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US Army Edgewood Arsenal
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Technical Report

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Effect of the Container on the Stability of Aqueous Solutions of Pralidoxime Chloride

by

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EDGEWOOD ARSENAL, MARYLAND 21010

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FOREWORD

The work described in this report was authorized under Task 1C622401A09709, Lethal Agents. The experimental data are contained in notebooks MN-1884, MN-1885, MN-1886, and MN-1916. This work was started in January 1964 and completed in March 1965.

Acknowledgment

The authors gratefully acknowledge the valuable assistance of the Analytical Research Branch, Chemical Research Division, for the iron-content and residue-on-ignition analyses.

Notices

The information in this report has not been cleared for release to the general public.

Disclaimer

The findings in this report are not to be construed as an official Department of the Army position, unless so designated by other authorized documents.

Disposition

When this report has served its purpose, DESTROY it.

DIGEST

Solutions of pralidoxime chloride (2-PAMCl) are significantly less stable in the metal container of the AtroPen Auto-Injector than in glass or plastic containers, when stored at temperatures ranging from ambient to 95°C. Catalysis by the metallic surface is probably the factor contributing to the decreased stability. In the event the AtroPen Auto-Injector is used for 2-PAMCl solutions (as it is presently used for atropine), a glass or plastic container should be used instead of the present metal container.

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EFFECT OF THE CONTAINER ON THE STABILITY OF AQUEOUS SOLUTIONS OF PRALIDOXIME CHLORIDE

I. INTRODUCTION.

An automatic injector, which permits the individual soldier to give himself (self-aid) or his buddy (first aid) a rapid and reliable intramuscular injection of atropine in the event of exposure to chemical nerve agents, has been classified Standard Type by the US Armed Forces Medical Services.* In this injector, 0.85 ml of a solution of the drug is contained in a small, stainless-steel (anodized) cylinder that is closed at each end by a nylon-coated rubber plug. The cylinder also encloses a stainless-steel needle (figure 1). An essential characteristic of the injector item is that the cylindrical container must be compatible with the atropine solution; i.e., neither contributing to the degradation of the atropine nor becoming corroded by the solution. The formula of the atropine solution used in the injector was developed to give maximum stability of the drug and to prevent corrosion of the metal container.

Pralidoxime chloride, chemically designated as 1-methyl-2-pyridinium aldoxime chloride and commonly referred to as 2-PAMCl, has become an important adjunct to atropine in the treatment of casualties caused by chemical nerve agents. An item containing 5 gm of the oxime as a powder in a 20-ml bottle with a rubber-diaphragm closure has been classified as Standard Type and identified as FSN 6505-082-2456, Pralidoxime Chloride, 5 gm, for inclusion in the Federal Catalog, Department of Defense Section Medical Materiel. Should the packaging of an aqueous solution of the oxime salt in the automatic injector be desired, a knowledge of the stability of this solution in the metal cylinder and of their compatibility is essential. Therefore, the stability of an unbuffered 50% aqueous solution of 2-PAMCl in the stainless-steel cylinder used in the automatic-injector item was determined. Cylinders having identical dimensions but made of glass and plastic were also included in this study. The rates of decomposition of the oxime in the various containers were studied at ambient temperature, 40°, 65°, and 95°C; the half-lives at these temperatures have been calculated.

II. EXPERIMENTATION.

A. Apparatus.

Cary Model 14 spectrophotometer

Beckman Model GS pH meter

Thomas-Hoover capillary melting-point apparatus

* FSN 6505-584-3067 and FSN 6505-823-8041, Atropine Injection, 2 mg; manufactured by Rodana Research Corporation, Bethesda, Maryland.

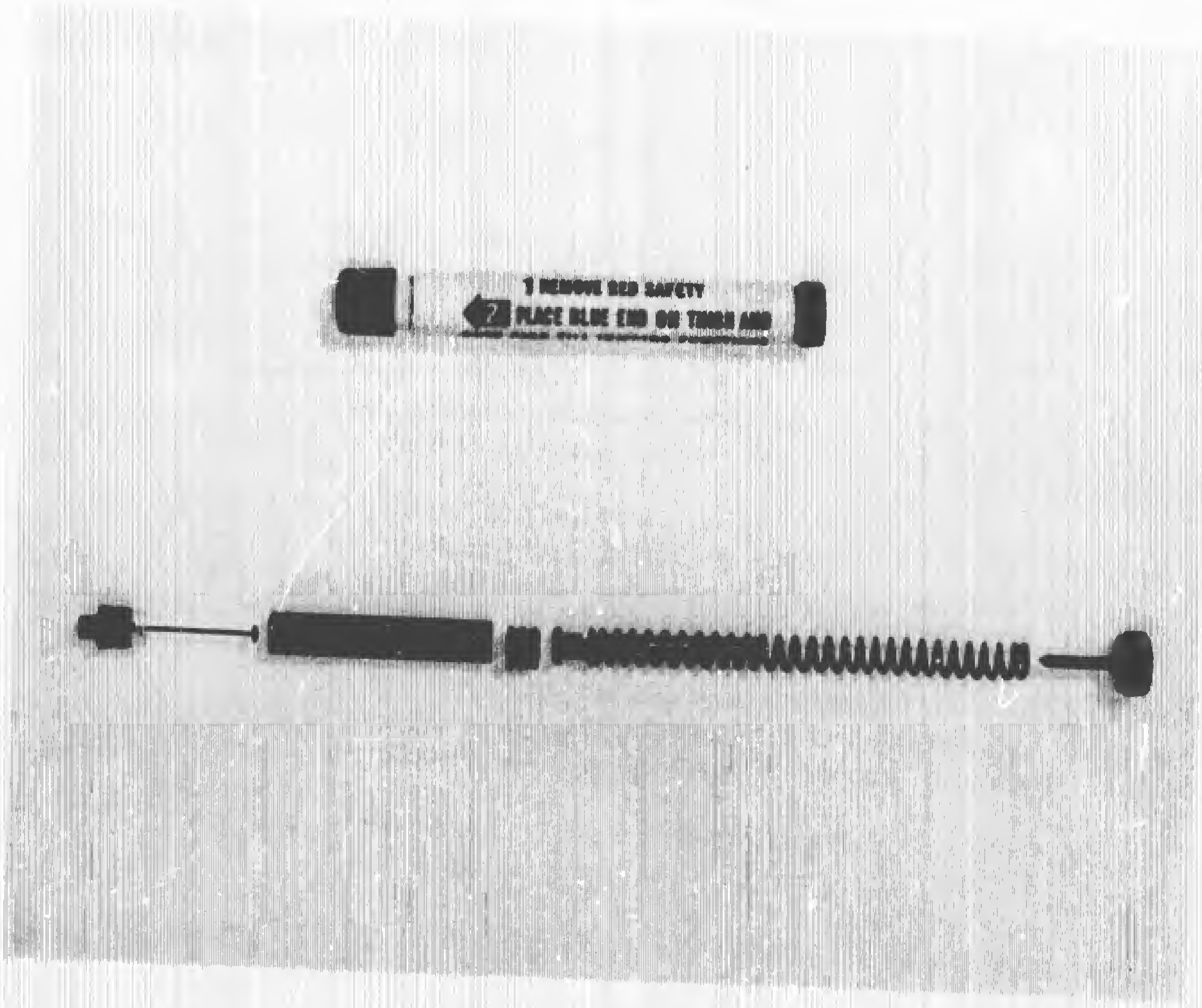

FIGURE 1

ATROPINE AUTOMATIC INJECTOR, FSN 6505-823-8041

(Assembled unit and internal components showing stainless-steel cylinder and needle)

B. Materials.

The 2-PAMCl was obtained from a commercial source and purified by repeated recrystallization from an ethanol-water system. The resulting product (lot M-1/24) was white and odorless and melted at 221° to 222°C with decomposition, when determined in accordance with the USP method for substances of Class 1.

Analysis:

Calculated: C, 48.7; H, 5.3; Cl, 20.5
Found: C, 48.7; H, 5.4; Cl, 20.7

The cylinders — glass, metal, and plastic — used in the experiments were furnished by the manufacturer of the AtroPen Auto-Injector. They were 1-11/16 in. long and 5/16 in. in diameter and were fitted at each end with nylon-coated rubber plugs. A stainless-steel hypodermic needle, which was attached to the forward rubber seal, was completely enclosed within the assembled unit; i.e., cartridge.

Holders were made that kept the filled cartridges in an upright, secure position and prevented the plugs from loosening and popping out at elevated temperatures. The holders consisted of two pieces of fiberboard of the same dimensions, in one of which holes had been drilled to accommodate the cartridges snugly; the other piece was placed on top of the cartridges as a template and was then secured at the corners with bolts and wing nuts.

C. Analytical Methods.

The 2-PAMCl concentration of each of the solutions was calculated from the spectrophotometric measurement of the absorbance at 336 mμ of an appropriately diluted solution in 0.1 N NaOH. A value of 1.84×10^4 for the molar absorptivity of the oxime salt under these conditions was used in the calculations. The breakdown product, 1-methyl-2-pyridinium carboxamide chloride, also designated as 1-methyl-2-carbamidopyridinium chloride and hereafter referred to as carboxamide, shows no absorption at 336 mμ in alkaline solution.

The concentration of the carboxamide was calculated from the absorbance at 275 mμ of an appropriately diluted solution in 0.1 N NaOH, after correcting for the absorbance (calculated) at this wavelength due to the 2-PAMCl present in the solution. Molar absorptivities used in the latter calculation are 4.4×10^3 and 6.0×10^3 for 2-PAMCl and the carboxamide hydrochloride, respectively.

The effect of cylinder composition, temperature, and time on the pH of the solutions was determined on the pooled, undiluted contents of two cartridges.

D. Procedure.

A 50% (w/v) solution of 2-PAMCl was prepared by adding sufficient triply distilled water (quartz still) to 50 gm of the highly purified oxime salt in a 100-ml volumetric flask. Approximately 1-ml quantities of the solution were pipetted into the cylinders, which were then assembled and placed in the fiberboard holders. The units were placed on the laboratory shelf for ambient-temperature studies and into hot-air ovens for controlled-temperature studies at 40°, 65°, and 95°C.

In those studies performed to determine the uptake of metal by the oxime solution, the cylinders were weighed before and after filling and assembling. Studies were also performed on glass and plastic containers with and without the stainless-steel needle.

III. RESULTS.

The results obtained on the stability of a 50% aqueous solution of 2-PAMCl in the metal, glass, and plastic containers of the AtroPen Auto-Injector that were stored at various temperatures are plotted in figure 2. The stability data on the glass and plastic cylinders were statistically identical and, therefore, have been combined in the graph in figure 2. The plots clearly show that the concentrated solution of 2-PAMCl is significantly less stable in the metal than in either the glass or plastic container. The presence or absence of the needle in the cylinder did not alter this finding. The half-lives of the solutions in the containers at the various temperatures are given in table 1, together with the calculated, apparent first-order rate constants. These constants show that the breakdown of the solution of 2-PAMCl was five and six times faster in the metal than in the glass and plastic cylinders at room temperature and 40°C, respectively. At higher temperatures, 65° and 95°C, the rate of breakdown in the metal was twice that in the nonmetal cylinders.

Figure 3 shows plots of the disappearance of the oxime salt and of the appearance of the carboxamide in the various containers at 65°C.

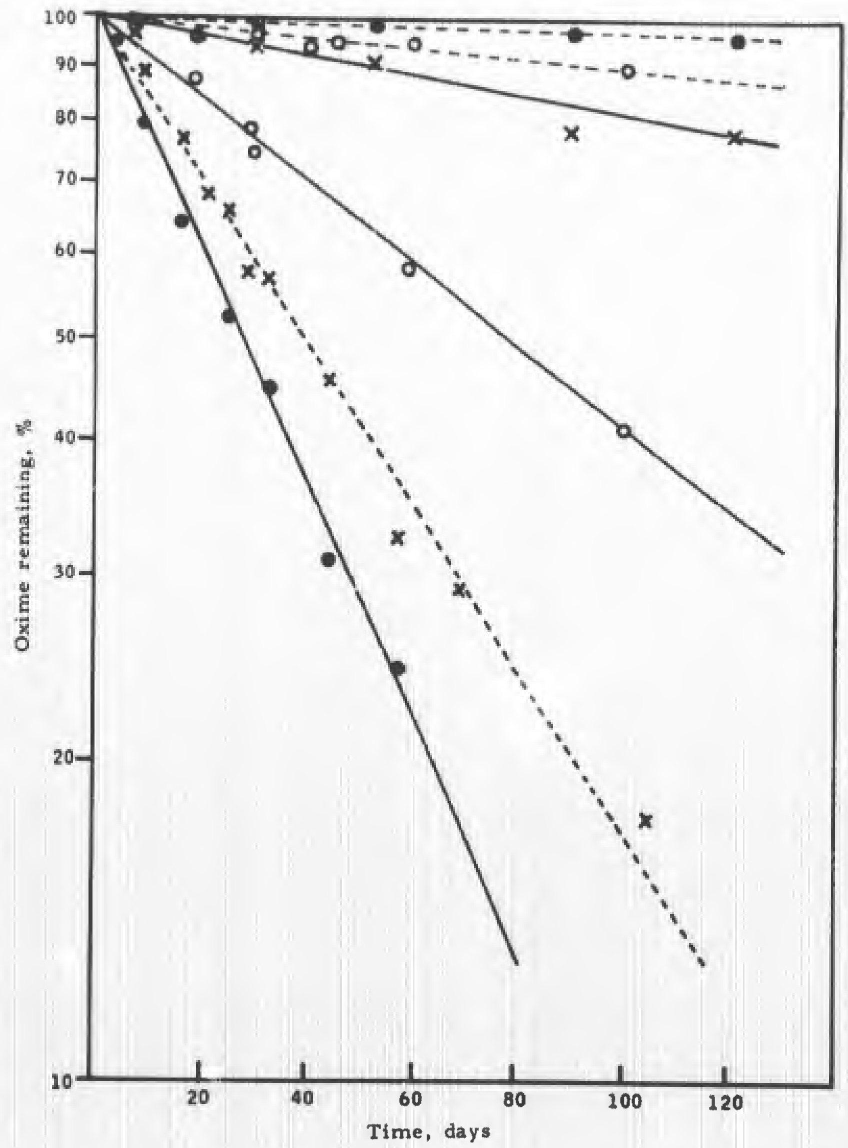

FIGURE 2

STABILITY AT VARIOUS TEMPERATURES OF 50% AQUEOUS SOLUTIONS OF 2-PAMCl IN METAL, GLASS, AND PLASTIC CYLINDERS OF ATROPEN AUTO-INJECTOR

● ---- ● In glass and plastic cylinders at room temperature
× —— × In metal cylinder at room temperature
○ ---- ○ In glass and plastic cylinders at 40°C
○ —— ○ In metal cylinder at 40°C
× ---- × In glass and plastic cylinders at 65°C
● —— ● In metal cylinder at 65°C

TABLE 1

OBSERVED RATE CONSTANTS AND HALF-LIVES FOR DEGRADATION OF 50% AQUEOUS SOLUTIONS OF 2-PAMCl IN GLASS, PLASTIC, AND METAL CYLINDERS

Cylinder composition	Temperature							
	Ambient		40°C		65°C		95°C	
	k	$t_{1/2}$	k	$t_{1/2}$	k	$t_{1/2}$	k	$t_{1/2}$
	day^{-1}	yr	day^{-1}		day^{-1}	days	day^{-1}	hr
Glass and plastic	4.54×10^{-4}	4.2	1.43×10^{-3}	1.33 yr	1.67×10^{-2}	42	8.43×10^{-1}	20
Metal	2.29×10^{-3}	0.83	8.88×10^{-3}	78 days	2.60×10^{-2}	27	1.63	10
$\frac{t_{1/2} \text{ (glass and plastic)}}{t_{1/2} \text{ (metal)}}$		5		6		2		2

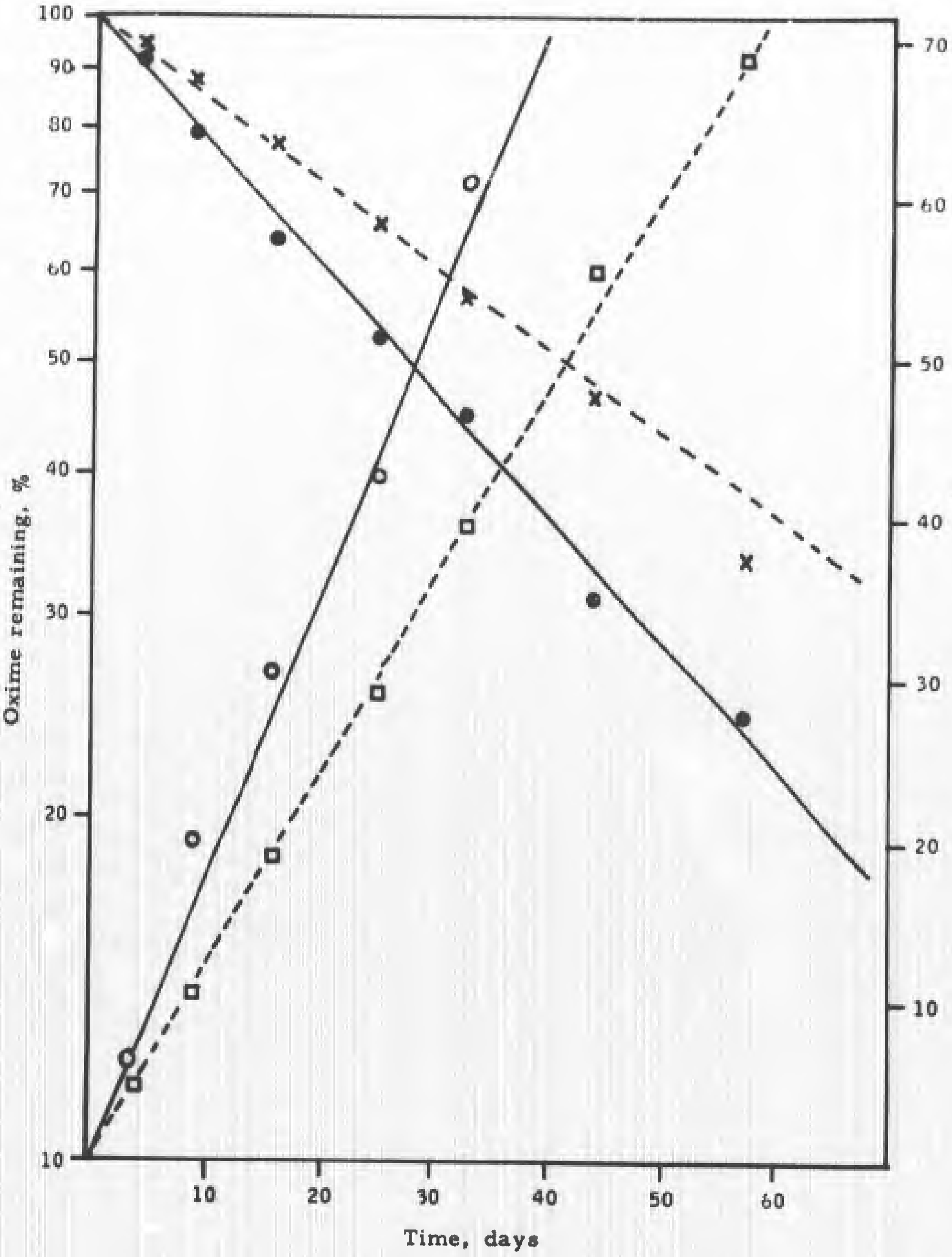

FIGURE 3

DECREASE IN CONCENTRATION OF 2-PAMCl AND INCREASE IN CONCENTRATION OF CARBOXAMIDE IN 50% AQUEOUS SOLUTIONS OF 2-PAMCl AT 65°C

× ---- × 2-PAMCl in glass and plastic cylinders

●——● 2-PAMCl in metal cylinder

□----□ Carboxamide in glass and plastic cylinders

○——○ Carboxamide in metal cylinder

The plots for each type of container intersect at the region of 50% of the total concentration, a finding that indicates that the amount of carboxamide formed is equivalent to the amount of 2-PAMCl disappearing and confirms the fact that carboxamide is the compound formed during the described storage of the 2-PAMCl solution. The plot of the rate constants against absolute temperature (figure 4) shows that the reaction involved in the disappearance of 2-PAMCl is not altered by temperature and, also, that the reaction is the same in the various containers.

To investigate the possibility that metallic ions or other material dissolved from the container by the oxime solution might be involved in the increased rate of breakdown observed in the metal cylinders, the iron content of the oxime solution and the loss in weight of the metal containers were determined after storage for various periods of time at 95°C. Cleaned, dried, empty cylinders and filled, assembled cartridges were weighed. The cartridges were allowed to cool to room temperature and were weighed and disassembled; the metal cylinders were thoroughly washed with water, rinsed with distilled water, dried, and weighed. The loss in weight of the filled, assembled unit during storage was a measure of the loss of water due to evaporation at the elevated temperature and was found to be an insignificant factor in the results. The data given in table 2 indicate that neither the iron content of the solution nor material dissolved from the container (as judged by residue on ignition of the solution and loss in dry weight of the metal cylinders) was a significant factor in the increased instability of the oxime solution in the metal containers.

The pH values obtained in the study at 65°C are illustrated in table 3. A comparison of the "intra" with the "inter" pH fluctuation of the solution from each type of cylinder indicates that this variable is not a significant factor in the stability results.

An attractive explanation of the decreased stability of the concentrated solution of 2-PAMCl in the metal cylinder in comparison with cylinders made of glass and plastic involves catalysis by the surface of the metal container; i.e., heterogeneous catalysis. The significantly increased rate of breakdown in the metal cylinders at room temperature and at 40°C is suggestive of processes that are catalyzed by metallic surfaces. Under the conditions of this study, the conversion of 2-PAMCl to the corresponding pyridinium carboxamide takes place in at least two steps: (1) dehydration of the oxime to the 2-cyanopyridinium compound, and (2) reaction with hydroxide ion to form the corresponding carboxamide. Neither the experimental approach nor the results obtained permit the designation of the step or steps involved herein that would be subject to catalysis by the surfaces of the metal cylinder.

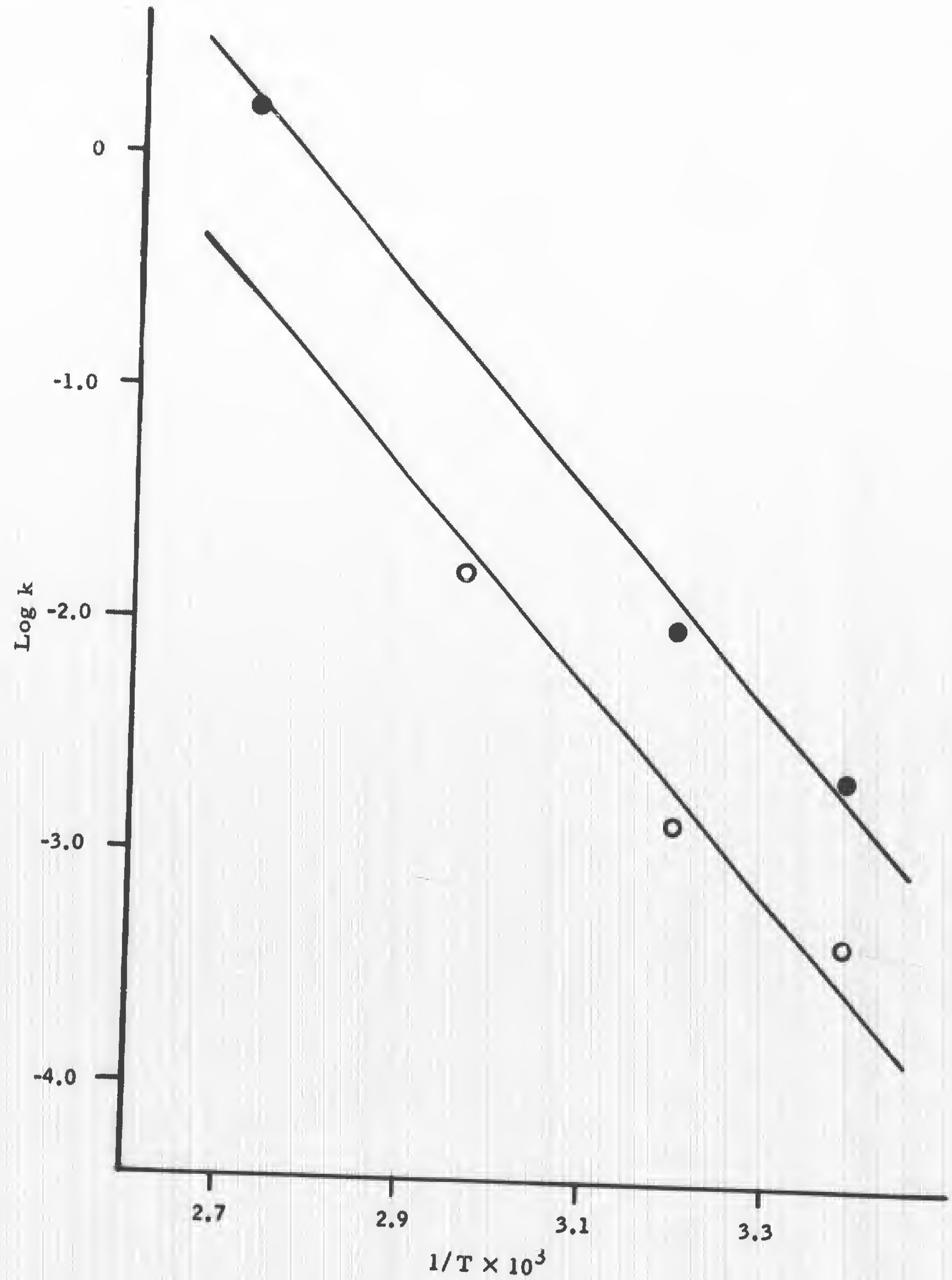

FIGURE 4

TEMPERATURE DEPENDENCE OF REACTION INVOLVING DEGRADATION OF 50% AQUEOUS SOLUTIONS OF 2-PAMCl IN VARIOUS CYLINDERS

○——○ In glass and plastic cylinders

●——● In metal cylinder

TABLE 2

ANALYSIS FOR IRON IN 50% AQUEOUS SOLUTIONS OF 2-PAMCl STORED IN STAINLESS-STEEL CYLINDERS UNDERGOING DECOMPOSITION AT 95°C

Time	2-PAMCl remaining	Wt*	Residue on ignition		Iron in solution		Wt loss of cylinder
hr	%	gm	mg	%	mg	%	mg
0	100.0	1.0247	0.2	0.02	0.02	0.002	–
18	43.5	1.7828	0.6	0.03	0.14	0.008	0.35
26	35.5	1.1454	0.7	0.06	0.08	0.007	0.85
42	13.7	1.5353	0.8	0.05	0.11	0.010	0.90
90	0.0	1.4134	0.4	0.03	0.03	0.002	0.55

* Weight of solution used for iron analysis.

TABLE 3

HYDROGEN-ION MEASUREMENT IN 50% AQUEOUS SOLUTIONS OF 2-PAMCl UNDERGOING DECOMPOSITION AT 65°C

Cylinder composition	pH							
	Time in days							
	0	4	9	16	25	33	44	57
Glass	3.68	3.62	3.65	3.67	3.56	3.55	3.55	3.74
Metal	3.68	3.68	3.83	3.71	3.69	3.59	3.65	3.77
Plastic	3.68	3.67	3.42	3.64	3.52	3.59	3.50	3.75

Evaluation of this point must be the object of another study; e.g., effect of a metallic surface on hydroxide-ion attack on the 1-methyl-2-cyanopyridinium ion.

IV. CONCLUSIONS.

Solutions of 2-PAMCl are significantly less stable in the metal container of the AtroPen Auto-Injector than in glass or plastic containers, when stored at temperatures ranging from ambient to 95°C. Catalysis by the metallic surface is probably the factor contributing to the decreased stability. In the event the AtroPen Auto-Injector is used for 2-PAMCl solutions (as it is presently used for atropine), a glass or plastic container should be used instead of the present metal container.

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13. ABSTRACT

The storage stability of solutions of pralidoxime chloride (2-PAMCl) in metal containers was studied. The metal containers were a component part of the AtroPen* Auto-Injector. The oxime was placed in various containers, and its rate of decomposition was observed at ambient temperature, 40°, 65°, and 95°C. Results are presented graphically. Decreased stability may be used to catalysis by the metallic surface. If the AtroPen* Auto-Injector is to be used for the administration of 2-PAMCl solutions, glass or suitable plastic containers should be used.

14. KEYWORDS

Pralidoxime chloride	2-PAMCl	Storage
Stability	Atropine	Rate of decomposition
Catalysis	Glass cartridge	Plastic cartridge
Stainless-steel cartridge		
AtroPen* Auto-Injector		

* Rodana Research Corporation, Bethesda, Maryland

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