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Isoxazoles II: Kinetics and Mechanism of Degradation of Sulfisoxazole in Moderately Concentrated Acids

RUBEN H. MANZO* and M. MARTINEZ de BERTORELLO▲

Abstract ☐ The acid degradation of sulfisoxazole (*N*-sulfanilamido-3,4-dimethyl-5-isoxazole) in hydrochloric acid solutions in concentrations from 10 to 24% and at 108 ± 0.1° was studied. Two parallel pathways of molecular degradation which lead simultaneously to the formation of sulfanilic acid (pathway A) and sulfanilamide (pathway B) as final products were determined. The isoxazole ring is degraded as much in the sulfisoxazole molecule (pathway B) as in the 5-amino-3,4-dimethylisoxazole (pathway A), leading to formation of 2-butanone and hydroxylamine (and ammonia in the latter case) as final products. Both degradative pathways show pseudo-first-order kinetics. A study was also made of how the reaction rates are affected with the acid concentration. Degradative pathway B prevails at low acid concentrations and can be associated with a mechanism in which water participates in the rate-determining step; degradative pathway A prevails at higher acid concentrations and the mechanism implies nonparticipation of water in the rate-determining step.

Keyphrases ☐ Sulfisoxazole—kinetics and mechanism of acid degradation, ionization ratios ☐ Isoxazole derivatives—kinetics and mechanism of acid degradation of sulfisoxazole, ionization ratios ☐ Degradation—sulfisoxazole in hydrochloric acid solutions, rates, mechanisms, ionization ratios

The isoxazoles form a group of heterocycles that may be characterized by their chemical behavior; they exhibit properties that are typical of aromatic systems and also, under certain conditions, show ring lability, particularly at the oxygen–nitrogen bond (1).

At present, more attention is paid to the investigation of the mechanism of chemical reactions under extreme conditions (high and low temperatures, high and low pressures, effects of radiation, *etc.*); available data show that under such conditions the course of reactions often becomes uncommon.

Based on these findings and on some experimental data obtained in this laboratory, it appeared interesting to perform a thorough study of the cleavage reactions of the isoxazole ring in strong acid solutions and at high temperatures. These studies may contribute more basic information on the stability of the ring, especially since data related to the problem are quite scarce (1). Moreover, since numerous derivatives of the isoxazole ring have pharmacological properties (2), the importance of the conditions and mechanism by which these heterocycles are degraded is greatly increased.

This paper presents the results of a study of the influence of hydrochloric acid concentrations and high temperatures on the hydrolytic degradation of one isoxazole derivative: sulfisoxazole[1] (*N*-sulfanilamido-3,4-dimethyl-5-isoxazole).

EXPERIMENTAL[2]

Materials—All of the solvents used were commercial products, purified by the usual techniques. Hydrochloric acid, sulfuric acid, and sodium β-naphthoquinone-4-sulfonate were analytical[3] reagent grade. 2,4-Dinitrophenylhydrazine[4] was recrystallized from methanol. Sulfisoxazole USP[5] was recrystallized from ethanol, m.p. 193–194°. 5-Amino-3,4-dimethylisoxazole was prepared according to the method described (3) for other sulfonamides: 10 g. of sulfisoxazole was dissolved in 200 ml. of glacial acetic acid and 25 ml. of acetic anhydride. The solution was boiled for 5 min., cooled, and diluted with 500 ml. of distilled water. A precipitate

[1] Preferred USAN chemical name is N^1-(3,4-dimethyl-5-isoxazolyl)-sulfanilamide.
[2] Melting points were taken on a melting-point apparatus (Dr. Tottoli) and are uncorrected. The IR spectra were run on a Beckman IR 8 spectrophotometer in potassium bromide pellets. UV measurements were made in a Hilger & Watts H.700.308 spectrophotometer, using quartz cells 1 cm. thick. The complete absorption spectrum in the UV region was taken in a Cary 14 recording spectrophotometer. Absorbance measurements in the visible region were made in a Bausch & Lomb spectrophotometer.
[3] Carlo Erba G.R.
[4] Merck & Co.
[5] SOCRAM.

was formed, which was separated, dried, and subsequently solubilized in 25 ml. of 40% (w/v) sulfuric acid and boiled for 3 min. The solution was cooled, alkalinized with 10% sodium hydroxide solution, and extracted with ether (3 × 40 ml.). The ethereal extracts yielded 3.2 g. of 3,4-dimethyl-5-aminoisoxazole, which was recrystallized first from benzene and then from water, m.p. 123.5–124.5°.

Qualitative Identification of Degradation Products of Sulfisoxazole—*Sulfanilic Acid, Sulfanilamide, 5-Amino-3,4-dimethylisoxazole, and 2-Butanone*—A solution of 0.045 mole (1.200 g.) of sulfisoxazole in 100 ml. of hydrochloric acid (24%) was boiled at reflux for 100 min. Aliquots were taken every 10 min. of the reaction and were immediately cooled in an ice bath.

Sulfanilic Acid and Sulfanilamide—Approximately 5 μl. of each reaction sample was spotted on a 20 × 20-cm. silica gel[6] TLC plate. The chromatogram was developed with heptane–chloroform–ethanol–glacial acetic acid (2:2:3:1). The spots were detected by spraying with a 1% sodium nitrite in 0.5 *N* hydrochloric acid solution and coupling the diazo compounds formed with a 0.5% *N*-naphthylethylenediamine dihydrochloride[7] aqueous solution. The spot corresponding to sulfisoxazole (R_f 0.87) faded progressively and was not detectable in approximately 80 min. Two spots (R_f 0.72 and 0.42) appeared simultaneously, and their intensities increased progressively with reaction time. They were identified by comparison with known standard samples and were found to be sulfanilamide and sulfanilic acid, respectively.

5-Amino-3,4-dimethylisoxazole—Twenty-five milliliters of the solution hydrolyzed during 20 min. was alkalinized with 20% sodium hydroxide solution; three ether extractions (20 ml. each) were performed on the alkaline solution. The ethereal extracts were combined and dried with anhydrous sodium sulfate. Evaporation of the solvent yielded a solid, which was recrystallized from water and identified as 5-amino-3,4-dimethylisoxazole by a comparison of its melting point and mixed melting point with those of a known pure sample. Comparison of its R_f value (0.83) in TLC on a silica gel G plate, using heptane–chloroform–ethanol (2:2:3) as a developing solvent and a hydrochloric acid solution of *p*-dimethylaminobenzaldehyde as a spray reagent, resulted in further identification.

2-Butanone—To the rest of the solution, hydrolyzed during 100 min., a sodium bicarbonate solution was carefully added until it was neutralized. This solution was distilled, collecting approximately one-third of the original volume in a conical flask which contained a cooled solution of 2,4-dinitrophenylhydrazine in hydrochloric acid. A yellow precipitate was formed, which was separated, dried, and recrystallized from ethanol. It was identified as the 2,4-dinitrophenylhydrazone of the 2-butanone by comparison of its melting point, mixed melting point, and IR spectra with those of an authentic sample.

Qualitative Identification of Degradation Products of 5-Amino-3,4-dimethylisoxazole—*2-Butanone, Ammonia, and Hydroxylamine*—A solution of 7.5 mmoles (0.840 g.) of 5-amino-3,4-dimethylisoxazole in 150 ml. of 24% hydrochloric acid was refluxed for 60 min.

2-Butanone—One hundred milliliters of this solution was neutralized carefully by addition of a 20% solution of sodium bicarbonate. The neutralized solution was distilled, and one-third of the original volume was collected (this volume ensured the complete distillation of the 2-butanone formed) in a cooled 2,4-dinitrophenylhydrazine solution in hydrochloric acid. The precipitate was separated and recrystallized from ethanol and identified as the 2,4-dinitrophenylhydrazone of the 2-butanone by a comparison of its melting point, mixed melting point, and IR spectra with those of an authentic sample.

Ammonia—Thirty milliliters of the hydrolyzed solution, alkalinized with 20% sodium hydroxide solution and heated in a water bath, gave off vapors which changed the color of red litmus paper and had a typical ammonia odor.

Hydroxylamine—One milliliter of 40% potassium hydroxide solution was added to 1 ml. of the hydrolyzed solution together with 3 drops of ethyl acetate and then 0.4 ml. of the same potassium hydroxide solution. After standing for 10 min., 1 ml. of a 7.5% hydrochloric acid solution and 2 drops of ferric chloride solution were added. This produced a reddish-violet color typical of ferric hydroxamate complexes. The test proved negative when the ester was not added. These results indicate the formation of hydroxylamine during hydrolysis.

Quantitative Determinations and Kinetic Study—Hydrolysis rates in hydrochloric acid solutions of 24, 15, and 10% (w/v) concentrations at 108 ± 0.1° were studied.

Sulfisoxazole solutions were prepared by quantitatively transferring 5-mmole quantities to a volumetric flask of 100-ml. capacity and adding the hydrochloric acid solution until the volume was completed. The same procedure was followed with each acid solution.

Once the solutions were prepared, equal aliquots of 3 ml. were introduced in a series of 10-ml. ampuls. The ampuls were sealed and immersed in a constant-temperature bath. They were then withdrawn at appropriate intervals and quickly cooled in an ice bath for analysis at a later time.

Degradation of Sulfisoxazole—*Determination of Sulfisoxazole, Sulfanilamide, and Sulfanilic Acid*—All three compounds were separated by TLC using 20 × 20-cm. silica gel F_{254} PL chromatofolios[8]. Upon development the samples were evaluated using the Bratton–Marshall colorimetric technique (4) adapted to the present operating conditions. Determinations were performed in triplicate.

Three aliquots of 5 μl. each were taken from each ampul, using a 10-μl. graduated micropipet. The chromatogram was developed with a solvent system of heptane–chloroform–ethanol–glacial acetic acid (2:2:3:1) to 12 cm. The spots were localized by observing the plate under UV light and delineating the respective areas with a stylet, taking care to preserve a constant surface for each compound.

The areas were separated independently. The sulfisoxazole fraction was extracted with 10% hydrochloric acid (3 × 2 ml.), suspending and centrifuging the material each time. Sulfanilic acid was extracted in the same way but hot. Sulfanilamide was extracted at room temperature using 1 ml. of hydrochloric acid solution in each extraction[9].

For each component, the elution liquids were transferred and collected in a test tube where the Bratton–Marshall colorimetric technique was carried out as follows. Three milliliters[10] of 0.1% sodium nitrite aqueous solution was added to 6 ml. of eluate, mixing both solutions thoroughly. After 3 min. a further 3 ml. of 0.5% sulfamic acid aqueous solution and 4 ml. of 0.1% *N*-naphthylethylenediamine dihydrochloride aqueous solution were added. The absorbance of the colored solution that formed was determined

Table I—Pseudo-First-Order Rate Constants for Sulfisoxazole Hydrolysis in 24% (6.47 *M*) Hydrochloric Acid Solution and at 108 ± 0.1°

Reaction Time, min.	A(Average)	$\log A_0 - \log A$	$K_\psi \cdot 10^{-4}$ sec.$^{-1}$
0	0.355	0.000	
5	0.232	0.184	1.41
10	0.158	0.351	1.35
15	0.098	0.559	1.43
25	0.042	0.927	1.42
		Average K_ψ: $14.0 \cdot 10^{-4}$ seg.$^{-1}$	

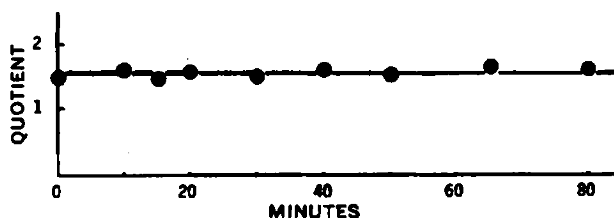
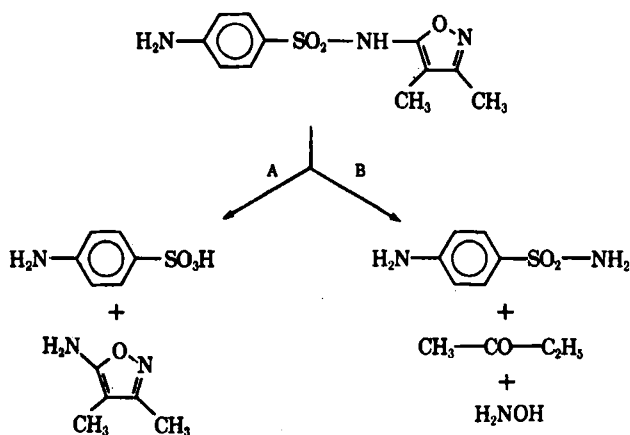


Figure 1—*Quotient between the absorbances of sulfanilamide and sulfanilic acid during sulfisoxazole hydrolysis.*

[6] E. Merck A.G., Darmstadt, W. Germany.
[7] Carlo Erba R.P.

[8] Merck.
[9] It was determined through a previous test with pure samples that the extraction of the three components in the way shown is quantitative.
[10] Half of each reagent was added in the determination of sulfanilamide.



Scheme I

in a spectrophotometer at 545 nm. against a blank with all of the reagents. The final result for each compound at a definite time was taken from the average of the three determinations.

From the values obtained it was possible to calculate the pseudo-first-order constant K_ψ for the degradation of sulfisoxazole, which was calculated according to Eq. 1:

$$K_\psi = \frac{(\log A_0 - \log A)\cdot 2.303}{t} \quad \text{(Eq. 1)}$$

where A_0 is the absorbance corresponding to the solution at $t = 0$, and A is the absorbance of a hydrolyzed solution during time t; $t = 0$ was the absorbance of a solution contained in an ampul which was submerged in the thermostatically controlled bath for 2 min. Table I shows the procedure used to calculate K_ψ for the degradation of sulfisoxazole in 24.5% hydrochloric acid. The values of K_ψ in 15 and 10% hydrochloric acid solutions were calculated using the same procedure.

Sulfanilamide and sulfanilic acid determinations made possible the calculation of the quotient between the absorbance of both compounds during hydrolysis of sulfisoxazole in 24.5% hydrochloric acid (Fig. 1). Sulfanilamide and sulfanilic acid concentrations were calculated in relation to a standard solution prepared as follows:

1. Sulfanilic acid, 191.9 mg. (1.107 mmoles), was introduced quantitatively in a volumetric flask of 50-ml. capacity and diluted to volume with a 24.5% hydrochloric acid solution.
2. A solution was prepared in the same way with 109.5 mg. (0.631 mmole) of sulfanilamide.

Both solutions were mixed in a 1:1 proportion and three aliquots were made with this solution on a TLC plate. Separation and determination were carried out exactly the same as when the problem samples were determined. The results were the following: microliters spotted, 5.0; sulfanilic acid absorbance, 0.170, 0.174, and 0.174; and sulfanilamide absorbance, 0.207, 0.202, and 0.207.

Calculations of the proportions of sulfanilamide and sulfanilic acid formed during hydrolysis were made relating the absorbances of the same samples to the absorbances determined with the standard solution of known concentration.

The fact that the absorbances produced by both compounds remained constant throughout the whole process of hydrolysis made possible the determinations of their final percentages without requiring the reaction to be carried out completely.

The proportions of sulfanilic acid and sulfanilamide were calculated through the relationship:

$$\frac{A_T}{C_T} = \frac{A_P}{C_P} \quad \text{(Eq. 2)}$$

where A_T and A_P are the absorbances of the standard solution and the problem, respectively; and C_P and C_T are the problem and the reference concentrations, respectively. The results were 29 moles% sulfanilamide and 71 moles% sulfanilic acid. These results permitted the estimation of the pseudo-first-order rate constants for the formation of sulfanilamide and sulfanilic acid through the following relationships:

$$K_\psi \text{ sulfisoxazole} \triangleq K_\psi \text{ sulfanilamide} + K_\psi \text{ sulfanilic acid} \quad \text{(Eq. 3)}$$

$$\frac{K_\psi \text{ sulfanilamide}}{K_\psi \text{ sulfanilic acid}} = \frac{29}{71} \quad \text{(Eq. 4)}$$

Table II—Pseudo-First-Order Rate Constants for Sulfisoxazole Hydrolysis and the Formation of Sulfanilamide and Sulfanilic Acid at Three Different Hydrochloric Acid Concentrations

HCl, moles/l.	$K_\psi \cdot 10^{-4}$ seg.$^{-1}$, Sulfisoxazole Degradation	Proportions, moles%, Sulfanilamide	Proportions, moles%, Sulfanilic Acid	$K_\psi \cdot 10^{-4}$ seg.$^{-1}$, Sulfanilamide	$K_\psi \cdot 10^{-4}$ seg.$^{-1}$, Sulfanilic Acid
6.47	14.0	29	71	4.1	9.9
4.10	2.4	49	51	1.2	1.2
2.74	1.1	59	41	0.65	0.45

Determination of 5-Amino-3,4-dimethylisoxazole during Sulfisoxazole Hydrolysis—Folin and Wu's colorimetric technique (5), adapted to the reaction system, was used. Samples were taken at adequate reaction times as described previously; accurately measured aliquots of these samples were diluted with distilled water in volumetric flasks of adequate capacity at concentrations of 1/50, 1/100, and 1/150. Then 1 ml. of each diluted sample was neutralized to phenolphthalein with potassium hydroxide solution[11] (a parallel tube was used to calculate the necessary quantity so as not to introduce phenolphthalein into the system). Then 2 ml. of 0.1 M phosphate buffer solution of pH 11.6 was added to the neutralized solutions, as well as 2 ml. of 0.13% sodium β-naphthoquinone-4-sulfonate; the solutions were shaken and allowed to stand for 2 min. Subsequently, 1.2 ml. of 7.5% hydrochloric acid solution was added and the colored substance that formed was extracted with 5.0 ml. n-hexane. The absorbances were determined at 450 nm. against a pure solvent blank.

Concentrations of 5-amino-3,4-dimethylisoxazole were calculated from a standard solution prepared with pure sample in adequate concentration in 24.5% hydrochloric acid solution, applying the procedure described for the problem. The system obeyed Beer's law in the concentration range used. The results of these determinations are shown in Fig. 2.

The extractions with n-hexane offer a specific method for the determination of 5-amino-3,4-dimethylisoxazole in the presence of hydroxylamine, ammonia, sulfisoxazole, sulfanilamide, and sulfanilic acid; these compounds also react with the reagent, but the compounds they form cannot be extracted by the solvent, which selectively extracts the colored substance formed between the reagent and 5-amino-3,4-dimethylisoxazole.

Determination of Carbonyl Groups—The opening of the isoxazole ring in aqueous solutions implies the formation of compounds having carbonyl groups. They were determined using a colorimetric method adapted from the one proposed by Clarck and Lappin (6), which consists of allowing 2,4-dinitrophenylhydrazine to react with the compound to be determined and measuring the color yielded by the 2,4-dinitrophenylhydrazones in an alkaline medium.

The procedure used was as follows. One milliliter of distilled water and 0.1-1 ml. of hydrolyzed acid solution containing the compound to be determined were placed in a test tube, and this

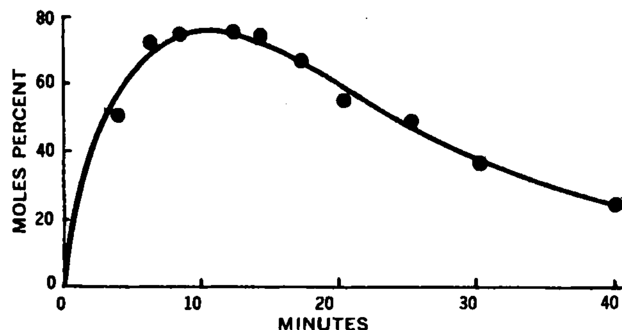
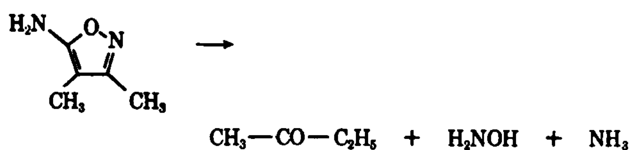
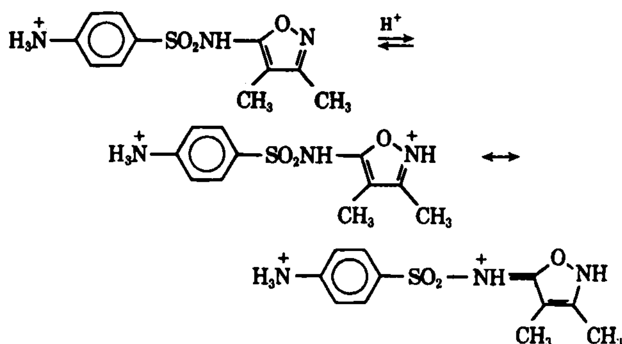


Figure 2—*Formation and degradation of 5-amino-3,4-dimethylisoxazole during sulfisoxazole hydrolysis.*

[11] Prepared by diluting in the same way as the sample from the 40% potassium hydroxide solution.



Scheme II



Scheme III

solution was completed to 2 ml. with 24.5% hydrochloric acid solution where necessary. Later, 5.0 ml. of methanolic solution saturated with 2,4-dinitrophenylhydrazine was added and the tubes were heated to 50° for 30 min. in a water bath. After cooling, 10 ml. of 10% sodium hydroxide solution was added and the resulting solution was quantitatively transferred to a 50-ml. volumetric flask, diluting to volume with methanol. The absorbance was determined at 480 nm. against a blank with all of the reagents; these were prepared according to the recommendations already indicated (6).

The concentration of the carbonyl groups formed was calculated from a standard curve prepared by means of a series of determinations made on a solution of 44.76 mmoles/l. of pure 2-butanone.

The determination of the carbonyl groups in a sulfisoxazole solution hydrolyzed during 140 min. yielded the following results: initial concentration of sulfisoxazole (moles per liter), 4.47×10^{-3}; and concentration of carbonyl groups in hydrolyzed solution, 4.42×10^{-3}. The results indicate that 1 mole of sulfisoxazole leads to the formation of 1 mole of the carbonyl groups.

Influence of Acid Concentration on Reaction Rates—A determination was made of the pseudo-first-order rate constants for the degradation of sulfisoxazole and the proportions of the final products, sulfanilamide and sulfanilic acid, at three different acid concentrations. Table II shows these results.

DISCUSSION

Experimental results indicate that, in the degradation of sulfisoxazole by the action of moderately concentrated hydrochloric acid at 108°, two degradative pathways (Scheme I) coexist in the concentration range studied. Degradative pathway A implies hydrolytic cleavage of the molecule at the sulfonamide group bond and is common to all sulfonamides. Degradative pathway B implies the opening of the isoxazole ring and leads to the formation of sulfanilamide as one of the final products.

Von Ernst and Seydel (7) studied the hydrolysis of sulfisoxazole in 1 *N* hydrochloric acid within the 50–90° temperature range and postulated one single degradative way, which agrees with pathway A proposed in the present paper.

An opening of the ring also takes place in the 5-amino-3,4-dimethylisoxazole, formed in degradative pathway A, similar to that which takes place in the sulfisoxazole molecule in degradative pathway B (Scheme II).

These degradative processes can be associated with a mechanism of acid catalysis which implies a preequilibrium between the substrates and protonated substrates (Scheme III). Sulfisoxazole possesses an aromatic primary amino group which, under reaction conditions, is in its complete protonated form; the respective activated states for the two degradative pathways can be associated with a second protonation in the isoxazole ring (8).

To study the influence of acidity changes on the velocity of the two degradative pathways, the ionization ratio *I* between diprotonated and monoprotonated forms of sulfisoxazole for the three concentrations of hydrochloric acid used was determined. Calculations were made starting from the regression line of the linear free energy relationships correlation for the second sulfisoxazole protonation (8) using values of *Ho*[12,13]. This implies taking the behavior of sulfisoxazole ionization in sulfuric acid as a reference.

To recognize how the rates of reaction for pathways A and B are affected when acidity conditions vary, velocity coefficients were correlated by the classical Zucker and Hammett method (9) (log K_ψ against $-Ho$) and by the treatment proposed by Bunnett and Olsen (10) which correlates (log K_ψ − log *I*) with (log [H⁺] + *Ho*).

Both treatments supply linear correlations for the two degradative pathways. Correlation slopes between log K_ψ and $-Ho$ were 1.01 and 0.52 for A and B, respectively (Fig. 3). The values of ϕ parameter which appear from correlations between (log K_ψ − log *I*) and (log [H⁺] + *Ho*) were 0.05 and 0.74 for A and B, respectively (Fig. 4).

The behavior of pathway B with the variations in acidity conditions, interpreted according to the Bunnett and Olsen (10) criterion, suggests the participation of water in the rate-determining step;

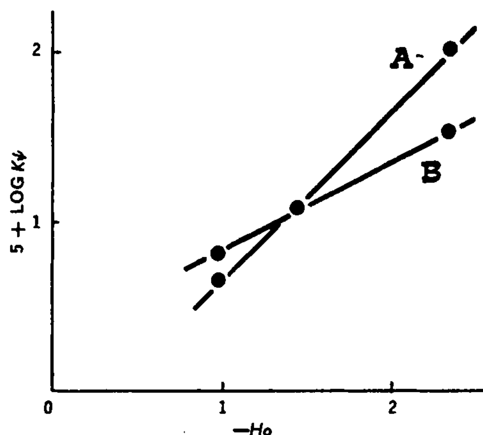


Figure 3—*Correlation between log* K_ψ *and* −Ho *for degradative pathways A and B.*

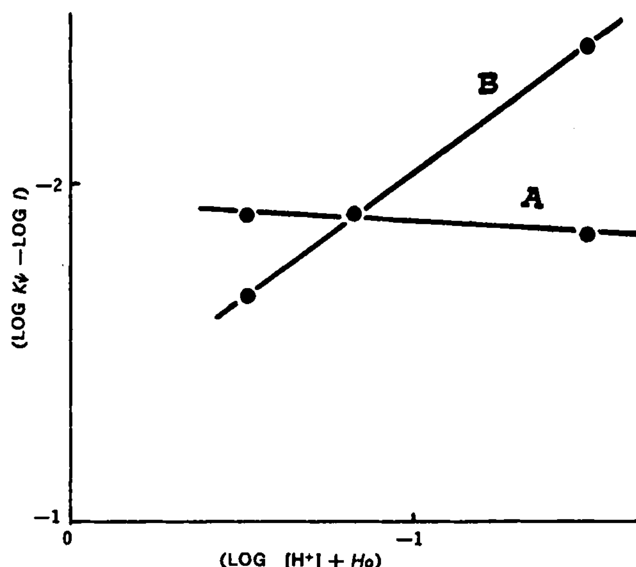


Figure 4—*Correlations between log* K_ψ − *log* I *and* (Ho + *log*[*H*⁺]) *or degradative pathways A and B.*

[12] *Ho* values for hydrochloric acid solutions were taken from the scale given by Paul and Long, *Chem. Rev.*, 57, 1(1957).
[13] Part I (8) discusses the utilization of *Ho* in the treatment of the equilibrium of a biprotonated compound.

in the A degradative process with ϕ value near zero and a 1.01 slope in plots of (log K_ψ against $-Ho$), water would not participate in the rate-determining step, displaying a typical A-1 mechanism according to Zucker and Hammett (9). Therefore, degradative pathway B prevails at low acid concentrations and A prevails at high acid concentrations.

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New Compounds: *N,N*-Dimethyl-[3-(1-alkylpiperidyl)]carbamates, Potential Cholinesterase Inhibitors

IAN W. MATHISON▲, KATHLEEN C. FOWLER, and ELIZABETH R. PETERS

Abstract □ The synthesis of 10 piperidine carbamates was carried out by condensation of various 3-hydroxypiperidines with dimethylcarbamyl chloride or, alternatively, by treatment of the hydroxy compound with phosgene followed by dimethylamine. Changes were made in the length of the alkyl chain substituted on the heterocyclic nitrogen. The compounds were developed as potential cholinesterase inhibitors as a continuation of previous studies.

Keyphrases □ *N,N*-Dimethyl-[3-(1-alkylpiperidyl)]carbamates—synthesized as potential cholinesterase inhibitors □ Cholinesterase inhibitors, potential—synthesis of *N,N*-dimethyl-[3-(1-alkylpiperidyl)]carbamates □ Piperidine carbamates—synthesized as potential cholinesterase inhibitors

The established interest of these laboratories in the synthesis and evaluation of potential cholinesterase inhibitors (1, 2) led recently to the completion of the synthesis of some compounds intimated in earlier work (1). The studies related to the effects on inhibitory potency of a series of compounds showing isosteric replacements of known cholinesterase inhibitors. The compounds possessed the general structural formulas indicated for I and II and were correlated with compounds of general formula III which were synthesized earlier (3) and shown to be active inhibitors. The data suggested (1) that the compounds having the urea moiety (II) provided a better "fit" in the area of the esteratic site than those possessing the acetamide function (I). To complete the series of isosteric modifications of the acetylcholine skeleton, the synthesis of carbamate derivatives of piperidines was considered appropriate. This approach was further substantiated by the presence of the carbamate moiety in physostigmine—a potent cholinesterase inhibitor. The compounds reported in this paper possess the general formula shown for IV and can be readily related to compounds of the general structures I–III.

The synthetic route adopted involved a preliminary quaternization of 3-hydroxypyridine followed by catalytic hydrogenation to the corresponding *N*-alkyl-3-hydroxypiperidine (Scheme I).

Two methods were chosen to introduce the carbamate function: treatment of the 3-hydroxypiperidine with di-