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Nucleophilic Displacement Reactions at the Thiol-Ester Bond of δ -ThiolvalerolactoneBY THOMAS C. BRUCE, J. J. BRUNO¹ AND WEI-SHIN CHOU

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The kinetics of the reaction of δ -thiolvalerolactone with nineteen bases (H_2O , T 30°, $\mu = 1.0 M$) has been determined. Three types of kinetic expressions were obtained: (A) $v = k_r(\text{base})(\text{lactone})$; (B) $v = k_r(\text{base})^2(\text{lactone})$; and (C) $v = k_r(\text{base})^2(\text{lactone}) + k_r'(\text{base}) \times (\text{conjugate acid})(\text{lactone})$. In C, $k_r = k_r'$ so that the second-order rate of reaction of the thiolactone with the base species is equally sensitive to the concentration of the base or its conjugated acid. As in previous studies, nucleophiles with unshared pairs of electrons α to the nucleophilic atom are unusually reactive. When the rate constants for the reaction of the various nucleophiles are compared to the rate constants for the reaction of the same nucleophiles with *p*-nitrophenyl acetate *via* a log k_r plot it is found that the majority of the points provide a fit to a line of slope 1.0 passing through zero (*i.e.*, most of the nucleophiles possess approximately the same numerical rate constants for reaction with *p*-nitrophenyl acetate and the thiolactone). The points for H_2NNH_2 , NH_2OCH_2 and NH_2OH fit the plot quite well establishing the " α -effect" to be of approximately the same importance in the displacement reaction on both substrates. Those nucleophiles whose rate data do not fit the plot of slope 1.0 are more reactive with *p*-nitrophenyl acetate than the thiolactone. Arguments are presented which support the hypothesis that for those nucleophiles having near identical rates of reaction with *p*-nitrophenyl acetate and the thiolactone the determined rate constant is that for nucleophilic attack at the carbonyl carbon atom. For those nucleophiles which exhibit much greater rates of reaction with *p*-nitrophenyl acetate it is reasoned that the partitioning of the tetrahedral intermediate is of kinetic significance so that the rate constants reflect the greater leaving tendency of *p*-nitrophenoxide ion *vs.* mercaptide ion.

Introduction

In view of the large literature on displacement reactions at the sp^3 carbon,²⁻⁴ it is quite surprising that, until relatively recently, nucleophilic displacements at the ester carbonyl group⁵ received scant attention (with the exception of studies involving OH^- and H_3O^+ catalyzed hydrolysis).⁶ The only ester that has received what might be considered to approach thorough exploration in its reaction with nucleophiles of divergent nature is *p*-nitrophenyl acetate.⁷⁻¹⁸ From the latter studies, it became evident that the empirical² and semi-empirical³ correlative equations developed from the literature on displacement reactions at the sp^3 carbon had little utility in correlating the rates of displacements of *p*-nitrophenol from its acetyl ester.¹⁰⁻¹² In particular, for a base series (*i.e.*, imidazoles, oxyanions, etc.), the logarithms of the second-order rate constants for *p*-nitrophenol appearance are a linear function of the pK_a' of the base (the familiar Brønsted relationship). In addition, each base series provides a different linear plot, each being more or less parallel to the other ($\alpha = 0.6$ to 0.8) but displaced one from the other. Nitrogen bases (imidazoles, pyridines and anilines) were found to be better nucleophiles than oxyanions of the same pK_a' . Thus, imidazole and phosphate dianion (both $pK_a' 7.0$) differ in their rates of reaction with *p*-nitrophenyl acetate by 10^3 . The linear dependence of $\log k_{rate}$ on pK_a' for a particular base series was found to hold over many powers of 10 in K_a' . Thus, for a series of oxyanions a good Brønsted plot is obtained over $5 pK_a'$ units,¹³ the dependence of nucleophilicity on basicity only becoming inoperative for oxyanions of $pK_a' > pK_w$.¹⁴ In fact, nucleophiles of low pK_a' but of high

nucleophilicity toward the sp^3 carbon are ineffective in displacement reactions at the sp^2 carbon of *p*-nitrophenyl acetate (see particularly ref. 12). An important adjunct to basicity in increasing nucleophilicity, toward the ester bond of *p*-nitrophenyl acetate, is the possession of a pair of unshared electrons on the atom α to the nucleophilic center (as in H_2NOH).¹¹ This has been termed the α -effect¹⁹ and postulated to involve the participation of the unshared pair of electrons in the resonance stabilization of the transition state.

For oxygen esters in which the leaving group is a stronger base than *p*-nitrophenol, general base or general acid assistance to nucleophilic attack is usually encountered when possible (*i.e.*, aminolysis reactions involving 1° and 2° amines,^{15,16,20} hydroxyl aminolysis,^{21,22} general base-catalyzed hydrolysis,^{23a,b} etc.) and even in the case of *p*-nitrophenyl acetate, general base-catalyzed nucleophilic attack may be encountered in certain instances.²⁴ As useful as *p*-nitrophenyl acetate has been as a substrate, it is essential to obtain comprehensive kinetic data for displacement reactions at other ester and amide bonds in order to comprehend better the factors which determine nucleophilicity and the role of general acid and general base assistance. It is the purpose of this communication to describe our initial studies into the kinetics and mechanisms of nucleophilic displacement reactions at the thiol-ester bond. For this purpose we have chosen δ -thiolvalerolactone as substrate. Thiol-esters are particularly suited to our stated purpose because of the ease in following, spectrophotometrically, their disappearance and also due to the fact that displacement reactions at the thiol-ester bond are subject to the complexities of general acid and general base catalysis.^{25a,b} A thiolactone rather than an *n*-alkyl thiol ester was chosen on the basis of the known greater reactivity of lactones as compared to esters²⁶ and the expectation that this would also be true of thiolactones. δ -Thiolvalerolactone was found to be particularly interesting on the basis that the second-order rate constant for its alkaline

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hydrolysis is very nearly identical with the corresponding rate constant for *p*-nitrophenyl acetate.²⁷

Experimental

Apparatus.—The spectrophotometer employed was a Zeiss PMQIT. The cell compartment of the spectrophotometer was modified to accommodate a hollow brass block cuvette holder through which was circulated water at a constant temperature of $30 \pm 0.1^\circ$ (Precision Scientific Co., circulating water-bath). All *pH* measurements were made with a Radiometer model 22 *pH* meter. The combined glass-calomel electrode (Radiometer GK 2021 C) and electrode-cell compartment were thermostated at $30 \pm 0.1^\circ$ during the course of these investigations.

Compounds. δ -Thiolvalerolactone was that used in a previous study²⁷ and stored at 0 – 5° until used.

The piperidine and ethylenediamine hydrochlorides were prepared by passing dry HCl gas through alcoholic solutions of the bases (piperidine, Eastman Kodak Co. practical; ethylenediamine, Eastman Kodak Co. White Label) cooled in an ice-water bath. The precipitated salts were collected by filtration, recrystallized several times from ether-alcohol mixtures, and dried *in vacuo* over phosphorus pentoxide.

Morpholine (Eastman Kodak Co., practical) was purified by distillation, after refluxing for 24 hr. over sodium metal, under an atmosphere of dry nitrogen; b.p. 125 – 126° (740 mm) (lit.²⁸ b.p. 128.3°).

Hydroxylamine hydrochloride (Baker and Adamson reagent grade) was recrystallized from 95% alcohol before using and dried over P_2O_5 *in vacuo*.

Triethylenediamine (1,4-diazabicyclo(2.2.2)octane) was obtained from Aldrich Chemical Co. and was recrystallized from 95% alcohol and dried *in vacuo* over $CaCl_2$ and BaO before using. Tris-(hydroxymethyl)-aminomethane was of primary titrimetric grade (Sigma) and was used without purification.

Acetone oxime, hydrazine dihydrochloride, glycine, pentaerythritol and methoxylamine hydrochloride (all Eastman Kodak Co. White Label) were dried *in vacuo* before using.

Trifluoroethanol (Aldrich Chemical Co.) was distilled before using, b.p. 72 – 74° (738 mm).

Kinetics.—The reactions of δ -thiolvalerolactone with the various reagents were followed by observing the decrease in thiolactone absorption at $239.5 m\mu$.

Because of the high absorbance of the solutions of triethylenediamine used in this study, the rates of disappearance of thiolactone could not be followed at $239.5 m\mu$. At each point in the run, the absorbance was scanned over a 10 – $15 m\mu$ region and a "new peak" shifted to the high wave length side of $239.5 m\mu$ was obtained (see Results section). The rate was followed by observing the decrease in absorbance at a convenient wave length on the high wave length side of the "new peak."

A stock solution of about 0.20 g. of thiolactone in 5 ml. of ether was prepared. Two drops of this solution from a calibrated dropper, diluted to 10 ml. with water, gave a solution approximately $10^{-4} M$ in thiolactone. The absorption due to the various bases and nucleophiles was always compensated for by using a solution identical with the reaction solution (minus thiolactone) in the reference cell. The reactions were carried out in $\frac{1}{2}$ cuvettes. When the *pH* of the reaction mixture was greater than 7.5 – 8.0 , deaerated water was employed. In all cases, the $\frac{1}{2}$ cuvettes were filled to the stopper level during runs, so that no air space remained in the cell after the stopper was put on. The *pH* of solutions was determined at the beginning and end of each run. The concentration of basic reagent was far in excess of the thiolactone concentration, in all instances. Thus the *pH* remained constant during runs, and pseudo-first-order kinetics were obtained. Potassium chloride was used to bring all reaction solutions to a calculated ionic strength of $1.0 M$. The reactions were routinely followed to two half-lives or more and were found to be first order. The pseudo-first-order rate constants were obtained from the slope of plots of $\log O.D._0/O.D._t$ vs. time.

The kinetics of the reactions of morpholine, ethanolamine and piperidine with *p*-nitrophenyl acetate were followed as previously described.^{23b} The following results were obtained.

Nucleophile	<i>M</i>	<i>pH</i>	k_{obs} , min. ⁻¹	k_2 , 1. mole ⁻¹ min. ⁻¹
Morpholine	0.10	8.0	0.829	41.1
	.05		.449	
	.025		.229	
	.01		.073	
	.004		.029	
Piperidine	.01	9.40	.716	3030
	.008		.626	
	.006		.498	
	.004		.359	
	.002		.229	

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Ethanolamine	0.05	8.90	1.60	246
	.02		0.672	
	.01		0.319	
	.10	8.62	1.81	246
	.07		1.19	
	.04		0.804	
	.01		0.175	

where k_{obs} represents the pseudo-first-order rate constant obtained experimentally and k_2 the second-order rate constant calculated on the basis of the reaction of the free base species with the ester.

pK_a' Determinations.—A collection of pK_a' values employed in this study is provided in Table I. The values have been obtained from the literature or experimentally by the method of half-neutralization. The pK_2' of triethylenediamine (TEDA) was determined spectrophotometrically by the method previously outlined²² and found to be 9.28 (half-neutralization gave a value of pK_2' of 9.13 and a pK_1' of 5.3).

TABLE I

THE pK_a' VALUES OF NUCLEOPHILES EMPLOYED IN THIS STUDY

Nucleophiles	pK_a'	Method
Tris-(hydroxymethyl)-aminomethane	8.15 ^f	$\mu = 1.0 M$, 30° , half-neutral.
Pentaerythritol	14.00 ^a	H_2O , 25°
CF_3CH_2OH	12.36 ^a	H_2O , 25°
Glycine	9.63 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Imidazole	7.10 ^b	$\mu = 1.0 M$, 30° , half-neutral.
Phosphate	6.90 ^c	H_2O , 25°
Hydroxylamine	6.04 ^b	$\mu = 1.0 M$, 30° , half-neutral.
Methoxylamine	4.81 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Acetoxime	12.4 ^d	$\mu = 1.0 M$, 30° , half-neutral.
Ethanolamine	9.72 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Triethylenediamine	5.3 (pK_1) ^e	$\mu = 1.0 M$, 30° , half-neutral.
	9.28 (pK_2) ^e	$\mu = 1.0 M$, 30° , spectrophotometric
Hydrazine	8.11 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Morpholine	8.59 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Piperidine	11.10 ^e	$\mu = 1.0 M$, 30° , half-neutral.
Ethylenediamine	7.15 ^e (pK_1)	$\mu = 1.0 M$, 30° , half-neutral.
	10.1 ^e (pK_2)	$\mu = 1.0 M$, 30° , half-neutral.
Water	13.83 ^g	30°

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Results²⁹

The kinetic expressions and related rate constants for the reaction of nineteen nucleophiles with δ -thiol-

(29) Abbreviations employed are: a_H , hydrogen ion activity as determined with the glass electrode; K_w , the autoprotolysis constant of water at 30° (1.47×10^{-14}); k_{obs} , the experimentally determined pseudo-first-order rate constants: k_2' , k_3' , ..., etc., apparent second, third, ..., etc., order rate constants calculated on the basis of the concentration of total nucleophilic species (N_T); k_2 , k_3 , ..., etc., true second, third, ..., etc., order rate constants calculated on the basis of the concentration of the reacting species of the nucleophile; k_{OH} , the second-order rate constant for alkaline hydrolysis of δ -thiolvalerolactone.

The concentrations of the ionic and neutral species of the nucleophile in water are: (N_T) = (NH_2^{++}) + (NH^+) + (N_F) + (N^\ominus), etc.; where (N_T) represents the total concentration of all species; (NH_2^{++}) and (NH^\oplus) the

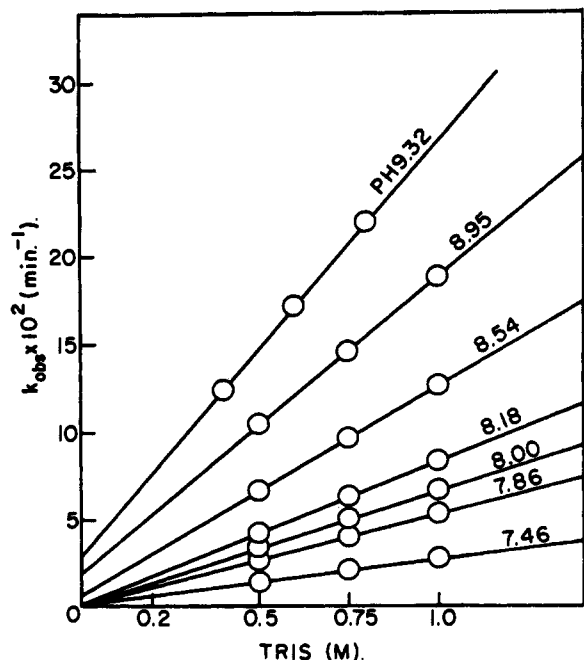


Fig. 1.—The linear dependence of the pseudo-first-order rate constants for the reaction of tris-(hydroxymethyl)-aminomethane with δ -thiolvalerolactone at seven pH values.

valerolactone in water at 30° and at a calculated ionic strength of 1.0 *M* (with KCl) are recorded in Table II. What follows is a description of the experimental results which lead to the data of Table II. The various nucleophiles have been divided into groups on the basis of the similarity of kinetic results. It was not possible to obtain useful experimental data for certain nucleophiles because of their very strong absorption in the region of 240 *m* μ (*i.e.*, anilines, pyridines, azide, bisulfite and thiosulfate).

Oxygen bases employed in this study were $\text{CF}_3\text{-CH}_2\text{O}^-$, HPO_4^{--} , borate, CO_3^{--} , acetone oxime anion and the mono-oxyanion of pentaerythritol. In these and all experiments reported in this paper (N_T) far exceeded that of the thiolactone so that the disappearance of the latter always followed pseudo-first-order kinetics (k_{obs}).

$$\frac{d(\text{lactone})}{dt} = k_2(N^\ominus)(\text{lactone}) + k_{\text{OH}}(\text{OH}^-)(\text{lactone}) \quad (1)$$

$$k_{\text{obs}} = \frac{k_2(N_T)K_a}{(K_a + a_{\text{H}})} + \frac{k_{\text{OH}}K_w}{a_{\text{H}}}$$

The values of k_2 were determined as the slope of the linear plots obtained when k_{obs} was plotted *vs.* the calculated values of the concentration of N^\ominus (except in the instance of carbonate when the stoichiometric concentration of carbonate in mixed carbonate-bicarbonate buffers was employed). In the case of borate and acetone oxime the disappearance of thiolactone was found to be independent of the oxyanion concentration (Table II). For the reactions with borate, carbonate and phosphate the nucleophile and its conjugate acid served as buffers to ensure constant pH. In the case of trifluoroethanol, acetone oxime and pentaerythritol, dilute (0.01 *M*) carbonate buffers were employed to maintain constant pH.

The reaction of tris-(hydroxymethyl)-aminomethane (TRIS) with δ -thiolvalerolactone was found to be first order in the total concentration of TRIS at all pH values employed (Fig. 1). The values of the pseudo-second-order rate constants (k_2') were obtained as the slopes of the plots of k_{obs} *vs.* (N_T) ($N_T = \text{NH}^+ +$

concentration of acidic species; (N_F) the concentration of neutral basic species; and (N^\ominus) the concentration of the basic anionic species. The concentration of δ -thiolvalerolactone has been abbreviated as (*L*).

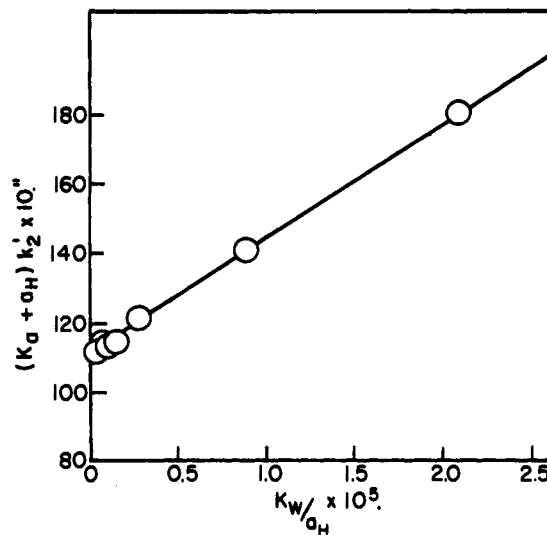


Fig. 2.—The linear dependence of the product of the apparent second-order rate constant and the sum of the dissociation constant and hydrogen ion activity upon the hydroxide ion activity in the reaction of tris-(hydroxymethyl)-aminomethane with thiolactone.

$N_F + N^\ominus$; where $\text{NH}^+ = (\text{HOCH}_2)_3\text{CNH}_3^+$, $N_F = (\text{HOCH}_2)_3\text{CNH}_2$ and $N^\ominus = (\text{HOCH}_2)_2\text{C}(\text{NH}_2)\text{-CH}_2\text{O}^-$.

$$k_2' = (k_{\text{obs}} - k_{\text{OH}}(\text{OH}^-))/N_T \quad (2)$$

A cursory inspection of the values of k_2' revealed to us that the reaction of TRIS with the thiolactone follows the same kinetic scheme as that previously found by us for the reaction of TRIS with *p*-nitrophenyl acetate (3).¹⁷

$$-dL/dt = k_2(L)(N_F) + k_3'(L)(N_F)(\text{OH}^-) + k_{\text{OH}}(\text{OH}^-)(L) \quad (3)$$

$$= \frac{K_a k_2(L)(N_T)}{(K_a + a_{\text{H}})} + \frac{k_3' K_w K_a(L)(N_T)}{(K_a + a_{\text{H}}) a_{\text{H}}} + k_{\text{OH}}(\text{OH}^-)(L)$$

$$k_2' = \frac{k_2 K_a}{K_a + a_{\text{H}}} + \frac{k_3' K_w K_a}{(K_a + a_{\text{H}}) a_{\text{H}}}$$

and

$$k_2'(K_a + a_{\text{H}}) = k_2 K_a + ((k_3' K_a K_w)/a_{\text{H}}) \quad (4)$$

It follows from 4 that a plot of $(K_a + a_{\text{H}})k_2'$ *vs.* K_w/a_{H} should yield a straight line of slope $k_3' K_a$ and intercept $k_2 K_a$ (Fig. 2). The values of k_2 and k_3' were so determined and are recorded in Table II. The value of k_2 is the true second-order rate constant for the reaction of the primary amino group of TRIS with the lactone, whereas the constant k_3' is related to the true second-order rate constant for the reaction of the mono-oxyanion of TRIS (k_3) with the lactone by the expression $k_3' = k_3 K_2/K_w$ where K_2 is the dissociation constant for the formation of the oxyanion from the neutral TRIS molecule. The value of K_a for TRIS is of course a readily determinable constant and has been used in the calculations (Table I), whereas the value of K_2 is most probably of the magnitude of K_w (see pentaerythritol in Table I) but has not been determined.

Triethylenediamine (TEDA) may be profitably discussed separately because of the experimental difficulties experienced in determining the rate constants. The absorbance of TEDA at 240 *m* μ is rather large ($\epsilon \cong 28$). Therefore, in the concentration range employed (0.02–0.2 *M* TEDA), the absorbance due to TEDA requires that the slit widths of the spectrophotometer be near maximum. The effect of these large slit widths is to give an apparent bathochromic shift of λ_{max} for δ -thiolvalerolactone absorption as well as a decrease in its extinction coefficient (specific absorption). In order to demonstrate that this effect was due to the slit opening

TABLE II
THE KINETIC EXPRESSIONS AND ASSOCIATED RATE CONSTANTS DETERMINED FOR
THE REACTION OF A SERIES OF BASES WITH δ -THIOLVALEROLACTONE
Solvent water, temperature 30°, ionic strength 1.0 *M* (with KCl)

Base	Reaction kinetics ^b	Rate constants ^a	pH range employed	No. of pH values at which k_{obs} was detd.	No. of k_{obs} values detd.	Concn. range for base, <i>M</i>
1 Borate	No reaction detected		9.1	1	1	0.27
2 $CF_3CH_2O^-$	$k(B)(L)$	1.27×10^1	9.61	1	4	.2-1.0
3 $(CH_3)_2C=N-O^-$	No reaction detected		10.4	1	4	.2-1.0
4 OH^-	$k(B)(L)$	740 ^c	5.94-8.40	12	12	
5 H_2O	$k(B)(L)$	$1.8 \times 10^{-6c,d}$				
6 CO_3^-	$k(B)(L)$	2.36×10^{-2}	9.11-9.42	2	8	.04-0.2
7 HPO_4^{--}	$k(B)(L)$	6.24×10^{-3}	7.16	1	4	.125-0.34
8 Triethylenediamine	$k(B)(L)$	1.7×10^{-2}	8.91-9.62	4	16	.01-0.11
9 Imidazole	$k(B)(L)$	2.8×10^{-3c}	5.94-8.40	12	52	.2-1.0
10 $HOCH_2CH_2NH_2$	$k(B)(L)$	5.29	8.76-9.90	5	20	.02-0.12
11 Tris-(hydroxymethyl)-aminomethane	$k(B)(L)$	1.57×10^{-1}	7.46-9.32	7	21	.40-1.0
	$k(B)(L)(OH^-)$	4.68×10^3	7.46-9.32	7	21	.40-1.0
12 $(HOCH_2)_3CCH_2O^-$	$k(B)(L)$	1.53×10^4	9.0	1	3	.3-0.5
13 Ethylenediamine	$k(NH_3^+CH_2CH_2NH_2)(L)$	1.68	6.76-10.18	13	56	.0035-0.14
	$k(NH_2CH_2CH_2NH_2)(L)$	1.04×10^2	6.76-10.18	13	56	.0035-0.14
14 Glycine	$k(B)(BH^+)(L)$	6.35×10^1	8.98-10.15	5	20	.02-0.10
	$k(B)^2(L)$	6.35×10^1	8.98-10.15	5	20	.02-0.10
15 H_2NOH	$k(B)^2(L)$	4.47×10^1	5.74-7.54	6	25	.025-0.10
16 CH_3ONH_2	$k(BH^+)(B)(L)$	7.6×10^{-1}	4.81-5.92	5	19	.05-0.50
	$k(B)^2(L)$	1.55	4.81-5.92	5	19	.05-0.50
17 Morpholine	$k(B)(BH^+)(L)$	6.6×10^{-1}	8.09-8.59	2	10	.2-1.0
	$k(B)^2(L)$	6.6×10^{-1}	8.09-8.59	2	10	.2-1.0
18 Piperidine	$k(BH^+)(B)(L)$	5.9	9.04-9.72	2	9	.4-1.0
	$k(B)^2(L)$	5.9	9.04-9.72	2	9	.4-1.0
19 H_2NNH_2	$k(BH^+)(B)(L)$	2.25×10^3	7.03-9.07	7	25	.005-0.04
	$k(B)^2(L)$	2.25×10^3	7.03-9.07	7	25	.005-0.04

^a Given in time units of minutes and concentration units of *M*. ^b The basic species is designated as B and the conjugate acid as BH⁺. Lactone concentration is designated by L. ^c Data from ref. 29 of this paper. ^d Spontaneous solvolysis rate divided by 55.5 *M*.

and not to some effect as complexing of reactants, an aqueous solution of the thiolactone and a solution of TEDA were placed in separate cuvettes. When the cuvettes were placed face to face and balanced against approximate blanks the same apparent "peak shift" and "absorption lowering" were obtained as when the lactone and TEDA were combined. Furthermore, the identical effect can be observed by substituting any solution for the TEDA solution that possessed the same O.D. Changes in concentration of thiolactone bring about only slight changes in absorbance and position of λ_{max} . A fivefold increase in thiolactone concentration (in the order of 10^{-4} *M*) caused a shift of 2 $m\mu$ to the higher wave length. A fivefold increase in TEDA (in the range of 0.02 *M*) caused a 10 $m\mu$ bathochromic shift of the observed λ_{max} .

The phenomenon noted above may be identical with that observed by Stadtman in the study of acetyl glutathiones.³⁰ In this case, it was reported that the λ_{max} associated with thiol ester absorption (232 $m\mu$) decreased in the presence of large excesses of thiol and disulfide, but not in the presence of sulfide. The phenomenon was rationalized by proposing the formation of thiol ester complexes with mercaptan and disulfide. The fact that sulfides did not show this phenomenon is most likely the result of their lacking a strong trailing absorption in the region of 230 $m\mu$.³¹

The kinetics of thiolactone disappearance in the presence of TEDA could not be followed in the region where the background absorption due to TEDA was very high. However, by following the decrease in absorb-

ance on the high wave length side of the thiolactone peak, in a region 4-5 $m\mu$ away from the apparent λ_{max} , it was possible to obtain good first-order kinetics. In Fig. 3 there is plotted the values of the observed pseudo-first-order rate constants obtained at four pH values vs. the concentrations of the conjugate base of TEDA. The slopes of the plots afford the second-order rate constant for the reaction of TEDA with lactone and the intercepts the pseudo-first-order constants for hydroxide ion catalysis. The fact that the plots of Fig. 3 are parallel at various pH values provides convincing evidence that the reaction involves an unassisted second-order reaction of the conjugate base of TEDA with the thiolactone.

Four other nitrogen nucleophiles investigated were morpholine, pyridine, hydrazine and glycine. These four may be conveniently discussed together because of the identity of the kinetic equations describing the reactions with the thiolactone. The reaction of hydrazine with δ -thiolvalerolactone from pH 7.0 to 9.0 was found to be second order in total hydrazine (N_T) as shown in Fig. 4. Plotting the pseudo-third-order constants (k_3') obtained from the slopes of this graph ($k_{obs}/(N_T)^2$) vs. pH provides a sigmoid curve of the type exhibited for the titration of a monobasic acid (Fig. 5). In Fig. 5 the points represent determined k_3' values, while the curve is a theoretical dissociation curve calculated for an acid of pK_a 8.17, which is the determined pK_a' of hydrazine. Equations 5 and 6 describe the kinetics of the reaction of hydrazine with δ -thiolvalerolactone

$$v = k_{obs}(L) = k_3'(N_T)^2 \left[\frac{K_a'}{K_a' + a_H} \right] (L) + k_{hyd}(L) \quad (5)$$

$$k_{obs} = k_3(N_T)^2 \left[\frac{K_a'}{K_a' + a_H} \right] + k_{hyd} \quad (6)$$

(30) E. E. Stadtman and L. B. Bradely, "Glutathione," Proc. Symp., Ridgefield, Conn., 1953, pp. 89-101.

(31) R. C. Passerini, in "Organic Sulfur Compounds," N. Kharasch, ed., Pergamon Press, New York, N. Y., 1961, Ch. 7.

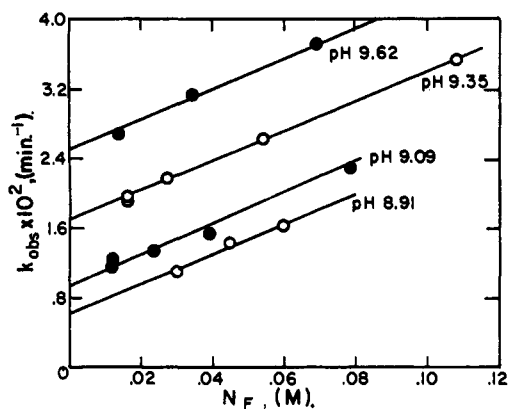


Fig. 3.—Plot of the concentration of neutral triethylenediamine vs. the pseudo-first-order rate constant for reaction with thiolactone at four pH values.

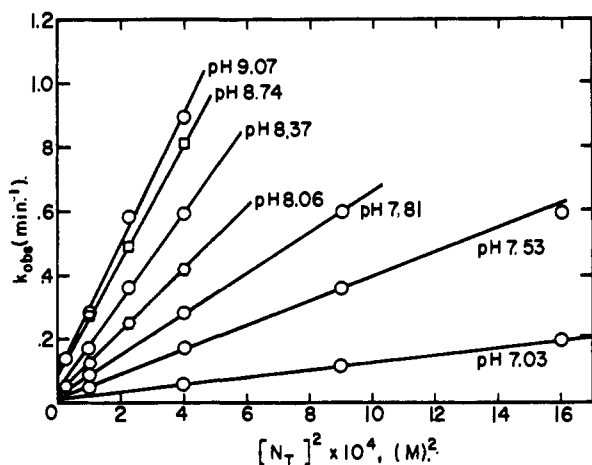


Fig. 4.—Plot of the square of the concentration of unprotonated hydrazine species vs. the pseudo-first-order rate of reaction of hydrazine with the thiolactone at seven pH values.

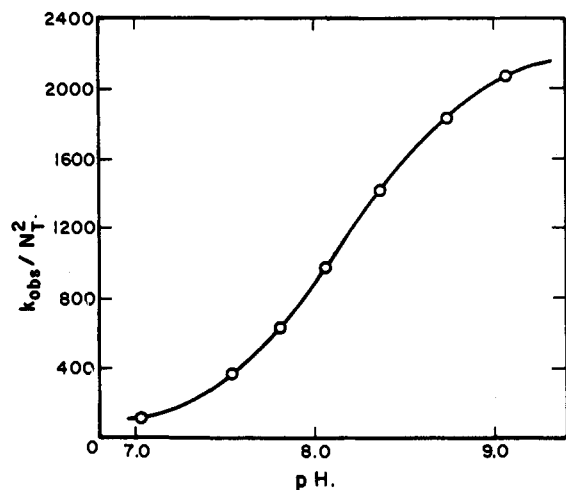


Fig. 5.—Plot of the apparent third-order rate constant for the reaction of hydrazine with thiolactone vs. pH .

in which K_a' corresponds to the second dissociation constant of hydrazine. A plot of $(k_{obs} - k_{hyd})$ vs. $(N_T)^2 K_a' / (K_a' + a_H)$ for all the pH 's is shown in Fig. 6, and from the slope of the plot we obtain k_8 ($2250 \text{ l.}^2 \text{ mole}^{-1} \text{ min.}^{-1}$). It should be recognized that the kinetic form of 6 is quite unique and in effect states that the rate of reaction of hydrazine with the lactone is approximately equally dependent on the concentration of the conjugate acid and conjugate base of hydrazine. This can

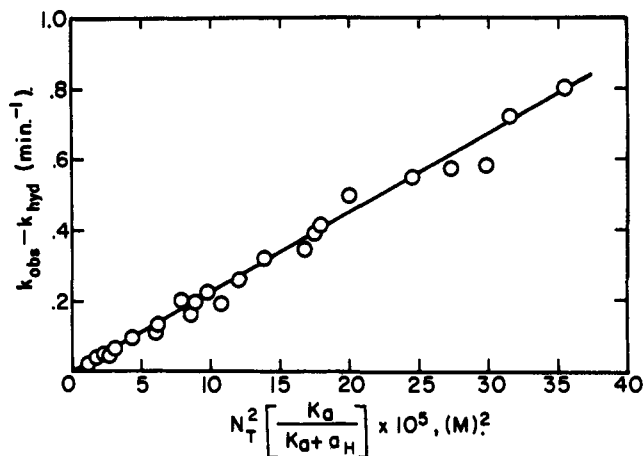


Fig. 6.—Plot of the pseudo-first-order rate constants for the reaction of hydrazine with the thiolactone vs. the product of the square of the concentration of total hydrazine and the mole fraction of neutral hydrazine species.

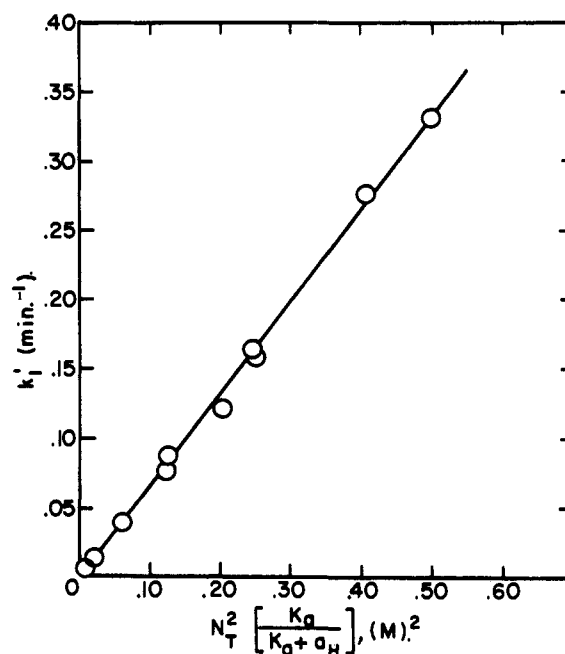


Fig. 7.—Plot of the pseudo-first-order rate constants for the reaction of morpholine with the thiolactone vs. the product of the square of the concentration of total morpholine and the mole fraction of neutral morpholine species.

be seen from the fact that substituting 7 and 8 into 6 provides 9, 10 and 11.

$$(N_F) = (N_T)K_a / (K_a + a_H) \quad (7)$$

$$(N_T) = (N_F) + (NH^{\oplus}) \quad (8)$$

$$k_{obs} - k_{hyd} = k_8'(N_T)(N_F) \quad (9)$$

$$k_{obs} - k_{hyd} = k_8'(N_F)(N_F + NH^{\oplus}) \quad (10)$$

$$k_{obs} - k_{hyd} = k_8'(N_F)^2 + k_8'(N_F)(NH^{\oplus}) \quad (11)$$

Other nucleophiles whose kinetic data fit the plot of k_{obs} vs. $(N_T)^2 K_a / (K_a + a_H)$ prescribed by eq. 6 most probably react with the lactone *via* a mechanism identical with that for hydrazine. The kinetic data for morpholine (Fig. 7), piperidine (Fig. 8) and glycine also fit eq. 6 and 11.

The kinetic data for **hydroxylamine and methoxyamine** do not fit eq. 6. The reaction of δ -thiolvalerolactone with methoxyamine is second order in base as indicated by the linearity of the plots of k_{obs} vs. $(N_F)^2$. Furthermore, a plot of $k_{obs} / (N_F)^2$ vs. a_H is linear and increases with increasing hydrogen ion concentration.

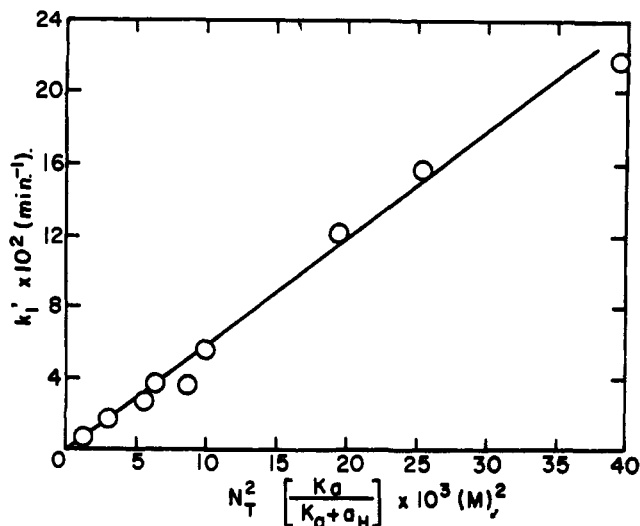


Fig. 8.—Plot of the pseudo-first-order rate constants for the reaction of piperidine with the thiolactone *vs.* the product of the square of the concentration of total piperidine and the mole fraction of neutral piperidine species.

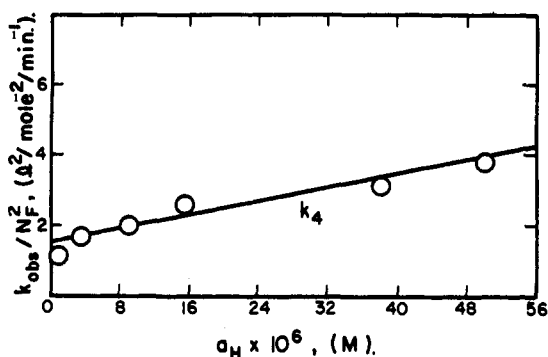


Fig. 9.—Plot of the apparent third-order rate constants for the reaction of methoxylamine with thiolactone *vs.* the hydrogen ion activity.

The plot has a positive intercept at $a_H = 0$. The kinetics are described by eq. 12.

$$k_{obs} = k_4(N_F)^2 a_H + k_3(N_F)^2 \quad (12)$$

The slope of the plot of $k_{obs}/(N_F)^2$ *vs.* a_H is k_4 while the intercept is k_3 (Fig. 9). The mechanisms that would be in accord with 12 are a general base-catalyzed nucleophilic attack (k_3) and a general base-specific acid-catalyzed nucleophilic attack (k_4). Alternatively, the term k_4 may be associated with a general acid-catalyzed nucleophilic attack (13).

$$k_4(N_F)^2 a_H = k_4 K_a (N_F)(NH^\oplus) \quad (13)$$

The reaction of **hydroxylamine** with δ -thiolvalerolactone is also second order in hydroxylamine species as can be shown by the linearity of the plots of k_{obs} *vs.* $(N_F)(NH^\oplus)$ at each pH . When the logarithm of the slopes of these plots (*i.e.*, $\log(k_{obs}/(N_F)(NH^\oplus))$) are plotted against pH a linear relationship of slope 1.0 is obtained from which it follows that the correct kinetic expression for the reaction is provided by 14.

$$k_{obs} = k_4(N_F)(NH^\oplus)(OH^-) \quad (14)$$

The value of k_4 was obtained as the slope of the plot of $k_{obs}/(N_F)(NH^\oplus)$ *vs.* K_w/a_H (Fig. 10). The expression 14 has the kinetic equivalence of 15 which corresponds to a general base-catalyzed reaction.

$$k_{obs} = k_4 K_w (N_F)^2 / K_a \quad (15)$$

The reaction of hydroxylamine with the thiolactone was too rapid to follow by determining the $\epsilon \cdot t$ hydroxamic acid produced *via* the Lippman-Tuttle procedure.³²

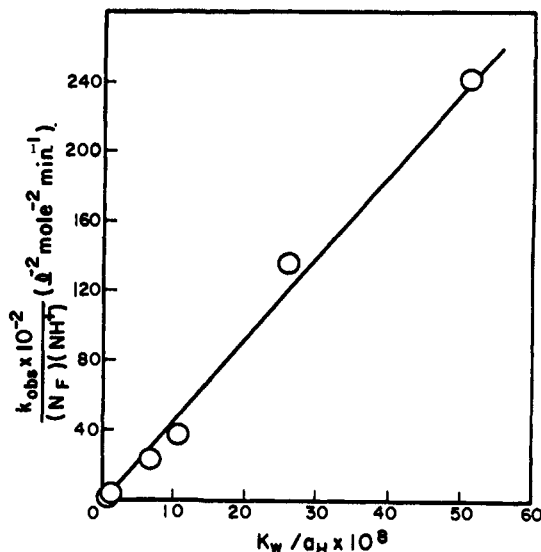


Fig. 10.—Plot of an apparent third-order rate constant for the reaction of hydroxylamine with the thiolactone *vs.* hydroxide ion activity.

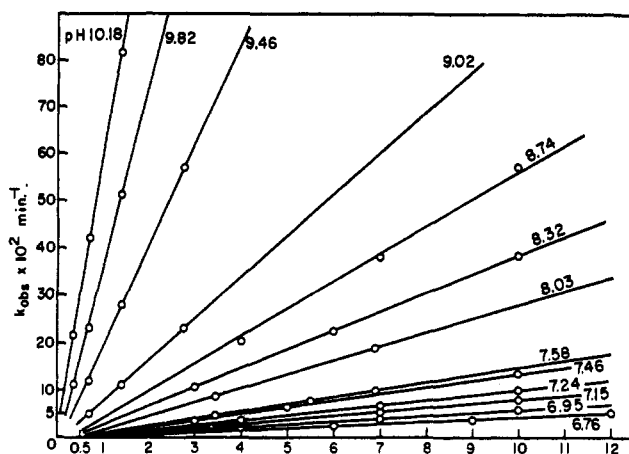


Fig. 11.—The linear dependence of the pseudo-first-order rate constant for the reaction of ethylenediamine with the thiolactone at thirteen pH values.

However, it was observed that at t_∞ an absorbance due to ferric hydroxamate could be developed and that this absorbance was proportional to the initial concentration of lactone employed.

The kinetics for the disappearance of thiolactone in the presence of varying amounts of **ethylenediamine** (ED) were studied at thirteen pH 's between pH 6.76 and 10.18. At all pH values the disappearance of thiolactone was found to be linearly dependent upon the first power of total diamine concentration (Fig. 11).

$$k_{obs} = k_2'(N_T) \quad (16)$$

Where $(N_T) = \oplus H_3N-CH_2CH_2-NH_2 + H_2N-CH_2CH_2-NH_2 + \oplus H_3N-CH_2CH_2-NH_3 = NH^\oplus + N_F + NH_2^\oplus$. On the basis of the presence of two distinct nucleophilic species (*i.e.*, N_F and NH^\oplus) one would anticipate that the pseudo-second-order rate constant (k_2' in 16) at any pH would be a composite constant containing the pseudo-second-order constants for N_F and NH^\oplus

$$v = \left[\frac{k_{NF}K_1K_2(N_T)}{K_1K_2 + K_1a_H + a_H^2} + \frac{k_{NH^\oplus}K_1(N_T)a_H}{K_1K_2 + K_1a_H + a_H^2} \right] (L) \quad (17)$$

$$k_2' = \frac{k_{NF}K_1K_2}{K_1K_2 + K_1a_H + a_H^2} + \frac{k_{NH^\oplus}K_1a_H}{K_1K_2 + K_1a_H + a_H^2} \quad (18)$$

where K_1 and K_2 are the first and second ionization con-

(32) F. Lippman and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

starts of ethylenediamine. The values of k_{NF}^{\oplus} and k_{NH}^{\oplus} were determined by means of successive approximations. The values of the constants which provided the best fit of eq. 19 to the experimental data were: $pK_{app}^1 = 7.15$, $k_{NH}^{\oplus} = 1.68$ l. mole⁻¹ min.⁻¹; $pK_{app}^2 = 10.06$, $k_{NF} = 104$ l. mole⁻¹ min.⁻¹.

A comparison of the experimental values of k_2' to those calculated from eq. 18 employing the determined rate constants is provided in Table III.

TABLE III

COMPARISON OF EXPERIMENTALLY DETERMINED PSEUDO-SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF ETHYLENEDIAMINE WITH δ -THIOLVALEROLACTONE TO THOSE CALCULATED FROM EQ. 17

pH	k_2' , l. mole ⁻¹ min. ⁻¹		pH	k_2' , l. mole ⁻¹ min. ⁻¹	
	Calcd.	Found		Calcd.	Found
6.76	0.50	0.50	8.03	2.31	2.96
6.93	.68	.64	8.32	3.25	3.97
7.15	.90	.89	8.74	6.17	5.83
7.24	1.01	1.08	9.02	10.0	8.74
7.46	1.30	1.42	9.46	21.9	21.50
7.58	1.46	1.55	9.82	38.8	39.40
			10.18	60.0	58.80

The reaction of ethanolamine with δ -thiolvalerolactone was found to be first order in free amine and first order in lactone

$$k_{obs} = k_2(N_F)$$

$$k_{obs} = k_2 K_a (N_T) / (K_a + a_H) \quad (19)$$

$$K_a k_{obs} / (N_T) = k_2 K_a - k_{obs} a_H / (N_T)$$

When the pseudo-second-order rate constant (*i.e.*, $k_{obs}/(N_T)$) is plotted *vs.* $k_2' a_H$, the value of K_a is obtained from the slope and the product $k_2 K_a$ from the intercept at $a_H = 0$ (Fig. 12). The kinetically determined value of pK_a' (9.73) was found to be that of the titrimetrically determined constant (9.72).

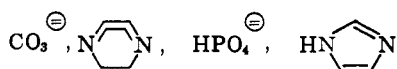
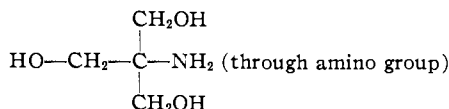
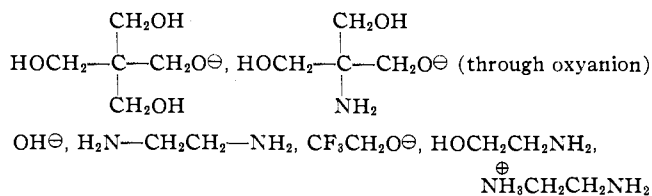
Discussion

Inspection of Table II reveals that the various nucleophiles investigated may be divided into three classes, dependent on the simplest equation which adequately describes the kinetic data for their reaction with δ -thiolvalerolactone:

(A) Uncomplicated second order

$$[v = k_r(N_F)(L) \text{ or } v = k_r(N^-)(L)]$$

In this category, in order of decreasing nucleophilicity are



(B) General-base-catalyzed third-order reaction

$$[v = k_r(N_F)^2(L)]$$

The only nucleophiles in this category are H_2NOH and H_2O . The rate of spontaneous solvolysis of δ -thiolvalerolactone in water is subject to a substantial deuterium solvent isotope effect ($k^{\text{H}_2\text{O}}/k^{\text{D}_2\text{O}}$ of 3.17 ± 0.32 as determined at four acidities between pH 7.0 and 8.0),²⁷

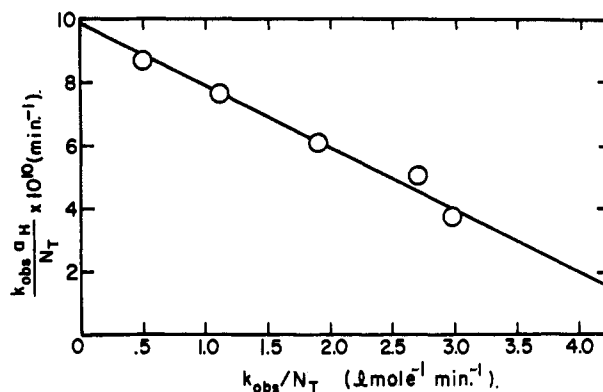


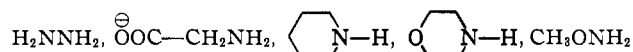
Fig 12.—The linear dependence of $K_{obs} \times a_H / (N_T)$ on $k_{obs} / (N_T)$ for the reaction of ethanolamine with the thiolactone.

suggesting that the reaction of water with the lactone is by way of general base catalysis involving a second molecule of water.

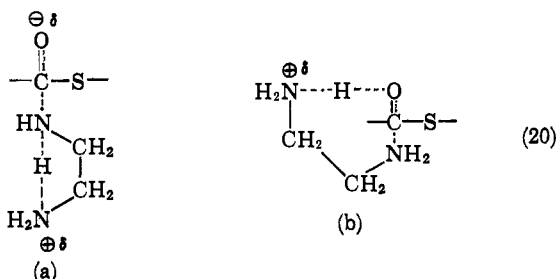
(C) General-base, general-acid catalysis in which the third-order rate constants for the two general catalytic processes are equal or approximately equal

$$[v = k_r(N_T)^2(L)K_a / (K_a + a_H) = k_r(N_F)^2(L) + k_r(N_F)(NH^\oplus)(L)]$$

In order of decreasing rate constants the nucleophiles in this class are



In order for a nucleophilic attack on the ester bond to be subject to assistance from general base catalysis *via* a proton abstraction from the nucleophilic center, it is essential that the nucleophilic center possess an acidic hydrogen. This requirement is met by the nucleophiles of group C but not by the oxyanions of pentaerythritol, tris-(hydroxymethyl)-amino methane, trifluoroethanol, and carbonate, phosphate, imidazole, triethylenediamine and hydroxide ion whose reactions with the thiolactone follow simple second-order kinetics. Because of the steric consequences of the location of the amino group of TRIS on a tertiary carbon it is also not surprising to find that the reaction of this primary amine exhibits no general acid nor general base assistance. It is possible that ethylenediamine, in its neutral or monocationic state, does exhibit general acid and general base catalysis (20) of an intramolecular nature but from the kinetic study of these species it is certain that they do not exhibit measurable intermolecular catalysis involving two amine species.



The magnitude of the rate constant for the neutral diamine does not suggest a transition state of the type 20a as being of importance. However, the possibility of intramolecular general acid catalysis as in 20b cannot be ruled out since the monocation would appear to have an enhanced nucleophilicity (Fig. 13). In the case of ethanolamine it is certain that neither intermolecular general base nor general acid catalysis is in operation and this is difficult to understand from the standpoint of the low steric requirements for this primary amine.

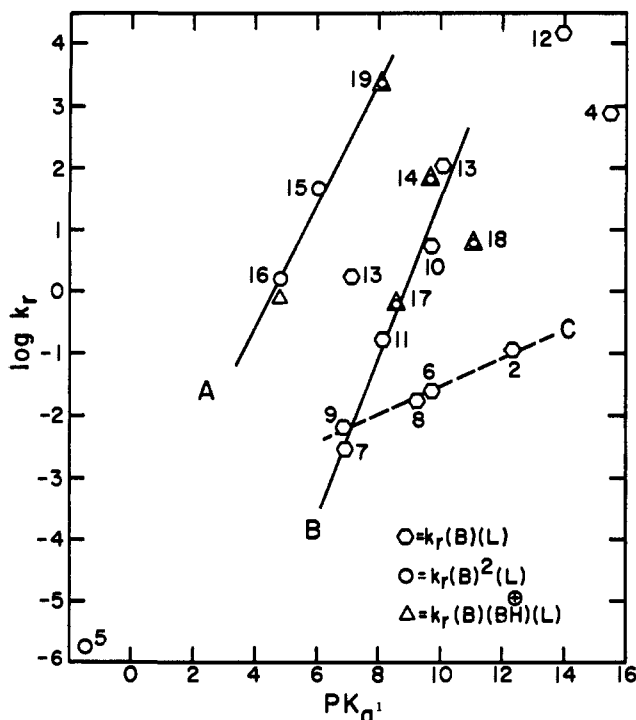


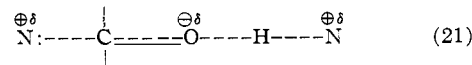
Fig. 13.—Brønsted plot for the reaction of nineteen assorted bases with δ -thiolvalerolactone. The numbers refer to the compounds of Table II.

Turning now to the categories of B and C: It is not obvious why hydroxylamine should exhibit general base catalysis only and methoxylamine and hydrazine exhibit equal sensitivity to both general base and general acid catalysis. In addition, it is not quite clear why glycine should exhibit general-acid and general-base catalysis and the closely similar ethanolamine exhibit only second-order kinetics. It is also strange that the secondary amines (piperidine and morpholine) should react with the thiolactone *via* general-acid- and general-base-catalyzed assistance when these same amines (in contrast to primary amines) react with phenyl acetate *via* kinetics which are first order in the secondary amine.¹⁵ It would appear that the steric effect is not so decisive in determining these mechanisms, as has been suggested.¹⁵

In Fig. 13 there is plotted the logarithm of the rate constants for the reaction of the various nucleophiles with δ -thiolvalerolactone *vs.* the pK_a of the nucleophilic species. The plot of Fig. 13 is of the conventional Brønsted type. Three lines have been drawn around which the points would appear to gather. It should be *understood* that the linear plots may have no theoretical significance but serve as a convenient means of presenting the data (*i.e.*, possibly another group of nucleophiles would provide an alternate relationship of $\log k_r$ to pK_a). For nucleophilic displacements on ester carbonyl groups Brønsted plots should only be constructed when bases of identical type are employed (*i.e.*, oxyanions, imidazoles, pyridines, etc., serving each as separate series).¹⁰ The values of the slopes of Brønsted plots when bases of divergent type are employed is of doubtful significance even though the proper choice of the bases may provide a reasonably good line. Inspection of Fig. 13 reveals that the three bases on line A (slope = 1.0) possess rate constants approximately 10^{4-5} greater than those of the nucleophiles of line B (slope = 1.2) and that both the nucleophiles of lines A and B represent nitrogen bases. The nucleophiles of line A owe their enhanced nucleophilicities to the possession of a pair of unshared electrons on the

atom α to the nucleophilic center (the α -effect¹⁹). Again, as in the case of other nucleophilic displacements of a varied nature, bases such as hydrazine and hydroxylamine appear to possess nucleophilicities far and away greater than anticipated on the basis of their pK_a' values. Inspection of Fig. 13 reveals also that the dependence on pK_a' for the nitrogen nucleophiles (B) is much greater than that for the oxygen nucleophiles (C) (*i.e.*, slope = 1.2 *vs.* slope = 0.19). No generalizations can be formulated, however, as can be seen by the positive deviation of OH^\ominus and pentaerythritol monoanion from line C. This would tend to indicate that the formation of the bond from the nucleophile to the ester carbonyl group in the transition state is more important in the case of those nucleophiles of line B than for those of line C. The ability to obtain Brønsted slopes greater than 1.0 in nucleophilic displacement reactions only requires that the $\log k_r$ for OH^\ominus attack exhibits a decided negative deviation from the Brønsted plot. This requirement is met by lines A and B.

In Fig. 13 all rate constants obtained in this study which could be related to the pK_a' of the nucleophile have been plotted. These include, in addition to the rate constants for simple second-order nucleophilic displacements, the third-order rate constants for general-base and general-acid catalysis. That the general-base rates follow, along with the simple nucleophilic constants, a positive dependence on the pK_a' of the base is expected. However, it should be noted that the rate constants for general-acid catalysis also exhibit a positive dependence on the pK_a' of the base species. In the general-acid catalysis the most probable transition state is one in which the nucleophilic base species ($\text{N}:$) is attacking the ester carbonyl group which is simultaneously receiving a proton from the conjugate acid species (NH^\oplus).



The formation of the N-C bond is favored by increasing the basicity of $\text{N}:$ while of course the protonation of the carbonyl oxygen should be a function of the acidity of the conjugate acid. The dependence of the general acid terms on basicity would tend to indicate that the bond between the nucleophile and the ester carbonyl carbon is essentially formed while the process of bonding to hydrogen has not proceeded extensively in the transition state. It is, of course, conceivable that the mechanisms do not represent general-acid and general-base catalysis, but the kinetically equivalent general-base-specific-acid and general-acid-specific-base catalysis

$$v = k_r(\text{N}_F)(\text{L}) + k_r(\text{N}_F)(\text{NH}^\oplus)(\text{L}) \quad (a)$$

$$v = \frac{K_a k_r}{K_w} (\text{N}_F)(\text{NH}^\oplus)(\text{OH}^\ominus)(\text{L}) + \frac{k_r K_L}{K_a} (\text{N}_F)(\text{LH}^\oplus) \quad (b)$$

(where K_L is the dissociation constant of the conjugate acid of the thiolactone). The kinetically identical expressions of 22a and 22b can, in our case, be differentiated. The following arguments establish our reactions to be mechanistically of the type given by 22a. The value of k_r for hydrazine is $2.25 \times 10^3 \text{ l.}^2 \text{ mole}^{-2} \text{ min.}^{-1}$. If in place of general base catalysis we were actually observing general-acid-specific-base catalysis of the reaction of neutral hydrazine with the lactone then the rate of this process would be $k_r' = k_a k_r / K_w = 1 \times 10^7 \text{ l.}^3 \text{ mole}^{-3} \text{ min.}^{-1}$. This rate constant would appear to be far in excess of that anticipated as possible for a proton transfer reaction involving the formation of a covalent bond.²³ If in place of a general-acid-catalyzed reaction of hydrazine with the lactone we had the alternate general-base catalysis of the reaction of hydrazine with the

(23) M. Eigen and G. G. Hammes, "Elementary Steps in Enzyme Reactions," to appear in *Advances in Enzymology*.

protonated lactone, then $k_r'' = k_r K_L / K_a$, and assuming any reasonable value for K_L provides a value of k_r'' greater than that for a diffusion-controlled process.

One might note, also, that the simple nucleophilic reactions as well as the general-base- and the general-acid-catalyzed reactions follow the same linear relationships (Fig. 13). Thus, neutral ethylenediamine and glycine possess approximately the same pK_a' values and almost the same numerical values for their rate constants even though the reaction of glycine is kinetically third order and that of ethylenediamine second order. The same type of relationship can be seen for TRIS and morpholine. It would appear, therefore, that the numerical values of the second- and third-order rate constants are very similar for bases of similar type and the same pK_a' . The near identity of these constants is dependent on the standard state of moles $l.^{-1}$ employed in the calculation of the various constants and must reflect a compensation of translational entropy and potential energy terms in proceeding from lower to higher order reactions.

Of considerable interest is the finding that trifluoroethanol anion is characterized by a second-order rate constant $10^{5.25}$ smaller than that of pentaerythritol monoanion. Both nucleophiles are oxyanions differing in pK_a' by only 1.64 units.³⁴ It is also surprising that no reactivity of the thiolactone with acetone oxime anion could be detected. At the concentrations employed in this study the reaction of acetone oxime anion with *p*-nitrophenyl acetate is easily discernible. The inability to detect a reaction of the oxime anion above that for hydroxide ion is explainable on the basis that this anion must belong to the class of bases which follows the relationship of pK_a' to $\log k_r$ or line C (Fig. 13). The oxime anion possesses almost the same pK_a' as trifluoroethanol whose rate of reaction with the lactone was barely detectable above that for hydroxide ion.

Comparison of Nucleophilicities of Bases toward *p*-Nitrophenyl Acetate and δ -Thiolvalerolactone.—As pointed out in the Introduction to this paper, only the phenyl acetates have received comprehensive attention as substrates in studies of displacement reactions at the carbonyl carbon of the ester bond. The most comprehensive work has been carried out with *p*-nitrophenyl acetate. With the exception of ethanolamine, morpholine and piperidine, the bases chosen for study as nucleophiles with δ -thiolvalerolactone have all previously been investigated with *p*-nitrophenyl acetate. We have now determined the second-order rate constants for the reaction of ethanolamine, morpholine and piperidine with *p*-nitrophenyl acetate (see Experimental) so that we are now in a position to assess the relative nucleophilicities of the bases in Table II toward two esters of very different nature. The value of such a comparison is found in the fact that differences in nucleophilicities due to solvation of nucleophiles^{35a,b,c} and steric factors cancel out or tend to cancel out if the same regime of solvent, temperature, ionic strength, etc., are employed in determining all rate constants and, therefore, the selectivity of one substrate over another for particular nucleophiles may be determined. By such a comparison, then, we are determining something of the differences and similarities in the transition states for the reaction of nucleophiles with different esters.

(34) Assistance of a general acid nature by the hydroxymethyl groups of pentaerythritol monoanion may be ruled out as a cause for its great nucleophilicity as compared to trifluoroethanol anion. Thus, hydroxide ion is also a much better nucleophile than trifluoroethanol anion (see also ref. 13 of this paper).

(35) (a) S. Winstein, *et al.*, *Tetrahedron Letters*, No. 9, 24 (1960); (b) A. J. Parker, *J. Chem. Soc.*, 1328 (1961); (c) A. J. Parker, *Quart. Rev.*, 36, 163 (1962).

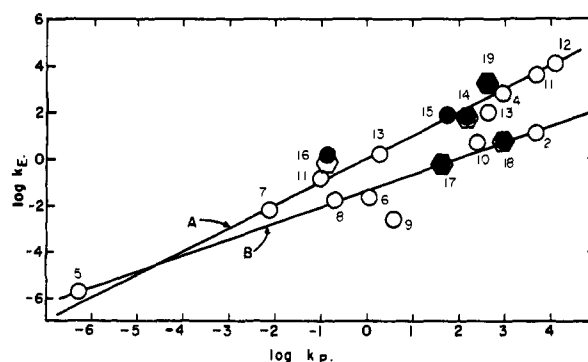
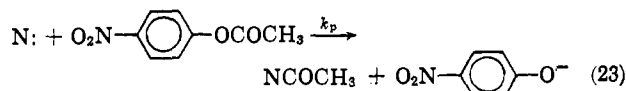


Fig. 14.—Plot of the log of the second-order rate constants for the reaction of nucleophiles with *p*-nitrophenyl acetate ($\log k_p$) vs. the log of the second order (○) and third order (● general base, ○ general acid) rate constants ($\log k_E$) for the reaction of the same nucleophiles with δ -thiolvalerolactone. The numbers refer to the compounds of Table II.





In Table III are presented the logarithms of the second-order rate constants ($\log k_p$) for the reaction of a series of nucleophiles (N:) with *p*-nitrophenyl acetate.



In Fig. 14 there is plotted the values of $\log k_p$ vs. the logarithms of the second-order rate constants ($\log k_E$) for the reaction of the same series of nucleophiles with δ -thiolvalerolactone (open circles). The solid line (A) drawn in Fig. 14 is of slope 1.0 and passes through zero so that the points falling on this line correspond to nucleophiles which exhibit essentially identical rates of re-

TABLE IV

LOGARITHMS OF THE SECOND-ORDER RATE CONSTANTS FOR THE DISPLACEMENT OF *p*-NITROPHENOL FROM *p*-NITROPHENYL ACETATE BY AN ASSORTMENT OF NUCLEOPHILES

Nucleophile	$\log k_p$	Ref.
$(\text{HOCH}_2)_3\text{CCH}_2\text{O}^-$	4.10	a
$(\text{HOCH}_2)_2\text{C}(\text{NH}_2)\text{CH}_2\text{OH} + \text{OH}^-$	3.68 ^g	a
$\text{CF}_3\text{CH}_2\text{O}^-$	3.67	b
	2.97	c
OH	2.95	d
H_2NNH_2	2.61	d
$\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$	2.62	d
$\text{HOCH}_2\text{CH}_2\text{NH}_2$	2.39	c
$\text{H}_2\text{C}(\text{COO}^-)\text{NH}_2$	2.19	e
HONH_2	2.04	d
	1.61	c
	1.3	f,g
		
$\text{H}_3\text{N}^+-\text{CH}_2\text{CH}_2\text{NH}_2$	0.3	d
	.29	d
CO_3^{--}	.025	d
CH_3ONH_2	-0.9	d
$(\text{HOCH}_2)_3\text{CNH}_2$	-1.17	a
HPO_4^{--}	-2.13	d
H_2O	-6.22	d

^a Ref. 17 of this paper. ^b Ref. 13 of this paper. ^c This study. ^d Ref. 11 of this paper. ^e Ref. 15 of this paper. ^f Ref. 10 of this paper. ^g The value of the third order rate constant (*i.e.*, $v = k_r(E)(\text{ROH})(\text{OH}^-)$) is employed here since the pK_a of the hydroxyl group is not known. The same expression is employed for the lactone in Fig. 14.

action with both the thiolactone and *p*-nitrophenyl acetate. Bases which are found to exhibit identical or near identical kinetics with both substrates include: pentaerythritol oxyanion, tris-(hydroxymethyl)-aminomethane oxyanion, hydroxide, ethylenediamine, the monocation of ethylenediamine, tris-(hydroxymethyl)-aminomethane, phosphate dianion and water. The linear correlation of line A of Fig. 14 extending from pentaerythritol anion to water covers some 10^5 in rate constants. Previous studies have shown that the $\log k_p$ value for hydroxide ion exhibits a very large negative deviation from the Brønsted plot for other oxyanions.^{10,11} In the present investigation hydroxide ion was again found to exhibit a large negative deviation from the principal Brønsted plot (Fig. 13) for δ -thiolvalerolactone. Hydroxide ion is also known to provide a negative fit to Brønsted plots for reactions proceeding *via* proton abstraction.³⁶ The fit of the hydroxide point to Fig. 14 suggests the possibility that the negative deviation of the hydroxide rate from the Brønsted plots for both the thiolactone and *p*-nitrophenyl acetate is due to solvation of the ion³⁷ in the ground state and that this is, as anticipated, of equal importance in the displacement reaction on either substrate.

The points for the second-order rate constants which follow line B of Fig. 14 represent nucleophiles which react much faster with *p*-nitrophenyl acetate than with the thiolactone. There is no sensible differentiation in base type between the nucleophiles of lines A and B. Carbonate and phosphate are both divalent oxyanions, yet *p*-nitrophenyl acetate is more selective toward the former. Pentaerythritol anion and trifluoroethanol anion are both alkoxide ions, yet *p*-nitrophenyl acetate is highly selective toward the latter. Ethanolamine and ethylenediamine are both primary amines, but *p*-nitrophenyl acetate is more selective toward the latter. The structure of the transition states for the reaction of the nucleophiles of line A must differ in some important detail(s) from the structure of the transition states for the reaction of the nucleophiles of line B with the thiolactone.³⁸ The fact that the rate constants for the nucleophiles of line A (Fig. 14) are essentially identical for reactions at the ester bond of *p*-nitrophenyl acetate and δ -thiolvalerolactone suggests that the leaving tendency of *p*-nitrophenoxide and mercaptide ion are identical or that the partitioning of the tetrahedral intermediate is not of importance for these reactions. The latter would appear to be the most reasonable alternative. Thus, *p*-nitrophenol possesses a pK_a of 7.14 while the pK_a of δ -thiolvaleramide has been determined to be 10.0.²⁷ In addition mercaptide ions are much better nucleophiles toward the ester bond than are oxyanions of comparable pK_a .³⁹ It can be argued that the carbonyl carbon of the thiolactone and *p*-nitrophenyl acetate would be expected *a priori* to be quite similar in that there should be very little electron release from the ether oxygen or the sulfur atom toward the ester carbonyl group. It is suggested, therefore, that for the nucleophiles of line A (Fig. 14) the value of k_r is given by the rate constant for nucleophilic attack on the carbonyl carbon and that there is no partitioning of the tetrahedral intermediate to starting material. The mechanism for the reaction of the nucleophiles of line B may then be proposed to involve the partitioning of the tetrahedral intermediate (at least in the case of the thiolac-

tone) so that the difference in leaving tendencies of mercaptide ion and *p*-nitrophenoxide ion are reflected in the rate constants. On the basis of this argument it is obvious that the partitioning of the tetrahedral intermediate must be subject to subtle influences.

As noted previously, the rate constants for the general acid- and general base-catalyzed reaction of various nucleophiles with δ -thiolvalerolactone increase with increasing basicity of the nucleophile. This is to be expected of the rate constants for the general base-catalyzed reactions and may be explained in the case of the general acid-catalyzed reactions by assuming that the formation of the bond between the nucleophile and the carbonyl carbon is of much greater significance in the transition state than is the proton transfer. It is then to be anticipated that the log of the rate constants for the general acid- and general base-catalyzed reactions of δ -thiolvalerolactone might also be correlatable with $\log k_p$. In Fig. 14 the log of the third-order rate constants for general base (shaded circles) and general acid (shaded hexagons) catalyzed nucleophilic attack of six nucleophiles on δ -thiolvalerolactone are plotted *vs.* $\log k_p$. Inspection of Fig. 14 reveals that the third-order rate constants associated with reactions with δ -thiolvalerolactone fall on the same two lines as do the second-order rate constants. This observation is particularly interesting in the case of those bases (hydrazine, hydroxylamine and methoxylamine) which possess enhanced nucleophilicity due to the " α -effect."¹⁹ These nucleophiles possess rate constants some $10^{4.5}$ greater than anticipated from their pK_a' values in reacting with the thiolactone. Reagents of this type have previously been shown to possess greatly enhanced nucleophilicities in displacement reactions on ester (including *p*-nitrophenyl acetate),¹¹ lactones,²² nitriles,⁴⁰ tetrahedral phosphorus,⁴¹ activated double bonds,⁴² and on an octahedral semi-metallo silicon complex.⁴³

Employing the standard state of moles per liter, the decrease in ΔF^\ddagger for the reaction of these bases with both *p*-nitrophenyl acetate and δ -thiolvalerolactone over the values of ΔF^\ddagger anticipated on the basis of their pK_a' values is nearly identical. This serves to show that the α -effect is of equal importance in enhancing nucleophilicity toward both *p*-nitrophenyl acetate and δ -thiolvalerolactone. The fact that all the rate constants for the third-order reactions correlate equally well as do the second-order reactions with lines A and B of Fig. 14 suggests that the additional translational entropy which must be frozen out in forming the transition states for the higher order reactions must be balanced by other potential and kinetic energy terms. That the numerical magnitude of the rate constants for the higher order reactions are comparable to those for the simple second-order reactions (identity of ΔF^\ddagger) must be considered fortuitous and dependent on the standard states employed in the calculation of rate constants.

In summary, this study has revealed many unusual results, a number of which will require further investigation prior to the presentation of hypotheses concerning mechanisms. Certainly this study has revealed the necessity to examine the susceptibility and kinetic nature of the reaction of series of nucleophiles with selected esters and amides in order that the ground work necessary to the understanding of the mechanisms

(40) K. B. Wiberg, *ibid.*, **77**, 2519 (1955).

(41) L. Larsson, *Acta Chem. Scand.*, **12**, 723 (1958); A. L. Green, G. L. Sainsbury, B. Saville and M. Stansfield, *J. Chem. Soc.*, 1583 (1958); J. Epstein, M. M. Demeck and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

(42) C. A. Bunton and C. J. Minkoff, *J. Chem. Soc.*, 665 (1949); H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958); H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *ibid.*, **81**, 108 (1959).

(43) R. G. Pearson, D. N. Edgington and F. Basolo, *ibid.*, **84**, 3233 (1962).

(36) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, Ch. V.

(37) C. G. Swain, R. B. Mosely and D. E. Brown, *J. Am. Chem. Soc.*, **77**, 3731 (1955).

(38) The mechanism of the reaction of imidazole with δ -thiolvalerolactone has been shown to be complex (see ref. 27 for experimental details and F. H. Westheimer and M. L. Bender (*J. Am. Chem. Soc.*, **84**, 4908 (1962)) for a reasonable interpretation.

(39) J. R. Whitaker, *ibid.*, **84**, 1900 (1962).

of displacement reactions at the ester and amide bond be provided. Finally, it is pointed out that the present study has been one of a kinetic nature which has presumed, in each case, a displacement of the thiol from the thiol ester carbonyl group. This assumption is felt to be quite safe on the grounds that thiol esters are much less prone to alkyl-sulfur cleavage than are oxygen esters prone to alkyl-oxygen cleavage^{25b} and that valerolactone shows no tendency to undergo alkyl-oxygen cleavage. Korte and Christoph have found no evidence for alkyl-S cleavage in the basic and acidic hydrolysis of a number of γ -butyro and δ -valerolactones.⁴⁴ It has also been

observed that δ -thiolvalerolactone yields with liquid ammonia only δ -thiolvaleramide.²⁷ It should also be pointed out that in certain cases water may be involved in the transition state as a nucleophile. This is possible in reactions which are first order in the basic species (*i.e.*, general base-assisted water solvolysis) but very unlikely for the higher order reactions. Investigation of this possibility is being pursued.

Acknowledgments.—This work was supported by grants from the National Institutes of Health and the National Science Foundation.

(44) F. Korte and H. Christoph, *Ber.*, **94**, 1966 (1961).

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH.]

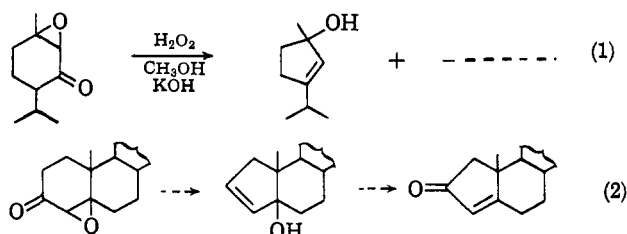
Rearrangements of 4,5-Oxidocholestane-3-one

BY WILLIAM REUSCH AND RONALD LEMAHIEU

RECEIVED NOVEMBER 3, 1962

The α - and β -epoxides derived from Δ^4 -cholestene-3-one are rearranged by methanolic base to 4-methoxy- Δ^4 -cholestene-3-one (IV). An isomer previously believed to be IV has been identified as 3-methoxy- Δ^2 -cholestene-4-one (VI). These isomeric enol ethers and the diosphenol V were reduced by hydrogen iodide in refluxing acetic acid to cholestane-4-one. Oxidation of the epoxyketones II and III with alkaline hydrogen peroxide gave, respectively, the lactone acids VIII and X.

Base-catalyzed rearrangements of piperitone oxide and related α,β -epoxyketones were first reported by Treibs¹ and have recently been confirmed by the precise and thorough study of House and Gilmore.² Since piperitone oxide was observed to undergo a Favorskii ring contraction, we felt that this rearrangement might provide a convenient route to nor-steroids. In particular, a remarkable oxidative modification described by Treibs (eq. 1)^{1d,3} seemed especially appropriate for this purpose (eq. 2).

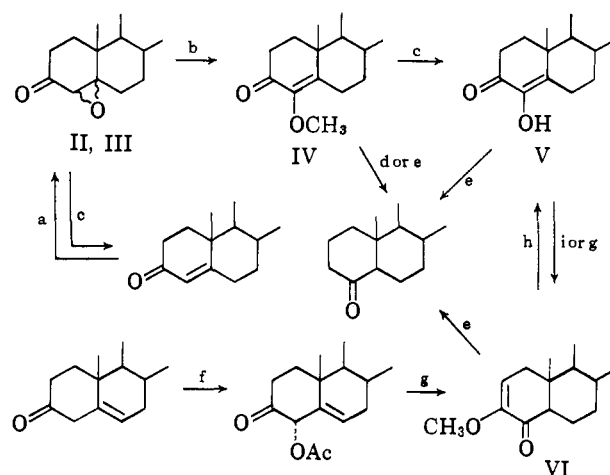
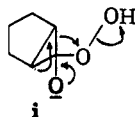


This paper reports the results from a study of the base-catalyzed reactions of β -(II) and α -(III) 4,5-oxidocholestane-3-one. These steroid isomers are found to differ from the previously reported cases^{1,2} in that reaction with methanolic base is much slower and ring contraction does not occur. The major product from both the α - and β -isomers was 4-methoxy- Δ^4 -cholestene-3-one (IV), m.p. 136–138°. This structural assignment rests upon the elemental analysis, infrared spectrum ($\lambda_{\text{max}}^{\text{CCl}_4}$ 5.97, 6.25 μ), ultraviolet spectrum ($\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 255 m μ , log ϵ 4.1), n.m.r. (OCH₃ at 6.48 τ), hydrolysis to the diosphenol V and conversion *via* the corresponding ethylene-thioetal to cholestane-4-one. In addition to the above evidence, an isomeric enol ether previously regarded as IV⁴ has been shown to have structure VI.

(1) (a) W. Treibs, *Ber.*, **63**, 2423 (1930); (b) **64**, 2178, 2545 (1931); (c) **65**, 163, 1314 (1932); (d) **66**, 610, 1483 (1933).

(2) H. House and W. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972 (1961).

(3) We wish to thank Professor D. H. R. Barton for calling this unusual reaction to our attention and for suggesting mechanism i.



(a) CH₃OH, H₂O₂, NaOH at 0° (g) BF₃ in methanol at reflux
(b) CH₃OH, NaOH at reflux (h) HCl, 95% ethanol
(c) HCl, dioxane at reflux (i) (CH₃)₂SO₄, CH₃OH, NaOH
(d) 1, ethanedithiol + BF₃;
2, H₃O⁺; 3, Raney nickel
(e) HI in acetic acid at reflux
(f) Pb(OAc)₂ in acetic acid

The reaction of 4- α -acetoxy- Δ^5 -cholestene-3-one with refluxing methanolic boron trifluoride yields a C₂₈H₄₆O₂ enol ether,⁴ m.p. 149°, which is readily hydrolyzed to diosphenol V, and exhibits a n.m.r. spectrum having a pair of overlapping doublets at 4.55 τ (characteristic of C=CH—CH₂—) with an area roughly one third that of the OCH₃ group at 6.51 τ . The assignment of structure VI to this substance is supported by the infrared ($\lambda_{\text{max}}^{\text{CCl}_4}$ 5.95, 6.12 μ) and ultraviolet⁵ ($\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$

(4) L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **78**, 1409 (1956). Shortly after this paper was submitted for publication, we discovered that identical structural assignments were made by B. Camerino, B. Patelli and R. Sciaky, *Gazz. chim. ital.*, **92**, 709 (1962). These workers have also prepared the testosterone, analogs of IV and VI.

(5) The enhanced bathochromic influence of the α -methoxy group in enone VI (+37 m μ) as contrasted with that for enone IV (+12 m μ) requires further comment. We suggest that for maximum effect the bonding plane of the oxygen be parallel to the enone chromophore. This condition is easily satisfied when the α -substituent is a hydroxyl group (ii), and diosphenol V ($\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 278, log ϵ 4.1) exhibits a bathochromic increment of +35 m μ for this substituent. Coplanarity of the methoxy group in IV, however, is prevented by crowding of the O-methyl with either the carbonyl oxygen or the C-6 methylene group, and a much smaller substituent effect is ob-