Rates of Hydrolysis of the Dibromo Acid (I, X = Br) at 2, 14, and 20°.—The hydrolysis rates were determined by measuring the rate of H^+ formation from the reaction

$$RSCH_2CH_2Br + H_2O \longrightarrow RSCH_2CH_2OH + H^+ + Br^-$$

All the measurements were made with the automatically recording Radiometer Titrigraph fitted with a glass electrode. Reaction solutions were maintained at the appropriate temperatures in jacketed vessels connected to a thermostated water bath. For each series of runs approximately 70 mg. of the dibromo acid was dissolved in 10 ml. of dry acetone. A 1-ml. aliquot of this solution was added to 20 ml. of water at the required temperature and containing the exact equivalent of decinormal NaOH required to neutralize the carboxyl group (approximately 0.2 ml.). Decinormal NaOH was automatically added to maintain the pH of the solution at its initial value of 8.3. The rate of addition was recorded on a time-scale graph.

Table I shows details of results obtained in a typical run. Dibromo acid (6.55 mg.) dissolved in 1 ml. of acetone was added at zero time to 20 ml. of water at 2° containing 0.14 ml. of 0.1 *N* NaOH. A plot of log $[a/(a - x)]$ against t gave a straight line for all runs showing that the reaction is first order with respect to dibromo acid. In the case of the data in Table I, the slope of this line is 0.053 and this equals $k/2.303$. Hence the rate constant is 0.124 min.$^{-1}$.

A series of runs was made at 2, 14, and 20° and from the mean values of the rate constants at each temperature the rate constant at 37° was computed graphically using the Arrhenius equation: $2.303 \log k = -E/RT +$ constant. The plot of $\log k$ against $1/T$ (°K.) gave a straight line (Figure 1). From the point on the graph whose abscissa corresponded to 37° the ordinate gave the required rate constant. Table II shows the measured rate constants and times for half-reaction ($t_{1/2}$ or "half-life") and the extrapolated values for 37°. The energy of activation of the reaction calculated from the slope of the line in Figure 1 is 20,700 cal.

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Reactivity of Some 2-*p*-Nitrophenoxy-1,3,2-dioxaphospholane 2-Oxides and -dioxaphosphorinane 2-Oxides[1]

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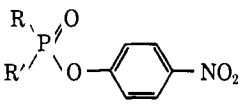
A number of 2-*p*-nitrophenoxy-1,3,2-dioxaphospholane 2-oxides and -dioxaphosphorinane 2-oxides have been prepared and examined for alkaline hydrolysis and anticholinesterase activity. Although the six-membered ring dioxaphosphorinane 2-oxides and the acyclic analog diethyl *p*-nitrophenyl phosphate (paraoxon) gave comparable rates of liberation of *p*-nitrophenol in aqueous NaOH, the cyclic esters were almost void of anticholinesterase activity. The five-membered ring dioxaphospholane 2-oxides gave instantaneous liberation of *p*-nitrophenol in water and were inactive as anticholinesterases.

The relationship between structure of phenyl esters of phosphoric, phosphonic, and phosphinic acids, their anticholinesterase properties, and toxicity to animals has been examined in great detail.[2-4] It has been shown that the inhibition of the cholinesterase enzymes is directly related to the reactivity of the phosphorus atom and correlations have been made between enzyme inhibition, alkaline hydrolysis rates, changes in P–O–aryl stretching frequencies, and Hammett σ-constants. The evidence shows that the organophosphorus poisons inhibit acetylcholinesterase and other esterases by phosphorylating the enzyme at one of the essential sites. Previous work from this and other laboratories have shown that in compounds of the general structure below, R and R′ may be varied to



considerable extent before extensive changes in the antiesterase properties become evident, provided the electrophilic character of the phosphorus atom is not altered to any large degree. For example, R and R′ may be alkyl or alkoxy groups of varying chain lengths and branching, and anticholinesterase activity is still maintained.

Steric factors must also be considered when assessing the reactivity of phosphorus esters, *e.g.*, when R or R′ is *t*-butyl, the compound is quite stable to alkaline hydrolysis, and anticholinesterase activity is low. In order to assess further the effect of steric factors in the inactivation of acetylcholinesterase by organophosphorus compounds, it was considered of interest to examine the activity of *p*-nitrophenyl esters in which the phosphorus atom was part of a ring system. Although five- and six-membered ring phosphorothionate esters of *p*-nitrophenol (2-sulfo-1,3,2-dioxaphospholanes and -phosphorinanes) have been proven to be poor anticholinesterases,[5] the corresponding oxygen esters have not been examined and their study seemed warranted since phosphorothionate esters are generally poor inhibitors because of the stabilizing effect of the sulfur atom. Further, five-membered ring cyclic phosphates are known to be quite susceptible to hydrolysis, but their activity toward cholinesterase has not been examined.

(1) Paper No. 1615, Citrus Research Center and Agricultural Experiment Station, University of California, Riverside, Calif. This investigation was supported in part by Public Health Service Research Grant CC-00038-07 from the Communicable Disease Center.

(2) W. N. Aldridge and A. N. Davison, *Biochem. J.*, **51**, 62 (1952).

(3) T. R. Fukuto and R. L. Metcalf, *J. Am. Chem. Soc.*, **81**, 372 (1959).

(4) G. Schrader, "Die Enwicklung neuer insektizider Phosphorsäure-Ester," Verlag Chemie, Weinheim, 1963.

(5) R. S. Edmundson and A. J. Lambie, *Chem. Ind.* (London), 1048 (1959).

Experimental Section

Chlorodioxaphospholane 2-Oxides.—The five-membered ring cyclic phosphorochloridates were prepared according to Arbuzov, *et al.*,[6] from the appropriate 1,2-glycol, phosphorus oxychloride, and diethylaniline in ether. Thus, 4-methyl-2-chloro-1,3,2-dioxaphospholane 2-oxide[6] was obtained in rather poor yield from 1,2-propanediol and $POCl_3$; b.p. 74–80° (0.5 mm.), $n^{26}D$ 1.4552. By the same procedure racemic 2,3-butanediol, prepared from *cis*-butene,[7] gave racemic 4,5-dimethyl-2-chloro-1,3,2-dioxaphospholane 2-oxide, b.p. 78–80° (0.5 mm.), $n^{25}D$ 1.4462, yield 56%.

Anal. Calcd. for $C_4H_8ClO_3P$: Cl, 20.8. Found: Cl, 20.6.

meso-2,3-Butanediol, from *trans*-butene,[7] gave the *meso*-4,5-dimethyl isomer in comparable yield, b.p. 84–86° (0.5 mm.), $n^{25}D$ 1.4545. Redistillation of this substance resulted in considerable residue as a polymeric material.

Anal. Calcd. for $C_4H_8ClO_3P$: Cl, 20.8. Found: Cl, 20.5.

Several attempts to prepare 2-chloro-1,3,2-dioxaphospholane 2-oxide, the ethylene cyclic phosphorochloridate, resulted in polymeric product only.

Chlorodioxaphosphorinane 2-Oxides.—Most of the six-membered ring cyclic phosphorochloridates were prepared according to Lanham[8] from the appropriate 1,3-diol and $POCl_3$. By this procedure the following compounds previously reported in the literature were prepared: 2-chloro-1,3,2-dioxaphosphorinane 2-oxide,[1] m.p. 38–39°, and 4-methyl-2-chloro-1,3,2-dioxaphorinane 2-oxide,[9] distilled at 80° (0.2 mm.) in a falling-film still, $n^{25}D$ 1.4560. In a like manner, racemic 2,4-pentanediol,[10] b.p. 75–78° (3 mm.), $n^{21}D$ 1.4359, gave racemic 4,6-dimethyl-2-chloro-1,3,2-phosphorinane 2-oxide, b.p. 70–72° (1 mm.), $n^{25}D$ 1.4552.

Anal. Calcd. for $C_5H_{10}ClO_3P$: Cl, 19.2. Found: Cl, 18.7.

meso-2,4-Pentanediol,[10] b.p. 75–78° (3–4 mm.), $n^{25}D$ 1.4314, gave *meso*-4,6-dimethyl-2-chloro-1,3,2-dioxaphosphorinane 2-oxide, b.p. 80–82° (1.5 mm.), $n^{25}D$ 1.4519.

Anal. Calcd. for $C_5H_{10}ClO_3P$: Cl, 19.2. Found: Cl, 18.8.

5,5-Dimethyl-2-chloro-1,3,2-dioxaphosphorinane 2-oxide, m.p. 38–39°, was prepared according to McConnell and Coover[11] from 2,2-dimethylpropane-1,3-diol and $POCl_3$.

It should be noted that attempts to distil some of the six-membered ring cyclic phosphorochloridates through a Claisen head under vacuum ended in violent decomposition of the crude material at about 120°.

2-Fluoro-1,3,2-dioxaphosphorinane 2-Oxide.—A mixture of 4.0 g. of 2-chloro-1,3,2-dioxaphosphorinane 2-oxide and 1.2 g. of NaF was heated in dry benzene at reflux for 5 hr. The reaction mixture was filtered through Celite, and the product was distilled, b.p. 96–98° (0.5 mm.), $n^{25}D$ 1.4087.

Anal. Calcd. for $C_3H_6FO_3P$: C, 25.72; H, 4.32. Found: C, 25.51; H, 4.73.

2-*p*-Nitrophenoxy-1,3,2-dioxaphospholane 2-Oxides and -dioxaphosphorinane 2-Oxides.—The *p*-nitrophenyl esters of the cyclic phosphorochloridates were prepared by heating a mixture of the appropriate 2-chloro-1,3,2-dioxaphospholane 2-oxide or -phosphorinane 2-oxide and anhydrous sodium *p*-nitrophenoxide in toluene. The following preparation for 2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide is typical. To a mixture of 10 g. of anhydrous sodium *p*-nitrophenoxide (0.062 mole) and 75 ml. of anhydrous toluene was added 9 g. of 2-chloro-1,3,2-dioxaphosphorinane 2-oxide (0.057 mole). The mixture was stirred and heated at reflux for 1 hr. at which time most of the red sodium *p*-nitrophenoxide had disappeared. The cooled mixture was filtered through Celite, and removal of the solvent gave a yellow oil which crystallized upon chilling. The product was recrystallized several times from benzene, m.p. 99–101°. The elemental analysis is given in Table I.

In some cases a chloroform–ether mixture was used for recrystallization. The physical constants and elemental analyses for all new compounds are given in Table I.

2-(2,4-Dinitrophenoxy)-1,3,2-dioxaphosphorinane 2-oxide was prepared in the usual manner from sodium 2,4-dinitrophenoxide and 2-chloro-1,3,2-phosphorinane 2-oxide, m.p. 125–126°.

Anal. Calcd. for $C_9H_9N_2O_8P$: C, 35.53; H, 29.8. Found: C, 35.39; H, 3.36.

All melting points were taken in capillary tubes and are uncorrected.

TABLE I

MELTING POINTS AND ELEMENTAL ANALYSES OF 2-*p*-NITROPHENOXY-1,3,2-DIOXAPHOSPHOLANE 2-OXIDES AND -DIOXAPHOSPHORINANE 2-OXIDES

Compd.	M.p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2-*p*-Nitrophenoxy-1,3,2-dioxaphosphorinane 2-Oxide					
Unsubstituted (I)	99–101	41.70	3.89	40.97	3.94
4-Methyl (II)	110–111	43.96	4.43	43.55	5.00
Racemic 4,6-dimethyl (III)	77–81	46.15	4.93	45.58	5.17
meso-4,6-Dimethyl (IV)	120–122	46.15	4.93	46.11	5.19
5,5-Dimethyl (V)	122–123	46.15	4.93	46.01	5.17
2-*p*-Nitrophenoxy-1,3,2-dioxaphospholane 2-Oxide					
4-Methyl (IX)	160 (0.03)[a]	41.70	3.89	41.10	3.96
meso-4,5-Dimethyl (X)	82–85	43.96	4.43	43.70	5.27
Racemic 4,5-dimethyl (XI)	97–100	43.96	4.43	43.77	4.56

[a] B.p., °C. (mm.); distilled in falling-film molecular still.

Hydrolysis Rates.—The rate of displacement of *p*-nitrophenol from the dioxaphospholanes and dioxaphosphorinanes by OH^- was determined in approximately 0.01 *M* NaOH solution. An acetone solution (1 ml.) containing 1 mg. of compound was added to standard NaOH and made up to 100 ml. Samples were taken at various time intervals and absorption by *p*-nitrophenoxide ion was estimated at 400 mμ in a Beckman DU spectrophotometer. The rate of liberation of *p*-nitrophenol was found to follow good pseudo-first-order plots. 2,4-Dinitrophenoxide ion was estimated at 362 mμ. The bimolecular rate constants (K_{OH^-}) at 30.0°, determined from the integrated form of the equation $-d[P]/dt = K_{OH^-}[P][OH^-]$, where P is cyclic *p*-nitrophenyl ester, are given in Table II.

The method to determine the anticholinesterase activity of these compounds with house fly head cholinesterase has been described previously.[12] The values for I_{50} given in Table II are molar concentrations required to inhibit 50% of the enzyme in our standard fly head homogenate after 15 min.

Results and Discussion

Second-order hydrolysis constants (K_{OH^-}) in 0.01 *M* NaOH and the molar concentrations needed to give 50% inhibition of fly head cholinesterase (I_{50}) are given in Table II. The data indicate that the six-membered ring 2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane oxides are similar to the acyclic analog paraoxon (XII) in sensitivity to alkaline hydrolysis. In fact, 2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide (I), the least substituted of the series, and the 5,5-dimethyl compound (V) are somewhat less stable in NaOH than paraoxon. Methyl substitution in the 4- or 6-position measurably increased stability to alkaline hydrolysis (II, III, and IV).

The fourfold lower hydrolysis constant for *meso*-4,6-dimethyl-2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide (IV) compared to the racemic isomer III permits us to speculate on the configuration of these isomers. The reaction between sodium *p*-nitrophenoxide and the isomeric 2-chloro-1,3,2-dioxaphosphorinane 2-oxides obtained from racemic and *meso*-2,4-pentanediol in each case gave predominantly a single crystalline product, III and IV, respectively. In the chair form the most probable configuration of the cyclic phosphorochloridate obtained from the

(6) B. A. Arbuzov, K. V. Nikonorov, and Z. G. Skishova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 823 (1954).

(7) C. E. Wilson and H. J. Lucas, *J. Am. Chem. Soc.*, **58**, 2396 (1936).

(8) W. M. Lanham, U. S. Patent 2,892,862 (1959).

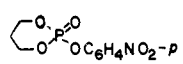
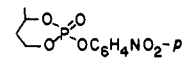
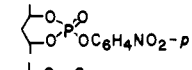
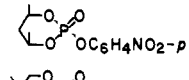
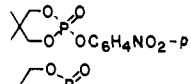
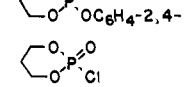
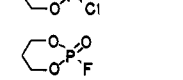
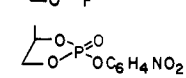
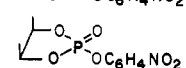
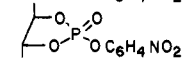
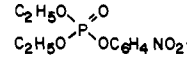
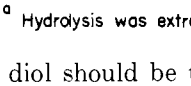
(9) H. R. Gamrath and R. E. Hatton, U. S. Patent 2,661,365 (1953).

(10) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

(11) R. L. McConnell and H. W. Coover, Jr., *ibid.*, **24**, 630 (1959).

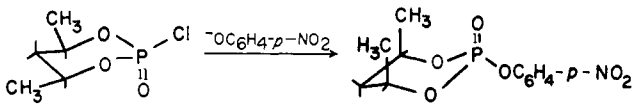
TABLE II

HYDROLYSIS CONSTANTS AND ANTICHOLINESTERASE ACTIVITY FOR FIVE- AND SIX-MEMBERED RING PHOSPHATE ESTERS.

	Compound	K_{OH^-} ($l \cdot mole^{-1} \cdot min.^{-1}$)	I_{50} (mol. conc.)
I		1.56	$> 1.3 \times 10^{-3}$
II		0.69	$> 1.3 \times 10^{-3}$
III		0.90	2.0×10^{-4}
IV		0.23	6.4×10^{-4}
V		1.49	$> 1.3 \times 10^{-3}$
VI		3.10	1.3×10^{-3}
VII		–	1.3×10^{-5}
VIII		–	1.2×10^{-6}
IX		–[a]	3.2×10^{-6}
X		–[a]	$> 1.3 \times 10^{-3}$
XI		–[a]	$> 1.3 \times 10^{-3}$
XII		0.94	2.6×10^{-8}

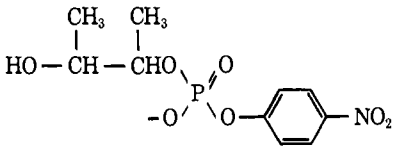
[a] Hydrolysis was extremely fast and K_{OH^-} was not determined.

meso diol should be the one in which the two methyl groups and the chlorine atom are equatorial, positions in which least interaction between the groups is expected. If it is assumed that displacement on phosphorus occurs with inversion, then the formation of the *p*-nitrophenyl ester by displacement of the chlorine atom should occur as shown below with concomitant change in the methyl groups to the axial positions. Thus, displacement of *p*-nitrophenoxide moiety by



OH^- is sterically hindered by two axial methyl groups. The methyl groups in the racemic isomer will each be axial and equatorial, hence, less interference to nucleophilic attack by hydroxide ion is expected. There is no ready explanation for the slower hydrolysis rate for the monomethyl ester II relative to III since II should be intermediate in stability between I and III, both on electronic and steric grounds.

The five-membered ring dioxaphospholanes were extremely sensitive to alkaline hydrolysis. In fact, compounds X and XI gave instantaneous and theoretical amounts of *p*-nitrophenol when added to 0.067 *M* disodium hydrogen phosphate buffer (pH 8.5). The rapid cleavage of the phosphorus–*p*-nitrophenoxy bond is consistent with the results reported by Ramirez, *et al.*,[13] for the fast reaction between water and 4,5-dimethyl-4,5-diacetyl-2-methoxy-1,3,2-dioxaphospholane 2-oxide in which methanol is liberated and the integrity of the cyclic ring system is maintained. The instantaneous liberation of *p*-nitrophenol suggests that the phosphorus–*p*-nitrophenoxy bond is broken prior to ring opening since the product from ring opening given below is expected to be somewhat stable in phosphate buffer due to the repulsion of hydroxide by the anion.



However, this point needs confirmation since it is known that the bond between the methoxy oxygen and the phosphorus atom in methyl 2-hydroxyethyl phosphate is easily split under mild alkaline conditions,[14] presumably because of participation of the β-OH.

The high reactivity of five-membered ring cyclic diesters and triesters of phosphoric acid has been well discussed by Cox and Ramsay,[15] and by Covitz and Westheimer.[16]

Inhibition measurements of house fly head cholinesterase by these cyclic esters gave results of considerable interest. The data in Table II show that these compounds were approximately 10^4–10^5 times less active in inhibiting cholinesterase than paraoxon (XII), in spite of their similar reactivity to OH^-. Further, the 2,4-dinitrophenyl ester (X) which hydrolyzed twice as fast as the corresponding mononitro compound showed little or no increase in anticholinesterase activity. However, in contrast to the nitrophenyl esters, the halo esters, 2-chloro- and 2-fluoro-1,3,2-dioxaphosphorinane 2-oxide, were moderately active anticholinesterases, the fluoro showing about 10 times higher activity than the chloro derivative.

Since the imidazole moiety in histidine has been implicated as a participant in the phosphorylation reaction between an organophosphorus inhibitor and an essential group in the esteratic site of the cholinesterase molecule,[17] the relative stability of I and paraoxon (XII) in 0.1 *M* imidazole was determined. As in aqueous NaOH I liberated *p*-nitrophenol at a slightly faster rate than paraoxon, the first-order constants ($min.^{-1}$) at 30.0° being 2.4×10^{-4} and 8.7×10^{-5}, respectively.

Since organophosphorus esters of the same order of reactivity as paraoxon are generally inhibitors of cholinesterase,[2,18] the low anticholinesterase activity of the six-membered ring esters is surprising and their inactivity must be attributed to steric effects. The data suggest that *p*-nitrophenoxydioxaphosphorinane oxides cannot be accommodated by the esteratic site of the enzyme, either in the enzyme–phosphate complex formation[19] or in the phosphorylation reaction. That in-

(12) T. R. Fukuto and R. L. Metcalf, *J. Am. Chem. Soc.*, **81**, 372 (1959).

(13) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *ibid.*, **85**, 2681 (1963).

(14) O. Bailly and J. Gaumé, *Bull. soc. chim. France*, [5] **3**, 1396 (1936).

(15) J. R. Cox, Jr., and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

(16) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963).

(17) J. A. Cohen and R. A. Osterbaan in "Handbuch der Experimentellen Pharmakologie," Ergänzungwerk XV, Springer-Verlag, Heidelberg, 1963, pp. 299–373.

(18) T. R. Fukuto in "Advances in Pest Control Research," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1957, pp. 147–192.

(19) A. R. Main, *Science*, **144**, 992 (1964).

activity is due to steric factors is strengthened by the moderately high activity of the smaller fluoro derivative.

With the exception of IX, the five-membered ring dioxaphospholanes were poor anticholinesterases, probably due in part to their rapid breakdown in water. The I_{50} value of IX, a liquid, must be taken with caution since its instability to heat and moisture made purification difficult.

None of the compounds in Table II showed topical toxicity at 500 γ/g. to house flies, *Musca domestica*, or at 10 p.p.m. in water to mosquito larvae, *Culex pipiens quinquefasciatus*.

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Potential Antiradiation Drugs. II.[1] 2-Amino-1-alkanethiols, 1-Amino-2-alkanethiols, 2-Thiazolines, and 2-Thiazoline-2-thiols[2]

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Syntheses and radioprotective properties are described for 21 compounds drawn from the title classes. With few exceptions all compounds studied showed some protective activity in either mice or bacteria. The best protection was shown by 2-amino-1-pentanethiol (**24**), 2-amino-3-methyl-1-butanethiol (**25**), and 1-amino-2-propanethiol (**27**). Three thiazolines offering good protection (**15**, **16**, and **10**) are the precursors of these same aminothiols. Radioprotective activities observed in the present work are compared with those observed in other laboratories with the same or analogous compounds.

The purpose of the present work was to continue the preparation of pure organic compounds which might protect against the lethal effects of ionizing radiation.[3] As part of an extensive program directed by the sponsoring agency,[4] we prepared 10 g.–1 kg. of the aminoalkanethiol hydrochlorides shown in Table III. The radioprotective activities of some of these substances had been reported previously by several investigators, but we felt it desirable to re-examine these substances, along with new compounds, using a standard testing technique.

When radioprotective activity was observed with some of the 2-thiazoline intermediates isolated during the aminothiol syntheses, all such intermediates (Table II) were purified and tested.

Chemistry.—We chose to prepare aminoalkanethiols from the related amino alcohols because of the availability of the latter. From among a variety of routes that have been devised for the replacement of an alcohol function by a thiol function, that involving a 2-thiazoline intermediate[5,6] proved to be completely satisfactory, not only with respect to yield but particularly with respect to purity of product. At the beginning of our work we prepared **21** and **27** by way of appropriate 2-thiazoline-2-thiol intermediates (**19** and **20**) but abandoned this route when a repetition of the synthesis of **27** by way of a 2-thiazoline showed clearly the superiority of this latter route.

Amino alcohols were acetylated effectively by reaction with ethyl acetate[7] (method A). In early work we sought to acetylate by heating the acetate salt of the amino alcohol[5] (method B) but found that yields were low and that the desired amide was difficult to separate from unreacted acetate salt. In addition, we observed that at the temperature needed for this reaction the amide sometimes cyclized to the oxazoline. In the case of the acetate salt of 2-amino-2-methyl-1-propanol, 2,4,4-trimethyl-2-oxazoline was the only product formed; this facile cyclization, noted by others with the benzoyl derivatives,[8] appears to be another example of the so-called *gem*-dimethyl effect.[9] When acetylation was effected with acetic anhydride (method C), the acetate salt of the amino alcohol interfered with the isolation and purification of the amide (as in method B) and diacetylation of the amino alcohol also occurred.

The hydroxyalkylacetamides (Table I) were converted smoothly to the 2-thiazolines (Table II) when heated with phosphorus pentasulfide.[5,6] An important modification of the published procedures, introduced in our work, was the use of mineral oil as a diluent to moderate the otherwise violent reaction. This modification permitted us to carry out large-scale runs. The mechanism of this cyclization reaction has been studied recently.[10]

Hydrolysis of the 2-thiazolines by boiling overnight with dilute HCl[11] gave the desired aminoalkanethiol

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