STABILITY OF CHLORAMINE ANTISEPTICS.*

BY JULES BEBIE.

The synthetic organic chlorine antiseptics chloramine-T and dichloramine-T have found successful application in recent war surgery and filled the great demand for powerful, non-toxic and comparatively non-irritating disinfectants. As a natural consequence they are finding their place in civilian surgery and are beginning to be widely used. Investigation of their properties and applications was therefore desirable.

Too great stress cannot be laid on the necessity of working with pure products and it is safe to assume that most of some of the contradictory statements regarding properties and therapeutic action of the chloramines are entirely due to variable purity of these products in the hands of the different investigators. This refers particularly to the question of stability of the chloramine antiseptics and it is this phase of the subject which has received chief attention in our work.

1. CHLORAMINE-T.—SODIUM PARA TOLUENE SULPHONCHLORAMIDE.

$$CH_3.C_6H_4.SO_2.NClNa + 3H_2O.$$

The commercial product is on the market in form of the crystallized material containing 3 molecules of water of crystallization. The theoretical percentage for chlorine is 12.6, for water 19.2; the limits of the N. N. R.[1] standard are 11.5–13% Cl and 17–20% H_2O. The importance of the purity of the chloramine products justifies a critical survey of this standard.

If we take the extreme case of a product containing the minimum allowable amount of water, namely 17%, and the minimum allowable amount of Cl, namely 11.5%, we arrive at a Cl content of the anhydrous product of 13.85%, against the theoretical percentage of 15.6%. The purity of such a chloramine-T, based on the chlorine percentage, would be only 88.7%.

It was found in factory experience that it is feasible, without throwing any particular burden on the manufacturer, to obtain regularly products of 96–98% purity. Since water content of 18–20% and chlorine of above 12% are quite compatible with normal factory practice it would appear to be desirable to raise the standard of chloramine-T to 18–20% H_2O and 12.25–13% Cl. The minimum percent purity which could pass with such requirements would be represented by a product containing 18% H_2O and 12.25% Cl. The chlorine on the dry basis figures out 14.94% and the percent purity 95.8.

On account of the great usefulness of chloramine-T and its many advantages over other antiseptics it was of importance to establish the stability of this product on storing in the dry form as well as in solution. It was found that the stability of chloramine-T is directly contingent upon the purity of the product, and the latter is dependent on the purity of the intermediate, the method of manufacture and the kind of apparatus in which it is made. Impure products were found to show considerable gradual decomposition until they were completely decomposed. But it is quite feasible to produce in regular manufacture a product of constant high purity and uniform quality. Such a product is very stable both in

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[1] New and Non-Official Remedies, 1919.

crystal form and in solution as shown by the following tabulated results. A high standard of purity for chloramine-T is therefore an essential condition for ensuring stability of the product.

The first table gives the results obtained with chloramine-T in dry form, when made into tablets. No. 1 represents a hand-moulded tablet without any addition, No. 2 a hand-moulded tablet made with addition of 1% $NaHCO_3$.

TABLE I.

	No. 1. % Cl.	No. 2. % Cl.
Originally	12.29	12.22
After 1 month	12.27	12.24
After 2 months	12.23	12.21
After 4 months	12.21	12.18
After 6 months	12.26	12.30

The original product used for these tests contained 0.05% NaOH and the alkalinity was not changed after six months, which is another indication that no deterioration took place.

Table II gives the results on chloramine-T crystals in dry form from various manufactured lots when kept for one year in glass bottles.

TABLE II.

	1.	2.	3.	4.	5.	6.
% chlorine originally	12.37	11.56	12.16	12.11	12.01	11.76
% chlorine after one year	12.06	11.77	11.91	12.26	11.90	11.94

The slight differences are mostly within the limits of experimental errors, which is also indicated by the fact that on some products the chlorine percentage after one year was found slightly higher than originally.

Since after one year's storing of chloramine-T no indication of decomposition can be observed it can be safely claimed that chloramine-T in dry form, loose or in tablets is a stable product.

The results of the investigation with aqueous chloramine-T solutions are given in Table III. The recorded figures represent the percent available Cl in 10 Cc.

TABLE III.

Chloramine-T.	In brown bottle. 2%.	In white bottle. 2%.	In brown bottle. 4%.	1/2% Na_2CO_3. 4%.	1% $NaHCO_3$. 4%.	1% NaCl. 2%.	30% glycerine. 2%.	15%.
Originally	2.38	2.31	4.76	4.68	4.78	2.35	2.39	16.44
1/2 month	....	....	....	....	....	...	2.30	.....
1 month	2.30	2.35	4.76	4.68	4.81	2.30	2.30	16.38
2 months	2.31	2.35	4.76	4.70	4.85	2.28	1.76	16.38
3 months	2.32	2.29	4.75	4.65	4.79	2.28	0.23	16.62
4 months	2.32	2.25	4.64	4.86	4.86	2.31	0.123	.....
5 months	2.35	2.26	4.77	4.72	4.85	2.32	0.032	.....
8 months	2.28	2.22	4.82	4.70	4.88	2.34	.....	.....

These results demonstrate that chloramine-T solutions of 2–15% on 8 months' standing show no loss of available chlorine and can safely be considered stable. Color of container has no bearing.

Addition of NaCl, $NaHCO_3$, Na_2CO_3 does not influence the stability of the chloramine-T. In a 30% glycerin solution containing 2% chloramine-T the

latter shows very little decomposition after one month, towards the end of the second month the decomposition is very much advanced and after three months' decomposition has progressed to the extent of about 90%.

II. DICHLORAMINE-T. PARA TOLUENE SULPHONDICHLORAMIDE.

$CH_3.C_6H_4.SO_2.NCl_2$.

A pure product should comply with the following specifications:

Appearance: Yellowish crystals.

Available chlorine: 29%.

Water extract: Neutral reaction (1 Gm.–100 Cc.).

Solubility: 1 Gm. completely soluble in 1 Cc. of benzol.

Based on the chlorine percentage such a product would represent a purity of 98.8%.

Dichloramine-T can be obtained as a white powder by direct chlorination of an alkaline solution of para toluene sulphamide.[1] This product, even when made and washed with every precaution, is not very satisfactory in regard to stability. After three months' storing the solubility in benzol is not complete any more and after four months of storing a strong odor of chlorine develops, indicating decomposition. The highest degree of stability of dichloramine-T can only be obtained with a crystallized product. All of the following figures and remarks refer to the crystallized dichloramine-T which is on the market in form of yellowish crystalline granules.

Various samples were examined monthly for chlorine percentage, melting point and solubility in benzol. On all of these samples no change at all was noticeable after six months, after eight months a slight decomposition was indicated in some samples by slightly lower melting point, and after eleven months solubility in benzol was not complete any more, also indicating slight decomposition. After thirteen and fourteen months lower Cl percentage and presence of benzol insoluble matter are noticeable. However, since the difference in the Cl percentage and melting point are almost within the limits of experimental errors, and since the reaction of the water wash is still neutral, the degree of decomposition after fourteen months may be considered minute.

A few of the results of this investigation are tabulated in Table IV.[1]

TABLE IV.

	Sample A.			Sample B.			Sample C.		
Time.	% Cl.	M. P.	Sol. 1:1.	% Cl.	M. P.	Sol. 1:1.	% Cl.	M. P.	Sol. 1:1.
Originally..	29.21	80/81	Complete	29.32	80.5/81.5	Complete	29.13	80/81	Complete
1 month..	28.91	80/81	Complete	29.18	80.5/81.5	Complete	28.88	80/80.5	Complete
2 months.	29.10	80.5/81	Complete	29.08	80.5/81.2	Complete	28.86	80/81	Complete
3 months.	29.02	80.5/81	Complete	29.30	80.2/81.0	Complete	29.11	80/81	Complete
4 months.	29.07	80/80.8	Complete	29.07	80.5/81	Complete	29.19	80/81	Complete
6 months.	29.05	80/81	Complete	29.16	80.5/81	Complete	28.80	80/81	Complete
8 months.	28.97	79.5/80.5	Complete	29.28	79.5/80.4	Complete	29.05	79/80.5	Complete
11 months.	29.10	79.5/80.5	Complete	29.14	79.5/80.4	Complete	29.13	79/80.2	Complete
13 months.	28.91	79.5/80.5	Fair	28.91	79.5/80.4	Complete	29.06	79/80.2	Complete
14 months.	29.06	79.5/80.5	Fair	28.99	79.5/80.4	Complete	29.08	79/80	Fair

[1] R. B. Krauss and E. Crede, "Dichloramine-T and Chlorinated Eucalyptol 1.2," *Jour. Am. Chem. Soc.*, 1917, p. 2720.

It was anticipated that even the crystallized product might contain traces of impurities which might slowly react with the dichloramine and cause some decomposition. In order to decide whether or not the chemically pure dichloramine-T is a stable product a very pure material was prepared by several recrystallizations from chlorbenzol until a constant melting point was obtained. No definite signs of deterioration could be observed after fourteen months. The results are given in Table V and show that the deviations are about within the limits of experimental errors.

TABLE V.

	% Cl.	M. P.	Solubility.
Originally	29.39	81/82	Complete
1 month	29.36	81/82	Complete
2 months	29.27	81/82	Complete
4 months	29.23	81/82	Complete
6 months	29.30	81/82	Complete
8 months	29.30	80.7/81.3	Complete
11 months	29.22	80.5/81	Complete
13 months	29.31	80.5/81	Complete
14 months	29.20	80.5/81	Complete

STABILITY OF DICHLORAMINE-T IN CHLORCOSANE SOLUTION.

No solvent for dichloramine-T has been found yet which is at once entirely satisfactory from the surgical standpoint and which will give a permanently stable solution. Chlorcosane gave the most satisfactory results in this respect so far. Here again the highest degree of purity of the dichloramine-T is of greatest importance. In a recent publication by Sollmann[1] a very poor stability of dichloramine-T in chlorcosane is reported. After one month only 60% of the dichloramine-T added remained undecomposed. Our results with crystallized commercial dichloramine-T show a much slower degree of decomposition, as demonstrated in Table V.

TABLE VI.

	Percentage of the added dichloramine-T that remains undecomposed at the time stated.	
	2½% solution.	5% solution.
10 days	98.8	99.6
1 month	93.4	96.8
5 weeks	....	92.8
2½ months	85.0	84.7

It was also found that drying of the solution by shaking with anhydrous calcium chloride has a favorable effect on its stability and such a solution had decomposed less than one percent after three weeks, and contained only traces of HCl and Cl.

Stock solutions prepared in this manner, and when not exposed to light and heat, could be considered serviceable for hospital use for at least a couple of weeks. The results given in Table VI were obtained in March and April. A similar investigation carried out during the summer gave a somewhat greater speed of decomposition.

[1] Torald Sollmann, *Journal of the Amer. Med. Assn.*, 1919, p. 992.

TABLE VII.

	Percentage of the added dichloramine-T that remains undecomposed at the time stated.	
	Dichloramine-T solution not treated.	Dichloramine-T solution treated with $CaCl_2$.
3 weeks	97.4	99.2
5 weeks	94.3	95.7

Since the preparation of the dichloramine-T chlorcosane solution requires heating and therefore cannot be conveniently made at any place it would be desirable to have a solvent which would give a permanently stable solution. From theoretical consideration, only a completely chlorinated hydrocarbon can be considered for this purpose. The results obtained with a 10% solution of dichloramine-T in tetrachlorcarbon are given in Table VIII.

TABLE VIII.

	Tetrachlorcarbon.		Tetrachlorcarbon.	
Time.	Commercial Total solids.	% Cl.	Commercial. Total solids.	Redistilled. % Cl.
Originally	11.61	28.55	11.12	28.28
After 1 month	11.43	28.55	11.31	28.23
After 2 months	11.42	28.53	11.21	28.29
After 3 months	11.48	28.53	11.24	28.30
After 4 months	11.48	28.35	11.24	28.30
After 6 months	11.58	28.46	.....	.....

The results obtained so far up to a period of observation of six months would indicate that dichloramine-T in tetrachlorcarbon is stable. However, such a solution seems to have some objectionable features from the surgical point of view, but it might be considered to make a 20% stock solution of dichloramine-T in tetrachlorcarbon and dilute it before use with the required amount of chlorcosane.

III. HALAZONE: PARA SULFONE DICHLORAMIDOBENZOIC ACID.

$$COOH.C6H4.SO_2NCl_2.$$

This product is not used as an antiseptic but as a disinfectant of water only. It is on the market in dry form as a white, insoluble powder or in form of tablets mixed with sodium carbonate or borax to make it water-soluble. The observation was made that when 1 part of halazone was mixed with $^1/_2$ part of anhydrous Na_2CO_3 the product dissolved only with difficulty in water, but if it was mixed with $^1/_2$ part of the monohydrate of sodium carbonate containing 15% of water the resulting mixture dissolved quite readily in water. It was also found that mixtures of equal parts of halazone and sodium carbonate monohydrate dissolve readily and without decomposition in water, in concentration not higher than one per mille. When higher concentrations are used some decomposition takes place under development of chlorine and deposition of some insoluble material.

The loss in chlorine and percent of several samples of halazone which have been stored in glass containers for nine months is given in Table IX.

TABLE IX.

				Purity based on chlorine percentage. Theory = 26.26% Cl.		
No.	% Cl originally.	After 9 months.	Loss Cl in %.	Originally.	After 9 months.	% loss pure halazone.
1	24.45	23.80	0.65	93.1	90.6	2.5
2	24.40	23.35	1.05	92.9	89.0	3.9
3	25.17	24.20	0.97	95.8	92.0	3.6

The loss in Cl amounts to about 1% equivalent to about $3^1/_2$% deterioration of the halazone.

Since this product is not used as an antiseptic the deterioration, combined with slight acidity, is not serious. Halazone can be considered fairly stable for one year at least. It should be remembered that the deterioration of the chloramines is a function of the temperature and that under tropical conditions, for instance, considerably higher speed of decomposition may take place than reported in our investigation.

To sum up we arrive at the following:

CONCLUSIONS.

1. In order to assure the greatest possible degree of stability of chloramine-T, dichloramine-T and halazone, these products should be produced with a high degree of purity.

2. Judging from observation extending over the period of one year chloramine-T can be considered stable in crystal form and in aqueous solution, by itself and in mixture with NaCl, Na_2CO_3 or $NaHCO_3$.

3. Dichloramine-T in amorphous powder form begins to deteriorate after about three months. The crystallized commercial product, however, is stable for about eight months and after fourteen months shows only slight degree of decomposition. A specially prepared and exceptionally pure product showed no definite signs of deterioration after fourteen months' storing.

4. Solutions of dichloramine-T in chlorcosane, of $2^1/_2$–5% strength, particularly when previously dried with $CaCl_2$, are sufficiently stable to be serviceable for use for a couple of weeks.

5. Solutions of dichloramine-T in tetrachlorcarbon of 11% strength showed no signs of decomposition after six months.

6. Halazone is fairly stable and can be stored for one year without serious decomposition. The latter amounts to a loss of about 1% chlorine in the first year equivalent to a decomposition of about $3^1/_2$% of the halazone.

7. Above conclusions on halazone and dichloramine-T refer to conditions, whereby the products are protected from undue action of light and heat.

MONSANTO CHEMICAL WORKS,
ST. LOUIS.

PRESCRIPTION CLINIC.*

BY IVOR GRIFFITH AND ADLEY B. NICHOLS.[1]

In submitting the following list of prescriptions and comments the writers beg to call attention to the fact that they are bona-fide prescriptions and not of the type frequently referred to as arm-chair incompatibilities. It is quite possible to encourage the mind and the hand to formulate prescriptions that would easily present the most freakish incompatibilities imaginable. All of us have seen good journal space dedicated to a ponderous discussion of this type of a

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[1] Department of Pharmacy, Philadelphia College of Pharmacy.