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PROTECTIVE AND THERAPEUTIC AGENTS FOR WAR GASES - SOLUTIONS OF BAL

to
January 1, 1945
by

P. L. Salzberg, W. A. Lazier, G. W. Rigby
and C. G. Wortz -- Chemical Department of
E. I. duPont de Nemours & Co.

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Division 9

NATIONAL DEFENSE RESEARCH COMMITTEE
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OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT

PROTECTIVE AND THERAPEUTIC AGENTS FOR WAR GASES - SOLUTIONS OF BAL

Service Directive CWS-4

Endorsement (1) Homer Adkins, Member of Division 9, to Walter R. Kirner, Chief, Division 9.

Forwarding report and noting:

> "The main objective of this investigation was the development of a chemically stable solution of BAL which was therapeutically satisfactory as an antidote for Lewisite contamination of human eyes. It was shown that systems containing water were unstable. Assistance was given to the Army Medical Corps in writing specifications for the anhydrous ethylene glycol solution issued as "M-1 eye solution." Detailed studies were made of the factors influencing the stability of the ethylene glycol solution and a search was made for other satisfactory solvents for BAL."

(2) from Walter R. Kirner, Chief, Division 9, to Dr. Irvin Stewart, Executive Secretary of the National Defense Research Committee.

Forwarding report and approving:

This is a progress report under Contract 9-274, OEMsr-377, with E. I. duPont de Nemours & Company.

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TABLE OF CONTENTS

INTRODUCTION

Early in the work on BAL, the principal use contemplated was as an antidote for Lewisite (L) contamination of the eyes. For this purpose it was considered desirable to have a liquid vehicle miscible with the eye fluids. The solution was then to be included in the medical kit issued to Medical Corpsmen. At the time it was considered impractical for individual soldiers to treat themselves, even though it was realized that decontamination within 10-15 minutes was probably necessary if a satisfactory cure was to be obtained. Meanwhile, the U. S. Public Health Service had been experimenting with the injection of BAL as a means of controlling systemic arsenical poisoning which occasionally complicated the rapid mapharsen treatment of syphilis. Both of these uses required a chemically stable solution of minimum irritancy and maximum therapeutic efficacy. The present report covers the chemical work incident to developing a solution of BAL suitable for these two applications. The experimental work was carried out by George W. Rigby and C. G. Wortz under the direction of W. A. Lazier.

OBJECTIVES

The primary objective of this investigation was to develop a chemically stable solution of BAL which was therapeutically satisfactory as an antidote for Lewisite contamination of human eyes. In achieving this objective it was considered desirable to study in detail the factors affecting the stability of BAL in solution.

SUMMARY AND CONCLUSIONS

After a detailed investigation of aqueous and aqueous-glycol solutions of BAL, it was concluded that these systems are not sufficiently stable to be practical for field use in the treatment of Lewisite burns. On the other hand, anhydrous glycol solutions have a reasonably good life under tropical storage conditions. The Army Medical Corps has accordingly issued an anhydrous ethylene glycol solution under the label "M-1 Eye Solution". Assistance was given in writing the specifications for the preparation and in developing the required test methods.

Meanwhile, a detailed study was made of the factors influencing the stability of the glycol solution. Experimental evidence was obtained that pH, heavy metals (particularly iron), water, oxygen, light and stabilizers all influenced the keeping qualities of the solution. However, even under the most favorable conditions, deterioration under tropical storage conditions persisted at a rate sufficient to somewhat limit the useful life of the solution. Moreover, as deterioration progressed, a white polymer separated from the solution, although the amount bore no apparent quantitative relation to the extent of depletion.

These difficulties with glycol solutions led to a renewed and broadened investigation of other solvents for BAL. As a result of this study it became evident that non-hydroxylated solvents gave solutions of strikingly improved stability. Moreover, these solutions not only possessed remarkable heat stability but were also stable to oxidation and did not deposit a solid phase even on prolonged heating. Among the solvents which appeared most useful for therapeutic application of BAL were peanut oil, benzyl benzoate, diethyl phthalate, and triacetin. Although pH, water, heavy metals, light, and stabilizers all had an effect on these solutions, their influence was superimposed at a higher level of inherent stability. For injection of BAL a solution in 90% peanut oil and 10% benzyl benzoate is finding interesting clinical applications.

PROGRAM

Experimental work on solutions of BAL in this laboratory has been discontinued.

EXPERIMENTAL SECTION

A. Development of "M-1 Eye Solution"

In July 1942, as soon as the most pressing BAL manufacturing problems had been solved, attention was shifted to the preparation of a BAL solution suitable for the treatment of human eyes which had been exposed to Lewisite vapors. Since it was considered desirable to have a solution miscible with the eye fluids, the first thought was, logically, to use aqueous solutions. While these solutions were highly effective therapeutically, it soon became evident that they were quite unstable chemically since an oily polymer rapidly separated at room temperature. On analysis, this oil was found to consist of an insoluble polymer which had carried out of solution a considerable proportion of the BAL. A detailed study of the effect of pH, oxygen, metals and solution stabilizers failed to disclose conditions for preventing precipitation, although each of these factors had a bearing on the time required for the precipitate to form.

By the middle of August 1942, attention turned to aqueous glycol solutions of BAL. When freshly prepared these were as effective therapeutically as aqueous solutions. However, on standing at room temperature an oily precipitate formed, although much more slowly than from aqueous solutions. Attempts to prepare a usefully stable solution by control of pH, oxygen, heavy metal content and solution stabilizers were unsuccessful. Late in August 1942, it became evident that water catalyzes the decomposition of BAL and that aqueous solutions probably could not be prepared which were chemically stable. A review of the physiological and toxicity testing data, meanwhile, indicated that anhydrous ethylene glycol, propylene glycol and thiodiglycol had been used by the various investigators with satisfactory therapeutic results, although when applied to the eye there was a certain amount of smarting and discomfort, possibly caused by the dehydrating action of these solvents. Chemical stability tests were nevertheless undertaken with these solvents, all of which proved better than aqueous solutions.

An investigation of commercial availability revealed that the Carbide and Carbon Chemicals Corporation regularly produce an "iron and chloride free" grade of ethylene glycol which is exceptionally dry and otherwise free from deleterious impurities. Therefore, most of the detailed investigation of chemical stability was carried out with this solvent. It was soon established that the most favorable conditions required a solution having an iron content of less than 0.1 part per million, a water content of less than 0.5% and a pH of about 4.5. Moreover, the solution should be protected from light and air.

During September 1942, assistance was given to the Army Medical Corps in writing suitable specifications for an anhydrous ethylene glycol solution of BAL to be designated as "M-1 Eye Solution". Soon thereafter we were approached by representatives of John Wyeth and Brother of Philadelphia who had been awarded a contract to manufacture and package this solution. Assistance was given them in selecting suitable equipment for handling the solution and in establishing chemical control over the final product.

By the middle of January 1943, actual packaging began. This contract, which was completed in July 1943, consisted of about one and a quarter million one-half ounce brown glass bottles filled with 5.6% BAL solution (wt. %) in ethylene glycol. These bottles were nitrogen blanketed, closed with Vinylite lined screw caps held in place with cellophane bands and packaged in a cardboard container together with a suitable medicine dropper for dispensing. The contract for procurement of this solution was not renewed because of the favorable development of a BAL ointment (reported elsewhere).

In the meanwhile, further attention was given to improving the stability of BAL in solution. A substantial advance toward this goal was made when it was discovered that solution stabilizers such as Vitamin B_1 function as metal deactivators as well as antioxidants. However, in spite of all improvements, the stability of glycol solutions left much to be desired. At about this time, April 1943, partly as a result of experience gained under the ointment program, a renewed and broadened investigation of solvents was undertaken. This study revealed a startling improvement of stability in nonhydroxylated solvents. Consequently, if a new contract were to be given for "M-1 Eye Solution" it would now be recommended that a nonhydroxylated solvent such as triacetin should be considered.

B. BAL Solution for Injection

On May 28, 1943, we were approached by a representative of the U. S. Public Health Service who reported extremely interesting data on the use of BAL solutions for combating general systemic arsenical poisoning which occurs in a small proportion of cases of syphilis treated by the intensive arsenical therapy (mapharsen) method with which they have been experimenting. Their problem was to prepare a solution of BAL in a vehicle which could be injected intramuscularly. This solution was required to be stable to sterilization temperatures. From the earlier work on nonhydroxylated solvents it was recommended that peanut oil and benzyl benzoate might prove satisfactory. Based on this recommendation a 5% solution in a solvent composed of 90% peanut oil and 10% benzyl benzoate is undergoing extensive clinical testing under the supervision of the Public Health Service. Chemically, our experience showed only 5% loss of active ingredient during 56 days at 78°C. thus indicating a very satisfactory margin of stability for this type of solution.

C. Problems Incident to "M-1 Eye Solution" Procurement

Glycol. Before procurement of an anhydrous ethylene glycol solution of BAL could be started, it was necessary to set up specifications for each of the components. Samples of the best glycol obtainable from each of the major producers were examined chemically and physiologically. As a result of this investigation it was found that the so-called "technical grade iron and chloride free" material produced by the Carbide and Carbon Chemicals Corporation was the most suitable for the preparation of "M-1 Eye Solution". A typical analysis of a good sample of this quality ethylene glycol is as follows:

Water	0.165%
Chlorine	6.4 parts per million
Iron	40 parts per billion
Freezing point	-13.2°C.
Color	A.P.H.A. 3
Carbonyl No.	0

The methods by which these analyses were made will be found appended to this report, together with the specifications adopted by the Army.

Materials of Construction. In order that commercial preparation of an "M-1 Eye Solution" could be undertaken, it was necessary to determine the effect of materials of construction on the stability of the solution. Since previous experience with BAL and its solutions (see below) had shown most metals to be deleterious the next thought was to use plastics materials as extensively as possible. A series of experiments were, therefore, undertaken to determine the effect of a 5.6% by weight solution of BAL in anhydrous ethylene glycol on a number of plastics materials (see Table I). Among these, Tenite II, Saran, and Vinylite were found to be unaffected by the solution.

In view of these findings the John Wyeth Company of Philadelphia mixed the solution in a 2000 gal. glass lined tank with a stream of oxygen-free nitrogen and constructed transfer lines for the solution from Tenite tubing. The filling pipettes were constructed of glass. This arrangement proved very satisfactory in operation. The screw caps for the bottles in which the solution was to be packaged were lined with cardboard coated on the inner side with a thin layer of Vinylite. Accelerated test experiments in the laboratory indicated that Vinylite was unaffected by the solution and that the BAL was not adversely affected by the Vinylite. Experiments were also undertaken with medicine dropper bulbs molded from "Tygon". This plastic did not swell or lose its rubbery quality even after contact with the "M-1 Eye Solution" for a prolonged period at 50°C.

Bottles. It was proposed to package the solution in 1/2 oz. brown screw cap bottles. Since brown bottles are colored with ferric oxide it was feared that BAL would pick up a considerable portion of iron from this source. To test this point 100 bottles selected at random from each of 10 one hundred gross cartons (representing a total of 1.5 million bottles) were taken, filled with "M-1 Eye Solution", fitted with screw caps, and placed in a 50° oven. At the end of one week the iron content in each of the bottles was measured with a photometer. The solution was replaced in the bottles and heated for a second week and the iron pickup again determined. The results of these tests are indicated in Table II. It will be noted from this table that the bottles imparted an average of 15 parts per billion of iron to the solution during one week and this increased to only 22 parts per billion after two weeks. Moreover, it will be seen that the bottles from one carton (B) contained an abnormal amount of iron. It was recommended to the John Wyeth Company, therefore, that samples of bottles taken at random be tested as a routine procedure before packaging the BAL.

"M-1 Eye Solution" Specifications. On the basis of laboratory experience, tentative specifications were written for "M-1 Eye Solution". The specifications and the analytical methods will be found appended to this report. It will be noted that a specification for iron content was not included since it was emphasized that as low a concentration as practicable should be maintained. However, the exact value was to be established from plant experience. The John Wyeth Company were able to keep this to less than 100 parts per billion of iron in the completed solution. This is a remarkably low value considering the handling and mixing of the glycol solutions in commercial quantities.

5% Volume In Volume Solution. For some obscure reason, procurement of the anhydrous ethylene glycol solution ("M-1 Eye Solution") was based on a 5% volume in volume solution; thus making it necessary to determine accurately the weight composition of the solution. This was done using 2 samples of BAL (NDR-133-11 and NDR-133-15). The determinations were made in triplicate using considerable care in determining the densities of BAL, the densities of the anhydrous glycol, and the densities of the resulting 5% volume in volume solution. Thus, by calculation, the weight of BAL equivalent to 5 ml. at 25° was added to the weight of ethylene glycol equivalent to 95 ml. at 25° and the resulting solution, after thorough mixing was titrated for thiol sulfur and the density accurately determined. The numerical values will be found in Table III. In Table IV will be found a summary of the data.

Table IV

	NDR-133-11	133-15	Average
D_4^{25} (BAL)	1.2409	1.2390	1.23995
S(H)	51.36	51.81	51.58
5% volume in volume solution at 25°C.			
% BAL	5.463	5.535	5.499
D_4^{25}	1.11566	1.11560	1.11563

Comparing the actual density with that calculated from the densities of the materials used, it appears that on mixing the solution expands about 0.07% (the density found is approximately 99.934% of the calculated value).

D. Effect of Solvent on BAL Stability

1. Aqueous Solutions

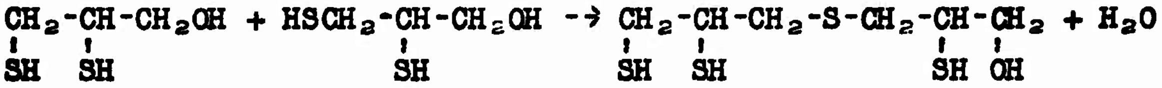
Physical Properties. A 5% solution of BAL in distilled water should have approximately the following properties:

N_D^{25}	1.3423
D_4^{25}	1.0080
Surface tension	42 dynes/cm.at 25°C.
Viscosity	1.12 cps. at 25°C.
pH	About 5.0

It should be understood that these properties will vary somewhat with the sample of BAL used.

The solubility of BAL in water at 25° is approximately 7.97% by weight. This value will vary directly with the quality of the BAL, solubility being a sensitive criterion of purity.

Stability. When a clear aqueous solution of BAL was boiled, a colorless oily precipitate separated rapidly. Refluxing was continued for 18 hours and the oil separated and analyzed. The composition corresponded to dimeric BAL formed through loss of one molecule of water:



$$\underset{\mathrm{SH}}{\mathrm{CH_2}}-\underset{\mathrm{SH}}{\mathrm{CH}}-\mathrm{CH_2OH} + \mathrm{HSCH_2}-\underset{\mathrm{SH}}{\mathrm{CH}}-\mathrm{CH_2OH} \rightarrow \underset{\mathrm{SH}}{\mathrm{CH_2}}-\underset{\mathrm{SH}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{S}-\mathrm{CH_2}-\underset{\mathrm{SH}}{\mathrm{CH}}-\underset{\mathrm{OH}}{\mathrm{CH_2}} + \mathrm{H_2O}$$

	Found	Calculated for $C_6H_{14}S_4O$
C	31.6%	31.2%
H	6.4%	6.13%
S	55.24%	55.7%
M.W.	229.	230.
S(H)	38.3%	41.6%

pH. The rate at which polymeric material separates from an aqueous solution of BAL is a function of the pH and of the BAL quality as well as the temperature. Thus, at room temperature, as illustrated by the data in Figure I, the solution is considerably more stable between pH 3 and 5 than at pH 6. The optimum stability appears to lie at about pH 4.5. These data were obtained by preparing a clear 5% aqueous solution of BAL, adjusting the pH with ammonia or HCl (use of NaOH and HBr gave the same result) and keeping 25 ml. of the solution in a 2 oz. screw cap bottle at room temperature. Samples were taken at frequent intervals blown free of H_2S with oxygen-free nitrogen and titrated with standard iodine solution. (It should be pointed out that a "thiol depletion" of 10% might correspond to about 50% transformation of BAL into the dimeric form.)

Qualitatively a solution of pH 6 rapidly becomes cloudy with streamers of precipitate falling from the surface towards the bottom of the bottle. On the other hand a clear solution of pH 3 will remain clear for several hours. Again the quality of the BAL, as well as the pH, determines the time required for the solution to become cloudy. The effect of pH on oxidation rate is discussed below and in Figure III.

Iron. An aqueous solution of BAL containing iron becomes cloudy more rapidly at a given pH than does a solution free from iron. This parallels the catalytic loss of S(H) from the BAL:iron complex and the accelerated oxidation rate catalyzed by iron. (For a more detailed discussion see below under "Anhydrous Glycol".)

Using a glass electrode and a Beckman pH meter, it was found that the iron:BAL complex changes from pink at pH 3.6 to green at pH 3.3. This change in color at the end point appears much sharper than with the usual type of acid:base indicator.

Container. The container material rather definitely affects the stability of an aqueous BAL solution (see Figure 1 A). Thus, a solution at pH 5 is about 1.2 times more stable in a bottle coated with paraffin than in a soda glass bottle previously cleaned with acid to remove surface alkali. Moreover, the pH of the solution in glass increases with time (evidently by slight erosion of the glass).

Oxygen. Oxidation is one of the causes for instability of aqueous BAL solutions. As indicated in Figure III, the rate of oxidation in contact with air is greatest at high pH's, e.g. solutions below pH 5 oxidize much more slowly than solutions at pH of 6 or above. Iron particularly accelerates the rate of oxidation of aqueous BAL.

Heat. In the absence of oxygen, heat alone causes BAL in aqueous solution to decompose. Thus, an aqueous solution at pH 5 was divided among several 12 mm. glass tubes which were sealed under nitrogen and heated at 50° in a device which caused the tubes to rotate end over end. In this manner the separated oil was kept in equilibrium with the aqueous solution. Tubes were removed (in duplicate) from time to time and the contents analyzed for BAL. The rate of decomposition is indicated in Figure IV. The best solution stabilizers (vitamin B_1 and d-iso-ascorbic acids) had no measurable effect on the heat stability of aqueous BAL possibly because of the inherent instability which made small improvement hard to detect.

In the absence of oxygen, aqueous solutions of BAL deteriorate many times more rapidly than glycol solutions as may be seen from Figure II.

Quality. The quality of the BAL has a profound influence on the time required for a 1% aqueous solution to become cloudy. Thus, the very best BAL which we have been able to prepare required 120 hours for a 1% aqueous solution to become cloudy, whereas a sample of the same material which had been allowed to stand on the shelf in the presence of air would give only a cloudy 1% solution.

Stabilizers. An intensive search was made for a compound or a combination of compounds which would prevent precipitation from aqueous BAL solution. Although this hope was not realized, several compounds were found (among about 60 compounds tested) which approximately doubled the life of an aqueous BAL solution. In Table V are given relative values at 5 months for the stability of a 5% aqueous solution containing 0.01% stabilizer, pH about 5, room temperature. These values are relative to an aqueous solution of the same BAL containing no stabilizer taken as unity. It will be seen that "Gardinol" and "Alkanol" WXN are near the top of the table. It is believed that these compounds function principally by improving the distribution ratio of BAL between water and polymeric BAL. This may be the function of most of the stabilizers since in this early work the titrations for BAL were made on the clear supernatant aqueous solution, these experiments being designed to simulate shelf storage conditions.

The experiments were carried out by placing 25 ml. of aqueous BAL in a square type 2 oz. screw cap bottle (35 x 35 x 35 mm. O.D.), adding 5 mg. of the stabilizer and allowing the solution to stand at room temperature. One ml. of the clear aqueous solution was removed at various time intervals and titrated with standard iodine solution. In all cases it was necessary to blow the solutions with oxygen-free nitrogen to remove H_2S before making the thiol sulfur determination.

In connection with Table V it will be noted that some compounds such as sodium salicylate and sodium benzoate, actually increased the rate at which thiol sulfur disappeared.

S-Diethanolaminomethyl Ethers. A second method of stabilizing aqueous BAL solutions was to prepare a derivative by the reaction of formaldehyde with BAL and an amine (suggested by Dr. Kharasch). The solution obtained from BAL, diethanolamine and formaldehyde had a pH of about 8.5 and proved relatively unstable because of the high pH. Moreover, the formation of the derivative did not prevent BAL precipitation from the aqueous solution or evolution of H_2S. Adjusting to pH 5 or 6 by addition of acid somewhat improved the stability but did not prevent the formation of a precipitate. It appears that at these lower pH values the derivative is actually decomposed. It will be noted from Figure V that formaldehyde alone stabilizes the BAL solution much more effectively than the reaction product of formaldehyde and diethanolamine with BAL. The disappointing stability of this derivative led to its abandonment as a means of making aqueous solutions usable.

2. Aqueous Glycol Solutions

Ethylene Glycol

Physical Properties. A 5% solution of BAL in a 50:50 mixture of ethylene glycol and distilled water has approximately the following properties:

N^{25}_{4} - - - - - - - - - - - - 1.3910
D^{25}_{4} - - - - - - - - - - - - 1.0714
Viscosity - - - - - - - - - 3.36 cps. at 25°
pH - - - - - - - - - - - - Approximately 4.6
Surface Tension - - - - - - About 48 dynes/cm. at 25°

It should be understood, of course, that these physical constants will vary somewhat with the quality of the glycol and of the BAL.

Stability. An aqueous ethylene glycol solution of BAL requires a considerably longer time (under similar conditions) before an oily precipitate separates than does an aqueous solution. The rate at which the thiol sulfur depletes at room temperature in the presence of air will be seen in Figure VI as contrasted with the rate for propylene glycol (see below).

Heat Stabilizers. A number of the more promising stabilizers previously found for aqueous BAL were studied with the aqueous ethylene glycol solution. In Table VI will be found a tabular presentation of the relative stabilizing effect of these substances. It should be emphasized that in no case was it possible to prevent the separation of an oily precipitate from the aqueous glycol solution, although it was possible to prolong considerably the period before the precipitate formed. In this series (as in the previous one) it was noted that even in the absence of air an oily precipitate will form and that none of the solution stabilizers were notably effective in decreasing the rate at which nonoxidative decomposition took place.

Effect on Plastics. A number of commercially available plastic materials were tested at 50° in contact with an aqueous ethylene glycol solution to determine the practicality of using these plastics as container materials. It will be noted in Table VII that a number of the newer plastics showed considerable promise for this use. Among those substantially unaffected by the solution were polyacrylonitrile, polythene, ethylene/vinyl acetate, Type 2 nylon, Type 3 nylon, Type 6 nylon, Saran, and Vinylite.

Propylene Glycol

Physical Properties. A 5% solution of BAL in 50:50 mixture of propylene glycol and water has approximately the following physical constants:

N_D^{25} - - - - - - - - - - -	1.3953
D_4^{25} - - - - - - - - - - -	1.0444
Viscosity - - - - - - - -	5.16 cps. at 25°
pH - - - - - - - - - - -	About 5
Surface Tension - - - -	About 39.9 dynes/cm. at 25°

Stability. The stability of an aqueous propylene glycol solution of BAL is given in Figure VI as contrasted with the corresponding ethylene glycol solution. These results were obtained at room temperature using 25 ml. of the glycol solution in a square type 2 oz. screw cap bottle. The only significant observation in connection with these results is that the aqueous propylene glycol required a longer period before oily drops began to separate than did the corresponding ethylene glycol solution. In both cases, however, the separation of polymer is a serious handicap to the use of this type of solution.

Effect on Plastics. In Table VII are given the observations made when a 5% solution of BAL in a 50:50 mixture of propylene glycol and water was allowed to come in contact with a piece of plastic in the form of a film 1/2" by 2-1/2" and 50 mils thick at 50°C. It will be noted that in general the plastics behaved toward the aqueous propylene glycol in a manner similar to that observed with aqueous ethylene glycol.

3. Anhydrous Glycol Solutions

Physical Properties. A 5.6% by weight solution of BAL in anhydrous ethylene glycol has approximately the following properties:

N_D^{25}	1.4362
D_4^{25}	1.1158
Viscosity	16.64 cps. at 25°
pH	about 4.15
Surface tension	about 45.8 dynes/cm. at 25°

It will be understood, of course, that these values will vary with the quality of the ethylene glycol and with the sample of BAL.

Factors Affecting Thiol Stability. The following eight factors are of particular importance in their influence on the stability of BAL in ethylene glycol: pH, water content, presence of metals, presence of stabilizers, quality of the BAL, the temperature of storage, the atmosphere (i.e., presence or absence of oxygen), and light. Each of these factors was investigated individually to determine the optimum conditions.

pH. As may be seen from Figure VII, the optimum pH for a stable ethylene glycol solution of BAL lies at about 4.5 for nonoxidative degradation and below 5.3 for oxidative degradation as shown in Figure III. These data on heat stability were derived from a series of experiments in which a 5.6% solution of BAL in anhydrous ethylene glycol was divided into 6 portions. Each portion was adjusted to a predetermined pH by means of anhydrous ammonia or anhydrous HCl. Solutions having pH values of 3.5, 4, 4.5, 5, 5.5, and 6 were thus prepared. Four ml. portions of each of these solutions were then sealed under nitrogen in 12 mm. glass ampoules. One series of these tubes was heated at 78°C. in boiling carbon tetrachloride and a second series was placed in a 50° thermostat. At predetermined time intervals tubes were removed from each of these baths and analyzed by titration with iodine. (In each case it was necessary to blow the solution with oxygen-free nitrogen before making the thiol determination since a certain amount of H_2S was always present.) The effect of pH on polymer separation may be seen in Plate I.

It will be noted from Figure VIIA that decomposition was progressive. Moreover, it was noted that the amount of H_2S produced was qualitatively greater at pH 6 than at lower pH's. Finally from Plate I it will be observed that the solutions became turbid more rapidly at low pH's, i.e., at pH 3.5 and 4, than at the higher pH's. Moreover, the first precipitate is solid from low pH solution and oily from high pH solutions. On further depletion all samples yield liquid polymer. It appears, therefore, that turbidity, polymer precipitation, and thiol depletion are not necessarily related factors.

In one series of experiments, 5.6% solutions of BAL in ethylene glycol were prepared from 4 samples of BAL to which had been added 1% of Vitamin B, (solution pH 4.0). The solutions were kept under nitrogen in sealed ampoules for 167 days at 50°C. and the solid filtered off for analyses. The thiol depletions were 21.1, 17.5, 18.9 and 18.4% while the amount of polymer collected amounted to 4.51, 2.60, 2.03 and 2.06% of the BAL respectively.

Analysis gave	C, 32.86	H, 5.55	S, 60.02
	32.90	5.80	59.26
			39.64
$C_3H_6S_2$ requires:	C, 34.0	H, 5.6	S, 60.4

A second sample of polymer was prepared by heating (under N_2) 400 grams of a 5.6% glycol solution (pH 4.0) of BAL containing 1% of Vitamin B_1 (based on the BAL) for 190 hours at 78°C. The polymer passed through the solid stage and had begun to separate as a liquid.

Analysis gave:	C, 31.51 31.45	H, 5.32 5.29	S, 57.10 57.50
BAL requires:	C, 29.0	H, 6.49	S, 51.6

From these data it is evident that the main reaction has involved splitting out water from BAL.

A third sample of polymer separated at pH 6, on the other hand, was liquid and showed the main reaction at the higher pH to be one of splitting out H_2S.

Analysis gave:	C, 29.89	H, 6.06	S, 48.06 48.41
BAL requires:	C, 29.0	H, 6.49	S, 51.6

Water. The effect of adding small amounts of water to an anhydrous ethylene glycol solution was determined in two ways. In the first series of experiments 0.5, 1, and 5% of water was added to a 5.6% solution in ethylene glycol and the solutions placed in 2 oz. screw cap bottles stored at 50°C. From time to time samples were removed and analyzed for thiol sulfur. In this series of experiments it was noted that while 1% of water did not cause particularly aggravated decomposition, 5% of water was definitely detrimental.

Metals. The most usual metal to contaminate BAL solutions is iron which is derived either from dust or from container materials used in the manufacture of glycol or the BAL.

As was pointed out previously, iron gives a pink complex with BAL. The color of the complex serves as a quantitative measure of the amount of iron present since the logarithm of the intensity is directly proportional to the concentrations; i.e., the solutions follow Beer's Law up to about 10 parts per million of iron. Above this concentration there is definite deviation. The color of the iron complex has a maximum absorption (minimum transmittance) at 5220 Angstrom units as may be seen from Figure IX. Therefore, in the photometric determining of iron this wave length (λ5300Å) has been employed.

Other metals such as copper, cobalt, and nickel likewise form colored complexes with BAL. The absorption curves of these complexes will be found in Figures X, XI, and XII, respectively. Only in the case of nickel would it seem theoretically sound to determine concentrations photometrically. In connection with these metal complexes it should be pointed out that the maximum intensities were obtained on the alkaline side.

The effect of iron on the stability of BAL in the absence of oxygen has been measured and found to be appreciable. Thus, a solution containing 1 part per million of iron at 50°C. rapidly evolves hydrogen sulfide with a resultant loss of BAL. The most pronounced effect of iron, however, is in accelerating the rate of oxidation. In Figure XIII will be found oxidation rate curves for glycol solutions containing 55, 80, 106, and 126 parts per billion of iron. It will be noted that these solutions are characterized by an increased rate of oxidation with an increased iron concentration. This emphasizes the necessity for close control of the quantity of iron in ethylene glycol solutions of BAL, particularly if the solution is to be opened and stored on a shelf for infrequent use.

Iron also has a particularly pronounced accelerating effect on the rate at which a glycol solution decomposes under the influence of light (see below).

In Figure XIV it will be noted that other metals have a similar accelerating influence on the rate at which BAL oxidizes as well as upon the rate of nonoxidative degradation.

Stabilizers. Since an ethylene glycol solution was selected for manufacture of "M-1 Eye Solution" it was considered desirable to study the effect of stabilizing agents, particularly those which act as iron and metal deactivators. In Table VIII are recorded the results obtained by adding known amounts of stabilizer to an anhydrous ethylene glycol solution of BAL. The numerical values are intended to show the relative effectiveness of these stabilizers. One series of experiments was carried out in which no iron was present and the other series had 1 part per million of added iron. In contrasting these two series it will be noted that Vitamin B_1 acts both as a stabilizer and as an iron deactivator.

These experiments were carried out by placing 25 ml. of the glycol solution in a 2 oz. square type screw cap bottle stored in a 50° thermostat. At intervals a 1 ml. sample was withdrawn, blown with oxygen-free nitrogen to remove H_2S, and analyzed for thiol sulfur by iodine titration. Decomposition in every case was progressive although with some stabilizers an initial drop in thiol sulfur took place followed by a slow and progressive decomposition.

In Tables IX and X are recorded the results obtained with other stabilizers and with mixtures of stabilizing agents. The value obtained for unstabilized solutions was taken as unity in each series of experiments. In a study of the most effective concentration for Vitamin B_1, Table IX, it will be noted that 0.1% was approximately as effective as 0.5% but that lower concentrations did not give optimum protection. It will be noted that tri-n-butyl phosphite was effective as a metal deactivator in protecting anhydrous glycol solutions. In Figure XV the effect of adding stabilizers to an anhydrous glycol solution is reported graphically.

The effect of several stabilizers on polymer separation may be seen from Plate II.

<u>BAL</u>. The stability of the ethylene glycol solutions of BAL depends partially upon the stability of the BAL itself. To test this point a number of solutions were prepared from representative lots of BAL and the deterioration at 50°C. was measured using 25 ml. samples in a square type 2 oz. screw cap bottle. While the rate of deterioration could not be directly related to any particular property of the BAL, it will be noted that a variation occurs between different samples. Typical results will be found in Figure XVI. (Each point on these curves represents check analyses.)

<u>Temperature.</u> Experiments carried out at room temperature, 50° and 78°, indicate that the rate of decomposition approximately doubles for a 10° rise in temperature. These experiments were carried out both in sealed tubes and in screw cap bottles.

<u>Atmosphere</u>. Since it had been observed that oxidation was one of the types of decomposition taking place in BAL solutions, a series of samples were stored under nitrogen and a parallel series stored under air. From Figure XVII it can be seen that an improvement results by displacing the air with nitrogen particularly when a small amount of iron

is present in the solutions. (Each point on each of these curves represents an average of 12 determinations using three samples of BAL.)

Light. The decomposition of BAL is catalyzed by light particularly the near ultraviolet. Thus a series of 2 oz. square type screw cap bottles each containing 25 ml. of 5% BAL solution were placed at a 45° angle in a water bath and exposed 3-1/2 inches from a capillary mercury arc. A second bottle from each series was covered with black paper, and placed in the same bath. Samples were removed at intervals and titrated for thiol sulfur. It will be noted from Figure XVIII and XVIIIA that decomposition was considerably higher in samples exposed to the ultraviolet radiation. Moreover, samples containing one part per million iron were decomposed at a very much higher rate than were samples relatively free from metal.

4. Nonhydroxylated Solvents

On the basis of work reported above the factors to be studied in connection with solutions of BAL can be divided into the following: (1) heat stability, (2) oxidation stability, (3) polymer separation, (4) catalytic effects (particularly of metals), and (5) solution stabilizers.

Heat Stability. Since one of the major defects of the glycol solutions of BAL was heat instability, the first experiments with other solvents were directed to measuring the effect of heat on solutions of BAL in different media. These experiments were carried out as follows: A 5% solution of BAL in the solvent in question was prepared and analyzed in duplicate for thiol sulfur. Five ml. portions were then sealed in glass ampoules under nitrogen. These ampoules were constructed of pyrex glass, 12 x 65 mm., previously cleaned with nitric acid, marked on the outside with glass marking ink and baked in a gas flame to insure dryness and adherence of the marks. Nine of these tubes were then placed in a flask containing refluxing carbon tetrachloride. Duplicate tubes were removed at 4, 8, 16 and 32 days and analyzed for thiol sulfur by iodimetric titration. The ninth tube acted as a spare and was removed when good checks were not obtained at any time interval. Analysis was conducted as follows: Using a sharp file, a score mark was made across the glass tube above the liquid level. A crack was then started by applying a small button of hot glass to the score mark. The tube and contents were weighed on an analytical balance, the contents washed from the tube with methanol and the tubes reweighed after careful drying. The methanol solution was blown with oxygen-free nitrogen for 20 minutes, or until free from H_2S (as determined by holding a section of filter paper moistened with aqueous lead acetate in the vapors). When H_2S free, the solution was titrated with 0.1 N iodine solution.

The average of two good check determinations was used for each time interval and the thiol depletion in terms of the original value was calculated. The depletion values for a number of solvents are recorded in Table XI. The effect of several solvents on polymer separation are shown in Plate III. It should be noted that with most solvents there was an initial drop after which depletion continued at a uniform rate.

Scanning Table XI one notes the following: First, there is a striking improvement in the stability of BAL in nonhydroxylated as contrasted with hydroxylated solvents (see Figures XIX and XX). Second, the higher the percentage of hydroxyl groups in the solvent the more rapid the depletion (contrast glycol with 55% (OH) with BAL containing 13.7% (OH)). Third, the initial drop (not shown in the table) is greatest for those solvents forming peroxides most readily (diethyl carbitol contrasted with glycol diacetate). This was confirmed by purifying a sample of diethyl carbitol until it was free of peroxide when the rate more nearly approximated that of glycol diacetate.

Oxidation Stability. The next important property of BAL solutions is stability toward oxidation. To measure this, the accelerated test described in the appendix was used. A five gram sample was placed in the oxidation flask and the test was carried out at 50°C. The oxygen absorbed was measured at intervals and corrected to ml. at standard temperature and pressure.

It will be noted from Figures XIX and XX that the oxidation rate for the most heat stable solutions are quite low. Diethyl carbitol appears to be the exception, although it is believed that the very early uptake of oxygen by this solution is largely a matter of the solubility of oxygen in this solvent. In general, these low rates of oxidation parallel the freedom of these solvents from metallic ions. This is borne out by the greatly increased rate noted when metals were deliberately added to the triacetin solution (see Figure XXI). Moreover, the effect of pH appears to be as great in these solvents as in glycol (see above).

Polymer Separation. The original interest in nonhydroxylated solvents arose from the separation of a white polymeric material from glycol solutions of BAL after aging. Work with other solvents showed no exact relation between the stability of BAL and the separation of polymer. Thus BAL is quite unstable in thiodiglycol solution even though polymer does not separate from this solvent on prolonged heating. On the other hand, BAL is quite stable in triacetin and no polymer separates. However, if the original BAL contains polymer this will not dissolve in triacetin and it is necessary to filter before a clear solution is obtained. BAL free from polymer gives a clear solution which does not become cloudy on heating for 52 days at 78°C. Similar results were obtained with peanut oil/benzyl benzoate, glycol diacetate, diethyl phthalate and pure diethyl carbitol. The effect of solvents on polymer separation may be seen in Plate III.

Catalysts. Nonhydroxylated solutions of BAL appear to have about the same range of susceptibility to catalytic influences as was displayed by glycol solutions although this is superimposed on much greater heat stability. Thus metals and pH both have a pronounced influence on heat stability and on oxidation stability. The optimum pH for the triacetin solution as measured by the Beckman glass electrode on a 20% suspension in water appears to lie between 3.5 and 4 (as contrasted with glycol solutions which display optimum stability at about pH 4.5). Metals have a pronounced effect on the rate of oxidation and on the evolution of H_2S. Numerical data for the effect of metals on a triacetin solution is given in Figure XXI. Metals catalyze the precipitation of polymer from BAL solutions in triacetin.

Stabilizers. Solution stabilizers are much less important for BAL in nonhydroxylated solvents than in hydroxylated solvents. The chief benefit is derived from metal deactivators such as Vitamin B_1 in triacetin solution containing iron. However, it is preferable to prepare triacetin out of contact with iron when a highly satisfactory stability for the solution is required. Vitamin B_1 and d-iso-ascorbic acid both have a limited solubility in triacetin.

G. W. Rigby

Approved by
W. A. Lazier
Group Leader

Table I

Effect of 5.6% BAL in Anhydrous Glycol on Plastic Materials at 50°C.

Plastic	Ethylene Glycol	Propylene Glycol
1. Saran (80/20)		
2. Saran (Normal)		
3. Aluminum foil		
4. Polythene		
5. 66 Polymer		
6. Vinylite sheeting	good	
7. Cellulose acetate		
8. Polystyrene		
9. Hycar (vulcanized)		
10. Neoprene ILS (vulcanized)		
11. Lead foil		
12. Type 8 nylon		
13. Type 8 nylon		
14. "Butacite" (vulcanized)		
15. "Tenite II" tubing (4966-64)	good	
16. "Tygon" (4966-83 & 135)	good	
17. Polythene/isobutylene (4966-109)		

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Table II

Iron Picked Up by 5.6% BAL in Fthylene Glycol From 1/2 oz. Brown Bottles

(figures in parts per billion of iron)

5 days at 50°C.

Bottle Number	Carton Number									
	A	B	C	D	E	F	G	H	I	J
1	10	32	5	6	42	13	8	30	10	20
2	10	30	13	6	6	3	8	5	18	13
3	30	40	8	10	28	28	26	15	15	10
4	8	20	10	15	13	10	5	6	15	32
5	18	10	6	10	9	28	20	6	10	9
6	13	9	6	40	9	8	28	6	10	13
7	13	8	18	15	6	13	34	8	60	13
8	6	(126)	8	8	18	15	28	6	34	15
9	10	24	13	20	15	20	18	8	13	10
10	8	(655)	9	9	18	38	5	20	9	8
Average	12.6	21.6	9.6	13.9	16.4	17.6	18.	10	19.4	14.3

Iron increase average 15.34 p.p.t. $Fe^{=}$ (excluding B-8 and 10)

12 days at 50°C.

Bottle Number	A	B	C	D	E	F	G	H	I	J
1	30	35	17	10	45	19	13	40	18	15
2	20	37	24	8	15	10	13	9	28	13
3	37	65	19	6	28	37	38	22	22	15
4	13	30	13	15	24	19	13	36	15	32
5	24	15	6	12	18	35	30	10	29	13
6	13	10	8	42	19	15	40	13	14	19
7	17	10	23	15	45	19	32	10	115	13
8	17	(152)	10	8	28	19	36	15	60	18
9	15	30	12	20	28	27	13	14	15	15
10	12	(3100)	12	9	20	52	10	33	12	12
Average	19.8	29	14.4	14.6	27	25.2	23.8	20.2	31.8	16.5

Iron increase average 22.23 p.p.b. $Fe^{=}$ (excluding B-8 and 10)

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Table III

Determination of 5% Volume and Volume Solution of BAL in Anhydrous Ethylene Glycol 25°C.

BAL		NDR-133-11	NDR-133-15
Thiol sulfur:		51.41	51.72
		51.24	51.82
		51.44	51.90
	S(H) **Average**	51.36	51.81
Density:		1.24087	1.23913
		1.24092	1.23880
		1.24103	1.23904
	D_4^{25} **Average**	1.24094	1.23899

Glycol	
Density:	1.10983
	1.10991
	1.10001
D_4^{25} **Average**	1.10992

BAL Solution			
Density:		1.11568	1.11556
		1.11574	1.11562
		1.11555	1.11563
	D_4^{25} **Average**	1.11566	1.11560
		D_4^{25} 1.11563	
BAL by titration		5.4541	5.526
		5.4534	5.532
		5.4827	5.546
	Average	5.4634	5.535
			5.499% by wt.

Table V

Stabilizer Tests on 5% Aqueous BAL

Original pH 5.0; room temperature; 5 months
using 0.01% of stabilizer

Stabilizer	Relative Effectiveness
Sodium hydrosulfite	1.80
Phenyl beta-naphthyl amine	1.74
Gardinol	1.73
"Alkanol" WXN	1.69
Hydroquinone	1.56
Eugenol	1.53
Ammonium acetate	1.43
Sodium sulfite	1.33
Diammonium phosphate	1.28
beta-Thiodipropionic acid	1.19
"Rhodol"	1.17
Phenyl alpha-naphthyl amine	1.16
1,5-Dihydroxy naphthalene	1.15
"Amidol"	1.13
Diphenyl amine	1.13
Sulfanilamide	1.12
Salicylic Acid	1.11
d-iso-Ascorbic Acid	1.09
Vitamin A	1.09
Hydrazine hydrochloride	1.08
d-Ascorbic Acid	1.07
Catechol	1.07
p-Toluene Sulfinic Acid	1.07
Formamidine Sulfinic Acid	1.07
Resorcinol	1.06
"Avonex" (extract of oat flour)	1.05
Sodium nitrite	1.04
Hydroxylamine hydrochloride	1.03
Thymol	1.01
p-Aminobenzoic acid	1.01
Silver salt	1.01
Blank	1.00
Coumarin	.98
Mannitol	.98
Sodium hydrogen sulfite	.96
p-Aminophenol	.96
alpha-Thionaphthol	.94
Vitamin B_1	.93
Methyl glucamine	.92
Dextrose	.89
Vanillin	.88
p-Nitro-aniline	.88
Boric acid (2%)	.87
Diphenylol octadecane	.87
Camphor	.85
Gum Guaicum	.83
Caffeine	.83
Sodium formaldehyde sulfoxalate	.82
Zinc sulfate	.79
Thiosorbitol	.79
Menthol	.78
Gum Tragacanth	.76
Glycine	.74
Ether	.69
Sodium benzoate	.67
Nicotinic Acid	.55
Boric Acid	.40
p-Phenylphenol	.38
Ethyl Tyrosin	.32
Sodium salicylate	.23

Table VI

Stabilizers for 5.6 BAL in 50/50 water/ethylene glycol 60°C.; initial pH 4.01 under air in 2 oz. screw cap bottles

Stabilizer	Relative Stability at 21 Days 0.01% Stabilizer	 0.2% Stabilizer
p-Aminobenzoic Acid	2.06	-
Hydrazine hydrochloride	-	1.61
Hydroxylamine hydrochloride	1.68	1.59
Nicotinic Acid	-	1.48
Sodium sulfite	1.21	-
Vitamin E	-	1.21
Boric Acid (2%)	1.16	-
Sodium hydrosulfite	1.13	-
Camphor	1.13	-
Sodium benzoate	1.08	-
Salicylic acid	1.07	-
Caffein	1.06	-
Coumarin	1.01	-
Zinc sulfate	1.00	-
Blank	1.00	-
Diphenylamine	0.98	-
Vitamin B_1	0.93	1.21
Ascorbic acid	0.83	1.37
Thymol	0.72	-
Avonex	-	0.89

Table VII

Effect of 5.6% BAL in 50/50 water/glycol on plastic materials at 50°C.

Test strips 2-1/2" x 1/2" x 50 mils

Plastic	Ethylene Glycol Solution	Propylene Glycol Solution
1. 92/8 Vinylidene chloride/vinyl chloride	good	good
2. 95/5 Vinyl chloride/diethyl fumarate + 30% MCAR	poor	bad
3. Polyacrylonitrile	good	good
4. 80/20 Vinylidene chloride/vinyl chloride	good	good
5. 95/5 Vinyl chloride/dimethyl fumarate + 30% MCAR/DBCS	bad	bad
6. Type 8 nylon	bad	bad
7. 95/5 Vinyl chloride/diethyl fumarate	bad	bad
8. Vinylite VYNW + 30% DBCS	bad	bad
9. Pliofilm	fair	fair
10. Aluminum foil	good	good
11. Polythene	good	good
12. Acrylonitrile/isobutylene	poor	poor
13. Ethylene/vinyl acetate	fair	poor
14. 66 + Octyl phenol	good	bad
15. 12-Aminostearic acid polymer	poor	bad
16. 610	good	good
17. Type 6 nylon (66/610/6)	good	good
18. "Butacite" RW 410	bad	bad
19. Poly p-aminoethyl benzene/10	good	good
20. Ethyl rubber (all varieties)	very poor	very poor
21. Ethylcellulose	very poor	very poor

Table VIII

Effect of stabilizers on anhydrous glycol solution containing 5.6% BAL (NDR-133-Q2); 50°C.; air; half filled 2 oz. screw cap bottles

Stabilizer	Relative Effectiveness at 0.18% stabilizer: Iron free; 117 days	Relative Effectiveness at 0.18% stabilizer: 1 p.p.m. iron 92 days
Vitamin B_1	3.4	2.5
"Amidol" (2,4-diaminophenol sulfate)	3.5	2.4
Hydroxylamine hydrochloride	1.5	2.4
Tri-n-butylphosphite	-	2.4
Salicylic acid	1.2	1.8
"Rhodol" (p-methylaminophenol sulfate)	2.7	1.6
Hydrazine hydrochloride	2.4	1.6
d-iso-ascorbic acid	2.7	1.5
Nicotinic acid	2.1	1.3
Ascorbic acid	3.1	1.3
"Avonex" (oat flour concentrate)	1.8	1.3
Sulfanilamide	2.0	1.2
Camphor	2.0	1.2
Menthol	-	1.2
Thiodiglycol	-	1.2
Diphenylamine	2.8	1.1
Thymol	2.2	1.1
Catechol	2.0	1.1
p-Aminobenzoic acid	2.0	1.1
p-Phenyl beta-naphthylamine	-	1.1
Di(p-aminophenyl) disulfide	-	1.1
Coumarin	2.0	1.0
Eugenol	-	1.0
Blank	1.0	1.0
o-Aminothiophenol	-	0.92
p-Aminothiophenol	-	0.72
Sodium hydrosulfite	-	0.0
p-Nitroaniline	1.9	-
Vitamin A	1.6	-
Ethyl tyrosin	1.5	-
p-Phenyl phenol	1.5	-
1,5-Dihydroxynaphthalene	0.2	-

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Table IX

Effect of Stabilizers on BAL in Anhydrous Ethylene Glycol
5.6% BAL; 50°C.; 1 p.p.m. iron; 2 oz. screw cap bottles
1/2 filled; under air

Stabilizer	Relative Effectiveness 88 Days
0.5% Vitamin B_1	1.20
0.11% " "	1.18
0.05% " "	1.08
0.01% " "	0.94
Blank	1.00
0.02% Vitamin B_1 0.20% d-iso-ascorbic acid	1.02
0.01% tri n-butylphosphite 0.01% Vitamin B_1	1.03
0.01% Vitamin B_1 0.20% tocophenols (40%)	1.02
0.01% Vitamin B_1 0.20% sulfanilamide	1.03
0.01% Vitamin B_1 0.20% sulfanilamide 0.20% camphor	1.03
0.01% Vitamin B_1 0.20% sulfanilamide 0.01% d-iso-ascorbic acid	1.02
Diammonium phosphate	1.02
Citric Acid	1.02
Tartaric acid	1.03
Iron-free solution	1.14
Tri-n-butylphosphite (Tech)	1.2
0.01% tri-n-butyl phosphite 0.20% ascorbic acid	1.2
0.01% tri-n-butylphosphite 0.20% Vitamin B_1	1.2
0.20% Vitamin B_1 0.20% Lecithin	1.1

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Table IX (Cont.)

Stabilizer	Relative Effectiveness 88 Days
Salicylaloxime	1.0
(0.20% hydroquinone (0.20% Lecithin	1.0
(0.01% tri-n-butylphosphite (0.20% Lecithin (0.20% ascorbic acid	1.0
Hydroquinone	0.9
Du Pont Metal deactivator GD689	0.9
Tetrasalicylalpentaerythrityltetramine	0.9
Disalicylalethylenediamine	0.6
alpha-phenyl biguanidine	0.6
2,4-Diamino N-n-butylaniline	0.0
Blank	1.0

	Relative Effectiveness 168 Days
Riboflavin	1.06
2-Imidazolidone	1.0
Anthracene	1.0
Sulfapyridine	0.9
Anthraquinone	0.9
Sulfathiazole	0.8
Thioacetamide	0.8
Monophthalidylurea	0.8
Quinone	0.8
Sodium dimethyl dithiocarbamate	0.5
Dimethylamine dimethyl dithiocarbamate	0.5
Blank	1.0

Table X

Effect of Stabilizers on BAL in Anhydrous Ethylene Glycol
5.6% BAL (NDR-133-15); 50°C.; 1 p.p.m. iron; 91 days;
0.18% stabilizer; air; 2 oz. bottle 1/2 filled

Stabilizer	Relative Effectiveness
Tri-n-butylphosphite	1.3
Dilauryl phosphate	1.2
Dithiobiuret	1.2
Thioglycolic acid	1.1
Thiourea	1.1
Methylsalicylate	1.1
alpha,alpha'-Dipyridyl	1.1
Phenol	1.1
Glycolic acid	1.1
Dimethyl glyoxime	1.1
Salicylanilide	1.1
Pinenethiophosphite	1.1
Pinene mercaptan	1.1
2-mercaptothiazoline	1.1
Adipic acid	1.1
Oxalic acid	1.1
Phenyl dithiobiuret	1.1
Diphenyloloctadecane	1.1
Pyrogallol	1.1
Soya Lecithin	1.1
2-Amino-5-ethoxythiophenol	1.1
Tocophenol	1.1
Thiosemicarbazide	1.0
Phenylthiocarbazone	1.0
Anthranilic acid	1.0
2-Mercaptobenzothiazoline	1.0
Maleic acid	1.0
Blank	1.0
Salicylaldoxime	0.9
Methyl p-hydroxybenzoate	0.9
Disalicylal ethylenediamine	0.7
Diphenyl guanidine	0.7
Phthalonitrile	0.5
Iron free solution	1.3

Table XI

Effect of Solvents on BAL Stability at 78°C.

Solvent	Relative Thiol Depletion
Triacetin	0.2
Benzyl benzoate	0.2
Diethyl phthalate	0.2
Dioxane	0.2
Peanut oil	0.2
Dimethyl Cellosolve	0.2
Peanut oil/benzyl benzoate 90/10	0.3
Diethyl Carbitol	0.3
Diethyl Cellosolve	0.4
Tetramethylene sulfone	0.5
Glycol diacetate	0.6
N-Butyl Carbitol	0.6
BAL	0.7
Benzene	<1
Tetraglycol dimethyl ether	<1
Polyethylene glycol "400"	1
Cellosolve acetate	1.4
Cellosolve	1.4
Carbowax 1500	2.9
Carbitol	3.2
Polyethylene glycol + ethylene glycol 50/50	4.2
Diethylene glycol	7.9
Propylene glycol	10
Ethylene glycol + B_1	12
Ethylene glycol	15
Thiodiglycol	17
Glycerol	21

APPENDIX

TENTATIVE SPECIFICATIONS FOR BAL

(Revised Sept. 10, 1942)

1. Color. The color shall be less than 10 as measured in 100 ml. Nessler tubes.

2. Refractive Index. The refractive index at 25°C. shall be not less than 1.5700.

3. Bromine. The bromine content shall be less than 0.1% as determined by the Carius method.

4. Thiol Sulfur. The thiol sulfur content as determined by iodometric titration shall be not less than 50.0%.

5. Heat Stability. The viscosity shall increase not more than 40% on heating for 5 hours at 156°C. as described in the attached method.

6. Acidity. The pH of a 1% aqueous solution shall be not less than 4.0 as measured with a glass electrode.

Tentative Specification Methods for BAL

1. Color

The procedure is identical with that described for determining the color of water, "Standard Methods of Water Analysis," Ed. VIII, p. 12, section VI (American Public Health Association, 1936).

Tentative Specification Methods for BAL

2. Refractive Index

The refractive index is measured at 25°C. with an Abbe refractometer using the yellow D line of sodium.

Tentative Specification Methods for BAL

3. Bromine Determination

Objective

Determination of the percentage of bromine in BAL.

Reagents

(a) Fuming nitric acid, analytical grade.
(b) Silver nitrate, analytical grade.

Equipment

A heavy walled Pyrex reaction tube, about 750 mm. x 19 mm. I.D. x 25 mm. O.D. (A. H. Thomas Co., No. 3881-C).

Procedure

A small sample tube is prepared by closing one end of an 8-cm. section of 6 or 7 mm. glass tubing, and an accurately weighed sample (about 0.6 g.) of BAL is introduced. Into the heavy walled reaction tube is placed 4.5 to 5.0 cc. of fuming nitric acid and 0.2 g. of silver nitrate. The sample is lowered gently into the reaction tube in such a way that it does not come into contact with the nitric acid. The reaction tube is then sealed and heated in a horizontal position in a Carius or similar furnace for four hours at 270°C. The tube is then opened and the contents washed out thoroughly with water into a beaker. The suspension is heated to boiling and filtered through a Pregl filter tube (Pregl, Analytical Organic Analysis, Ed. III, p. 98). The precipitate is washed thoroughly with water, then with acetone, dried to constant weight (35 minutes at 125-140°C.) and weighed.

The percentage of bromine in the sample is equal to:

$$\frac{\text{wt. ppt.} \times 42.55}{\text{wt. sample}}.$$

Accuracy

The method is believed to be accurate to within ±.02%.

Tentative Specification Methods for BAL

4. Iodine Titration for Thiol Sulfur

Objective

Determination of the thiol sulfur in BAL, the theoretical value being 51.6%.

Reagents

(a) 0.1 Normal standard sodium thiosulfate solution.

(b) 0.1 Normal iodine solution, prepared by dissolving 25 g. of potassium iodide in 25 cc. of water, then dissolving 13 g. of iodine in the solution and diluting to one liter. The solution should be standardized against standard sodium thiosulfate solution every two or three days.

Equipment

250 cc. Iodine flasks (Scientific Glass Apparatus Co.)

Procedure

About 0.2 cc. of BAL is introduced into a weighed iodine flask, the flask is stoppered and the sample weight determined by difference. About 50 cc. of ethanol is then rinsed into the flask around the stopper, and the solution is titrated with 0.1 N iodine solution until addition of a single drop produces a faint yellow color. If required 0.1 N sodium thiosulfate solution can be used for back titration.

The percentage of thiol sulfur in the sample is equal to: $\frac{\text{cc. iodine solution} \times N \times 3.206}{\text{wt. sample}}$, where N is the normality of the iodine solution.

Interfering substances

Hydrogen sulfide or other substances which reduce an iodine solution interfere with the test.

Accuracy

The determination is believed to be accurate to within ±0.2%.

Tentative Specification Methods for BAL

5. Heat Stability Test

Objective

Determination of the heat stability of BAL.

Equipment (See attached drawing)

Specially designed capillary tip pipette.
Vapor bath.
Bromobenzene for use as vaporizing liquid.
Long test tube (25 mm. x 35.6 cm.)
Stopcocks, corks, rubber tubing, deoxidized nitrogen, gas burner, stop watch.

Procedure

Referring to the attached drawing, the apparatus consists of a vapor bath (8) containing bromobenzene to maintain a constant temperature of 156°C. in a centrally located test tube (7) which contains the BAL. Within the test tube (7) is suspended the capillary tipped pipette (6) which is held in position by passing through a T-tube (2) to the upper end of which is attached a short length of rubber tubing (3) fitting snugly around the stem of (6). The rubber stopper supporting the capillary carries an outlet tube (10) which permits maintaining the system under deoxidized nitrogen by means of the rubber tubing system and stopcock (1). The capillary in the pipette should be small enough to require at least 28 seconds flow time as measured below.

To carry out a heat stability test place 20 to 25 ml. of BAL in the test tube (7). Lower the pipette (6) near to the bottom of the tube, turn the stopcock (1) so that a rapid stream of nitrogen passes through (5). Place a finger over the outlet at (5) and force gas through (6) until the air has been displaced from the system through (10). Now lift (6) above the surface of the liquid and change stopcock (1) so that a slow stream of gas passes through (2) to maintain a blanket of inert gas in (7).

Start heating the vapor bath (8) by applying the gas flame (9) and maintain sufficient heat to keep the bromobenzene vapors condensing at the lower end of the vent (11). Within about five minutes the liquid in (7) will have attained the bath temperature. At this time make the first viscosity observation.

To make a viscosity measurement first turn stopcock (1) and close the outlet of (5) so that gas passes through (6). Lower (6) so that the tip is just below the surface of the liquid and blow nitrogen through the system for 30 seconds. This insures removal of water vapor which may cause trouble in the next step. Now lower (6) to the bottom of the liquid, turn stopcock (1) so that gas passes through (2) and close (10) so that gas pressure forces the liquid well above the scratch mark in (6). Quickly raise (6) above the surface of the liquid, change stopcock (1) so that gas passes out (5) and start the stop watch when the liquid level in (6) falls to the mark. Note the time required for the liquid to fall to the tip of the capillary in (6). This time interval is the initial time of flow (proportional to the viscosity) of the EAL at 156°C. Reverse stopcock (1) so that gas passes through (2) and continue heating for a total of 5 hours taking viscosity readings every 30 minutes or less depending on the rate at which the sample decomposes. Water is given off during the decomposition; hence the gas stream must be strong enough to carry the vapors out of the system.

$$\frac{\text{(Flow time at 5 hrs.)} - \text{(Initial flow time)}}{\text{Initial flow time}} \times 100 = \%\ \text{viscosity increase}$$

Precautions

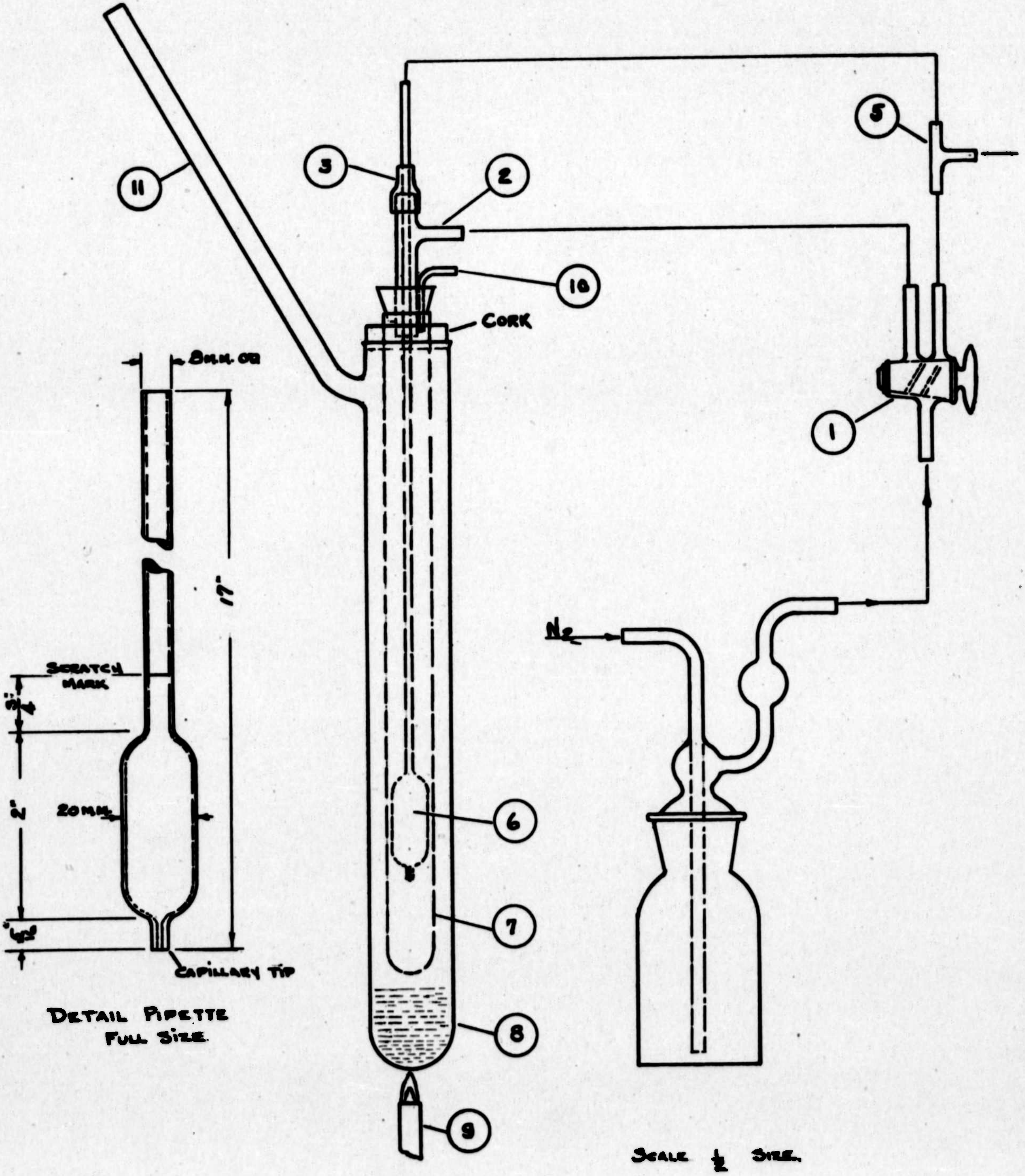
It is imperative that water vapors liberated during the decomposition be swept from the system with a gas stream before attempting to take a reading.

Readings are taken at frequent intervals since some samples decompose rapidly and at accelerating rates after an initial induction period.

The relative stabilities of a series of samples are best correlated by plotting log flow time vs. heating time. The slope of the straight portion of this curve is a measure of the relative stabilities.

Reference

Notebook 4927, p. 34 and following pages.



DETAIL PIPETTE
FULL SIZE

SCALE ½ SIZE.

HEAT STABILITY TESTER.

Tentative Specification Methods for BAL

6. Acidity

Make up a 1% solution (by weight) of BAL in distilled water and measure the pH electrometrically as described in manual accompanying the instrument (Beckman pH Meter, Laboratory Model G.)

eec
1-4-45

IRON CONTENT OF BAL

Reagents and Materials

Concentrated aqueous ammonia (iron-free).
Prismatic spectrophotometer.
5 cm. photometer cell.

Procedure

To a 50 ml. sample of BAL, add concentrated aqueous ammonia to a distinctly blue color measured with litmus paper. Fill the 5 cm. photometer cell with this solution and measure the relative transmission at λ 5300 Å as contrasted with water equalling 100. Repeat the measurement with a fresh filling of the sample cell.

From the attached curve, read parts per billion of iron in the BAL.

Notes

It is essential that the BAL be distinctly alkaline since the iron complex is red above a pH of approximately 4 and green below pH 3.5. With samples of BAL having a distinctly yellow color, it is possible to estimate the iron content by adding known amounts of iron (200 and 400 parts per billion respectively) to two samples of BAL and comparing the transmission with that of the unknown sample, the log. of the transmission being proportional to the concentration.

The absorption maximum of the BAL iron complex lies between wave lengths of 5500 Å and 5000 Å.

It is believed that with careful manipulation an accuracy of about ±6 parts per billion of iron can be achieved by this method.

Analyst______ Date______ File No.______ Method______

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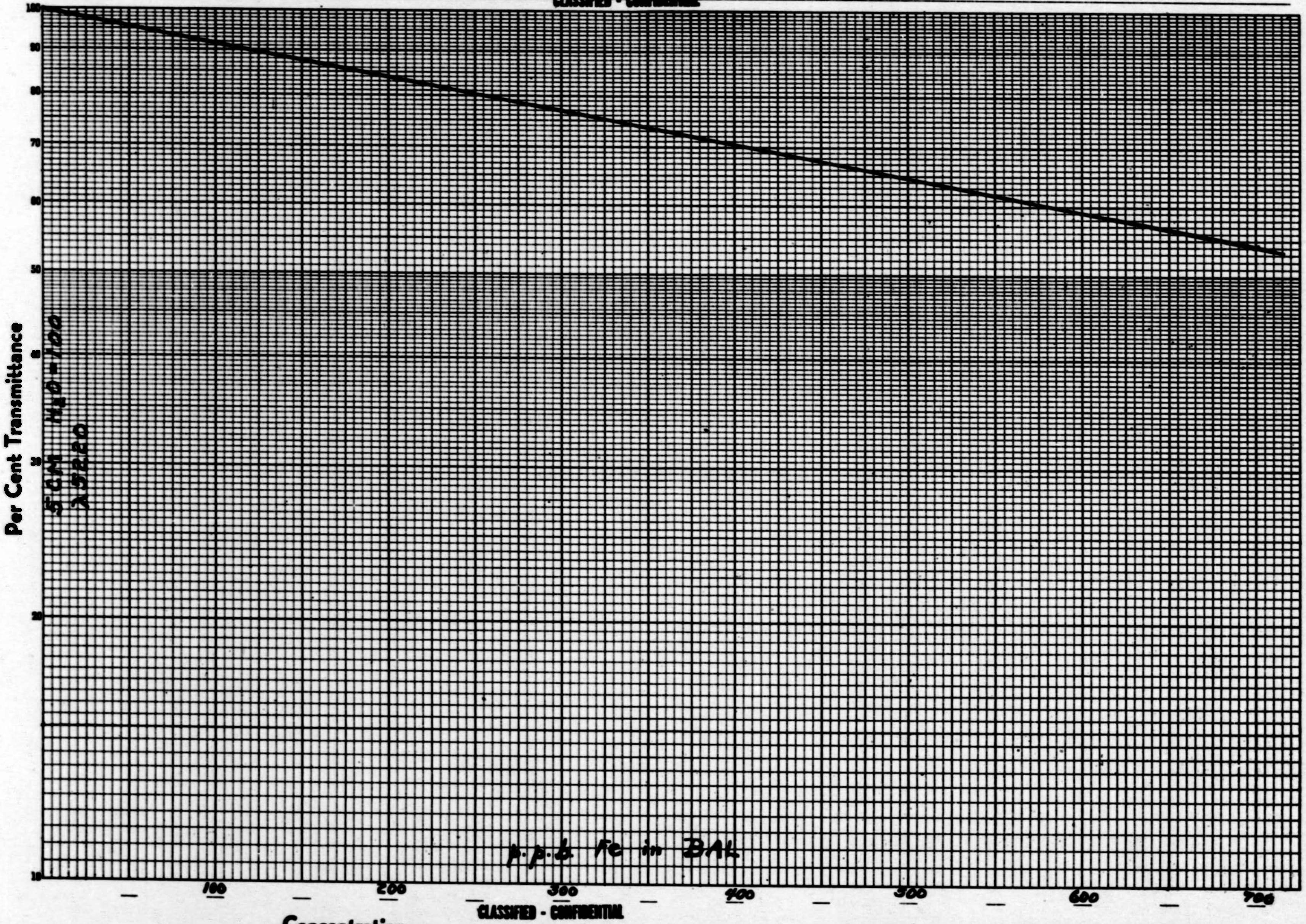

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Concentration______ MODEL______ COLEMAN SPECTROPHOTOMETER Serial No.______

Reference Sol.______

Cell Length mm.______ Remarks______

Wave Length mμ______

Slit Width mm.______

TENTATIVE SPECIFICATIONS FOR ETHYLENE GLYCOL

(Sept. 10, 1942)

1. Suspended Matter. The glycol shall be free from suspended matter as determined by visual observation in a test tube.

2. Color. The color shall be less than 10 as determined in 50 ml. Nessler tubes.

3. Freezing Point. The freezing point shall be not less than -14°C.

4. Water Content. The glycol shall contain less than 0.5% water as determined by the Karl Fischer method.

5. Halogen. The halogen content shall be less than 0.005% calculated as chlorine and as determined by the attached method.

6. Aldehydes and Ketones. The carbonyl number as determined by the hydroxylamine titration method shall be less than 5.

7. Iron. The iron content shall be less than 100 parts per billion as determined by the attached method.

Tentative Specification Methods for Ethylene Glycol

2. Color

The procedure for determining color shall be that described for determining the color of water, "Standard Methods of Water Analysis", Edition 8, page 12, Section VI (American Public Health Association, 1936).

Tentative Specification Methods for Ethylene Glycol

3. Freezing Point

Fit a 6" by 1" test tube with a two-hole rubber stopper. Through one hole insert a standardized thermometer graduated in tenths of a degree, and through the other a stiff wire agitator with a horizontal loop on the lower end encircling the thermometer stem and resting freely inside the tube. Flush out clean tube twice with sample, then quickly charge about one-half full. Insert stopper with clean thermometer and agitator. Supercool sample in carbon dioxide-methanol freezing bath to about 2°F., then seed with previously obtained glycol crystals. Remove the partly frozen sample from the bath and agitate steadily. Avoid pumping viscous material out of the hole in the stopper. Read the freezing point when equilibrium has been reached or when a thin slurry of crystals remains. The thermometer bulb should be midway between the bottom of the tube and not touching the walls.

Tentative Specification Methods for Ethylene Glycol

4. Water Content

Titration with Karl Fischer Reagent

A. REFERENCES

Angew. Chem. 48, 394 (1935)
J. Am. Chem. Soc. 61, 2407 (1939)

B. PRINCIPLE

Iodine oxidizes sulfur dioxide, in the presence of water, with the formation of sulfuric and hydriodic acids. Fischer gives the fundamental reaction as:

$$2H_2O + SO_2 + I_2 \text{ --------}\rangle\ H_2SO_4 + 2HI$$

Water is consumed in the reaction and, when all the water is gone, the reaction stops. In practice it is necessary to remove the sulfuric and hydriodic acids by combining them with pyridine in order to drive the reaction to completion. The iodine, sulfur dioxide, and pyridine are dissolved in methanol to form the Fischer reagent. According to Smith, Bryant, and Mitchell, who adduce convincing evidence to support their contention, the fundamental reaction is modified in the presence of methanol and takes place in two steps:

$$H_2O + SO_2 + I_2 + 3C_5H_5N \text{ ------}\rangle\ 2C_5H_5N.HI + C_5H_5N.SO_3$$

$$C_5H_5N.SO_3 + CH_3OH \text{ ------}\rangle\ C_5H_5N.HSO_4CH_3$$

According to these equations, one mole of iodine is equivalent to one mole of water, instead of two.

In applying the method, the material to be analyzed is titrated with the Fischer reagent, either directly or after solution or suspension in methanol of known water content. The reagent itself indicates the endpoint of the reaction, a slight excess producing a marked brown tinge in the yellow color of the solution being titrated.

The reagent is not stable and deteriorates rapidly enough to make daily standardization necessary, especially during the first week after preparation. After the first week the rate of deterioration diminishes. The weakening of the reagent is caused, according to Smith, Bryant, and Mitchell, by either or both of the following reactions:

$$I_2 + SO_2 + 2CH_3OH + 3C_5H_5N \text{ --- } 2C_5H_5N.HI + C_5H_5N.SO_4(CH_3)_2$$

$$I_2 + 2SO_2 + 3CH_3OH + 4C_5H_5N \text{ --- } 2C_5H_5N.HI + C_5H_5N.HSO_4CH_3 + C_5H_5N.SO_3(CH_3)_2$$

The reagent will also deteriorate if allowed to absorb moisture from the atmosphere. It should be set up for use in a bottle with an automatic burette attached, with $CaCl_2$ drying tubes protecting all openings to the air. Ground glass joints should be used throughout, as the reagent attacks rubber.

C. STATUS

The accuracy and precision of the method has been established as applied to refined and crude glycerin, ethylene glycol and nitroglycerin. It is believed that other applications of the method will be found after more experience.

The preparation of the solution takes several hours after the iodine has been dried, though constant attention is not required during this time. When all is ready, a determination of water can be completed in 10-15 minutes.

D. EQUIPMENT

1. Materials Required

Ace Automatic Overflow Burette #100, burette capacity 50 ml., bottle capacity 2000 ml., with 29/42 standard taper joint, and drying tubes #115. Ace Glass, Inc., Vineland, N.J.

Methanol, containing not more than 0.1% water. Du Pont synthetic methanol is usually sufficiently dry for use as received.

Pyridine, preferably containing not more than 0.1% water, but in no case more than 0.3%.

Iodine, resublimed, dried over conc. H_2SO_4 for 24 hours.

Sulfur dioxide, conveniently obtained from Matheson Co., Rutherford, N.J., in 10-lb. cylinders.

2. Preparation of Reagent

Mix 1334 ml. of methanol and 538 ml. of pyridine; add 170 grams of dry iodine and shake until the iodine is completely dissolved. It is advantageous to use a mechanical shaker, as complete solution requires several hours. Place the flask in an ice water bath in the hood and pass in 128 grams of sulfur dioxide through a calcium chloride drying tube. Some heat is developed during the addition of sulfur dioxide, but the contents of the flask should not be allowed to rise above room temperature. The above amounts give about two liters of reagent and more or less can be prepared as desired. The reagent should be put into the automatic burette bottle and calcium chloride drying tubes should be connected to all outlets to the air, including one between the pumping bulb and the reagent bottle.

Little if any loss of strength occurs before the addition of sulfur dioxide. Consequently, larger quantities of the mixture of methanol, pyridine, and iodine can be prepared, if desired, and stored for future use.

E. STANDARDIZATION OF REAGENT

Weigh 2.0 - 2.5 grams of water (an aniline weighing bottle is convenient for this purpose) into a dry 250 ml. volumetric flask and make up to 250 ml. with dry methanol. Shake well, pipette (use a suction bulb) 10 ml. into a 125 ml. Erlenmeyer flask, and titrate rapidly to the first permanent brown tinge. Do not agitate too violently or the solution may absorb enough moisture from the air to affect the result. Titrate 10 ml. of the dry methanol in like manner. From the difference between the titrations and the weight of water taken calculate the grams of water per ml. of reagent.

The water content of the methanol solution of water can be calculated from the first titration above, and is conveniently expressed as grams of water in 10 ml. This solution can then be kept in a rubber-stoppered bottle for future use as a standard. When an accurate determination of a relatively high percentage of water is required, the standard solution of water in methanol should be brought to the temperature at which it was prepared before pipetting out the 10 ml. for standardization of the Fischer reagent.

The Erlenmeyer flasks used for the titration will be sufficiently dry if they are rinsed with acetone and blown with dry air.

F. PROCEDURE

Weigh a suitable sample of ethylene glycol (5 - 10 grams weighed to the nearest milligram) into a dry, tared and stoppered 125 ml. Erlenmeyer flask. Titrate rapidly with the Fischer reagent to the first permanent brown tinge, as in the standardization.

Calculation:

$$\frac{\text{Ml. Fischer reagent} \times \text{g. } H_2O \text{ per ml.} \times 100}{\text{Wt. Sample}} = \%\ H_2O$$

Tentative Specification Methods for Ethylene Glycol

5. Halogen Content

Weigh about 50 g. of the glycol into a tared platinum dish and heat until the vapor continues to burn after the withdrawal of the flame. Allow the combustion to proceed until it dies out. Carefully protect the operation from draughts, especially during the latter part of the combustion, as a premature extinguishing of the flame, even by but a few seconds, materially lessens the carbonization of the residue. Ignite the residue in the platinum dish avoiding a greater heat than necessary to secure complete combustion of the carbonaceous residue.

Add about 10 ml. of hot distilled water to the ash residue in the platinum dish and triturate with the end of a glass rod. Finally wash the contents of the dish onto a filter and wash thoroughly with hot water, collecting the filtrate in a porcelain evaporating dish or casserole. Add 1 cc. of potassium chromate indicator and 1 to 2 mg. of Na_2CO_3. Titrate to the first permanent reddish tint with 0.01 N. $AgNO_3$ solution.

Calculation:

$$\frac{\text{Ml. } AgNO_3 \times \text{N.} \times 3.546}{\text{Wt. of Sample}} = \text{\% Chlorides as Cl.}$$

Tentative Specification Methods for Ethylene Glycol

6. Aldehyde and Ketone Content

A. REFERENCE

Journal of the American Chemical Society 57, 57 (1935).

B. PRINCIPLE

The aldehyde or ketone is reacted with hydroxylamine hydrochloride in the presence of pyridine to assist in the completeness of the reaction, and the acid which is set free is titrated with alkali. The equations for the reactions involved are as follows:

$$RCHO + HONH_3Cl + C_5H_5N = RCH{=}NOH + H_2O + C_5H_5NHCl$$

$$RCOR' + HONH_3Cl + C_5H_5N = RC({=}NOH)R' + H_2O + C_5H_5NHCl$$

$$C_5H_5NHCl + NaOH = C_5H_5N + NaCl + H_2O$$

The hydroxylamine hydrochloride solution (0.5 N) is prepared by dissolving 35 g. of Eastman hydroxylamine hydrochloride in 160 ml. of distilled water and diluting to 1 liter with 95% ethanol. This solution is adjusted to a pH of 2.50 ±0.01 by means of a pH meter. A solution of 20 ml. of pyridine, Baker's C.P., made up to 1 liter with 95% ethanol is used in conjunction with the above. The sodium hydroxide solution for titration is a standard solution of sodium hydroxide in 90% C.P. methanol (0.5 N). (Methanol is preferable to ethanol for this purpose since the resulting solution does not color with age.)

D. PROCEDURE

Using suitable dispensing cylinders or burettes, 30 ml. of hydroxylamine hydrochloride reagent and 100 ml. of pyridine solution are run into a clean 300-ml. "citrate of magnesia" bottle. The sample is then weighed or pipetted into the mixture, preferably in such proportion that not more than one-half and never less than one-third remains after the reaction is complete. The pressure bottle is then capped and heated in a steam bath at 100°C. for two hours. After heating, allow the sample to cool to approximately room temperature before titrating. Run a blank at the same time, using the same amounts of all reagents. When cooled, take the pH of the blank by means of a pH meter, then titrate the solution of the sample until the pH, as shown by the pH meter, is the same as for the blank. The number of moles of sodium hydroxide used is a direct measure of the number of moles of aldehyde or ketone in the 5-gram sample.

Calculation:

$$\frac{\text{ml. NaOH} \times \text{N} \times 56.11}{\text{Weight of Sample}} = \text{Carbonyl Number}$$

Tentative Specification Methods for Ethylene Glycol

7. Iron Content

(Revised 12/21/42)

Reagents and Materials

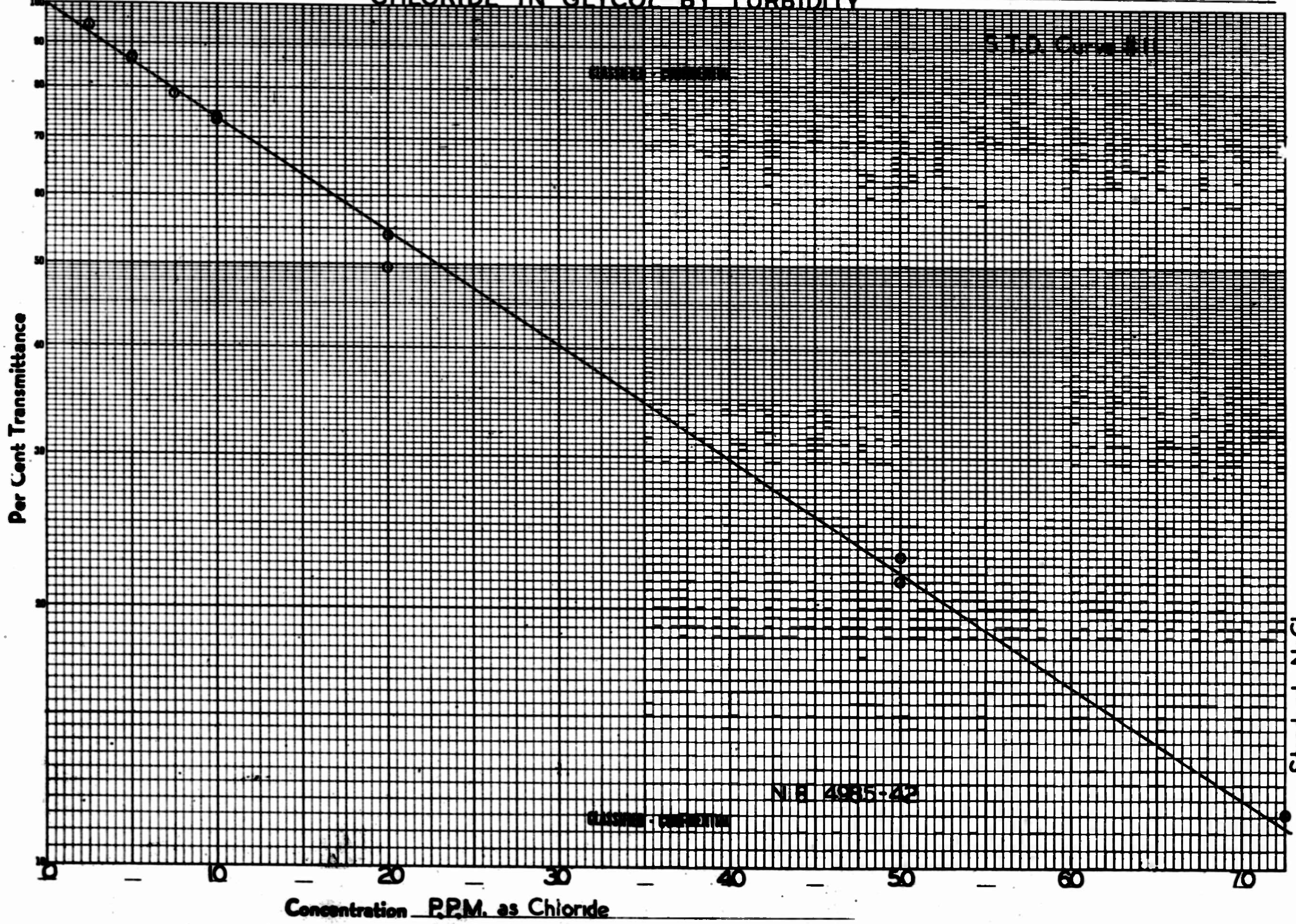
2% ethylene glycol solution of thioglycolic acid.
Conc. aqueous ammonia.
50 ml. volumetric flasks and suitable pipettes,
Photometer useful at λ5300Å provided with 5 cm. cell.

Procedure

By means of pipettes transfer 0.1 ml. of concentrated aqueous ammonia and 1 ml. of thioglycolic acid reagent to a 50 ml volumetric flask and dilute to 50 ml. with the ethylene glycol to be tested. Mix thoroughly and fill the 5 cm. photometer cell being careful to rinse out the cell with at least two small portions of the solution which are discarded. Measure the relative transmission λ5300Å using a sample of the untreated glycol in the comparison cell. Repeat the reading with a fresh sample of the solution.

From the attached curve read off the parts per billion of iron in the glycol.

Analyst ECD Date 6-23-43 File No.______ Method CHLORIDE IN GLYCOL BY TURBIDITY



S.T.D. Curve #11

NB 4985-42

Reference Sol. Standard NaCl
Cell Length mm. 10.0cm Remarks 10ml. Sample diluted to 100ml.
Wave Length mμ. 546 AMINCO FILTER PHOTOMETER, Tungsten Bulb Source
Slit Width mm.

Analysis of Chloride in Glycol by a Turbidimetric Method

Method No. 312

I. Reference:

"The Nephelometric Determination of Chloride" by I. M. Kolthoff and Henry Yetzy, J. Amer. Chem. Soc. 55, 1915-22 (1933).

II. Principle:

Upon addition of a glycol sample containing chloride (other halogen or halogenoids) to a reagent solution containing nitric acid, sodium sulfate and silver nitrate, a turbidity is produced whose light transmission is proportional to the amount of chloride present in the sample.

III. Status:

The method gives a satisfactory calibration curve and is reproducible. Not enough information has been obtained to say how accurate the method will be. The method should be used for a range of 1 to 50 p.p.m. of chloride. Do not use an ultraviolet light source.

IV. Reagents and Apparatus:

1-ml. pipet
10-ml. graduated pipet
100-ml. volumetric flask
A photometer with 10.0-cm. cells, filter
  for 546 millimicrons and a tungsten filament
  light bulb source.
Chloride-free glycol
1.0 N $AgNO_3$ (Keep in dark bottle)
5.0 N HNO_3
Na_2SO_4 solution, 0.1 N as $SO_4^{=}$
Distilled water

V. Detailed Procedure:

To a clean 100-ml. volumetric flask add about 40 ml. of water, 1 ml. of 1.0 N $AgNO_3$, 1 ml. 5 N HNO_3, and 10 ml. of 0.1 N Na_2SO_4. To this add 10 ml. of the glycol sample and dilute to 100 ml. Mix, but do not shake vigorously, set flask in a dark place for 60 minutes. Carry along a blank with the sample and treat in the same way except add 10 ml. of known chloride-free glycol or 40 ml. of chloride-free ethyl alcohol in place of the sample. After 60 minutes, and within the next 60 minutes, determine the per cent transmission of the sample with respect to the blank, using an Aminco photometer set for the filter to give light of a wave length of 546 millimicrons. Use the tungsten filament lamp for the light source and use 10.0-cm. cells.

Determine the per cent transmission and read the concentration of chloride in parts per million directly from the standard curve, the standard curve having been prepared by adding known samples of a standard NaCl solution covering the entire concentration range used and under the same conditions as the future experiments are to be carried out.

The use of alcohol in place of the glycol for the blank is permissible as it has been found that it will give almost exactly the same transmission.

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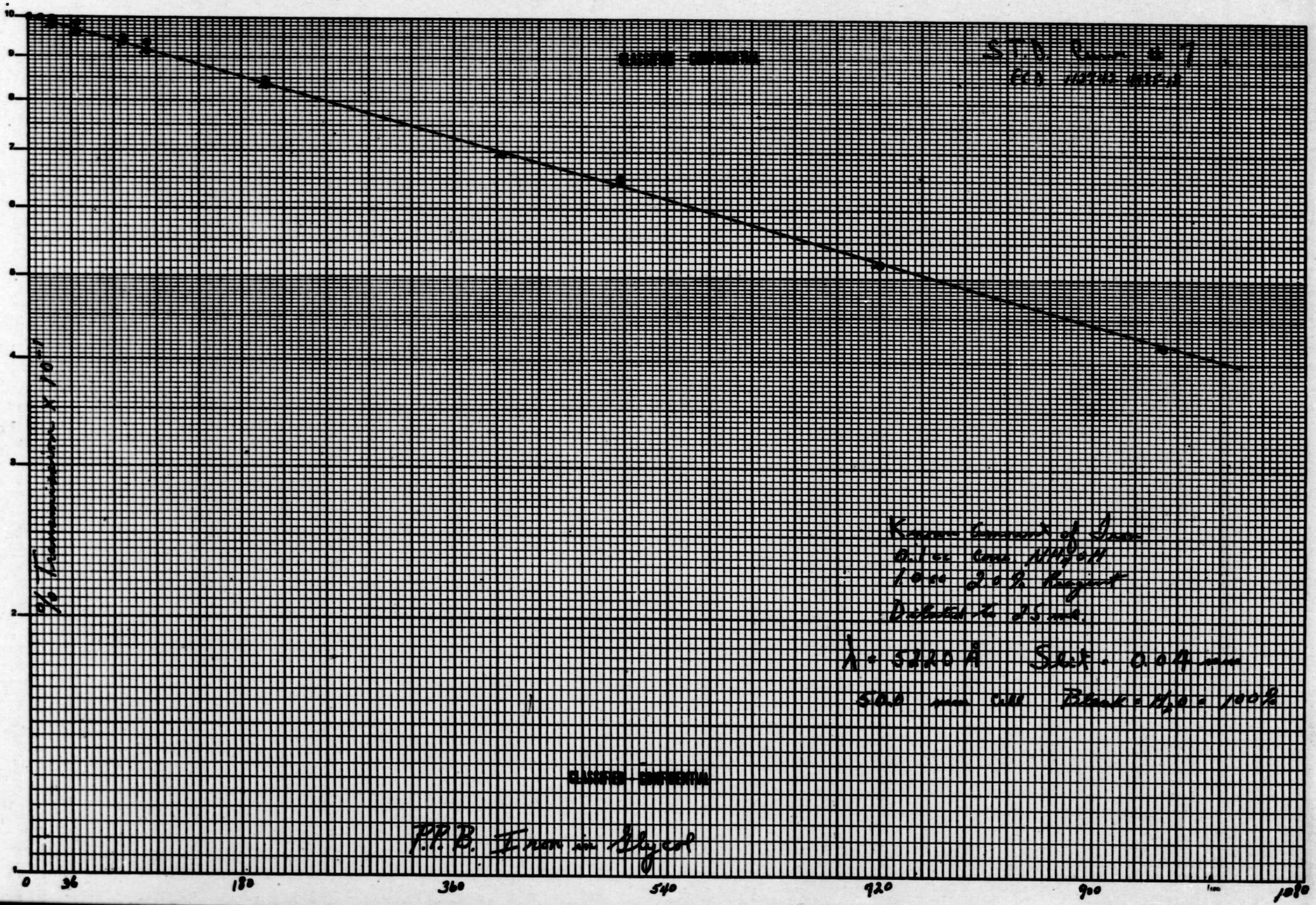

P.P.B. Iron in Glycol

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TENTATIVE SPECIFICATIONS FOR "M-1 EYE SOLUTION"

1. Suspended Matter: The solution shall be essentially free from suspended matter as determined by visual inspection of a sample in a test tube,

2. Color: The color shall be less than 10 on the A.P.H.A. color standard.

3. Density: The density of the solution shall be not greater than D_4^{25} 1.1160 nor less than D_4^{25} 1.1150.

4. Thiol sulfur: The thiol sulfur content as determined by the attached method shall be not more than 3.0% and not less than 2.7%.

5. Water content: The water content shall not exceed 0.5% as determined by the attached method.

6. Iron: To be specified on the basis of experimental work now in progress.

Tentative Specifications for "M-1 Eye Solution"

2. Color

The procedure for determining color shall be that described for determining the color of water, "Standard Methods of Water Analysis", Edition 8, page 12, Section VI (American Public Health Association, 1936).

If the solution has a pink color, add one or two drops of concentrated hydrochloric acid (as required to discharge the pink color) before comparing with the A.P.H.A. color standards.

Tentative Specifications for "M-1 Eye Solution"

3. Density

The density shall be determined by means of a pycnometer having a capacity of at least 50 ml. at 25° as compared with oxygen-free water at 4°C.

Tentative Specifications for "M-1 Eye Solution"

4. Thiol Sulfur

Objective: Determination of the thiol sulfur concentration in "M-1 Eye Solution".

Reagents:

(a) 0.1 Normal standard sodium thiosulfate solution.

(b) 0.1 Normal iodine solution, prepared by dissolving 25 g. of potassium iodide in 25 cc. of water, then dissolving 13 g. of iodine in the solution and diluting to one liter. The solution should be standardized against standard sodium thiosulfate every day. It is a good practice to standardize the solution with each series of determinations.

Equipment: 250 cc. Iodine Flasks (Scientific Glass Apparatus Co.)

Procedure:

Five (5) cc. of the eye solution is pipetted into a weighed iodine flask, the flask is stoppered and the sample weight determined by difference. About 20 cc. of methanol is then rinsed into the flask around the stopper, and the solution is titrated with 0.1 N iodine solution until addition of a single drop produces a faint yellow color. If required 0.1 N sodium thiosulfate solution can be used for back titration.

$$\frac{\text{Iodine solution} \times \text{Normality} \times 3.206}{\text{wt. sample}} = \%\ \text{Thiol sulfur}$$

Interfering Substances

Hydrogen sulfide or other substances which reduce iodine solution interfere with the test.

Accuracy

The determination is believed to be precise to within ±0.01% of thiol.

Tentative Specifications for "M-1 Eye Solution"

5. Water Content

Objective:

Determination of water content of glycol solutions of BAL.

Principle:

Iodine oxidizes sulfur dioxide, in the presence of water, with the formation of sulfuric and hydriodic acids. Fischer gives the fundamental reaction as:

$$2\ H_2O + SO_2 + I_2 \dashrightarrow H_2SO_4 + 2HI$$

Water is consumed in the reaction, and when all the water is gone the reaction stops. In practice it is necessary to remove the sulfuric and hydriodic acids by combining them with pyridine in order to drive the reaction to completion. The iodine, sulfur dioxide, and pyridine are dissolved in methanol to form the Fischer reagent. According to Smith, Bryant, and Mitchell, who adduce convincing evidence to support their contention, the fundamental reaction is modified in the presence of methanol and takes place in two steps:

$$H_2O + SO_2 + I_2 + 3C_5H_5N \dashrightarrow 2C_5H_5N\cdot HI + C_5H_5N\cdot SO_3$$

$$C_5H_5N\cdot SO_3 + CH_3OH \dashrightarrow C_5H_5N\cdot HSO_4CH_3$$

According to these equations, one mole of iodine is equivalent to one mole of water, instead of two.

In applying the method, the material to be analyzed is titrated with the Fischer reagent, either directly or after solution or suspension in methanol of known water content. The reagent itself indicates the endpoint of the reaction, a slight excess producing a marked brown tinge in the yellow color of the solution being titrated.

The reagent is not stable and deteriorates rapidly enough to make daily standardization necessary, especially during the first week after preparation. After the first week the rate of deterioration diminishes. The reagent will also deteriorate if allowed to absorb moisture from the atmosphere. It should be set up for use in a bottle with an automatic burette attached, with $CaCl_2$ drying tubes protecting all openings to the air. Ground glass joints should be used throughout, as the reagent attacks rubber.

The active ingredient of "M-1 Eye Solution" reacts with iodine; hence the method has been modified to separate the water from the solution as the azeotrope with n-butanol before making the titration. To insure complete absence of moisture from the n-butanol and from the distillation apparatus a sample of the butanol is distilled and titrated before introducing the sample into the distillation flask.

Apparatus:

1. Ace automatic overflow Burette #5870, burette capacity 50 ml., bottle capacity 2000 ml., with 29/42 standard taper joint and drying tubes #5765. Ace Glass, Inc., Vineland, N.J.

2. Weighing Burette #5625, burette capacity 10 ml., with #13/14 standard taper joint. Ace Glass, Inc., Vineland, N.J.

3. Distillation apparatus consisting of one 500 ml. flask with 24/40 and 13/14 standard taper grinds, one #8260-13 stopper, Distillation Column #6615, Adapter #5125. Condenser #6040, and Receiver #6665 all with 24/40 standard taper grinds. Ace Glass, Inc., Vineland, N.J.

4. 100 ml. Volumetric flasks with #13 standard taper grinds and stoppers.

5. Glass holices, #7527, pyrex glass, 1/8 inch. Ace Glass, Inc., Vineland, N.J.

Reagents:

Methanol containing not more than 0.1% water.

Pyridine preferably containing not more than 0.1% water, but in no case more than 0.3%.

Iodine, resublimed, dried over conc. H_2SO_4 for 24 hours.

Sulfur dioxide, conveniently obtained from Matheson Co., Rutherford, N.J., in 10 lb. cylinders.

n-Butanol, commercial first quality.

Preparation of Karl Fischer Reagent

Mix 1334 ml. of methanol and 538 ml. of pyridine; add 170 g. of dry iodine and shake until the iodine is completely dissolved. It is advantageous to use a mechanical shaker, as complete solution requires several hours. Place the flask in an ice water bath in the hood and pass in 128 g. of sulfur dioxide through a calcium chloride drying tube. Some heat is developed during the addition of sulfur dioxide, but the contents of the flask should not be allowed to rise above room temperature. The above amounts give about two liters of reagent and more or less can be prepared as desired. The reagent should be put into the automatic burette bottle and calcium chloride drying tubes should be connected to all outlets to the air, including one between the pumping bulb and the reagent bottle.

Little, if any, loss of strength occurs before the addition of sulfur dioxide. Consequently, larger quantities of the mixture of methanol, pyridine, and iodine can be prepared, if desired, and stored for future use.

Blank

Weigh 2.0-2.5 g. of water (use the weighing burette for this purpose) into a dry 250 ml. volumetric flask and make up to 250 ml. with dry methanol. Shake well, pipette (using a suction bulb) 10 ml. into a 100 ml. volumetric flask and titrate rapidly to the first permanent brown tinge. Do not agitate too violently or the solution may absorb enough moisture from the air to affect the result. Titrate 10 ml. of the dry methanol in like manner. From the difference between the titrations and the weight of water taken calculate the grams of water equivalent to one ml. of the reagent.

The water content of the methanol solution of water can be calculated from the first titration above, and is conveniently expressed as grams of water in 10 ml. This solution can then be kept in a rubber-stoppered bottle for future use as a standard. When an accurate determination of a relatively high percentage of water is required, the standard solution of water in methanol should be brought to the temperature at which it was prepared before pipetting out the 10 ml. for standardization of the Fischer reagent.

The volumetric flasks used for the titration should be rinsed with acetone and blown with air dried by passing through a calcium chloride tower.

Procedure

Assemble the apparatus taking care to protect all outlets to the air with $CaCl_2$ drying tubes.

Place 200 ml. of n-butanol together with a boiling chip in the distillation flask. Slowly distill off 20 ml. of butanol and discard. Distill a second fraction of 20 ml. and titrate with Karl Fischer reagent. Continue distilling and titrating until 20 ml. of distillate requires less than 1.0 ml. of reagent. Usually the second fraction meets this requirement.

Remove the heat from the flask, cool slightly and introduce 10 ml. (or for greater accuracy 10 g.) of sample through the side arm. Continue the distillation and titrations until 20 ml. of distillate requires less than 1.0 ml. of reagent. Usually the second 20 ml. will meet this requirement if the distillation has been properly carried out.

Calculate the % water in the sample by substitution of the proper values in the following equation.

$$\frac{\text{Ml. Fischer reagent} \times \text{g. } H_2O \text{ per ml.} \times 100}{\text{Wt. of Sample}} = \%\ H_2O$$

Precautions

Samples containing H_2S in amounts detectable by odor should be blown with oxygen-free nitrogen until the vapors no longer discolor filter paper moistened with 10% aqueous lead acetate. n-Butanol has proved quite satisfactory as a carrier for the water. Dioxane purified by refluxing with metallic sodium and distilling has also been used with fairly satisfactory results. The method is believed to be sensitive to about ±0.02% H_2O.

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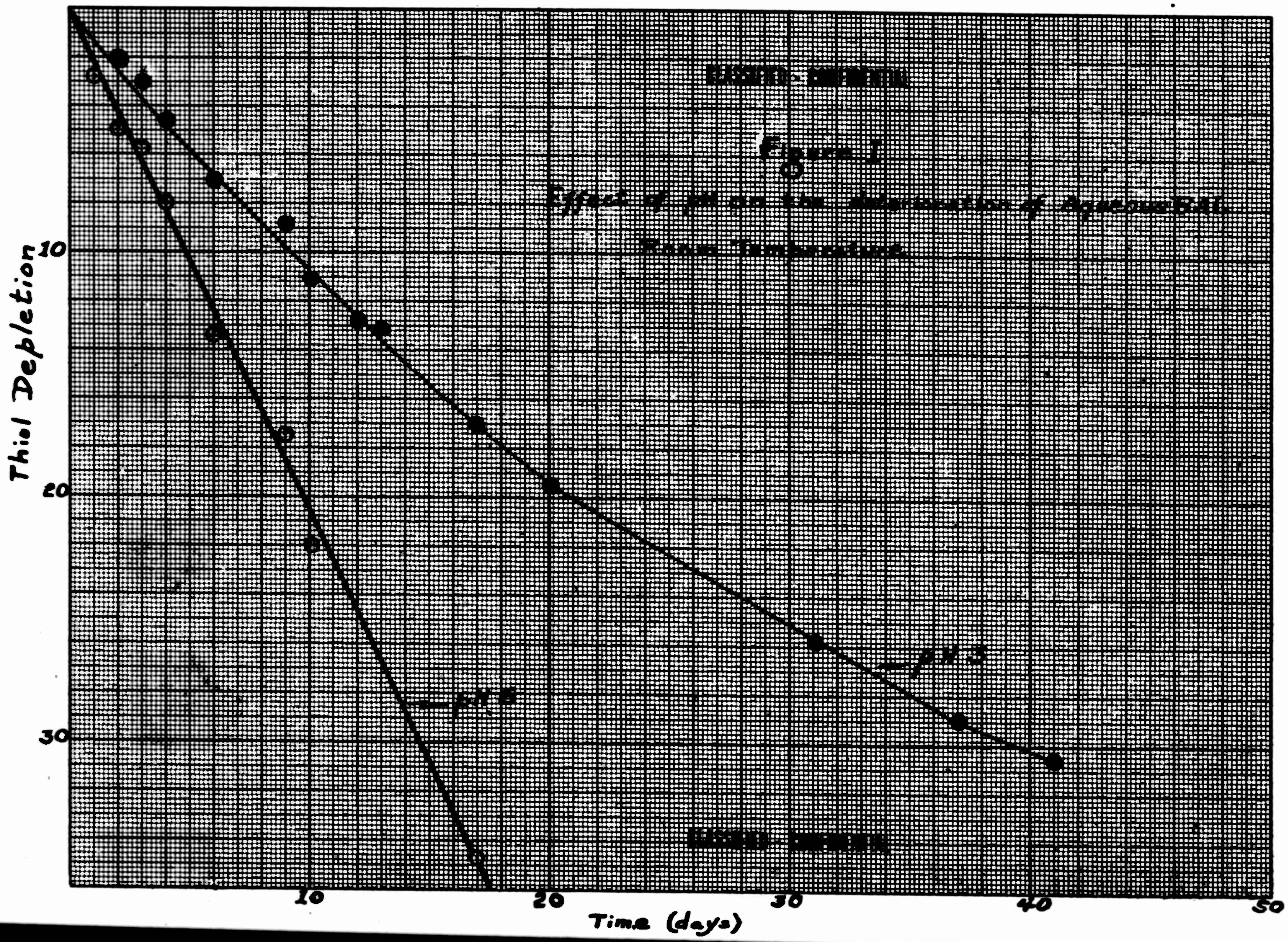

Figure 1

Effect of pH on the deterioration of Aqueous BAL

Room Temperature

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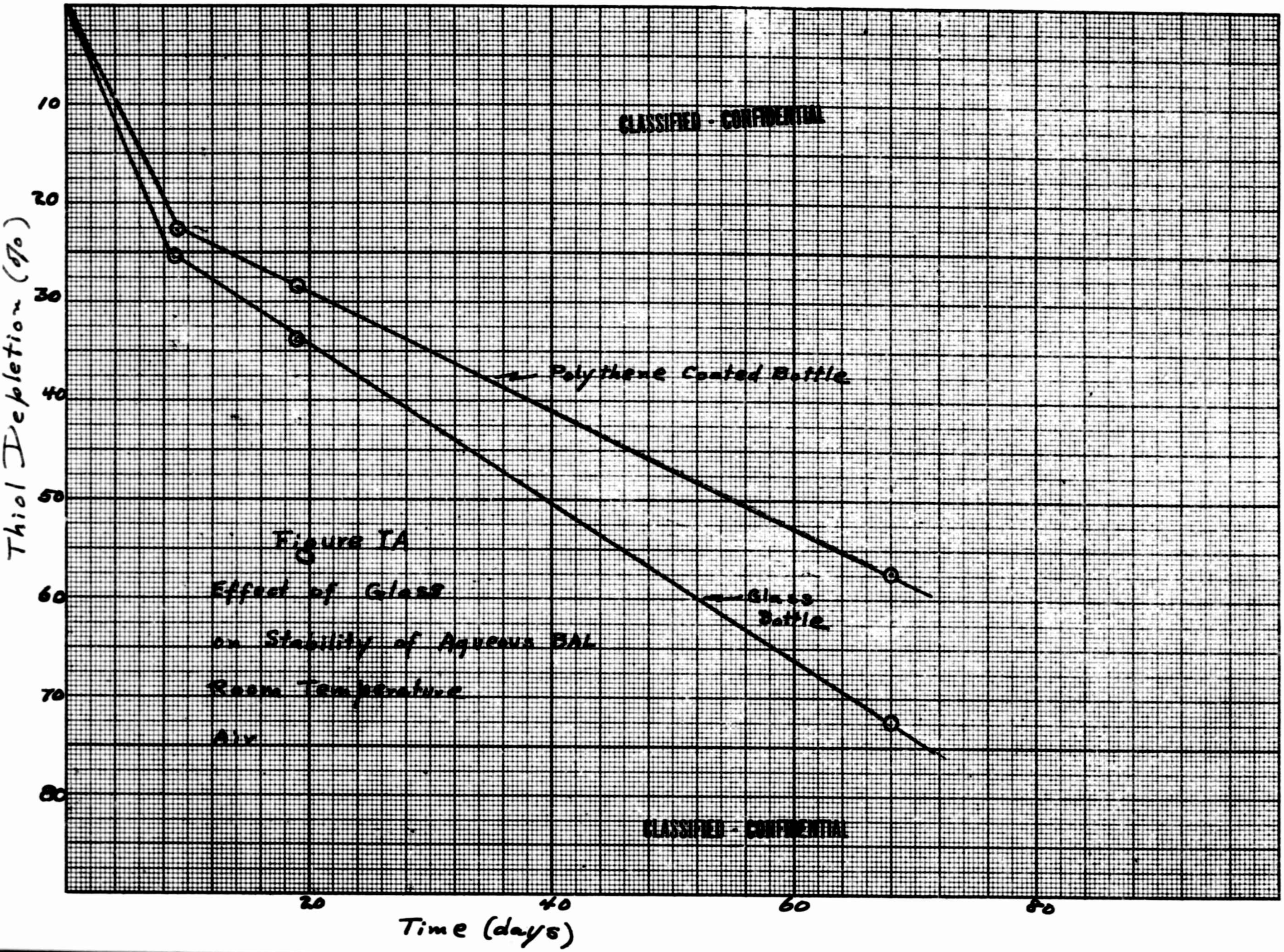

Figure IA

Effect of Glass on Stability of Aqueous BAL

Room Temperature

Air

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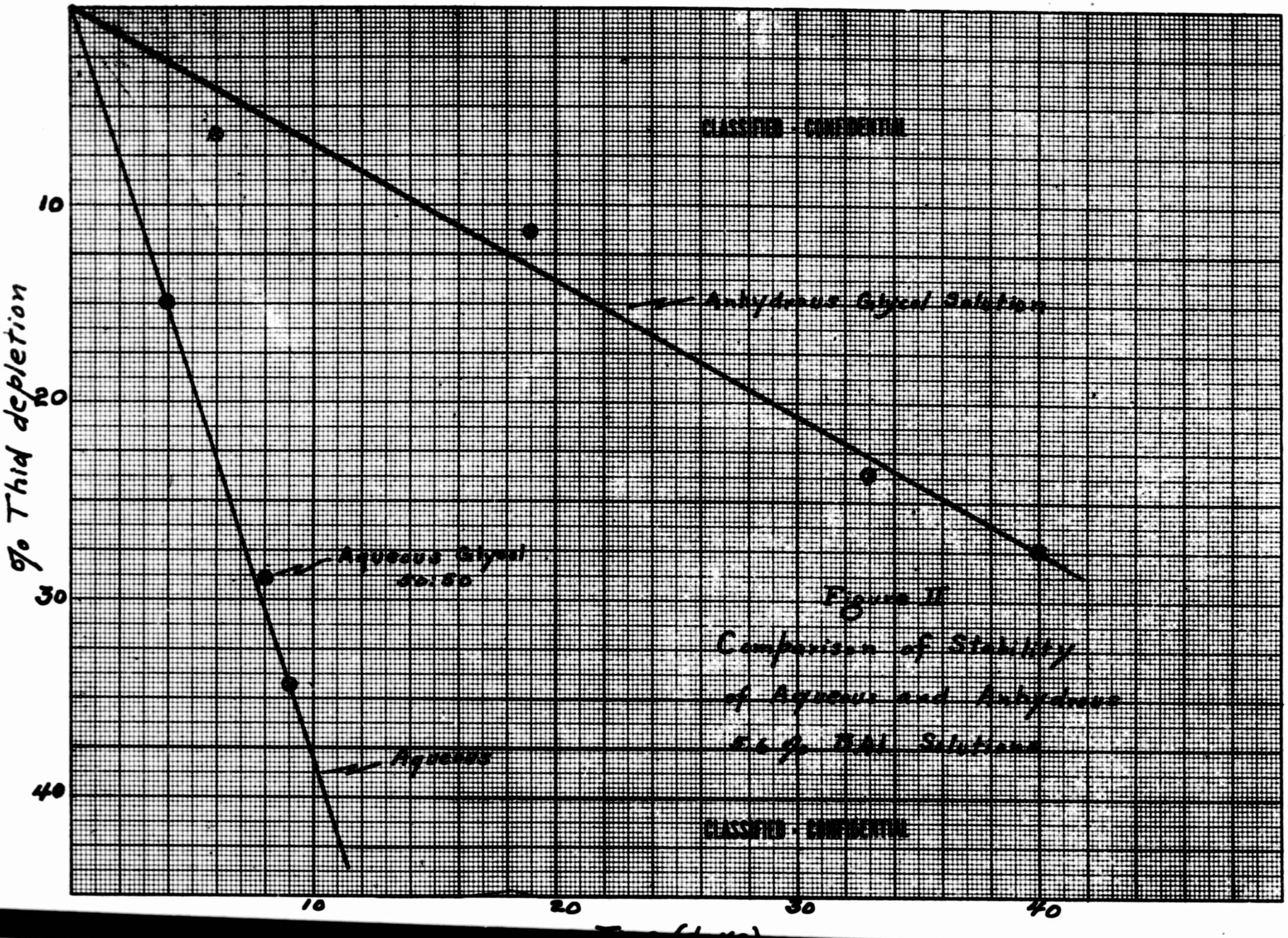

Figure II

Comparison of Stability of Aqueous and Anhydrous 5.6% BAL Solutions

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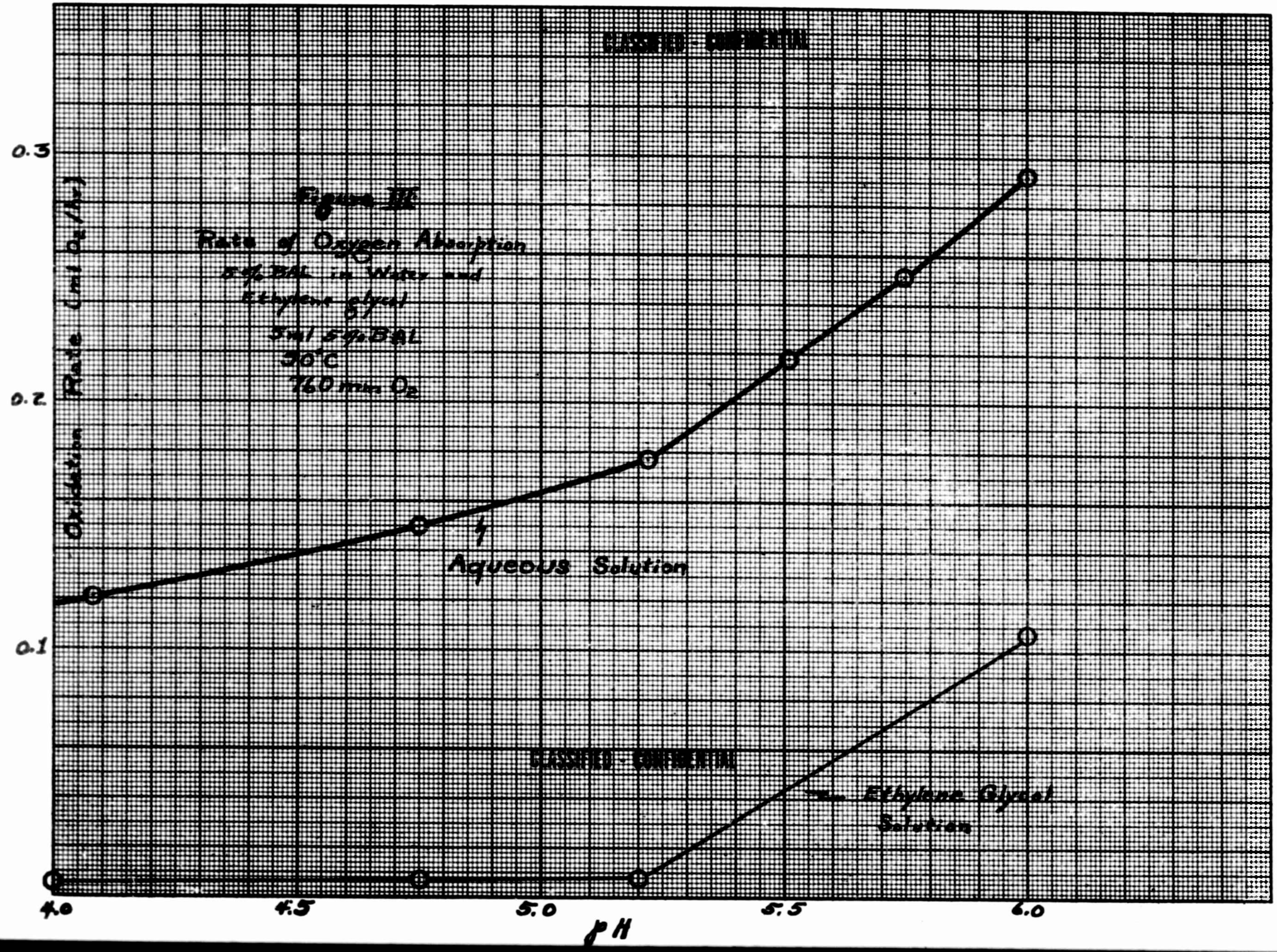

Figure III

Rate of Oxygen Absorption
5% BAL in Water and Ethylene glycol
5ml 5% BAL
30°C
760 mm O_2

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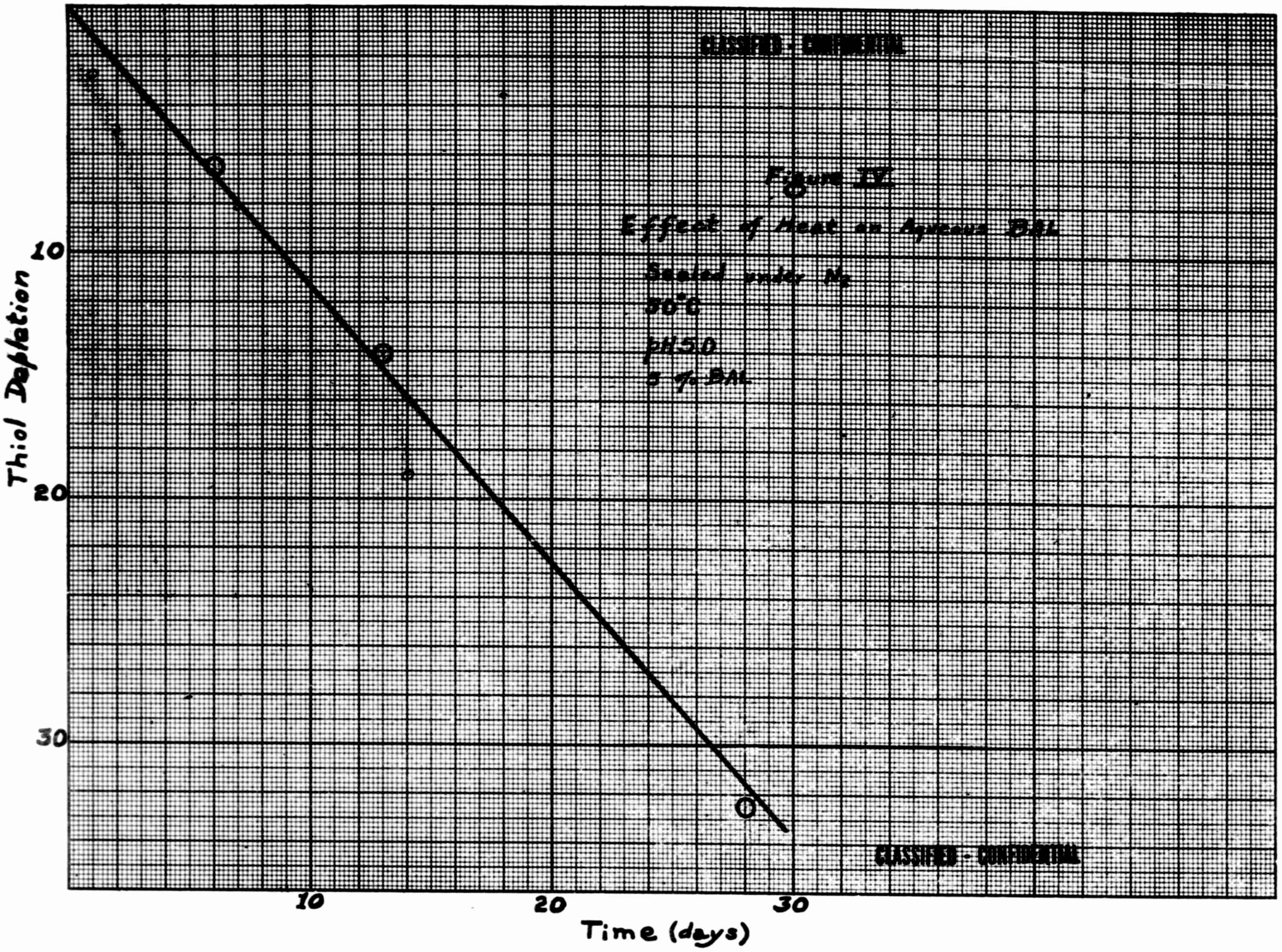

Figure IV

Effect of Heat on Aqueous BAL

Sealed under N_2

50°C

pH 5.0

5 % BAL

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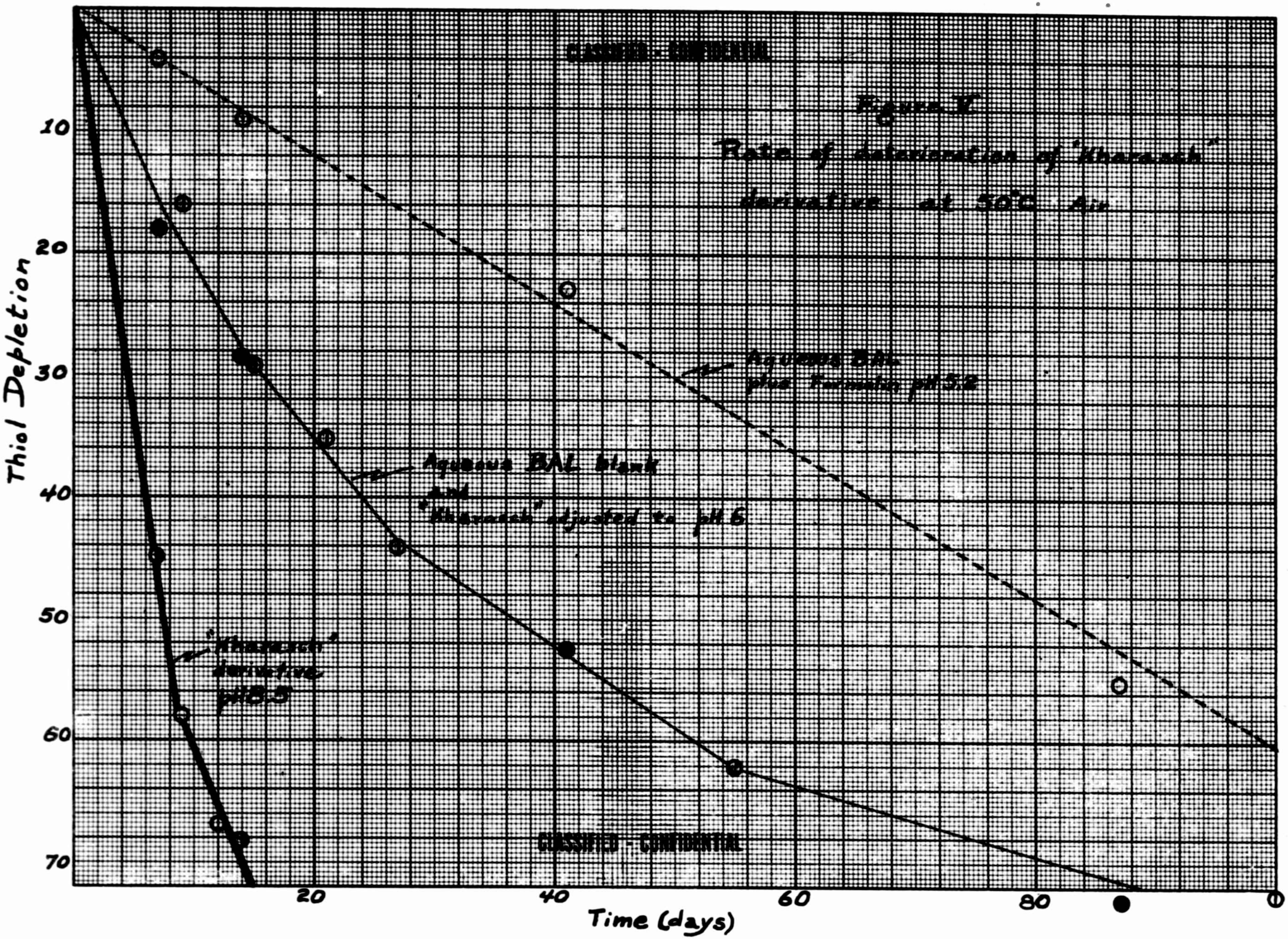
Figure V

Rate of deterioration of "Kharasch" derivative at 50°C Air

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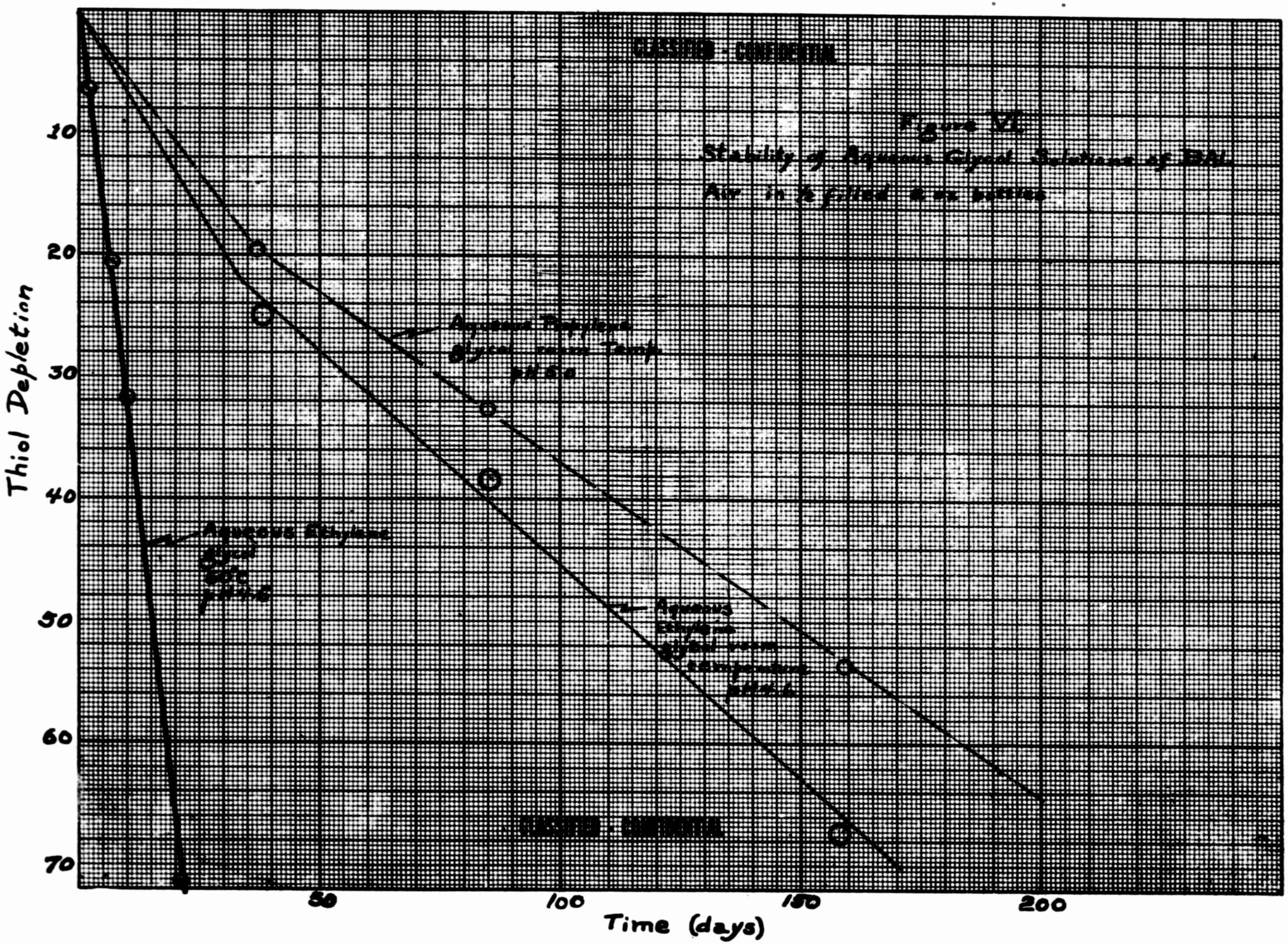

Figure VI

Stability of Aqueous Glycol Solutions of BAL

Air in ½ filled 4 oz bottles

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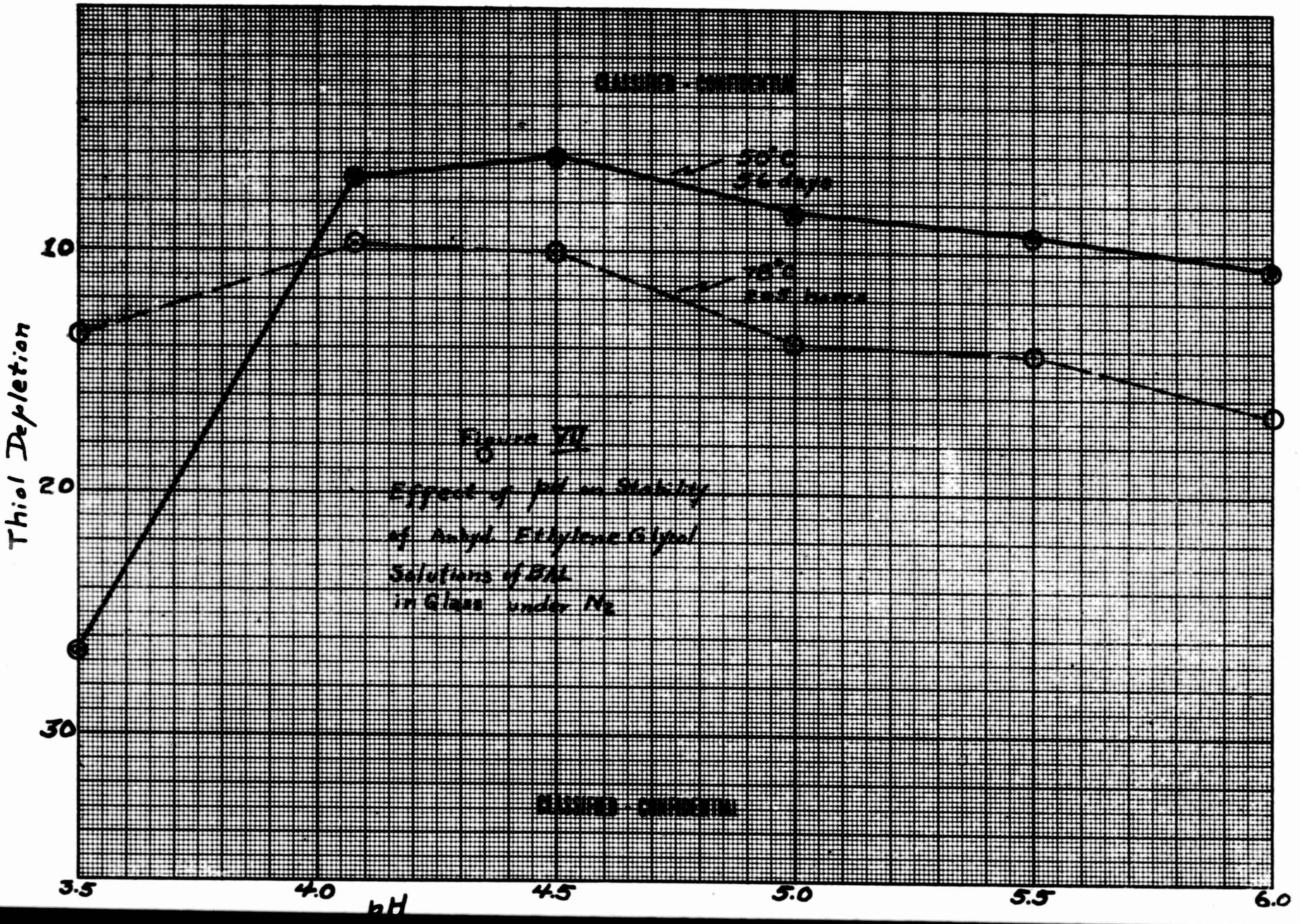

Figure VII

Effect of pH on Stability of Anhyd. Ethylene Glycol Solutions of BAL in Glass under N_2

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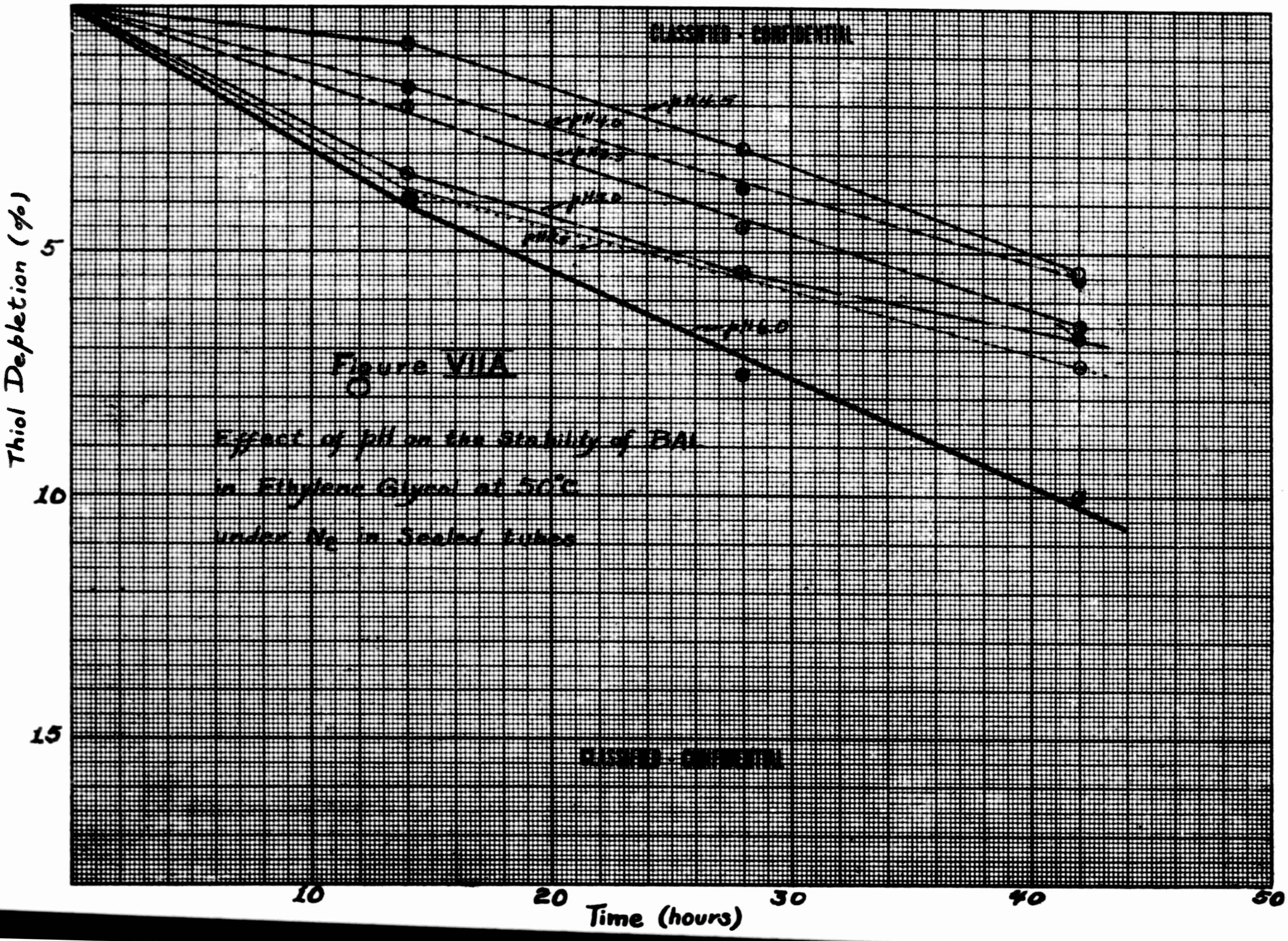

Figure VIIA

Effect of pH on the Stability of BAL in Ethylene Glycol at 50°C under N_2 in Sealed tubes

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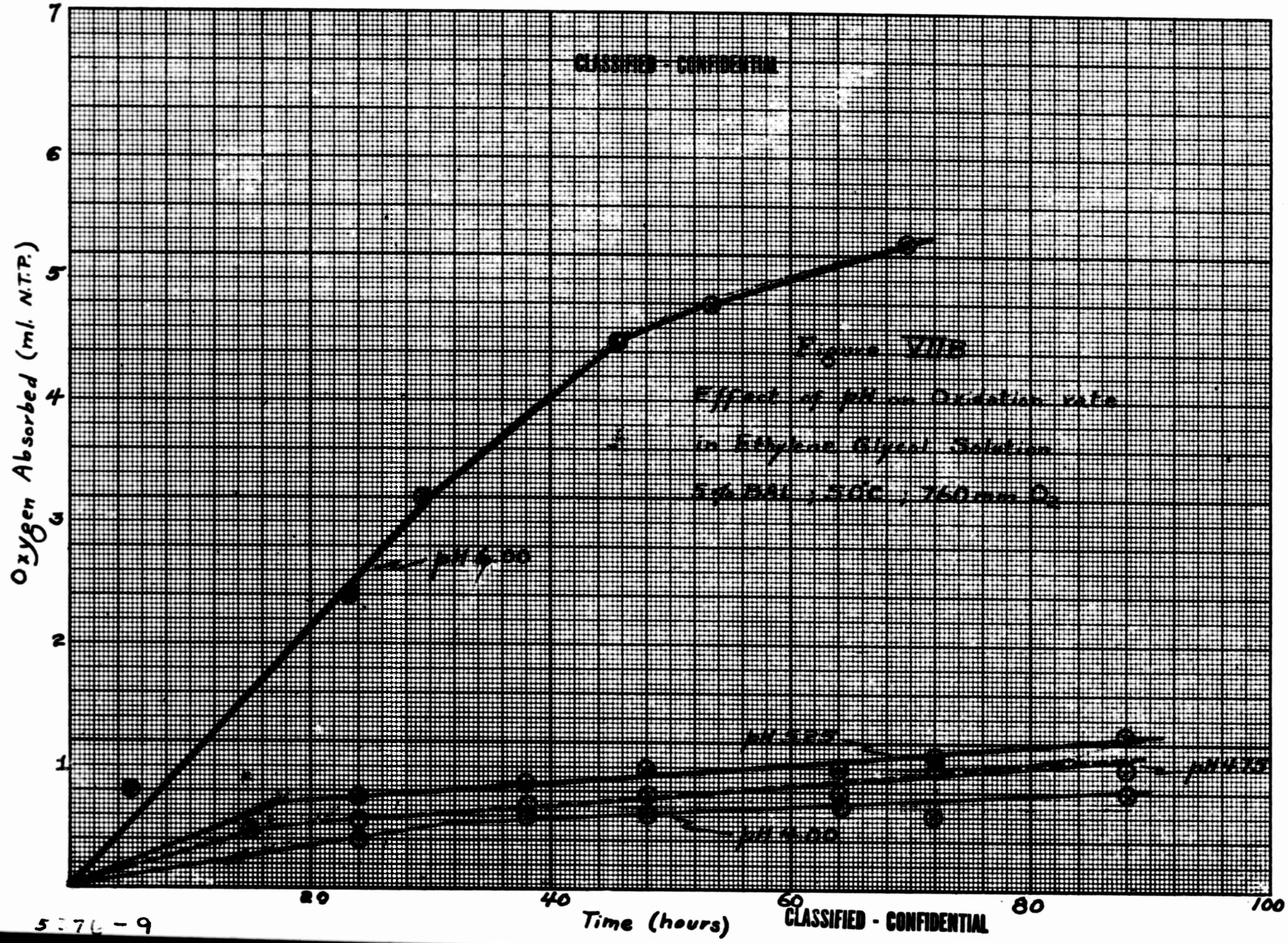

Figure VIIB

Effect of pH on Oxidation rate in Ethylene Glycol Solution

5% BAL, 50C, 760 mm O_2

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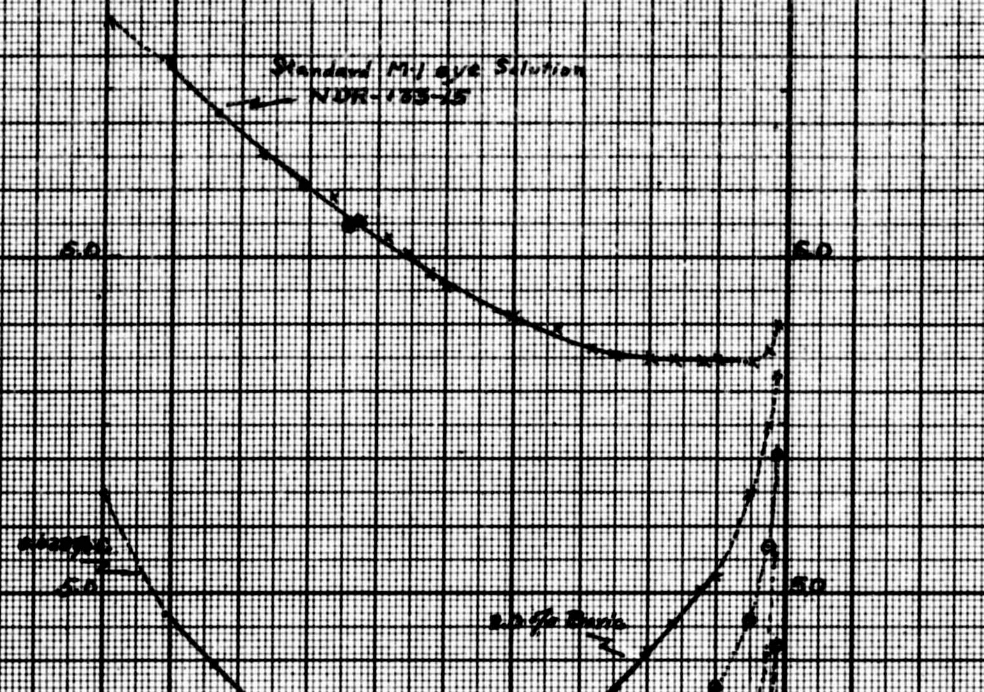

Figure XVII
Effect of adding H_2O to 5.6% BAL
in Ethylene Glycol solution

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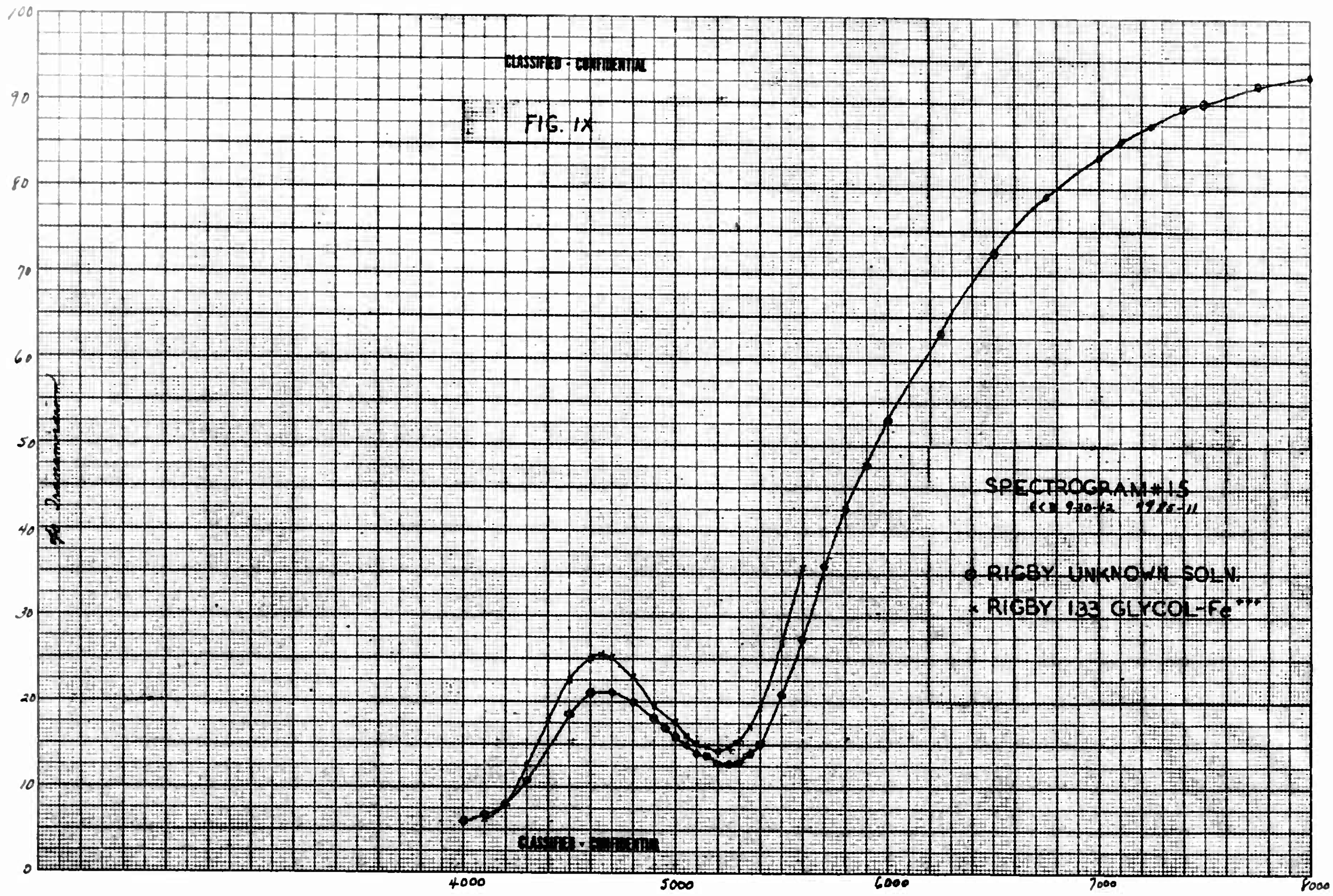
FIG. IX



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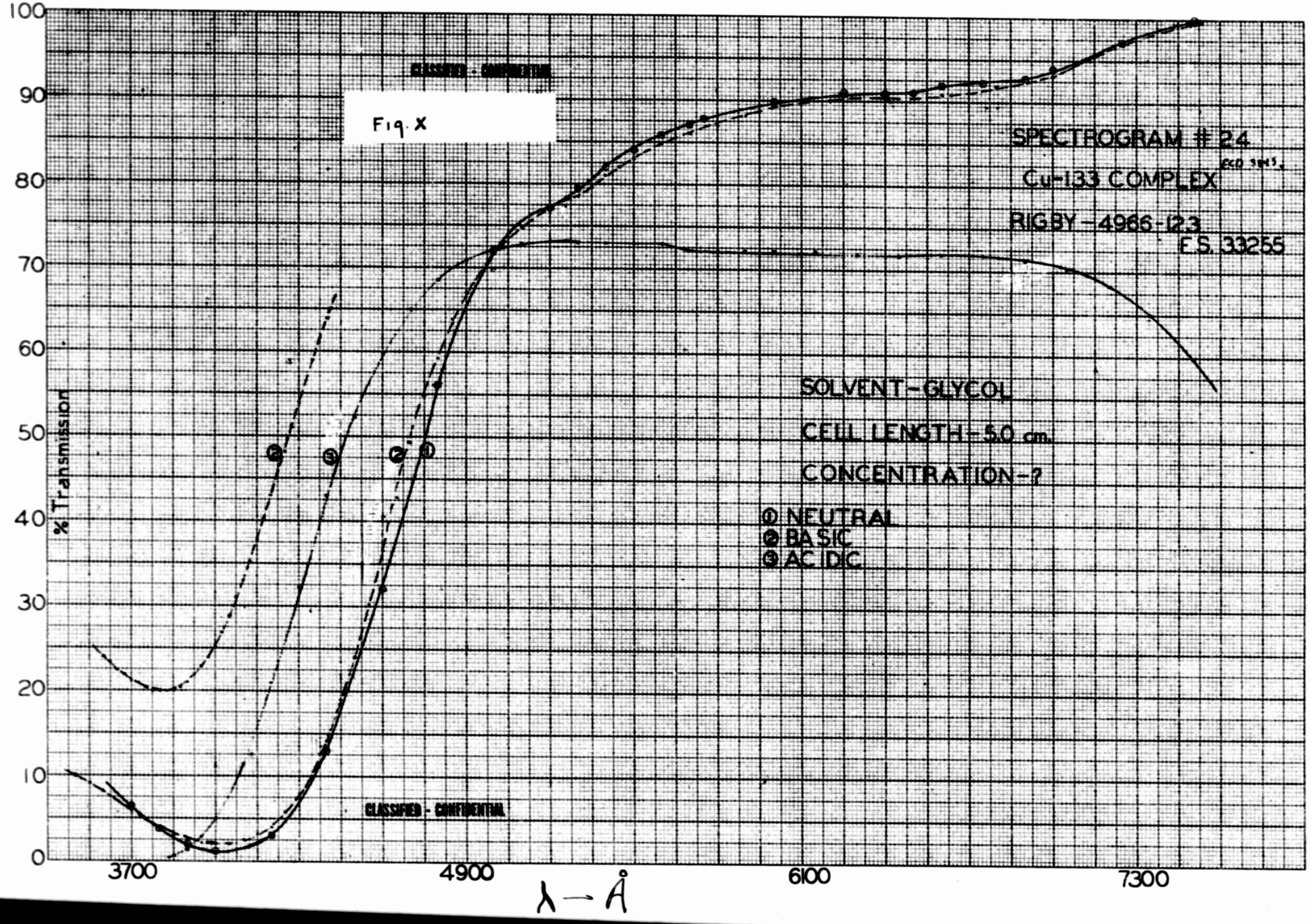

Fig. x

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SPECTROGRAM # 24
Cu-133 COMPLEX
RIGBY - 4966-123
E.S. 33255
SOLVENT - GLYCOL
CELL LENGTH - 5.0 cm.
CONCENTRATION - ?
① NEUTRAL
② BASIC
③ ACIDIC
①
②
③
②
% Transmission
100
90
80
70
60
50
40
30
20
10
0
3700
4900
6100
7300
λ → Å
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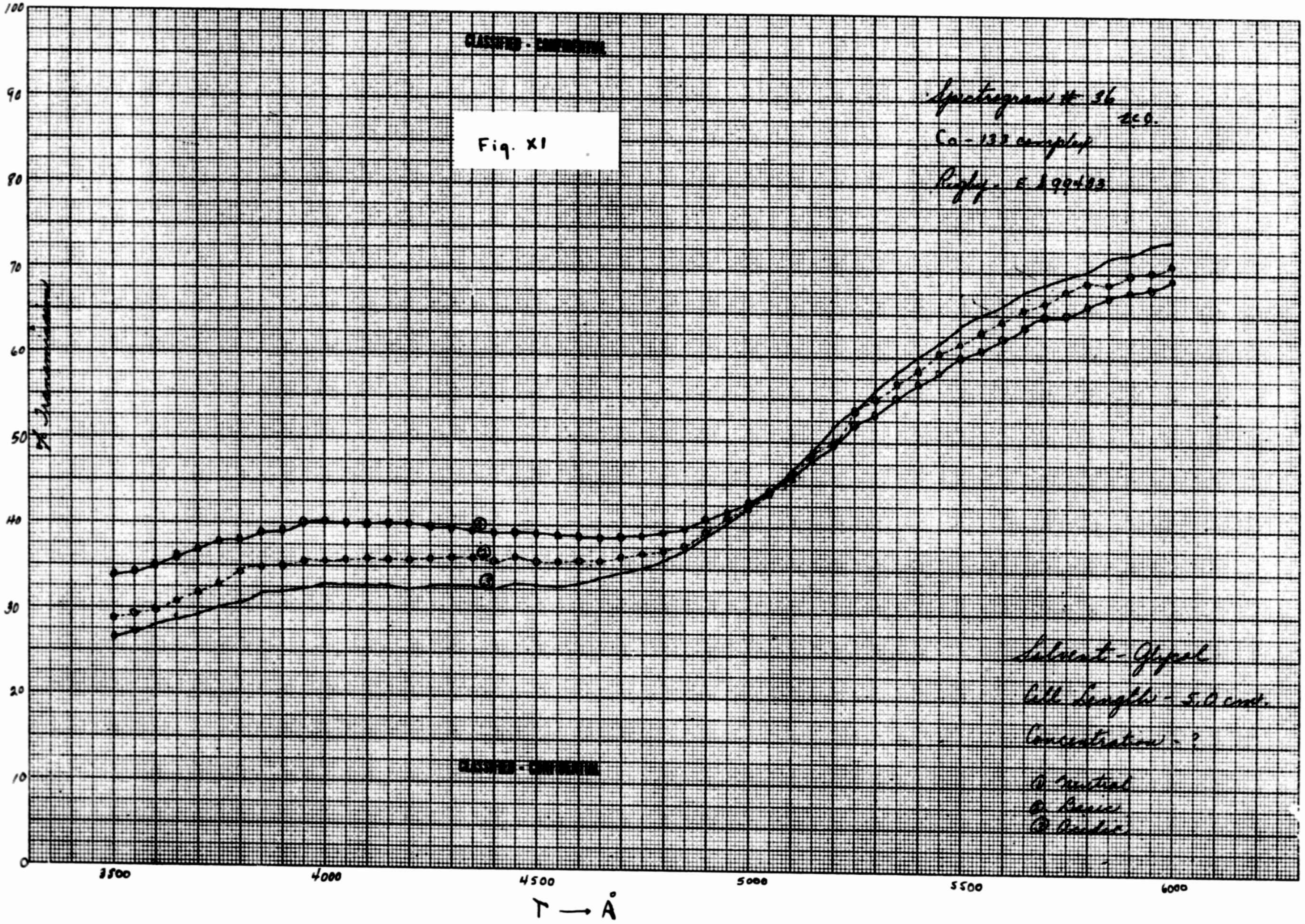

Fig. XI

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Spectrogram # 36
zco.
Co-133 complex
Reply - E 199493
% Transmission
100
90
80
70
60
50
40
30
20
10
0
3500
4000
4500
5000
5500
6000
T → Å
①
②
③
Solvent - Glycol
Cell Length - 5.0 cm.
Concentration - ?
① Neutral
② Basic
③ Acidic
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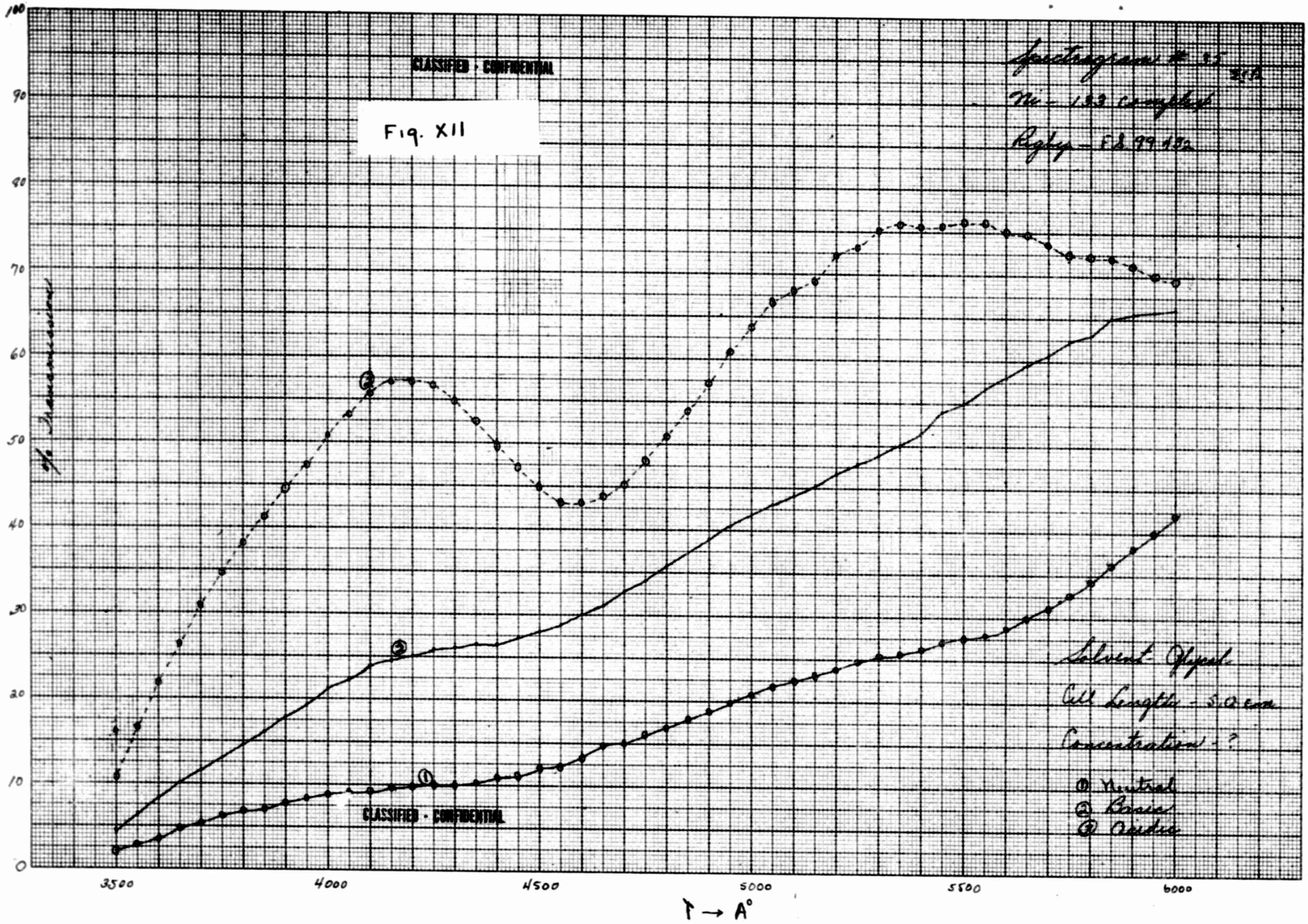
Fig. XII

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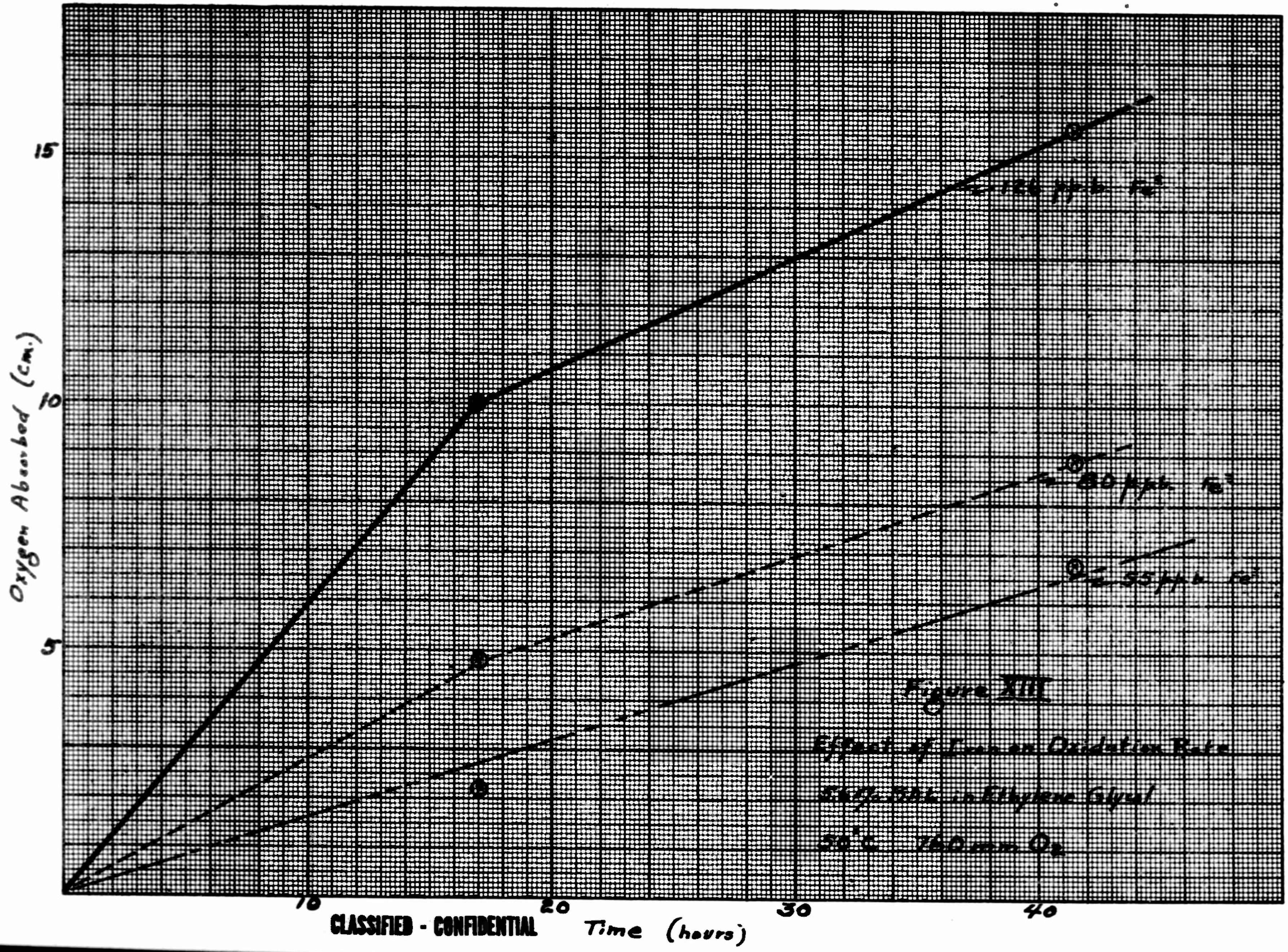

Figure XIII

Effect of Iron on Oxidation Rate

5% [illegible] in Ethylene Glycol

50°C 760 mm O_2

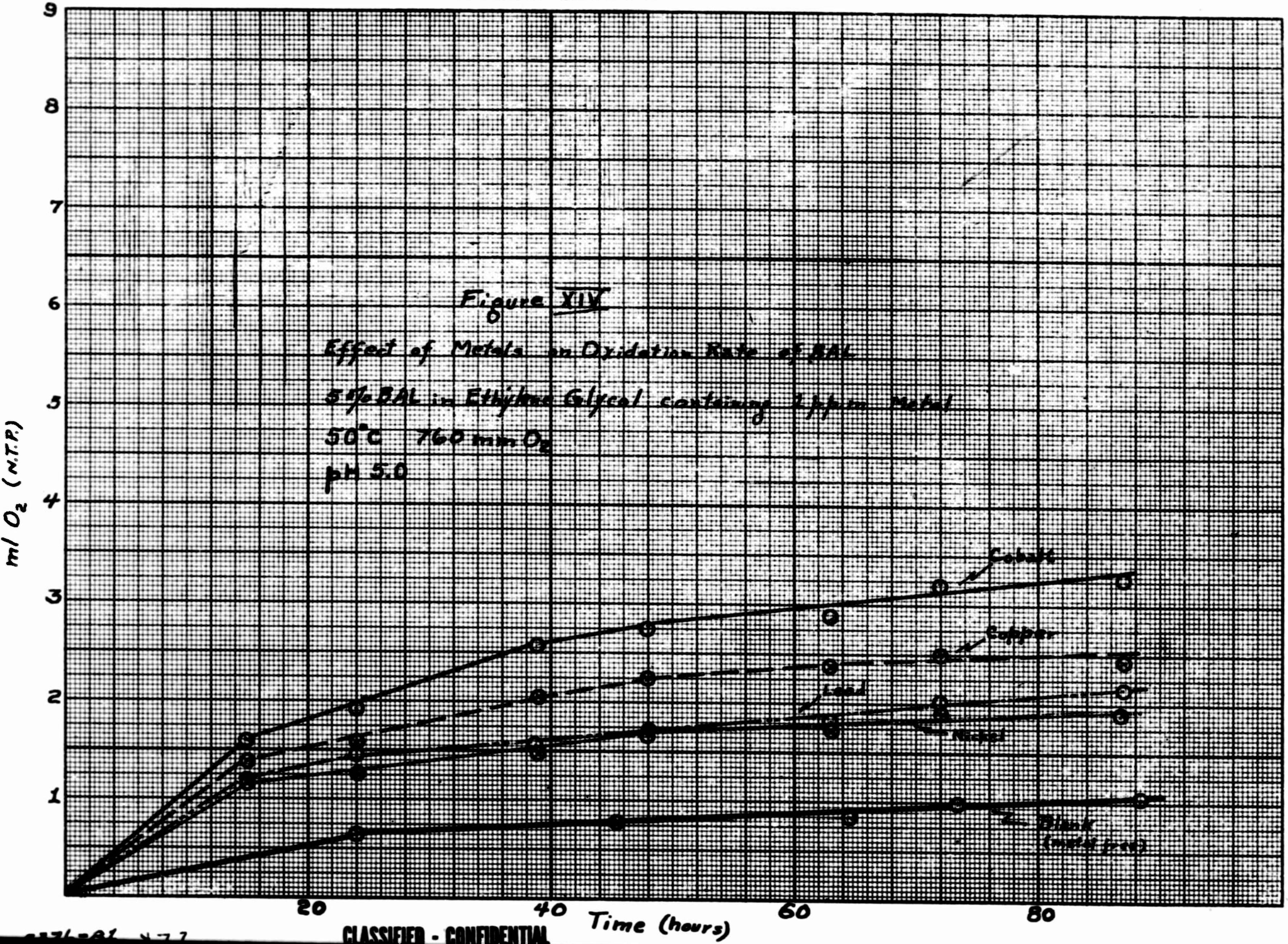

Figure XIV

Effect of Metals on Oxidation Rate of BAL

5% BAL in Ethylene Glycol containing 1 ppm Metal

50°C 760 mm O2

pH 5.0

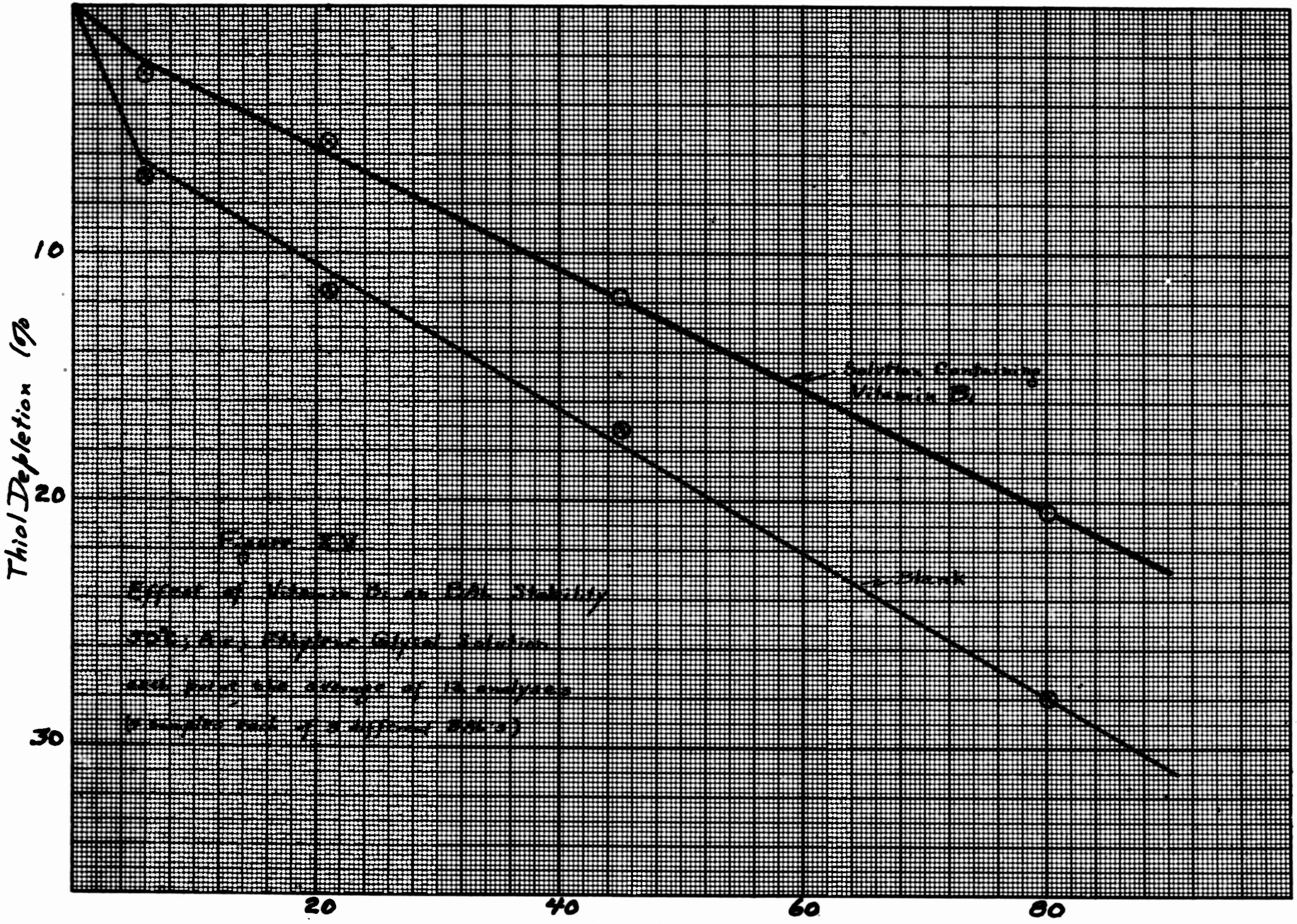

Figure XII

Effect of Vitamin B₁ on EAL Stability

30% Aq. Ethylene Glycol Solution

each point the average of 12 analyses

(4 samples each of 3 different EAL's)

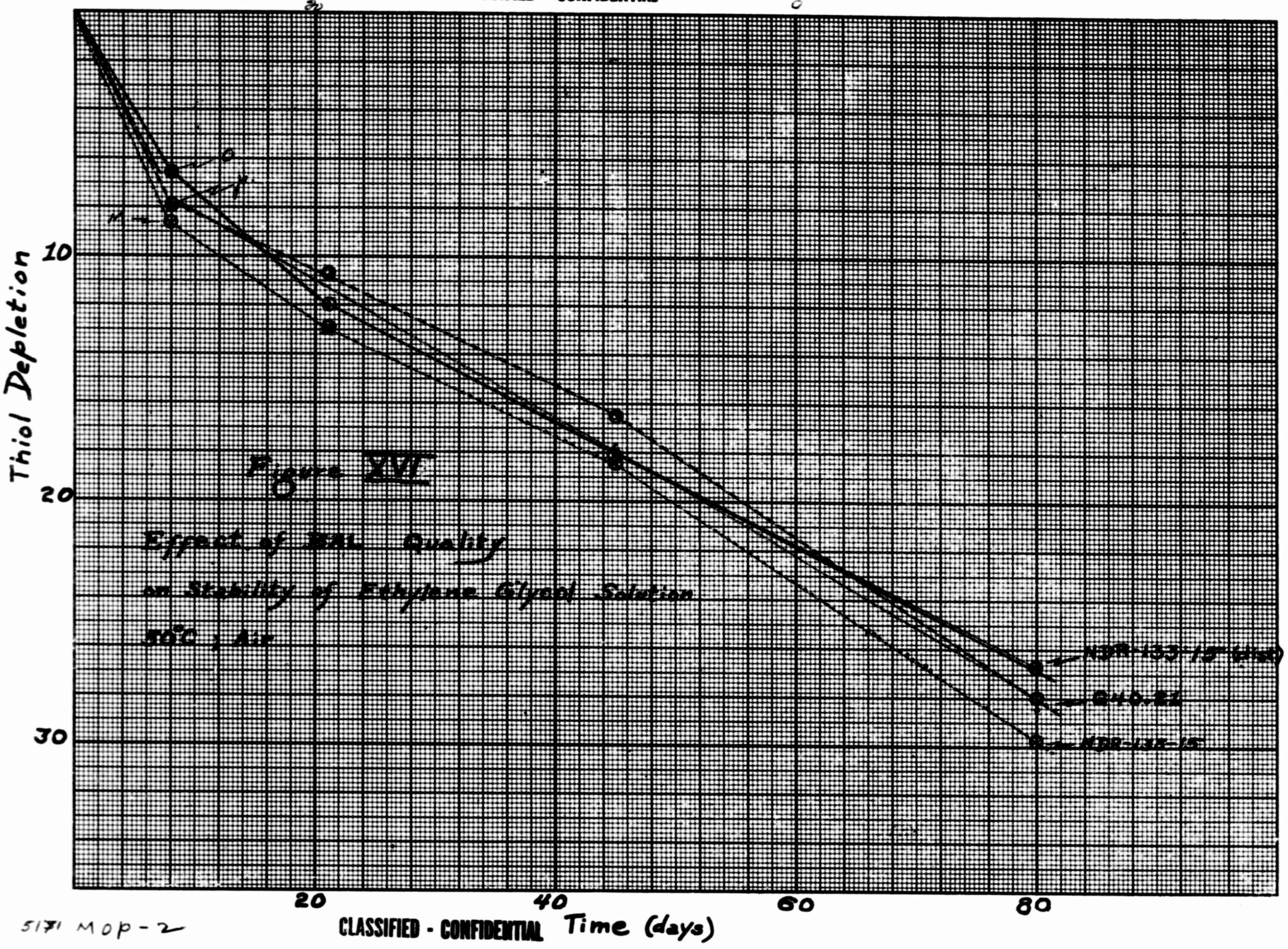

Figure XVI

Effect of BAL Quality on Stability of Ethylene Glycol Solution

50°C ; Air

5171 MOP-2

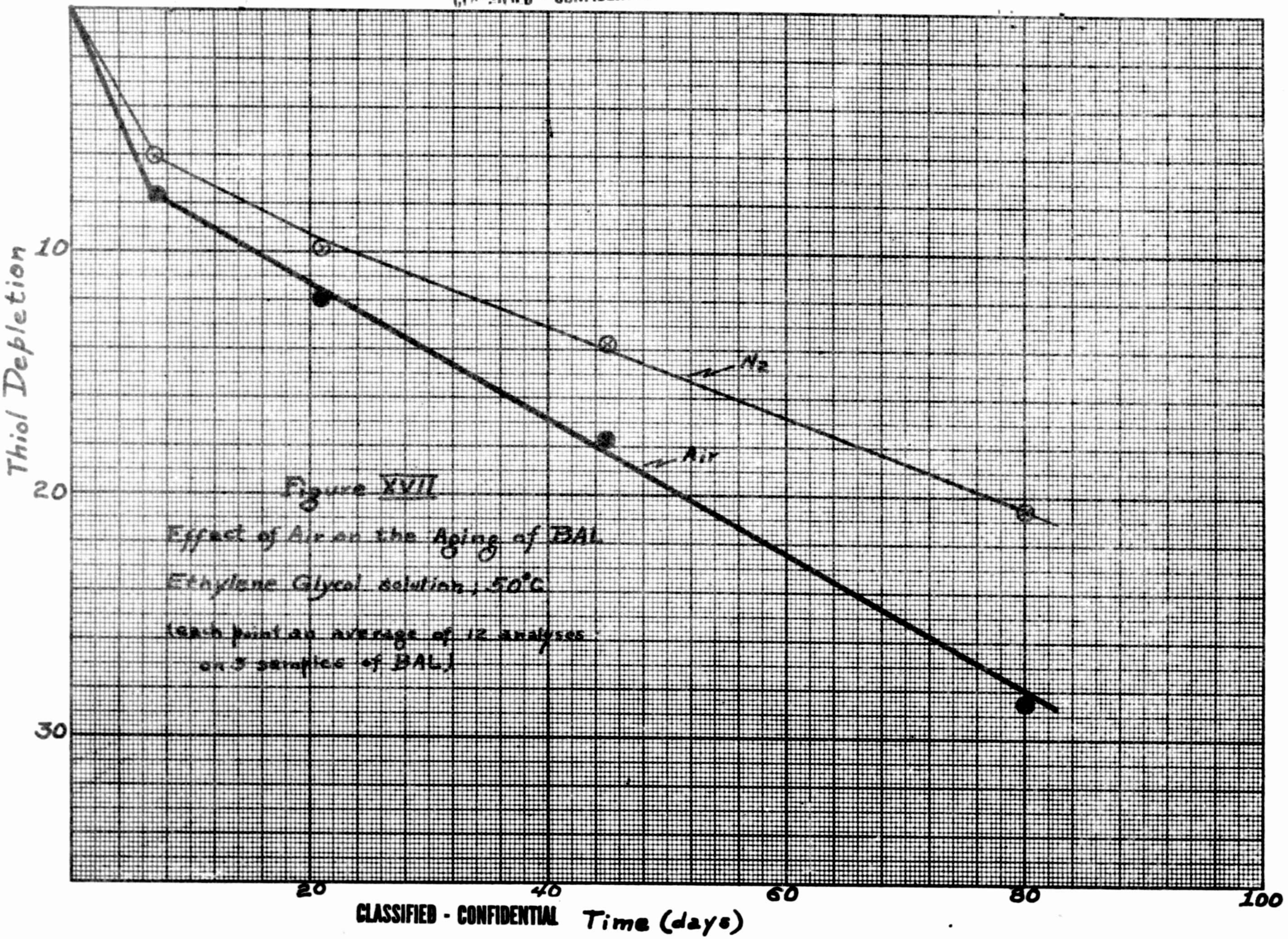

Figure XVII

Effect of Air on the Aging of BAL

Ethylene Glycol solution, 50°C

(each point an average of 12 analyses on 3 samples of BAL)

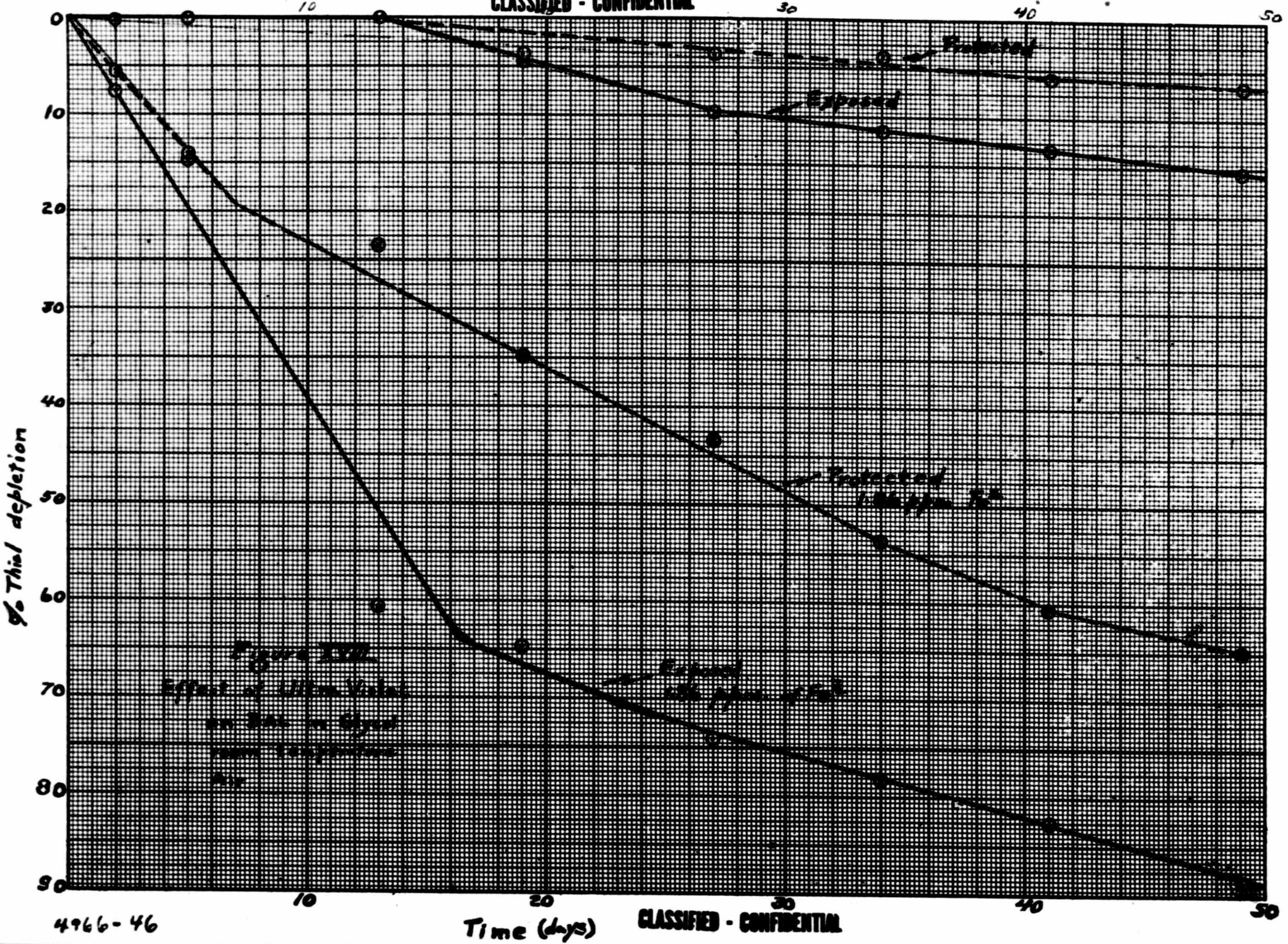

Figure XVII
Effect of Ultra Violet
on BAL in Glycol
room temperature
Air

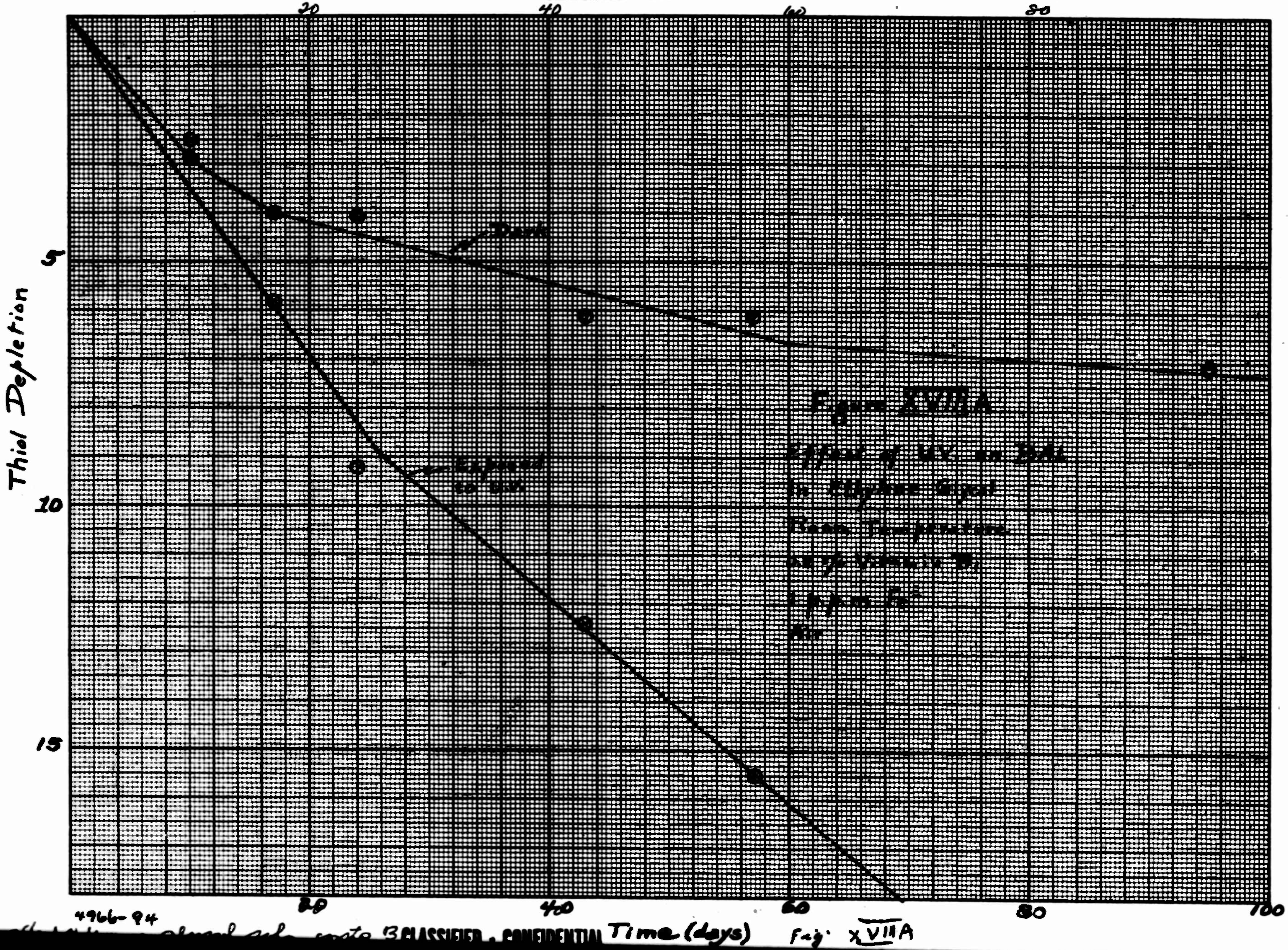

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Fig. XVIIA

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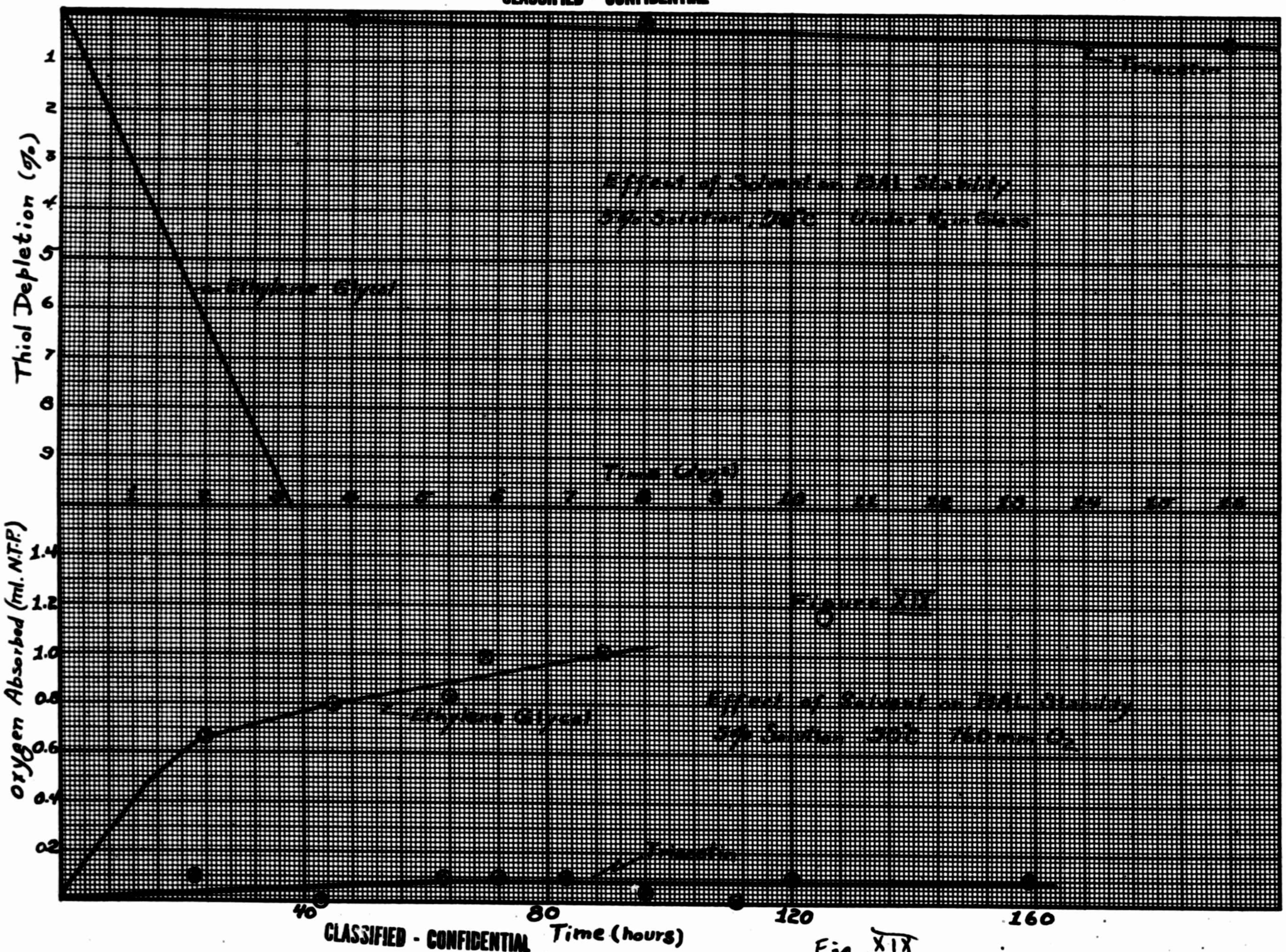

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Fig XIX

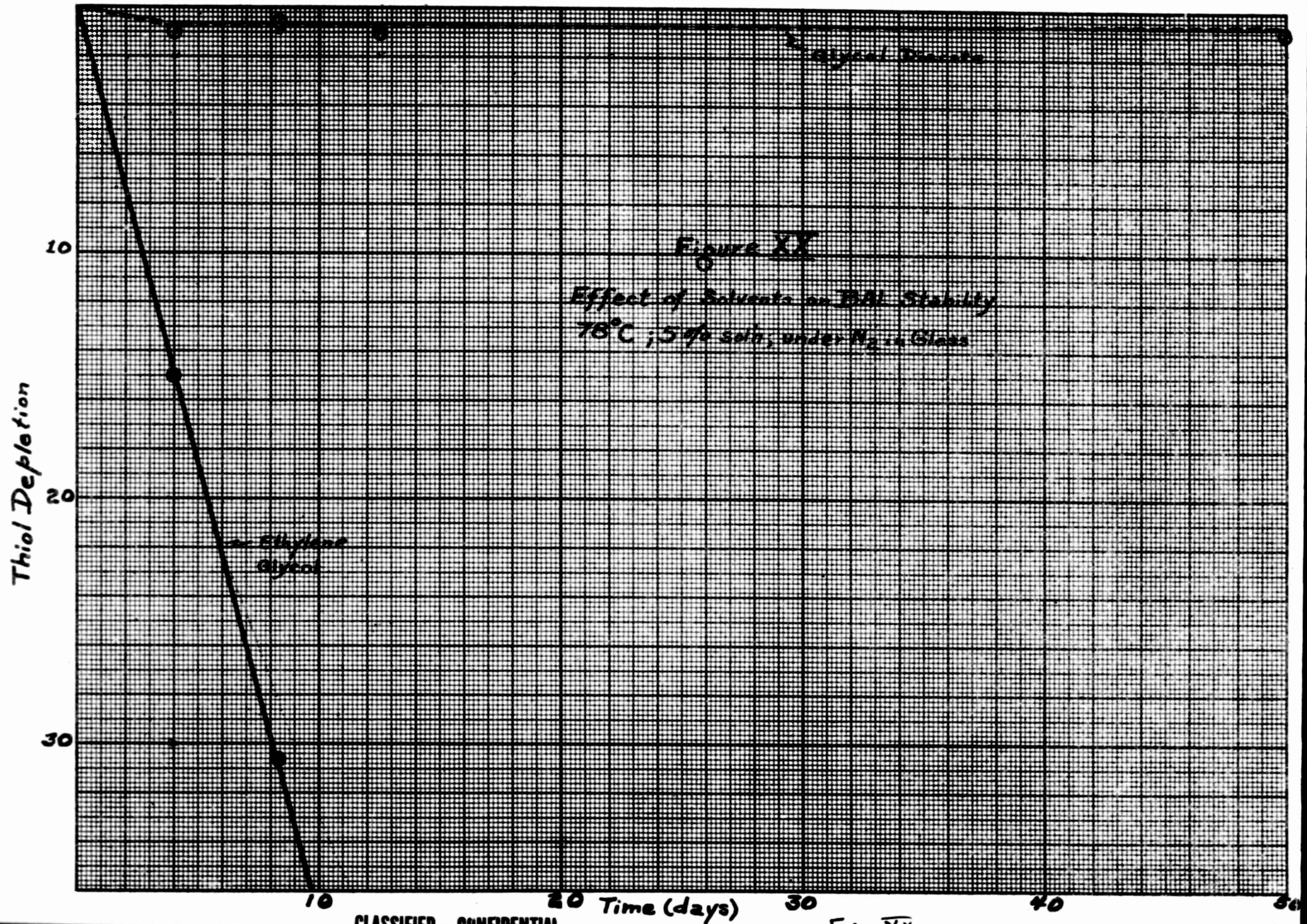

Figure XX

Effect of Solvents on BAL Stability

78°C ; 5% soln; under N_2 in Glass

Fig XX

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ABSTRACT:

A detailed study of aqueous and aqueous-glycol solutions of BAL showed that these systems do not possess sufficient stability to be practical for field use in the treatment of lewisite burns. These findings led to renewed investigation of other solvents for BAL. The results showed that nonhydroxylated solvents gave solutions of strikingly improved stability. Among the solvents which appeared most useful for the therapeutic application of BAL were peanut oil, benzyl benzoate, diethyl phthalate, and triacetin.

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