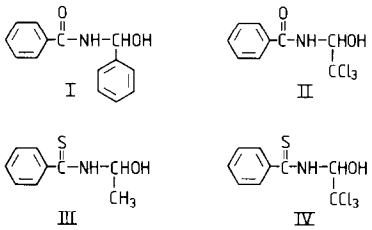
The most commonly used acyloxyalkyl derivatives are acyloxymethyl compounds, i.e. derivatives from which formaldehyde is released from an N-hydroxymethyl intermediate. Kinetic studies on the decomposition of a large number of N-hydroxymethyl derivatives have shown that these are cleaved quantitatively to formaldehyde and the parent NH-acidic compound in aqueous solution (Johansen and Bundgaard, 1979; Bundgaard and Johansen, 1980). The reaction rates were found to be directly proportional to the hydroxide ion concentration in neutral and weakly basic solutions and to increase sharply with increasing acidity of the parent NH-acidic compound. The following structure–reactivity relationship was established (Bundgaard and Johansen, 1980) for a variety of NH-acidic compounds including several carboxamides, hydantoins, thiobenzamide, succinimide and a carbamate:

$$\log t_{1/2} = 0.77\ pK_a - 8.34 \qquad (r = 0.986;\ n = 9) \tag{1}$$

where $t_{1/2}$ is the half-life for hydrolysis at pH 7.4 and 37 °C (in min) and pK_a refers

to the ionization constant of the parent NH-acidic compound. This relationship allows one to predict the reactivity of an N-hydroxymethyl derivative solely from a knowledge of the pK_a of the parent compound. Thus, it can be predicted that the requirement for a half-life of decomposition of less than 1 h at pH 7.4 and 37 °C is that the parent NH-acidic compound possesses a pK_a value of less than 13.1 or that a pK_a value of less than 10.8 is required for a half-life of less than 1 min. From this it is readily evident that N-acyloxymethylation is not a universally applicable approach to bioreversible derivatization of NH-acidic compounds but is limited to compounds possessing a pK_a value of less than about 10.5–11 when the requirement is to be fulfilled—that the intermediate N-hydroxymethyl derivative should only have a transistory existence in the overall process of drug release as outlined in Scheme 1. For example, N-hydroxymethyl derivatives of carboxamides (pK_a 14–15) are relatively stable at physiological conditions of pH and temperature, the half-lives for decomposition of the derivatives of, e.g., benzamide and nicotinamide being 183 and 37 h, respectively, at pH 7.4 and 37 °C (Johansen and Bundgaard, 1979).

In order to expand the usefulness of N-acyloxyalkylation as a means of obtaining prodrug forms of drugs containing NH-acidic moieties information is needed about the reactivity of N-hydroxyalkyl derivatives other than those derived from formaldehyde, i.e. N-hydroxymethyl derivatives. The purpose of the present work is to provide such information by describing the kinetics of hydrolysis of some N-hydroxyalkyl compounds (I–IV) derived from benzamide, thiobenzamide and various aldehydes (acetaldehyde, benzaldehyde and chloral).



Materials and Methods

Ultraviolet spectral measurements were performed with a Shimadzu UV-190 spectrophotometer equipped with a thermostated cell compartment. 1-cm quartz cells were used. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. Nuclear magnetic resonance (NMR) data were obtained using a Varian Type EM-360 L spectrometer. Infrared spectra were recorded using the potassium chloride disc technique on a Unicam SP 200 spectrophotometer. Melting points were taken on a capillary melting-point apparatus and are uncorrected. High-performance liquid chromatography (HPLC) was done with a Spectra-Physics Model 3500B instrument equipped with a variable wavelength detector and a 10-μl loop injection valve. A column, 250×4 μm, packed with Lichrosorb RP-8 (7 μm) (E. Merck, F.R.G.) was used.

Preparation of the N-α-hydroxyalkyl amide derivatives (I–IV)

N-(α-Hydroxybenzyl)benzamide (I) was prepared by hydrolysis of N-(α-morpholinobenzyl)benzamide (V). The latter compound was obtained in the following way, adopted from Macovski and Backmeyer (1944). Benzaldehyde (4.35 g, 0.041 mol) and morpholine (4.2 g, 0.048 mol) were added to a solution of benzamide (5 g, 0.041 mol) in methanol (50 ml). The reaction solution was kept in a water-bath at 37 °C for 2 days and cooled to about 5 °C. Upon addition of water (about 50 ml) and standing at 5 °C overnight compound V precipitated from the mixture as large needles. It was filtered off and recrystallized from ethanol, m.p. 166–167 °C, reported m.p. 166–167 °C, (Sekiya and Sakai, 1969). To prepare compound I, N-(α-morpholinobenzyl)benzamide (200 mg) was dissolved in 8 ml of ethanol and 0.1 M hydrochloric acid was added followed by 200 ml of water, the pH of the solution being adjusted to 4–4.5. The solution was kept at room temperature for 5 h with pH being maintained at 4–4.5. Upon standing overnight at 4 °C a precipitate was formed. It was filtered off, washed with water and dried in vacuo over phosphorous pentoxide to give 110 mg (72%) of pure title compound, m.p. 114–115 °C. Analysis: calculated for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%. Found: C, 74.08; H, 5.83; N, 6.09%. IR (KBr) ν: 3280, 1645 and 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.2 (2H, bs, NH and OH), 6.5–6.7 (1H, bd, CH) and 7.3–8.0 (10 H, bm, C_6H_5) ppm.

N-(α-Hydroxy-2,2,2-trichloroethyl)benzamide (II) was prepared by reacting benzamide with chloral as previously described (Jacobsen, 1881), m.p. 146–147 °C (from ethanol), reported m.p. 146 °C. N-(α-Hydroxyethyl)thiobenzamide (III) and N-(α-hydroxy-2,2,2-trichloroethyl)thiobenzamide (IV) were obtained as described by Böhme et al. (1974), m.p. (III) 109–110 °C, reported m.p. 109–110 °C; m.p. (IV) 115–116 °C, reported m.p. 114–115 °C.

Kinetic measurements

All rate studies were performed in aqueous buffer solutions at 37.0 ± 0.2 °C. The buffers used were hydrochloric acid, formate, acetate, phosphate, borate and carbonate buffers. A constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride.

The progress of the reactions was followed either by direct UV-spectrophotometry or by HPLC. In the former method absorbance changes were recorded at a wavelength where the absorption of substrate and products differed maximally. Reactions were performed in 2.5 ml aliquot portions of buffer solution in a thermostated quartz cuvette and were initiated by adding 25 µl of stock solutions of the derivatives in acetonitrile. The reaction rates for the thiobenzamide derivatives III and IV were determined in this manner by recording the absorbance increase at 310 nm, the initial substrate concentration being about 5×10^{-4} M. For the benzamide-chloral adduct (II) the decrease in absorbance at 240 nm during the decomposition was utilized, the initial concentration being about 5×10^{-3} M. In the case of compound I the rate of hydrolysis was followed by monitoring the increase in absorbance at 245 nm due to liberation of benzaldehyde (initial concentration about 6×10^{-5} M). Pseudo-first-order rate constants were determined from the

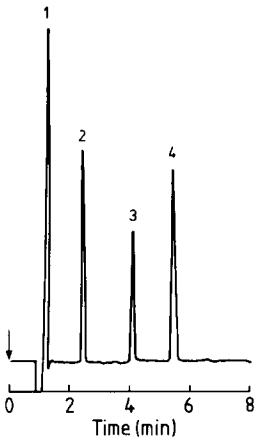


Fig. 1. Chromatogram of a partially degraded aqueous solution of compound I. Key: (1) solvent front: (2) benzamide; (3) benzaldehyde; (4) compound I.

slopes of linear plots of $\log(A_t - A_\infty)$ or $\log(A_\infty - A_t)$ vs time, where A_t and A_∞ are the absorbance readings at time t and infinity, respectively.

The rate of decomposition of compound I was also determined by using a reversed-phase HPLC procedure. The RP-8 column was eluted with a mixture consisting of 0.005 M acetate pH 4.5–methanol (1 : 1 v/v). The flow rate was 1.6 $ml \cdot min^{-1}$, and the column effluent was monitored at 230 nm. Under these conditions the N-hydroxybenzyl derivative (I) was separated from its products of decomposition, benzamide and benzaldehyde, and all 3 compounds could readily be determined (Fig. 1). Quantitation of the compounds was done from measurement of the peak heights in relation to those of standards chromatographed under the same conditions. Buffer solutions containing compound I at initial concentrations of about 0.015 $mg \cdot ml^{-1}$ were kept at 37 °C, and aliquots were removed at suitable intervals and chromatographed immediately. First-order rate constants for the hydrolysis were determined from the slopes of linear plots of the logarithm of the peak height due to the derivative against time. For reactions performed in 0.05 M phosphate buffer pH 7.40 containing 80% human plasma (at 37 °C), 200 μl samples were withdrawn at suitable intervals and added to 1000 μl of ethanol in order to deproteinize the plasma. After mixing and centrifugation for 2 min, 10 μl of the clear supernatant was analyzed by HPLC as described above.

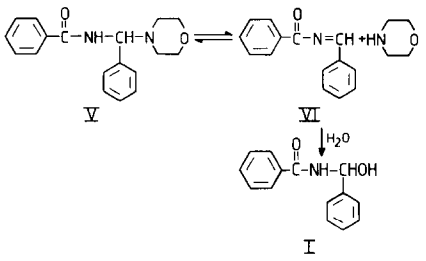
Results and Discussion

Availability of N-hydroxyalkyl derivatives

The lack of information on the stability of N-hydroxyalkyl derivatives of NH-acidic compounds (such as amides) other than N-hydroxymethyl derivatives may simply be due to the fact that the compounds are not readily synthesized. Whereas N-hydroxymethyl derivatives are easily prepared by reacting formaldehyde with the

NH-acidic compound in water, ethanol or another solvent (Johansen and Bundgaard, 1979; and references cited therein) most aliphatic and all aromatic aldehydes do not behave as formaldehyde does (Zaugg and Martin, 1965). The reaction with, e.g., amides usually does not stop at the N-alkylol stage, RCONHCHOHR′, but progresses further to the alkylidene- or arylidene-bisamide, $(RCONH)_2CHR'$. The only exceptions are the α-halogenated aldehydes such as chloral (e.g. Zaugg and Martin, 1965; LaRocca, 1961; Zinner et al., 1974) and also acetaldehyde toward thiobenzamide (Böhme et al., 1974). The present study is therefore limited to the known N-α-alkylol derivatives of benzamide with chloral (II) and those of thiobenzamide with acetaldehyde (III) and chloral (IV) but includes also the hitherto not described derivative of benzamide and benzaldehyde, N-(α-hydroxybenzyl)benzamide (I).

In agreement with the above noted, all attempts to prepare this compound by reacting benzamide with benzaldehyde in various solvents or using no solvents resulted in the formation of benzylidenebisbenzamide (VII) which has previously been characterized by Breuer et al. (1967). A study of the decomposition behaviour of N-Mannich bases of benzamide formed with benzaldehyde and various secondary amines revealed, however, the formation of a major degradation product in aqueous solution which proved to be N-(α-hydroxybenzyl)benzamide. N-(α-Morpholinobenzyl)benzamide (V, Scheme 2), in particular, was effectively degraded to compound I,



Scheme 2

in that kinetic studies showed a 100% conversion in aqueous solutions of pH 3–6. The decomposition most likely occurs as depicted in Scheme 2 with N-benzylidenebenzamide (VI) being an intermediate. In alkaline solutions where morpholine is in the free base form the hydrolysis of the N-Mannich base V did not follow first-order kinetics in contrast to that in acidic solutions and the rate of hydrolysis was inhibited by adding small amounts of morpholine to the reaction solutions (to be published elsewhere). This suggests the presence of an intermediate and the proposed compound (VI) has in fact previously been isolated by thermal decomposition of compound VII (Breuer et al., 1967) and has also been suggested to be an intermediate in the thermal decomposition of N-(α-morpholinobenzyl)benzamide (Chiacchio et al., 1983). As shown below the stability of compound I in aqueous solution is maximal at pH 4.5 and therefore, the conditions used for the formation and isolation of the compound as described in the Experimental section involved degradation of compound V at such pH value. It was separately shown that the half-life for the reaction V → I at pH 4.5 and 37 °C is about 2 min whereas the

subsequent hydrolysis of compound I exhibits a half-life of 37 h. Besides being in agreement with the given analytical and spectroscopic data the structure of compound I was confirmed by its degradation behaviour in aqueous solution. Using the HPLC method described above (cf. Fig. 1) the compound was found to be quantitatively converted to benzamide and benzaldehyde in solutions of pH 2–10.

It should already at this point be noted that although the availability of N-hydroxyalkyl derivatives other than those derived from formaldehyde is very limited this does not restrict a broad utility of N-acyloxyalkyl derivatives as prodrug forms. The reason is that besides being obtainable by esterification of the intermediate N-hydroxyalkyl derivative such derivatives are readily—and most often—obtained by reacting the NH-acidic drug substance with an α-acyloxyalkyl halide (e.g. Ozaki et al., 1978; Bodor, 1979; Bodor et al., 1980; Bodor, 1981). The latter compounds are easily available from the reaction of acid halides with a variety of aldehydes including, e.g., acetaldehyde and benzaldehyde besides formaldehyde (Adams and Vollweiler, 1918; French and Adams, 1921; Ulich and Adams, 1921; Bodor and Kaminski, 1980; Bodor et al., 1980).

Kinetics of hydrolysis

The kinetics of breakdown of the N-hydroxyalkylated amides (I–IV) was studied in aqueous solution at 37 °C over a wide range of pH. At constant pH and temperature the reactions displayed good first-order kinetics over several half-lives and all reactions proceeded to completion. Benzamide and benzaldehyde were formed in stoichiometric amounts from compound I as revealed by HPLC and for compounds whose breakdown was monitored by direct ultraviolet spectral measurements the spectra of the completed reaction solutions coincided exactly with those of the parent substances.

The rates of decomposition were found to be independent of buffer concentration from 0.02–0.1 M at constant ionic strength (Table 1). Thus, no significant general

TABLE 1

EFFECT OF VARYING BUFFER CONCENTRATION ON THE PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DECOMPOSITION OF N-HYDROXYALKYL DERIVATIVES OF BENZAMIDE AT 37 °C ($\mu = 0.5$)

Buffer		pH	k_{obs} (min^{-1})	
			Compound I	Compound II
Acetate	0.02 M	4.00	0.00089	
Acetate	0.10 M	4.00	0.00092	
Phosphate	0.02 M	6.15	0.0059	
Phosphate	0.05 M	6.15	0.0063	
Phosphate	0.10 M	6.15	0.0062	
Phosphate	0.02 M	7.40	0.10	0.0011
Phosphate	0.10 M	7.40	0.11	0.0010
Borate	0.02 M	9.01	4.0	0.041
Borate	0.10 M	9.01	4.0	0.039

acid–base catalysis appears to be involved which is also the case for the hydrolysis of N-hydroxymethyl derivatives (Johansen and Bundgaard, 1979).

The influence of pH on the hydrolysis rate is shown in Figs. 2–4, where the logarithms of the observed pseudo-first-order rate constants (k_{obs}) are plotted against pH. The pH–rate profile for compound I indicates the occurrence of specific acid- and base-catalyzed decomposition:

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

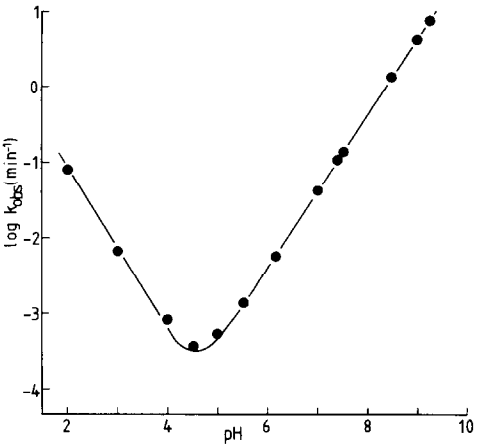


Fig. 2. The pH–rate profile for the decomposition of N-(α-hydroxybenzyl)benzamide (I) in aqueous solution at 37 °C and $\mu = 0.5$. The points are experimental while the curve is constructed on basis of Eqn. 2 and the rate constants given in Table 2.

Fig. 3.

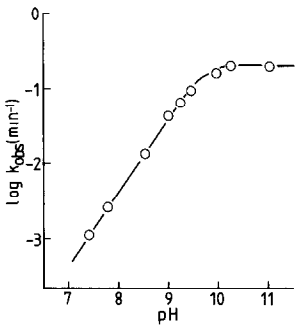


Fig. 3. The pH–rate profile for the decomposition of N-(α-hydroxy-2,2,2-trichloroethyl)benzamide (II) in aqueous solution at 37 °C and $\mu = 0.5$.

Fig. 4.

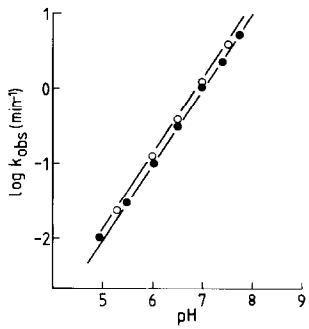
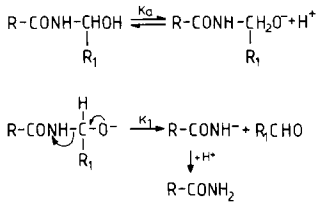


Fig. 4. Plots of the logarithm of the observed pseudo-first-order rate constants against pH for the decomposition of N-(α-hydroxyethyl)thiobenzamide (III) (●) and N-(α-hydroxy-2,2,2-trichloroethyl)thiobenzamide (IV) (○) in aqueous solution at 37 °C and $\mu = 0.5$.

where a_H and a_{OH} are the hydrogen ion and hydroxide ion activity, respectively. The values derived for the second-order rate constants k_H and k_{OH} are listed in Table 2. In the pH range 5–8 the k_{obs} values for the decomposition of the derivatives II, III and IV are directly proportional to a_{OH} as the slope of the log k_{obs}–pH plot is 1.0. The calculated k_{OH} values are given in Table 2. For compound II, however, the rate levels off with increasing pH and becomes constant at pH > 10. A similar levelling-off of the decomposition rate at high pH has been observed for N-(hydroxymethyl)benzamide (Johansen and Bundgaard, 1979) and is consistent with a reaction mechanism involving a stepwise pathway with anionic N-hydroxyalkyl amide as an intermediate undergoing rate-determining N–C bond cleavage (Scheme 3) (Ugelstad and de Jonge, 1957; Johansen and Bundgaard, 1979). According to this mechanism



Scheme 3

the rate law for the reactions occurring in neutral and alkaline solutions should be written as:

$$k_{obs} = k_1 \frac{K_a}{a_H + K_a} \tag{3}$$

where K_a is the ionization constant for the N-hydroxymethyl derivatives and k_1 is a first-order rate constant for cleavage of the ionized N-hydroxyalkyl compound (cf. Scheme 3). The rate data obtained for compound II were found to fit well to Eqn. 3, giving a value of k_1 of 0.20 min^{-1} and a K_a value of 1.8×10^{-10} ($\sim pK_a$ 9.75). The

TABLE 2

APPARENT HYDROXIDE ION CATALYTIC RATE CONSTANTS (k_{OH}) FOR THE DECOMPOSITION OF VARIOUS N-HYDROXYALKYL DERIVATIVES IN AQUEOUS SOLUTION ($\mu = 0.5$; 37 °C) AND HALF-LIVES ($t_{1/2}$) OF DECOMPOSITION AT pH 7.40 AND 37 °C

Compound	k_{OH} ($M^{-1}\,min^{-1}$)	$t_{1/2}$ (min)
N-(α-Hydroxybenzyl)benzamide (I) [a]	1.8×10^5	6.5
N-(α-Hydroxy-2,2,2-trichloroethyl)benzamide (II)	1.7×10^3	6.9×10^2
N-(Hydroxymethyl)benzamide [b]	1.1×10^2	1.1×10^4
N-(α-Hydroxyethyl)thiobenzamide (III)	2.3×10^6	0.5
N-(α-Hydroxy-2,2,2-trichloroethyl)thiobenzamide (IV)	4.5×10^6	0.3
N-(Hydroxymethyl)thiobenzamide [b]	6.3×10^4	18

[a] The value for k_H was determined to be 7.9 $M^{-1} \cdot min^{-1}$.

[b] The rate data for these compounds were determined previously (Johansen and Bundgaard, (1979)).

value of pK_a is reasonable since it should be expected to be close to that of chloral hydrate, and the pK_a value for the latter has been reported to be 10.04 at 25 °C (Bell and Onwood, 1962).

At pH values well below pK_a of the hydroxyalkyl compounds Eqn. 3 is reduced to:

$$k_{obs} = k_1 \frac{K_a}{a_H} \tag{4}$$

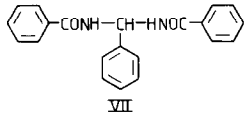
or

$$k_{obs} = k_1 \frac{K_a}{K_w} a_{OH} \tag{5}$$

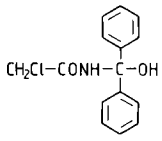
where K_w is the autoprotolysis constant of water. It is readily seen that Eqn. 5 is of the same form as the equation: $k_{obs} = k_{OH} a_{OH}$, and therefore, the observed linearity between k_{obs} and a_{OH} for compounds I, III and IV at the alkaline pH values studied is fully in agreement with the rate expression of Eqn. 3. The pK_a of N-(hydroxymethyl)benzamide has been determined to be 13.1 at 37 °C (Johansen and Bundgaard, 1979), and it is to be expected that the pK_a values of compounds I and III are of the same order of magnitude and not much lower.

The rate of decomposition of compound I was also determined in 80% human plasma (pH 7.4) at 37 °C. No significant effect of plasma was observed since the half-life observed (6.0 min) was similar to that for the reaction taking place in pure buffer solution (6.5 min). This lack of enzymatic catalysis is expected on the basis of the suggested reaction mechanism and has also been observed previously for an N-hydroxymethyl amide (Johansen and Bundgaard, 1981).

Inspection of the rate data in Table 2 shows that the N-α-alkylol derivatives (I–IV) are much more unstable than the corresponding N-hydroxymethyl (N-methylol) derivatives. Thus, whereas N-(hydroxymethyl)benzamide is decomposed with a half-life of 183 h at pH 7.4 and 37 °C, the derivatives of benzamide with benzaldehyde and chloral possess half-lives of 6.5 min (I) and 11.5 h (II). For the thiobenzamide derivatives a similar trend is seen. The derivatives with chloral (IV) and acetaldehyde (III) are 60-fold and 36-fold, respectively, more susceptible to undergo decomposition at physiological pH than the compound derived from formaldehyde. This difference in reactivity is suggested to be due to steric effects within the α-substituents. Sayer and Conlon (1980) have previously studied the hydrolysis of the carbinolamide VIII derived from chloroacetamide and benzophenone (generated in situ upon hydrolysis of the corresponding benzophenone N-chloroacetylimine) and detected spontaneous, specific acid and specific base catalysis. The value derived for k_{OH} was 7.2×10^6 $M^{-1} \cdot min^{-1}$ at 25 °C which is 40 times greater than the k_{OH} value for compound I. Although taken into account that substitution of benzamide by chloroacetamide results in a ~6-fold increase in reactivity (Johansen and Bundgaard, 1979) it is evident that the introduction of two α-phenyl groups results in a carbinolamide with a greater lability than one possessing only one α-phenyl group.



VII



VIII

In conclusion, therefore, the results of the present study show that it should be feasible to make use of N-acyloxyalkylation as a means of obtaining prodrug forms of also weakly NH-acidic drugs such as amides, carbamates and urea derivatives ($pK_a > 14$) if the (acyloxy)alkyl α-halide normally used for the N-acyloxyalkylation is prepared from other aldehydes than formaldehyde, e.g. benzaldehyde.

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