A STUDY OF THE STABILITY OF SOLUTION OF ARSENOUS AND MERCURIC IODIDE, U. S. P. X.[1,2,3]

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INTRODUCTION.

Following the introduction of arsenous iodide into medicine in 1826 (1), and in view of the use of combinations of arsenic, iodine and mercury in the treatment of certain diseases, Dr. M. Donovan of Dublin in 1839 prepared a solution containing compounds of these three elements. Solution of Arsenous and Mercuric Iodide, commonly called Donovan's Solution, is official in the U. S. P. and in the British Pharmacopœia; other pharmacopœias have not adopted it (2).

The U. S. P. X offers the following suggestion to retard the deterioration of Donovan's Solution: "Preserve in well-filled, amber-colored bottles." However, it is well known that in spite of these precautions the solution is notably poor in keeping qualities. In the present investigation a study was made of the various factors which might influence the deterioration of Donovan's Solution, and of possible means of retarding the deterioration.

CHEMICAL COMPOSITION OF DONOVAN'S SOLUTION.

Various explanations have been given of the reactions which take place in the preparation of Donovan's Solution.

Donovan (1) thought that a chemical action takes place with the formation of a double iodide of arsenic and mercury, which he called a "hydriodate of arsenic and mercury."

Dott (3) stated that when AsI_3 is dissolved in water, a very basic salt is produced. Similarly, Dupouy (4) reported that a solution of arsenous iodide does not contain AsI_3, but rather the products of hydrolysis, *i. e.*, arsenous anhydride and hydriodic acid.

In 1903, Duncan (5) reported that Donovan's Solution does not contain AsI_3 and HgI_2 or a double iodide, but is a solution of As_2O_3, with a little undecomposed AsI_3, HgI_2 and HI. He further stated that most of the acid is combined with HgI_2, forming soluble mercuro-iodic acid, H_2HgI_4.

Langenhan (6), in 1925, expressed the opinion that Donovan's Solution is "essentially an aqueous solution of arsenous acid and a compound of mercury di-iodide with hydrogen iodide, and that other substances, such as a double halide, arsenic tri-iodide, arsenic hydroxyiodide, etc., are present in minor phases, if at all in recognizable quantities."

In view of our present knowledge of the chemical properties of the substances involved, it appears quite certain that the original explanation as given by Donovan is incorrect. It is well known (7) (8) that the arsenic halides are considerably hydrolyzed in aqueous solution. In a one per cent solution of AsI_3, corresponding to Donovan's Solution, the hydrolysis is almost complete:

$$AsI_3 + 3H_2O \rightleftharpoons As(OH)_3 + 3HI$$

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[2] This paper is based on a thesis presented to the faculty of the Graduate School of the University of Florida by W. W. F. Enz, in partial fulfillment of the requirements for the degree of Master of Science in Pharmacy.

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Ten grams AsI_3 as represented in a liter of Donovan's Solution would form 8.42 Gm. HI on hydrolysis if hydrolyzed completely.

HgI_2 is practically insoluble in water, according to Bourgoin (9) 0.005 Gm. being soluble in 100 cc. of water at 22° C. It is well known, however, that HgI_2 is soluble in solutions of iodides with the formation of a complex anion (10):

$$\underset{\text{red, insoluble}}{HgI_2} + 2HI \rightleftharpoons H_2HgI_4$$

or, represented ionically:

$$HgI_2 + 2\bar{I} \rightleftharpoons (\bar{H}g\bar{I}_4)$$

Ten grams HgI_2 would require 5.63 Gm. HI to form the above soluble compound. This would leave 2.79 Gm. of free HI, assuming complete hydrolysis.

From these well-known reactions, it appears that the HgI_2 in Donovan's Solution goes into solution by reacting with the HI and that the finished product is essentially a solution containing arsenous acid, hydrogen mercuric iodide and hydriodic acid.

The name "Solution of Arsenous and Mercuric Iodide" tends to give the impression that the solution contains AsI_3 and HgI_2 or a double compound of the two. For this reason, the real nature of the solution has not been generally understood. Considering the actual composition, it would be more specific to designate it as "Solution of Arsenous Acid, Hydriodic Acid and Hydrogen Mercuric Iodide."

DETERIORATION OF DONOVAN'S SOLUTION.

Donovan realized (1) that constancy of composition and strength were important, for he states that "the compound must be permanent, not liable to spontaneous decomposition, nor to injuries arising from careless exposure to light or air." He thought his preparation fulfilled these requirements.

However, in course of time, the trivalent arsenic in Donovan's Solution is oxidized to pentavalent arsenic (2) (11) (12) (13). Light increases the rate of oxidation (14). Schulze (14) found that a commercial sample of Donovan's Solution was low in trivalent arsenic, although an assay for total arsenic showed no deficiency. In the present investigation, it was found that a sample of Donovan's Solution purchased from a wholesale drug house in the regular course of business was deficient in trivalent arsenic to the extent of 33.1 per cent.

It is an established fact that HI in aqueous solution in presence of air, liberates free iodine according to the following equation:

$$2HI + O \rightleftharpoons H_2O + I_2$$

In an aqueous solution containing only hydriodic acid, free iodine accumulates. The HI in Donovan's Solution is subject to this same oxidation; however, free iodine does not appear in the solution until all or most of the arsenous acid has been oxidized to arsenic acid according to the following equation:

$$As(OH)_3 + I_2 + H_2O \rightleftharpoons AsO(OH)_3 + 2HI$$

As shown by the equation, the free iodine is thus reduced to HI, which is again subject to oxidation by atmospheric oxygen as before. This cycle continues until all or most of the arsenic is in the pentavalent form. Before equilibrium is reached in the oxidation of the trivalent arsenic, no free iodine is present as shown by testing with starch T. S.

After all or most of the trivalent arsenic is oxidized to pentavalent arsenic, the free iodine accumulates, being no longer reduced to HI. As the amount of HI present becomes reduced, more HI is set free by causing the following equation to proceed toward the left:

$$HgI_2 + 2HI \rightleftharpoons H_2HgI_4$$

Eventually there is not sufficient HI to keep all of the HgI_2 in solution and as a result a red precipitate of HgI_2 appears in the solution. This was observed by Goodman (15) on a 5-year-old sample, which contained all its arsenic in the pentavalent form, also containing free iodine and precipitated HgI_2.

With reference to Donovan's Solution, the U. S. P. X states that "it must not be dispensed if darker than pale yellow." In this connection it should be noted, however, that almost all of the As^{III} may be oxidized to As^{V} before there is any change in the color of the solution.

EXPERIMENTAL DATA.

Experimental Methods.—In the present study of Donovan's Solution, the assay of AsI_3 was used as an index of the stability of the solution. The U. S. P. method of assay was used, which is as follows:

> Assay for arsenous iodide—Measure accurately 25 cc. of Solution of Arsenous and Mercuric Iodide into a flask, dilute with 25 cc. of distilled water, then dissolve 2 Gm. of sodium bicarbonate in this solution, and titrate with tenth-normal iodine, using starch T. S. as indicator.

The usual method of procedure for comparing the stability of the various solutions was to expose 50-cc. samples, contained in ordinary 2-oz. prescription bottles, in diffused light and sunlight. The deterioration under these conditions was more rapid than in well-filled, amber-colored bottles and it was thus possible to secure quicker results. The entire sample was used for analysis. When more than one sample of the same kind was analyzed, the average result was taken and recorded in the tables.

Effect of Different Utensils Used.—Tests were made to determine whether the different utensils that a pharmacist might use in preparing or storing Donovan's Solution had any effect on the stability of the solution. Solutions were prepared in glass, porcelain and wedgewood mortars and the deterioration of the solutions noted by analyses made at successive intervals. It was concluded that the type of mortar used had no material effect upon the stability of the solution. It was also found that the rate of deterioration in corked prescription bottles was the same as in glass-stoppered Pyrex bottles.

Effect of Differences in Chemicals Used.—As samples of arsenous iodide made by different manufacturers differ somewhat in purity and physical properties, tests were made of the stability of Donovan's Solution prepared from three different commercial samples of AsI_3. These samples varied in color from orange

to dark red, in luster from no luster to marked luster; one of the samples gave a test for free iodine. The solutions prepared from these different materials showed approximately equal rates of deterioration.

Effect of Having Elements in Atomic Proportions.—In 1847, William Procter, Jr., (16) suggested the use of the elements in atomic proportions in the preparation of Donovan's Solution. An experiment was performed, which showed that the rates of deterioration of samples of Donovan's Solution made by the official process and using the chemicals in atomic proportions were practically uniform. The proportions used in the two solutions were as follows:

	U. S. P. method.	Atomic proportions.
AsI_3 per liter	10.000 Gm.	10.028 Gm.
HgI_2 per liter	10.000 Gm.	10.000 Gm.

Effect of Different Concentrations and Proportions.—The composition of Donovan's Solution since its origin has remained fairly constant. In order to determine what effect different concentrations and proportions would have on the stability, the following experiment was performed. Five solutions were made. The first was made according to the U. S. P.; this was used as the control. The second was made four times the U. S. P. strength while the third was made one-fourth the U. S. P. strength. The fourth contained 1 per cent of AsI_3 but only 0.67 per cent of HgI_2, the AsI_3 therefore being in excess. The fifth contained 1 per cent of AsI_3 and 1.5 per cent of HgI_2; a slight amount of HgI_2 remained undissolved and was filtered out.

TABLE I.—EFFECT OF DIFFERENT CONCENTRATIONS AND PROPORTIONS.

	Percentage Deterioration in Sunlight. After 15 days.	After 22 days.
Control	30.3	36.9
Concentrated solution	9.2	8.9
Dilute solution	100.0	100.0
Excess AsI_3 solution	31.7	33.6
Excess HgI_2 solution	35.9	37.4

In sunlight, a solution more dilute than the official solution deteriorated more rapidly; one more concentrated deteriorated less rapidly. Changes in the proportions of the ingredients had practically no effect on the stability.

Effect of Filtration.—All pharmacopœias in which Donovan's Solution appeared have directed it to be filtered. The U. S. P. of 1850 also required that the solution be heated to boiling before filtering; it was later shown that boiling drives off some of the arsenic (6). The following experiment was carried out to determine the effect of non-filtration, and also to test a method of preparing the solution by agitation in a bottle.

TABLE II.—DETERMINATION OF THE EFFECT OF NON-FILTRATION AND OF PREPARING THE SOLUTION BY AGITATION IN A BOTTLE.

Method of preparation.	Percentage Deterioration in Diffused Light. 50 days.	85 days.	247 days.
Mortar and pestle (U. S. P. method)	15.4	26.6	43.9
Mortar and pestle (non-filtered)	5.2	9.5	26.6
Agitation in bottle (filtered)	10.3	12.3	46.7
Agitation in bottle (non-filtered)	8.1	10.3	23.5

It would appear that solutions which are not filtered deteriorate less rapidly than those which are filtered. The residue in the non-filtered solutions contains free arsenic (17); the effect of this on the keeping qualities of the solution will be discussed later. The solution prepared by shaking in a bottle is at least as stable as that made by the official method in a mortar.

Experiments were carried out in which decolorizing charcoal, wood charcoal, pipe clay, kaolin and pumice were added to Donovan's Solution just before filtering. None of these had a stabilizing effect upon the solution.

Effect of a Globule of Mercury.—According to Brown (18) the addition of a globule of mercury to Donovan's Solution exerts a stabilizing influence on the solution. Tests were made on this point.

TABLE III.—EFFECT OF A GLOBULE OF MERCURY.

	Percentage Deterioration in Diffused Light.			
	28 days.	57 days.	97 days.	177 days.
Control	3.4	6.3	9.1	15.1
Control plus Hg	4.4	6.3	13.2	26.3

The addition of a globule of mercury to the solution has no effect during the first few months. After that time, the solution containing the globule of mercury apparently deteriorates more rapidly than the control.

Effect of Free Arsenic.—It is stated in a textbook (19) that the addition of fine arsenic to Donovan's Solution largely obviates the deterioration. Tests were therefore made on this point. It was found that some of the free arsenic went into solution in the course of time, making the arsenic content several times as great as the U. S. P. strength. Obviously this method of preservation is impractical.

Effect of Completeness of Filling of Bottle.—The U. S. P. directs that Donovan's Solution should be kept in well-filled bottles. Tests were made on two bottles completely filled and two bottles half-filled. There was less deterioration in the completely filled bottles, the deterioration after 71 days in diffused light being 3.1 per cent as compared with 6.0 per cent deterioration in the half-filled bottles.

Effect of Paraffin, Etc.—It was thought that occasion might arise to seal some of the cork-stoppered bottles with paraffin. Tests for possible effects of paraffin were therefore made by the addition of pieces of paraffin to the solution, and by placing a coat of paraffin inside the bottle; in each case there was no change in the stability of the solution. It was also found that tobacco smoke had no effect on the rate of deterioration. A layer of chloroform in the bottom of the bottle had no effect on the keeping qualities of the solution in diffused light; however, it was observed that a pink tinge, apparently due to free iodine, appeared in the chloroform layer, varying in intensity from day to day, at times disappearing completely.

Effects of Other Solvents.—A series of experiments was carried out to determine the effect of replacing 25 per cent of the water in Donovan's Solution by other solvents.

Honey has a marked stabilizing influence when present in this proportion. The solution containing honey was not filtered and on standing an insoluble residue settled to the bottom. Syrup, glucose and glycerin stabilize the solution to a certain extent, while alcohol hastens the deterioration.

TABLE IV.—EFFECT OF REPLACING 25 PER CENT OF THE WATER BY OTHER SOLVENTS.

	Percentage Deterioration. Diffused Light. 23 days.	52 days.	92 days.	149 days.	Sunlight. 9 days.
Control	5.9	12.4	20.9	36.3	27.6
Alcohol	7.6	15.2	26.5	46.5	41.6
Glycerin	7.3	13.4	18.1	23.4	18.6
Honey	3.6	6.3	7.7	7.1	0.8
Syrup	5.9	20.9	14.3	13.2	0.9
Glucose solution (12.5%)	8.6	15.7	20.0	23.9	16.8

Effect of Storage in Refrigerator.—The following experiment was performed to see if storage in a refrigerator would reduce the rate of deterioration.

TABLE V.—EFFECT OF STORAGE IN AN AUTOMATIC ELECTRIC REFRIGERATOR.

	Percentage Deterioration. 127 days.	155 days.	178 days.
Room temperature (in the dark)	9.2		13.0
Refrigerator (in the dark)	2.8	3.0	

The results in Table V indicate that storage in a refrigerator reduces the rate of deterioration of Donovan's Solution.

Effect of a Layer of Liquid Petrolatum.—Since a layer of liquid petrolatum is used to protect liquid preparations of ferrous carbonate from the air above the solution, a test was made to see whether this method was applicable to Donovan's Solution.

TABLE VI.—EFFECT OF A LAYER OF LIQUID PETROLATUM.

	Percentage Deterioration in Diffused Light. 28 days.	57 days.	97 days.	177 days.
Control	3.4	6.3	9.1	15.1
Control plus petrolatum	2.8	4.9	7.0	13.7

The results indicate a very slight preservative effect but this is too small to be of practical value.

Effect of Displacement of the Air in the Bottle by an Inert Gas.—It was thought that displacement of the air in the bottle containing Donovan's Solution with an inert gas might result in a more stable preparation. A series of bottles of Donovan's Solution was therefore saturated with hydrogen and securely stoppered. Another series used as a control was not saturated with hydrogen. By immediately analyzing some of the bottles containing hydrogen it was found that this treatment had caused no change in the trivalent arsenic content.

TABLE VII.—EFFECT OF DISPLACEMENT OF THE AIR IN THE BOTTLE BY HYDROGEN.

	Percentage Deterioration in Sunlight. 13 days.	28 days.	56 days.
Atmosphere above solution:			
Air	30.8	53.6	29.3
Hydrogen	6.8	7.2	7.2
	Diffused Light. 28 days.	56 days.	Dark. 79 days.
Air	5.4	11.7	17.3
Hydrogen	4.6	9.6	6.1

The results indicate that displacement of the air in the bottle by hydrogen has a marked preservative influence on the solution.

In the course of the work it was noted that bottles of Donovan's Solution taken from the same batch and kept side by side under identical conditions would not always deteriorate uniformly, the percentage differences in deterioration being greater than the experimental errors expected. For example, four bottles analyzed at the end of 56 days showed the following deterioration:

TABLE VIII.—PERCENTAGE DETERIORATION.

Diffused light.	Sunlight.
11.96 (variation of 6.1%)	30.98 (variation of 11.2%)
11.25	27.71

As a corked bottle limits the amount of oxygen available for oxidation of the trivalent arsenic, a calculation was made to determine how much oxygen would be necessary to completely oxidize the trivalent arsenic in Donovan's Solution. For the complete oxidation of the trivalent arsenic in 50 cc. of the solution, 12.3 cc. of oxygen or 61.5 cc. of air are required.

However, the amount of oxygen available in a securely corked 2-oz. bottle containing 50 cc. of Donovan's Solution is very much less than this. There is approximately 13 cc. of air above the solution below the cork. This is equivalent to 2.6 cc. of oxygen. In addition to this, there would also be a slight amount of oxygen dissolved in the water; assuming the solubility in Donovan's Solution as being the same as in water, the amount of dissolved oxygen in 50 cc. of Donovan's Solution would be 0.40 cc. Assuming all the available oxygen in the bottle to be consumed, this would oxidize only 24.4 per cent of the trivalent arsenic.

Due to the absorption of the oxygen used to oxidize the HI, a partial vacuum would be formed. While precautions were taken to see that the bottles were securely corked, there is a possibility that there was a certain amount of leakage through or around some of the corks; this would introduce a variable factor which may be the cause of the variation in the results as different corks might allow this vacuum to draw in different amounts of additional air.

To eliminate the possibility of infiltration of air, an experiment was carried out in which Donovan's Solution was sealed up in 5-cc. ampuls and exposed on the roof to sunlight for 5 days. The solution was then analyzed and was found to have deteriorated 24.0 per cent. By calculation, the amount of air in the sealed ampul could account for only 16.6 per cent deterioration; it is evident, therefore, that some other factor besides oxidation of HI enters into the deterioration of Donovan's Solution.

Warburg and Rump (20) observed that in an atmosphere of CO_2, HI solutions decomposed by the absorption of light energy into hydrogen and iodine. It appears from this that in Donovan's Solution light alone, by liberating iodine, may cause oxidation of the trivalent arsenic.

In view of this decomposition observed by Warburg and Rump (20) it is likely that part of the deterioration of Donovan's Solution takes place as follows:

$$2HI \rightleftharpoons H_2 + I_2$$

$$As(OH)_3 + I_2 + H_2O \rightleftharpoons H_3AsO_4 + 2HI$$

Oxidation of trivalent arsenic may thus take place without atmospheric oxygen; this would explain why greater deterioration was observed than could be

accounted for by the amount of air in the bottle. The failure of an inert gas to completely preserve Donovan's Solution may also be explained by these reactions.

Effect of Neutralization.—Duncan (5) suggested that the deterioration of Donovan's Solution may be checked by neutralizing the HI with alkali. Guyot (21) offered this same suggestion for checking the deterioration of a solution of arsenous iodide. Accordingly, an experiment was carried out on Donovan's Solution containing various amounts of acid and base. In order to have the Donovan's Solution of U. S. P. strength after the acid or base was added, the solution, was first prepared in a slightly more concentrated form, so that 40 cc. contained AsI_3 and HgI_2 equivalent to 50 cc. of U. S. P. solution. The control was diluted with 10 cc. of distilled water. In the others, varying amounts of acid or base were added, and then sufficient distilled water to bring the final volume to 50 cc.

TABLE IX.—EFFECT UPON THE STABILITY OF DONOVAN'S SOLUTION OF ADDING VARYING AMOUNTS OF ACID AND BASE.

Amount of acid or base added.*	Percentage deterioration after 133 days.	Amount of acid or base added.*	Percentage deterioration after 133 days.
10 cc. acid	62.7	1 cc. base	40.5
8 cc. acid	50.6	2 cc. base	49.1
6 cc. acid	57.3	4 cc. base	34.0
4 cc. acid	43.0	6 cc. base	22.3
2 cc. acid	52.9	6.2 cc. base (neutral to methyl orange)	19.2
1 cc. acid	47.2	8 cc. base	26.6
Control	49.5	10 cc. base	55.4

* Approximately *N*-1 HCl and KOH.

The results indicate that Donovan's Solution is more stable near the neutral point, the rate of deterioration increasing with increasing acidity or basicity.

Apparently no previous work has been done on the determination of the p_H value of Donovan's Solution. By the use of indicators, it was found that the p_H of freshly prepared Donovan's Solution is approximately 1.2.

Preparation of Donovan's Solution by a New Method.—In the preparation of Donovan's Solution, Donovan originally used the free elements; later Souberin modified this method by using the iodides of the metals. Since then, apparently, no thought has been given to the preparation of this solution by any other method. Considering the real nature of the solution as being essentially a solution of arsenous acid, hydriodic acid and hydrogen mercuric iodide, there seems to be no necessity of starting with AsI_3, particularly in view of the fact that AsI_3 probably varies somewhat and is itself quite unstable unless properly preserved. The same result could be obtained by starting with As_2O_3, putting it in solution with HCl and then neutralizing the acid; the HgI_2 could be put in solution in the presence of an excess of KI, the KI being present in an amount sufficient to make the total iodide content equivalent to that present in the official formula.

In accordance with this idea, a modified solution was prepared. The directions for preparation are as follows:

"As_2O_3	2.1717 Gm.
HgI_2	10.0000 Gm.
KI	10.9286 Gm.

Diluted HCl, U. S. P.	10.86	cc.
Normal KOH solution	q.s.	
Distilled water, q.s.	1000	cc.

With the aid of heat dissolve the As_2O_3 in a mixture of the diluted HCl and 55 cc. of water. Dilute the solution to 150 cc. and neutralize with *N*-1 KOH solution, the amount of KOH solution needed being determined by titration of an extra portion of the solution, using methyl orange as indicator. Dilute to 500 cc. Prepare another solution containing the HgI_2 and KI in water sufficient to make 500 cc. Mix the two solutions."

The quantitative composition of the official Donovan's Solution, which is acid in reaction, is probably per liter:

As_2O_3	2.17 Gm. (Equivalent to 10 Gm. AsI_3)
H_2HgI_4	15.63 Gm. (Equivalent to 10 Gm. HgI_2)
HI	2.79 Gm.

The quantitative composition of the modified neutral solution, is probably per liter:

As_2O_3	2.17 Gm. (Equivalent to 10 Gm. AsI_3)
K_2HgI_4	17.30 Gm. (Equivalent to 10 Gm. HgI_2)
KI	3.63 Gm.
KCl	2.32 Gm. (Calculated as KCl from the amount of HCl used in the preparation)

The quantitative amounts of the elements arsenic, mercury and iodine in the two solutions are identical, the modified solution containing K and Cl ions in the amounts indicated instead of H ions as in the official preparation.

Comparisons between the rates of deterioration of the modified Donovan's Solution and the official solution are given in Table X. Samples of the modified solution which were made slightly more basic and slightly more acidic were also placed under observation; these were made by adding 0.3 cc. of *N*-1 KOH and *N*-1 HCl, respectively, to 50 cc. of the modified Donovan's Solution. The approximate p_H of the solutions, as determined with the La Motte Roulette Comparator, is also given in the table; these determinations were made after the solutions had been standing in diffused light for several months.

TABLE X.—STABILITY OF MODIFIED DONOVAN'S SOLUTION.

	Percentage Deterioration in Diffused Light.			
No. of days' exposure.	Control.	Modified solution p_H 5.5.	Modified solution p_H 6.5.	Modified solution p_H 4.0.
9 days		0.4	0.3	0.3
38 days	3.8	0.8	2.0	1.9
59 days	5.0	0.7	2.2	2.5
78 days	7.3	0.7	2.7	3.9
93 days	9.1	0.3	3.1	4.0
135 days	14.5	1.1	3.7	7.1
158 days		0.9	4.7	9.4
		IN SUNLIGHT.		
9 days	21.9	24.7	18.9	23.0
38 days	78.2	90.5	83.3	84.3
		IN THE DARK.		
107 days	8.2	0.5	0.5	3.9
158 days		0.3	0.7	6.5

		IN REFRIGERATOR.		
107 days	2.7	0.4	0.5	1.3
135 days	3.0	0.1	0.0	1.4

When kept in the direct sunlight, the modified solution showed no advantage, but under the usual conditions of storage in diffused light the modified solution was remarkably stable. In the dark, both at room temperature and in the refrigerator, the modified solution of p_H 5.5 and the modified solution of p_H 6.5 were both very stable, showing less deterioration than the modified solution of p_H 4.0 and the official Donovan's Solution.

Study of Stabilizers.—As it seemed possible that a negative catalyst of oxidation might be discovered which would stabilize the solution, experiments along this line were carried out.

Before a substance could be tested for its possible stabilizing effect, it was necessary to determine whether it would interfere with the subsequent assay of the Donovan's Solution. To do this, 0.2 Gm. of the substance was placed in 50 cc. of Donovan's Solution. This was then titrated with standard iodine solution. Any variation from a blank of Donovan's Solution alone showed interference, due usually to covering up of the end-point or reaction of the substance with the iodine solution.

In carrying out the tests, 50-cc. portions of Donovan's Solution were placed in 2-oz. prescription bottles by means of a calibrated pipette, and 0.2 Gm. of the substance to be tested was added. In each case one bottle was placed in the sunlight, one in diffused light and one in the dark, for a period of from 113 to 125 days.

Some of the substances tried as stabilizers were acid or basic in character. As this property in itself might affect the stability of Donovan's Solution; these substances, before being added to the solution, were neutralized with the appropriate amount of KOH or HCl, as previously determined by titration, using methyl orange as indicator. Experiments were also run in which these substances were tested without being neutralized.

The following substances had no effect on the rate of deterioration of Donovan's Solution:

Acacia, acetanilid, phosphoric acid, picric acid, stearic acid, tartaric acid, alcohol, benzaldehyde, caffeine, camphor, chloral hydrate, dextrin, dextrose, diphenyloxide, ethyl bromide, ethylene glycol, glycerin, honey, menthol, methylamine hydrochloride, methyl iodide, naphthalene, nickel sulphate, nitrobenzene, phenolphthalein, piperine, potassium chloride, salicin, saponin, sodium acetate, sodium chloride, sodium citrate, sodium hypophosphite, sodium salicylate, sodium silicate, sodium thiosulphate, sucrose, sulphur, thymol, tragacanth; (the following substances both with and without neutralization), anthranilic acid, boric acid, citric acid, lactic acid, aniline hydrochloride, phenol, potassium bitartrate, saccharin, sodium borate and vanillin.

The following substances hastened the deterioration under at least one condition of exposure and failed to show any stabilizing effect under any of the conditions:

Barium carbonate, benzene, chrysarobin, copper tartrate, ethylene chlorhydrin, ethyl iodide, gelatin, iodoform, potassium iodide, uranium acetate and urea.

The following substances had a stabilizing effect under at least one condition of exposure:

Ammonium carbonate, anethol, tincture of benzoin, calcium carbonate, copaiba, ethyl methyl ketone, eucalyptol, fuchsin, methenamine, oil of caraway, oil of cinnamon, oil of rosemary, terebene, terpin hydrate; the following substances both with and without neutralization: Hypophosphorous acid, oxalic acid, diethyl amine, nicotine; (the following neutralized substances) tartaric acid and benzaldehyde.

After further tests, it appeared that the following substances retarded the deterioration of Donovan's Solution:

Methenamine, hypophosphorous acid, oxalic acid, terpin hydrate and calcium carbonate.

Since methenamine is incompatible with Donovan's Solution because of the production of a heavy yellow precipitate, it is not suitable for use as a stabilizer for the solution.

As hypophosphorus acid is used as a stabilizer in official preparations of hydriodic acid, it was hoped that it would be effective in the stabilization of Donovan's Solution, since this depends on the stability of HI formed by hydrolysis of AsI_3; however, hypophosphorous acid cannot be used for this purpose on account of the fact that it gives a black precipitate, which is probably free arsenic, with Donovan's Solution.

Oxalic acid chemically seems to be quite suitable as a stabilizer; however, it is objectionable because of its poisonous character. The least objectionable stabilizers appear to be terpin hydrate and calcium carbonate. Calcium carbonate has a two-fold stabilizing effect: it neutralizes the acidity, and the CO_2 evolved displaces some of the air. Using a slight excess of $CaCO_3$, there was 0.1% deterioration after 56 days in diffused light, as compared with 11.7% deterioration in the control. However, if the solution had been filtered, much of the CO_2 would probably have been lost.

The Effect of Different Wave-Lengths of Light.—If light is passed through a colored solution, the solution will transmit chiefly light of the wave-length corresponding to its color and will absorb the major portion of the remainder of the spectrum of the incident light. Using colored solutions as light filters, some tests were carried out, the 2-oz. sealed bottles of Donovan's Solution being placed in 600-cc. beakers, the beakers then being filled with the colored solutions. The beakers were covered by larger beakers and exposed to direct sunlight on the roof.

TABLE XI.—EXPERIMENT USING COLORED SOLUTIONS AS LIGHT FILTERS.

Solution surrounding bottle.	Percentage Deterioration in Sunlight. 7 days.	28 days.
Control	32.2	59.0
Water	32.0	56.6
Cresol	1.3	5.3
Cochineal	2.0	7.6
Methyl red in acid solution	27.6	41.4
Saturated potassium dichromate solution	0.8	15.4
Saturated picric acid solution	1.2	5.0
Phenolphthalein in alkaline solution	27.3	55.1
Saturated copper sulphate solution	27.2	47.1

Table XI indicates that Donovan's Solution deteriorates less rapidly in light passed through a saturated solution of picric acid or potassium dichromate, these solutions probably acting as partial light filters of the rays which are most effec-

tive in oxidizing Donovan's Solution. The protective influence of cresol and cochineal solution is probably due to their dark color, which cuts out most of the light of all wave-lengths.

Tests of Donovan's Solution in the dark, in diffused light and in sunlight in Pyrex glass-stoppered bottles, ordinary prescription bottles, and glass-stoppered Erlenmeyer flasks indicated that the type of colorless glass container used has no appreciable influence upon the stability of the solution. Tests were also made with bottles of colored glass. It was impossible to secure bottles of different colored glass of the same size and shape; however, experiments were carried out in such bottles of colored glass as were available. The brown bottles had a marked protective influence, but rapid deterioration took place in bottles of blue, green and colorless glass.

In order to secure more definite information as to what part of the spectrum is chiefly responsible for the deterioration, tests were made using light filters obtained from the Corning Glass Works. These light filters were in the form of plates of special glass about six inches square. Light-proof and water-proof wooden cabinets were constructed, in which the special glass plates served as windows. The cabinets were placed on the roof in direct sunlight, the Donovan's Solution in prescription bottles being placed within the cabinet. Eleven different light filters were used. The trade names of the light filters which appreciably retarded the deterioration of Donovan's Solution are as follows: "Noviol C," "HR Yellow-Yellow," "HR Yellow-Red," "Red" and "Heat Transmitting." From a study of the results obtained and the data on the light transmitted by the various filters, it was concluded that the wave-length of the light which causes most of the deterioration of Donovan's Solution stored in ordinary glass prescription bottles lies between 3200 and 4600 Å. This range includes the blue end of the visible spectrum.

SUMMARY.

1. A study has been made of the various factors which might influence the deterioration of Solution of Arsenous and Mercuric Iodide, U. S. P. X, commonly known as Donovan's Solution, and of possible means of minimizing this deterioration.

2. The name "Solution of Arsenous and Mercuric Iodide" tends to give the impression that the solution contains AsI_3 and HgI_2, or a double compound of the two. However, this preparation is essentially a solution of arsenous acid, hydrogen mercuric iodide and hydrogen iodide.

3. The deterioration of Donovan's Solution results in the oxidation of As^3 to As^5, which takes place as follows:

$$2HI + O \rightleftharpoons H_2O + I_2$$

$$As(OH)_3 + I_2 + H_2O \rightleftharpoons H_3AsO_4 + 2HI$$

In the present investigation, it was found, however, that frequently more deterioration took place than could be accounted for by the amount of air in the bottle. In view of this, and on the basis of the observation by Warburg and Rump that solutions of HI exposed to light undergo decomposition into H_2 and I_2, it appears that a part of the deterioration takes place as follows:

$$2HI \rightleftharpoons H_2 + I_2$$
$$As(OH)_3 + I_2 + H_2O \rightleftharpoons H_3AsO_4 + 2HI$$

4. The following factors had no effect on the stability of Donovan's Solution: (*a*) use of porcelain, glass or Wedgewood mortar; (*b*) changes in the proportions of the ingredients; (*c*) use of chemicals made by different manufacturers; (*d*) preparation of the solution by shaking the ingredients in a bottle.

5. The following factors were found to increase the stability of Donovan's Solution: (*a*) storage in amber bottles; (*b*) storage in well-filled bottles; (*c*) storage in a refrigerator; (*d*) replacement of the air in the bottle by an inert gas; (*e*) replacement of 25 per cent of the water by honey or syrup.

6. It has been reported that a globule of mercury placed in Donovan's Solution exerts a stabilizing influence. Tests on this point in the present study have shown that a globule of mercury does not increase the stability of the solution.

7. According to a statement in a textbook, the addition of fine arsenic to Donovan's Solution largely obviates the deterioration. This method was found to be impractical, as some of the free arsenic goes into solution in course of time, making the arsenic content several times as great as the U. S. P. strength.

8. The p_H of freshly prepared Donovan's Solution is approximately 1.2. Experiments on the effect of adding varying quantities of acid and base indicate that the solution is more stable near the neutral point, the rate of deterioration increasing with increasing acidity or basicity.

9. The addition of an amount of calcium carbonate sufficient to neutralize the acid in Donovan's Solution has a marked preservative influence, which appears to be due to a combination of two factors: (*a*) a more favorable p_H; (*b*) replacement of air by the inert gas, CO_2.

10. A neutral solution corresponding identically with the official U. S. P. solution as to As, Hg and I content, but varying in chemicals used, method of preparation, and p_H value, was found to be much more stable than the official solution.

11. The addition of 0.4 per cent of oxalic acid, methenamine, terpin hydrate or hypophosphorous acid retards the deterioration of Donovan's Solution. Oxalic acid is objectionable because of its poisonous character; methenamine and hypophosphorous acid are incompatible with Donovan's Solution, due to the formation of precipitates; terpin hydrate seems least objectionable.

12. From experiments with light filters, it was concluded that light of the wave-length lying between 3200 and 4600 Å. causes most of the deterioration of Donovan's Solution.

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ABSTRACT OF DISCUSSION.

E. Fullerton Cook inquired if it is desirable to widen the range of possible deterioration, because of deterioration of the product.

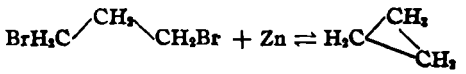
W. J. Husa replied that this would hardly seem feasible since the solution commonly shows 30 to 50 per cent deterioration. So many methods of increasing the stability have been found that it is difficult to select the best one. Further work is in progress in which ten solutions stabilized in different ways have been stored under drug store conditions and are being analyzed every three months. He concluded by saying that unless the formula is changed the solution should be freshly prepared.

THE PREPARATION OF CYCLOPROPANE.*

BY W. A. LOTT AND W. G. CHRISTIANSEN.

Trimethylene (cyclopropane) is the simplest cyclic hydrocarbon; its preparation in the pure state and in large quantities has been studied by a number of investigators whose various results are not entirely in agreement. We found none of the recorded methods entirely satisfactory.

All of the practical methods are based on the reduction of[1] trimethylene dibromide with metallic zinc in an alcoholic solution.



Freund, (*J. prakt. Chem.* (2), 26 (1886), 368) reduced trimethylene dibromide with sodium, in alcoholic solution. His product was not entirely pure, but he mentioned only propylene, its more stable isomer, as an impurity.

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* Scientific Section, Rapid City meeting, 1929.

[1] Made according to method outlined in Organic Syntheses, Vol. I, R. Adams.