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## Prodrugs as Drug Delivery Systems XXV: Hydrolysis of Oxazolidines—A Potential New Prodrug Type

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**Abstract** □ The hydrolysis kinetics of several oxazolidines derived from (–)-ephedrine and various aldehydes and ketones were studied to assess their suitability as prodrug forms for  $\beta$ -amino alcohols and/or carbonyl-containing compounds. The oxazolidines were found to undergo a facile and complete hydrolysis in the pH range of 1–11 at 37°. The hydrolysis rates were subject to general acid–base catalysis by buffer substances and depended strongly on pH. Most oxazolidines showed sigmoidal pH–rate profiles with maximum rates at pH > 7–7.5. At pH 7.4 and 37° the following half-lives of hydrolysis for the various ephedrine oxazolidines were found: 5 sec (formaldehyde), 18 sec (propionaldehyde), 5 min (benzaldehyde), 5 sec (salicylaldehyde), 30 min (pivalaldehyde), 4 min (acetone), and 6 min (cyclohexanone). The reaction rates in neutral and basic solutions were shown to decrease with increasing steric effects of the substituents derived from the carbonyl component and to decrease with increasing basicity of the oxazolidines. The oxazolidines are weaker bases ( $pK_a$  5.2–6.9) than the parent  $\beta$ -amino alcohol and more lipophilic at physiological pH. It is suggested that oxazolidines can be considered as potentially useful prodrug candidates for drugs containing a  $\beta$ -amino alcohol moiety or carbonyl groups.

**Keyphrases** □ Ephedrine—oxazolidine derivatives, potential prodrugs for  $\beta$ -amino alcohols and carbonyl-containing compounds □ Oxazolidines—potential prodrugs for  $\beta$ -amino alcohols and carbonyl-containing compounds, ephedrine □ Prodrugs—potential, oxazolidine derivatives, for  $\beta$ -amino alcohols and carbonyl-containing compounds, ephedrine

Bioreversible derivatization of drug substances to produce prodrugs with altered physicochemical properties can improve substantially both drug efficacy and safety (1–3). As a part of current studies involving new chemical approaches (4, 5), an investigation was carried out to obtain prodrug candidates for the  $\beta$ -amino alcohol moiety and/or carbonyl groups (aldehydes and ketones). There are several drugs containing a  $\beta$ -amino alcohol moiety (e.g., various sympathomimetic amines and  $\beta$ -blockers) which may exhibit delivery problems, e.g., due to unfavorable solubility or lipophilicity characteristics. For this moiety no prodrug types have apparently been described, and likewise, only few bioreversible derivatives of carbonyl-containing drugs have been explored (6, 7). We recently suggested (8) that oxazolidines should be considered as potentially useful prodrug candidates for  $\beta$ -amino alcohols

or drugs containing carbonyl groups. Oxazolidines (II and III) derived from (–)-ephedrine (I) and benzaldehyde or salicylaldehyde were found to undergo a facile and quantitative hydrolysis in the pH range of 1–11, the half-lives of hydrolysis at pH 7.4 and 37° being 5 min (II) and 5 sec (III). To further explore the potential of oxazolidines as prodrug types and to delineate some structure–activity relationships, this study has been extended to include oxazolidines derived from (–)-ephedrine and the ketones acetone and cyclohexanone, as well as the aliphatic aldehydes formaldehyde, propionaldehyde, and pivalaldehyde. In the present paper the kinetics of hydrolysis of these oxazolidines (IV–VIII) are described along with data for the lipophilicity of the compounds.

#### EXPERIMENTAL

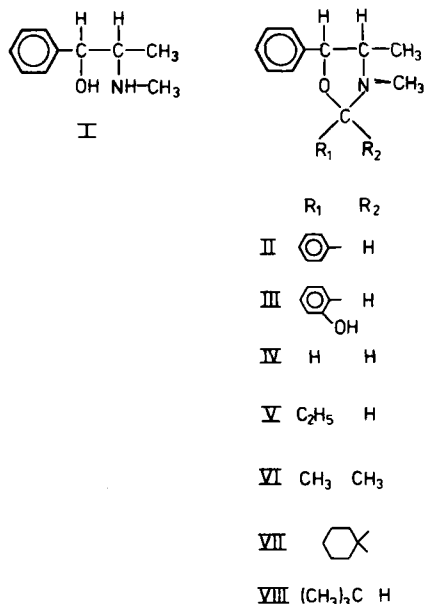
**Chemicals**—The oxazolidines IV–VIII were prepared by treating (–)-ephedrine<sup>1</sup> with the appropriate aldehyde or ketone, according to previously described procedures (9–11), and these materials were purified by distillation *in vacuo*. The boiling or melting points observed agreed with those previously reported (9–11), and satisfactory elemental analysis data (C, H, and N) were obtained. Buffer substances and all chemicals or solvents were of reagent grade.

**Kinetic Studies**—All rate studies were performed in aqueous buffer solutions at 37.0 ± 0.2°. The buffers used were hydrochloric acid, formate, acetate, phosphate, borate, and carbonate solutions. A constant ionic strength ( $\mu$ ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. The rates of hydrolysis were followed by one or more of three methods depending on the reaction rate.

**Direct UV spectrophotometry**—In this method the progress of decomposition of the oxazolidines was followed spectrophotometrically<sup>2</sup> by recording the decrease in absorbance at 220 nm. At this wavelength the absorption of substrate and products differed maximally. Reactions were performed in 2.5-ml aliquot portions of buffer solutions in a thermostated quartz cell and were initiated by adding 20  $\mu$ l of a stock solution of the oxazolidines in acetonitrile to give a final concentration of  $\sim 5 \times 10^{-4}$  M. Rate constants were calculated from the slopes of linear plots of  $\log(A_t - A_\infty)$  against time, where  $A_t$  and  $A_\infty$  are the absorbance

<sup>1</sup> AG Fluka, Switzerland.

<sup>2</sup> Zeiss PMQ II equipped with a thermostated cell compartment.



readings at time  $t$  and at infinity (*i.e.*, when no further changes in absorbance occurred), respectively.

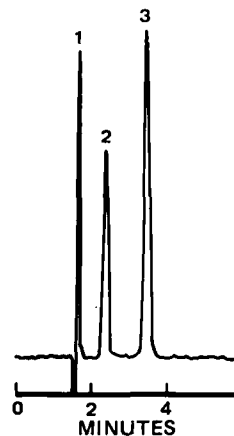
**Trapping of Carbonyl Product**—The rates of hydrolysis of IV and VII were measured at some pH values (pH 3–6) by trapping the formaldehyde or cyclohexanone formed with semicarbazide and following the increase in absorbance of the semicarbazone at 235 nm (12, 13). Semicarbazide hydrochloride was included in the buffer solutions at a concentration of  $5 \times 10^{-3} M$ . The concentration of the trapping reagent (and pH range) was such that there was no induction period in the observed pseudo first-order rate plots, *i.e.*, trapping of carbonyl compound was fast relative to its formation. The semicarbazide had no significant influence on the reaction rate in the concentration used; at higher concentrations a slight catalytic effect was noted. The initial oxazolidine concentration was  $\sim 2 \times 10^{-4} M$ , and the reactions were performed either directly in a thermostated cuvette or in flasks kept in a water bath. Pseudo first-order rate constants were determined from plots of  $\log(A_\infty - A_t)$  against time; in all cases stable end points ( $A_\infty$ ) were observed.

**High-Performance Liquid Chromatography (HPLC)**—Slower reactions were usually followed using an HPLC method. The apparatus<sup>3</sup> used was equipped with a variable-wavelength UV detector (8- $\mu$ l, 1-cm flow cells), a 10- $\mu$ l loop injection valve, and a reverse-phase column<sup>4</sup> (4.0 mm  $\times$  25 cm). The mobile phase consisted of methanol–0.04 M potassium dihydrogen phosphate (7:3 v/v). The flow rate was 1.6 ml/min, and the column effluent was monitored at 215 or 220 nm. Under these conditions the oxazolidines were separated from ephedrine and both 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. In the kinetic runs, buffer solutions containing the oxazolidines at initial concentrations of  $\sim 0.5$  mg/ml were kept at 37°, and aliquots were removed at suitable intervals and chromatographed. First-order rate constants for the hydrolysis were determined from the slopes of linear plots of the logarithm of residual oxazolidine against time.

**Measurement of Partition Coefficients**—The partition coefficients of the oxazolidine derivatives VI, VII, and VIII were determined in an octanol–phosphate buffer (0.05 M, pH 7.40) system as previously described (8). The solute concentration in the octanol phase was determined by the aforementioned HPLC method before and after partition, the equilibrium being obtained after mixing the two phases for only 3 min at 20° (for stability reasons). For each compound, determinations were carried out in triplicate, and the log P values thereby obtained were reproducible to within  $\pm 6\%$ .

## RESULTS AND DISCUSSION

**Kinetics of Hydrolysis**—The kinetics of decomposition of the oxazolidines IV–VII were studied in aqueous solution at 37° over the pH



**Figure 1**—Chromatogram of a partially degraded aqueous solution of VI. Key: (1) solvent front; (2) (–)-ephedrine; (3) VI.

**Table I**—Pseudo First-Order Rate Constants ( $k_{obs}$ ,  $\text{min}^{-1}$ ) for the Hydrolysis of Various Oxazolidines<sup>a</sup> as Determined by Different Methods

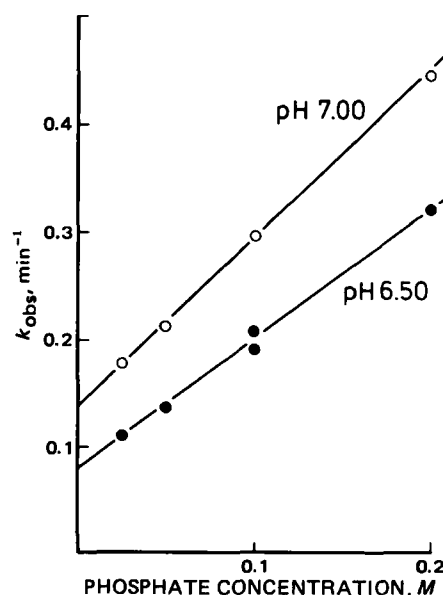
Compound	Buffer	Method <sup>b</sup>		
		A	B	C
V	0.05 M formate (pH 3.15)	0.10	—	0.11
VI	0.05 M phosphate (pH 7.40)	0.21	—	0.22
VII	0.1 M acetate (pH 5.55)	0.016	0.017	0.015

<sup>a</sup>  $\mu = 0.5$ ; 37°. <sup>b</sup> (A) Direct UV spectrophotometry; (B) trapping of carbonyl product with semicarbazide; (C) HPLC of oxazolidine.

range of 0.5–11. At constant pH and temperature the hydrolysis displayed strict first-order kinetics for  $>3$  half-lives, and in all kinetic runs followed by HPLC, ephedrine was found to be liberated in stoichiometric amounts. As described above, different experimental methods were used to follow the reactions. In several cases the rate of hydrolysis of oxazolidines at a given pH was determined using more than one of the methods and, as seen from the examples given in Table I, the values of the pseudo first-order rate constants ( $k_{obs}$ ) derived were in favorable agreement.

The hydrolysis of the oxazolidines was found to be subject to significant buffer catalysis, as has previously been observed for II (8). The hydrolysis rates showed in all cases a linear dependence on buffer concentration, as illustrated in Fig. 2 for the degradation of oxazolidine VI in phosphate buffers.

The influence of pH on the hydrolysis rate is shown in Fig. 3, where the logarithms of the  $k_{obs}$  values at zero buffer concentration ( $k_0$ , obtained



**Figure 2**—Effect of phosphate buffer concentration on the pseudo first-order rate constant for the hydrolysis of VI ( $\mu = 0.5$ ; 37°).

<sup>3</sup> Spectra-Physics Model 3500B.

<sup>4</sup> LiChrosorb RP-8 reverse-phase column; E. Merck, Darmstadt, West Germany.

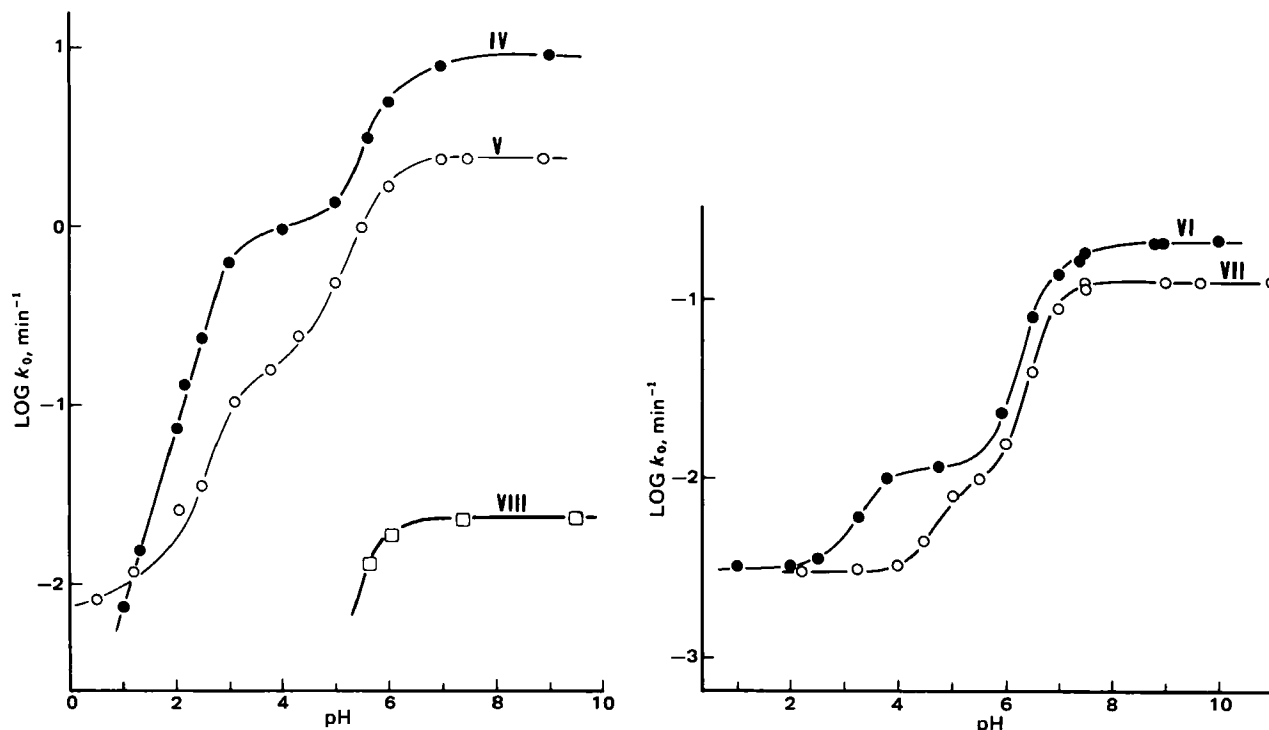


Figure 3—The pH-rate profiles for the hydrolysis of the oxazolidines IV–VIII at 37° ( $\mu = 0.5$ ).

by extrapolation of plots such as those in Fig. 2 to zero buffer concentration) are plotted against pH. The  $k_0$  values at pH < 2.2 were obtained directly from runs in hydrochloric acid solution.

Previous studies (14–16) have shown that the hydrolysis occurs in two separate reaction stages: reversible ring opening to give a cationic Schiff base species followed by hydrolysis of this intermediate to give the  $\beta$ -amino alcohol and the carbonyl component (Scheme I). These studies involving various 2-(substituted phenyl)-3-ethyloxazolidines, 2-[4-(dimethylamino)styryl]-3-phenyloxazolidine, and 2-(4-methylphenyl)-2,3-dimethyloxazolidine led to the proposed reaction scheme in which the ring opening proceeding with C—O bond breaking is subject to hydrogen ion catalysis as well as a possible unimolecular C—O bond breaking or a water-catalyzed ring opening. The cationic Schiff base intermediate formed is in equilibrium with the oxazolidine and undergoes both spontaneous and hydroxide-ion-catalyzed hydrolysis.

A similar mechanism may be involved in the hydrolysis of the oxazolidines IV–VIII. For these derivatives, however, no build up of a Schiff base intermediate occurs. Using UV spectrophotometry no such intermediate could be detected in the pH range studied, and furthermore, no lag time was observed in the rate of appearance of ephedrine as determined by HPLC. Thus, if formed, the Schiff base intermediate must be present in small steady-state concentrations. A similar conclusion was also reached in case of hydrolysis of the benzaldehyde derivative II (8). The sigmoidal pH-rate profiles obtained for the oxazolidines studied

indicate, on the other hand, that such an intermediate may be involved in the reaction pathway and that a change of the rate-determining step in the overall reaction with pH is taking place. In weakly acid to basic solution (pH > 5.5–6), the rate-determining step in the overall hydrolysis of the oxazolidines is suggested to involve a unimolecular or water-catalyzed breakdown of the free base form of the oxazolidines. Letting  $k_1$  be the apparent first-order rate constant for this process and  $K_a$  the apparent ionization constant of the protonated oxazolidines, the expression for  $k_0$  would be:

$$k_0 = \frac{k_1 K_a}{a_H + K_a} \quad (\text{Eq. 1})$$

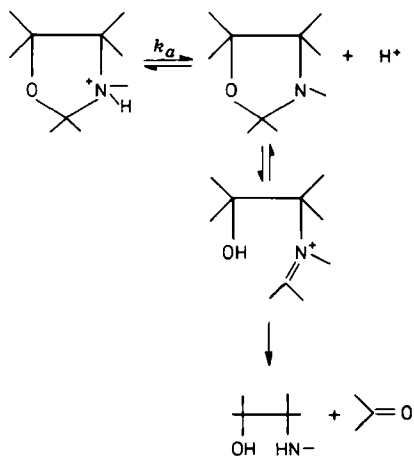
where  $a_H$  is the hydrogen ion activity. In Fig. 3 the lines at pH > 5.5–6 were constructed from Eq. 1 and the rate constants and  $pK_a$  values given in Table I. It is seen that the experimental data obtained in this pH region fit very satisfactorily to Eq. 1. Further support for this interpretation of the kinetic data is provided by the identical  $pK_a$  values obtained kinetically and by potentiometric titration for the oxazolidines VI and VII (Table II). Due to their facile hydrolysis the  $pK_a$  values of IV and V could not be determined titrimetrically. It should be added, however, that other kinetically equivalent reactions, e.g., hydroxide-ion-catalyzed hydrolysis of protonated oxazolidine, can equally account for the observed  $k_0$ -pH relationship in neutral and alkaline solutions.

As seen from Fig. 4 the oxazolidine derived from benzaldehyde (II) behaves quite differently from those from the aliphatic aldehydes (IV and V). The hydrolysis of this oxazolidine shows a bell-shaped pH-rate profile as previously reported (8). In contrast the pH-rate profile for the corresponding oxazolidine from salicylaldehyde (III) (8) is sigmoidal, as are those for IV, V, and VIII. The rate data for III at pH > 4 were analyzed in terms of Eq. 1, and the  $k_1$  and  $pK_a$  values derived are included in Table I.

Table II—Rate Data for the Hydrolysis of Various Oxazolidines and  $pK_a$  Values<sup>a</sup>

Oxazolidine	$k_1, \text{min}^{-1}$	$pK_a^b$
II	—	— (5.6) <sup>c</sup>
III	9.1	5.2
IV	9.1	6.0
V	2.4	5.9
VI	0.21	6.9 (6.9) <sup>c</sup>
VII	0.13	6.9 (6.9) <sup>c</sup>
VIII	0.023	5.9

<sup>a</sup>  $\mu = 0.5$ ; 37°. <sup>b</sup> Kinetically determined values; the values listed in parentheses were determined titrimetrically. <sup>c</sup> Values taken from Ref. 17.



Scheme I

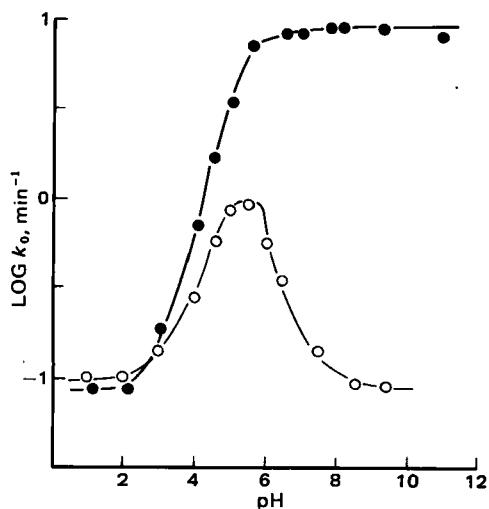


Figure 4—The pH-rate profiles for the hydrolysis of the oxazolidines II (O) and III (●) at 37° ( $\mu = 0.5$ ). (Taken from Ref. 8.)

The  $pK_a$  values derived for the oxazolidines are substantially smaller than the  $pK_a$  value (9.6) for ephedrine. The difference can most likely be attributed to the presence of the electronegative ring oxygen atom in the oxazolidines, *cf.*, the difference in the  $pK_a$  values for piperidine (11.1) and morpholine (8.3).

**Lipophilicity of the Oxazolidines**—The apparent partition coefficients ( $P = C_{\text{octanol}}/C_{\text{aqueous}}$ ) for the oxazolidines VI–VIII were measured using an octanol–aqueous buffer system, using 0.05 M phosphate buffer, pH 7.40. The values found for log P were 0.92 (VI), 1.83 (VII), and 1.68 (VIII). The log P values for the free base forms of the compounds can be calculated from these values when correction is made for the degree of ionization at pH 7.4; the values thus obtained are 1.04 (VI), 1.94 (VII), and 1.69 (VIII). The log P value for the benzaldehyde derivative (II) was previously reported to be 1.58 at pH > 7. The log P value for ephedrine ( $pK_a$  9.6) in a similar octanol–phosphate buffer (pH 7.4) system has been reported to be –1.35, with a log P value of 1.02 for the free base form (18). These results show that the oxazolidines prepared from acetone, cyclohexanone, or benzaldehyde are more lipophilic than the parent ephedrine, especially at physiological pH where the oxazolidines are largely in the free base form and ephedrine is largely protonated. Due to stability reasons the log P values for the oxazolidines III–V could not be experimentally determined, but could be estimated on the basis of hydrophobic substituent constants (19) and the values for derivatives described above.

**Structural Effects on Reaction Rate**—The rate data obtained show that the structure of the carbonyl component has a pronounced effect on the rate of oxazolidine hydrolysis in both acidic, neutral, and alkaline

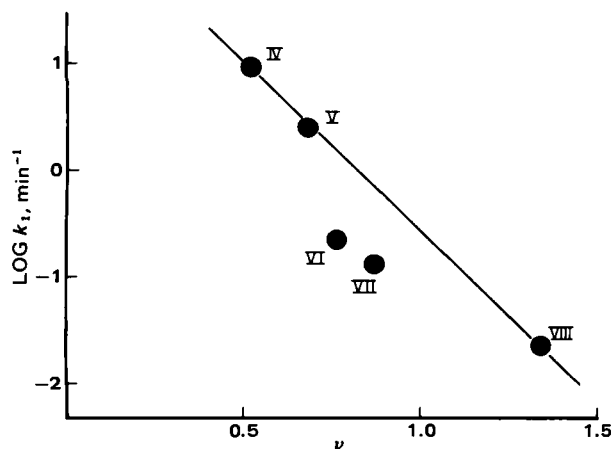


Figure 5—Plot of  $\log k_1$  against the steric substituent parameter  $\nu$  for various oxazolidines. The correlation plot was made for IV, V, and VIII possessing the same  $pK_a$  values. The  $\nu$  values used refer to the moiety of the oxazolidines derived from the carbonyl compounds including the ring carbon atom in the oxazolidines, e.g., for IV and VI the  $\nu$  values are those for methyl and isopropyl, respectively.

Table III—Half-lives of Hydrolysis of Various Oxazolidines at pH 1 and 7.4<sup>a</sup>

Oxazolidine	$t_{1/2}$ , min	
	pH 1	pH 7.4
II <sup>b</sup>	7	5.0
III <sup>b</sup>	8	0.08
IV	96	0.08
V	70	0.3
VI	220	4.0
VII	230	5.9
VIII	—	30

<sup>a</sup>  $\mu = 0.5$ ; 37°. <sup>b</sup> The rate data are from a previous study (8).

solutions. Considering the rate constant  $k_1$  and accordingly, the hydrolysis rate in weakly acidic to basic aqueous solutions, the structural effects appear to involve both electrical and steric effects. The oxazolidines derived from the three aliphatic aldehydes (IV, V, and VIII) possess almost the same  $pK_a$  values (Table II), and the variation of the rates of hydrolysis of these derivatives can be accounted for in terms of different steric properties of the aldehyde part. As seen in Fig. 5, an excellent linear correlation exists between  $\log k_1$  and the steric substituent parameter  $\nu$  (20). The regression equation between  $\log k_1$  and  $\nu$  for these oxazolidines is given by:

$$\log k_1 = -3.2\nu + 2.6 \quad (k_1 \text{ in } \text{min}^{-1}; 37^\circ) \quad (\text{Eq. 2})$$

This result implies that the reactivity of oxazolidines in neutral and basic solutions decreases with increasing steric effects within the carbonyl moiety. As seen from Fig. 5 such a correlation also appears to hold for oxazolidines derived from ketones, although only rate data for two derivatives have been obtained. The decreased reactivity of the ketone-oxazolidines as compared to the aldehyde-oxazolidines (Fig. 5) may most likely be due to differences in the  $pK_a$  values of the oxazolidines, *i.e.*, increased  $pK_a$  results in decreased reactivity. As previously suggested (8) the considerably greater reactivity of III compared with II may be attributed to some kind of intramolecular catalysis by the *ortho*-situated hydroxyl group in III. It is obvious, however, that the present data are insufficient to delineate the structural factors (steric and electrical), both within the aldehyde or ketone part and the amino alcohol moiety, that may influence the stability of oxazolidines.

**Consideration of Oxazolidines as Prodrug Types**—The results obtained extend the previous suggestion (8) that oxazolidines may have potential as prodrug forms for  $\beta$ -amino alcohols or carbonyl-containing compounds. The derivatives undergo a quantitative conversion to the parent compounds in aqueous solution with rates highly dependent on pH. As shown in Table III the decomposition of the oxazolidines at pH 7.4 and 37° is quite rapid, whereas a greater stability is achieved in acid solutions. These rates might not be expected to change much *in vivo*. The oxazolidines are much weaker bases than the parent  $\beta$ -amino alcohol, and this results in higher lipophilicity at physiological pH. Such increased lipophilicity may become advantageous in situations where delivery problems for  $\beta$ -amino alcohol-type drugs are due to low lipophilicity. Thus, by appropriate selection of the carbonyl moiety of oxazolidines it may be feasible to obtain prodrugs of  $\beta$ -amino alcohols with varying physicochemical properties, such as lipophilicity and rate of drug release, and hence to control and modify the delivery and overall activity characteristics of the parent drugs. In considering oxazolidines as prodrug candidates for carbonyl-containing substances, their weakly basic character may also be advantageous in that the transformation of such substances into oxazolidines introduces a readily ionizable moiety, which may allow the preparation of derivatives with increased aqueous solubilities at acidic pH values. For example, a potentially useful purpose of transforming a carbonyl-containing drug substance into a bioreversible oxazolidine derivative could be to enhance its dissolution behavior in an effort to improve the oral bioavailability.

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## Determinants of Bumetanide Response in the Dog: Effect of Indomethacin

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**Abstract** □ Four male unanesthetized dogs each weighing 22.0–29.0 kg received 0.250 mg/kg iv of bumetanide before (treatment I) and after (treatment II) indomethacin pretreatment. Lactated Ringer's solution was administered intravenously throughout both treatments at a flow rate of 2 ml/min to avoid fluid and electrolyte depletion. Unchanged bumetanide and indomethacin concentrations were analyzed using high-performance liquid chromatography. Sodium was measured by flame photometry and creatinine by colorimetry. Indomethacin pretreatment did not significantly change the pharmacokinetics of bumetanide, affecting neither the total amount of drug nor time course of drug delivered into the urine. In contrast, indomethacin pretreatment resulted in a dramatic reduction in the 4-hr sodium excretion and urine volume. Therefore, a pharmacokinetic interaction may be eliminated as a possible mechanism for the attenuation, by indomethacin, of the natriuretic and diuretic response of bumetanide. Instead, it appears that indomethacin diminishes the response to bumetanide *via* prostaglandin inhibition.

**Keyphrases** □ Bumetanide—pharmacokinetics, sodium excretion, dogs, effect of indomethacin pretreatment □ Indomethacin—pretreatment, effect on sodium excretion, pharmacokinetics of bumetanide, dogs □ Pharmacokinetics—bumetanide, sodium excretion, pharmacokinetics in the dog, effect of indomethacin pretreatment

Bumetanide [3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid] is a high-ceiling diuretic with pharmacological action similar to that of furosemide (1–3). The diuretic appears to act primarily at the medullary portion of the ascending limb of the loop of Henle, where it inhibits solute reabsorption, although inhibition of sodium transport in the proximal nephron also occurs (4–7). In addition, bumetanide induces intrarenal hemodynamic changes (8–12). Since bumetanide is highly bound to plasma proteins (13, 14), the drug gains access to the kidney lumen predominantly at the pars recta of the proximal tubule *via* the nonspecific organic acid secretory pathway (1, 13).

Indomethacin has been shown recently to attenuate the natriuretic and diuretic response to bumetanide in experimental animals (12), healthy volunteers (15, 16), and patients (17). These authors proposed that indomethacin,

a potent inhibitor of prostaglandin synthetase, interferes with the prostaglandin-mediated effect of bumetanide. However, it is also possible that indomethacin may compete with bumetanide (both drugs are weak organic acids) for active secretion into the lumen of the kidney tubule, thereby modifying either the total amount of diuretic delivered to its active site or the time course of drug delivery. Since previous investigators (12, 15–17) did not measure concentrations and/or amounts of bumetanide in the plasma and urine, this alternative hypothesis (pharmacokinetic interaction) cannot be eliminated. Therefore, the present investigation was undertaken to clarify the mechanism by which indomethacin diminishes the pharmacodynamic response to bumetanide.

### EXPERIMENTAL

**Materials**—An aqueous solution dosage form of bumetanide<sup>1</sup> was prepared using 0.4 N NaOH immediately prior to use. Indomethacin capsules<sup>2</sup> were obtained commercially. Indomethacin powder<sup>3</sup> was used as received. All other chemicals and solvents were reagent grade or better, as previously reported (18).

**Methods**—Four male, mongrel, conditioned, unanesthetized dogs weighing 22.0–29.0 kg received 0.250 mg/kg of bumetanide before (treatment I) and after (treatment II) pretreatment with indomethacin. Each dog was fasted the night before and throughout the entire study period. Bumetanide was administered intravenously over a 3-min infusion<sup>4</sup> period, with the beginning of the infusion being considered as time zero. A 100-mg dose of indomethacin (two 50-mg capsules) was ingested the night before (11:00 to 11:30 p.m.) and on the study day (60 min prior to bumetanide administration). An interval of at least 1 week elapsed between studies, and identical lots for each drug were used throughout.

Heparinized scalp vein needles<sup>5</sup> were placed in the forelegs of each dog:

<sup>1</sup> Lot A-29; Hoffmann-La Roche, Inc., Nutley, N.J.

<sup>2</sup> Lot D2520; Merck Sharp and Dohme, West Point, Pa.

<sup>3</sup> Merck Sharp and Dohme, Rahway, N.J.

<sup>4</sup> Harvard Compact Infusion Pump; Harvard Apparatus Co., Inc., South Natick, Mass.

<sup>5</sup> E-Z Set—PRN Intermittent Infusion Set; The Deseret Co., Sandy, Utah.