Sym. Cymyl Phenyl Urea.—Phenylisocyanate and amino-2 cymene react vigorously on being brought together. The product recrystallized from 5 per cent. alcohol forms light, fluffy, white crystals of m. p. 192° C.

$$C_{10}H_{13}—NH—CO—NH—C_6H_5.$$

SUMMARY.

1. Hydrazino-2 cymene (synonyms; cymyl hydrazine, carvacryl hydrazine) has been prepared from amino-2 cymene, together with its hydrochloride; monoacetyl derivative; glucose, mannose, and galactose hydrazones.

2. The cymyl hydrazones of benzaldehyde and furfural were not obtained in crystalline form.

3. Cymyl hydrazine reacts readily with acetoacetic ester, but the exact nature of the product has not been determined.

4. There is evidence that the side chains of the cymene residue exert a steric hindrance in some reactions of hydrazino-2 cymene.

5. Cymyl and sym. cymyl phenyl urea have been prepared.

SYNTHETIC DRUGS—IV.*

EXAMINATION OF AMERICAN-MADE CHLORAMINE-T, DICHLORAMINE-T, HALAZONE AND PREPARATIONS.

BY PAUL NICHOLAS LEECH, PH.D., CHICAGO.

Six years ago Dakin, Cohen and Kenyon[1] introduced into medicine the first "chloramine" antiseptic, "Chloramine-T;" the other members of the family, "Dichloramin-T" and "Halazone," followed soon afterward. The history of their introduction and of their commercial preparation has been detailed repeatedly in the pharmaceutical and medical literature; discussion now would be repetition.

The Council on Pharmacy and Chemistry of the American Medical Association kept pace with the therapeutic progress attendant on war times and described these chlorine antiseptics in "New and Nonofficial Remedies" after standards had been drawn up by the A. M. A. Chemical Laboratory. Since then a number of American firms have been marketing the products. It seemed opportune at this time to determine the purity of the market supply of those products described in "New and Nonofficial Remedies" and particularly to investigate the stability of the compounds containing a somewhat unstable atom. Hence this present report.

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* Contribution from the Chemical Laboratory of the American Medical Association.

The previous articles were: "Examination of American-Made Acetylsalicylic Acid," *J. Ind. and Eng. Chem.*, April, 1918, p. 228 (see also editorial, *Ibid.*, April 1918, p. 225); "American-Made Synthetic Drugs—II. Examination of Procaine (Novocain), Barbital (Veronal), Phenetidyl-acetphenetidin (Holocain), Cinchopen (Atophan), Manufactured under Federal Trade Licenses" (with Wm. Rabak and A. H. Clark), *J. A. M. A.*, 73, 754 (Sept. 6), 1919; "Synthetic Drugs—III. The Digestion of Tannin Compounds Used as Intestinal Astringents by Artificial Digestive Mixtures," *J. A. M. A.*, 75, 1120 (Oct. 23), 1920.

[1] *British Medical Journal*, Jan. 29, 1916, p. 160.

COMPARISON OF CHLORAMINES AND "SURGICAL SOLUTION OF CHLORINATED SODA."

The chloramines and their predecessor "Surgical Solution of Chlorinated Soda" ("Dakin's Solution") have one point in common which seemingly has been overlooked in the many comments on this topic. Both possess the positively charged and relatively unstable chlorine atom (Cl^+) and hence are active oxidizing agents in the proper medium.[1] Many writers have stressed the point that the Surgical Solution of Chlorinated Soda differs from the chloramines because it liberates oxygen and is, therefore, an oxidizing agent. This explanation is a relic of past days when sodium hypochlorite or hypochlorous acid was presumed to act as $2HClO \longrightarrow 2HCl + O_2$.

In the light of modern chemistry, however, we no longer hold the view that oxygen, directly or indirectly, is necessary for oxidation. Instead oxidation may "be considered to involve ultimately the assumption of positive or the loss of negative electrical charges by ions or atoms" and defined "as consisting fundamentally in the *loss of electrons by atoms or ions.*"[2] Thus hypochlorous acid [(ClOH) which besides ionizing to H^+ and ClO^-, dissociates to Cl^+ and OH^-]; hypobromous acid (Br^+OH^-) and their derivatives have a common characteristic, an atom with an unstable positive charge and a tendency to convert this atom to the common stable negative variety[3] (as for instance Chloride (Cl^-)).

There is convincing evidence to show that chloramine antiseptics contain positively charged chlorine: (1) The formulas and the methods of preparation (the replacing of a hydrogen atom of an amid group by chlorine) strongly suggest that the chlorine is positively charged. (2) On hydrolysis, they yield hypochlorous acid. (3) They are active oxidizing agents.

Thus the chloramines may be considered as simply more adaptable forms of administering the positive chlorine, which is well known medically in the form of sodium hypochlorite (Cl^+ONa), or bleaching powder. The antiseptic action of these is most probably due to the oxidizing action of a positively charged chlorine, in the case of the hypochlorite, the chlorine atom is bound to a hydroxyl group; in the case of the chloramine, to a nitrogen ($N\equiv$) atom.[4]

OXIDIZING ACTION OF CHLORAMINE-T.

Accepting the premise that Chloramine-T is an antiseptic by oxidation because it contains the relatively unstable chlorine atom (Cl^+), which tends to go over to the stable form (Cl^-), the question arises what effect will the reaction of the solvent have on the oxidation potential. Is it more active in acid; neutral or alkaline solution? In elaborating Chloramine-T standards for the Council on Pharmacy and Chemistry, one of the first reactions noted was that when a

[1] The two main attributes of the Surgical Solution of Chlorinated Soda are: (1) a definite degree of alkalinity sufficient to be of value in removing necrotic tissue but not too great to be unduly irritating; the p_H should be between 8 and 10; (2) the solution should be hypertonic. For methods of preparing such a solution see "New and Nonofficial Remedies," 1922, p. 137.

[2] Julius Stieglitz, "Quantitative Chemical Analysis," The Century Company, 1911, Part I, p. 252.

[3] Stieglitz and Senior, *J. Am. Chem. Soc.*, 38, 2727, 1916.

[4] Those interested in the electronic aspect of the nitrogen valences are referred to Stieglitz and Leech, *J. Am. Chem. Soc.*, Feb. 1914, 36, p. 272, and to references therein, also Stieglitz, *Ibid.*, June 1922, 44, p. 1293.

dilute solution of Chloramine-T was added to potassium iodide solution, iodine was freed, but in the case of potassium bromide solution, no bromine was freed; yet, when the latter solution was acidified, bromine was freed. In fact, this test can be used advantageously for a simple qualitative distinction between bromides and iodides. This shows that the oxidating action is increased in acid solution, and that, in common with ferric chloride, Chloramine-T in neutral solution has sufficient oxidizing action to oxidize an iodide ion, but not sufficient to oxidize the relatively more stable bromide ion (Br^-). Some experiments were made by utilizing the electrometric measurement of the oxidation potential. When 1 gram of Chloramine-T[1] was added to 100 cc of a solution having a p_H of 9, the voltage reading (using platinum electrode connected with the positive pole of the galvanometer[2]) was 0.12 V. When 1 gram of Chloramine-T was dissolved in 100 cc of water, having a p_H of 7 (the calomel[3] cell was connected to the positive pole of the galvanometer), the voltage reading was 0.4. When the solution was acidified, the voltage, of course, was increased enormously. Obviously this shows that Chloramine-T is greatly activated as an oxidizing agent when the medium is acid, whereas in alkaline solutions its oxidizing power is lowered proportionally to the concentration of the hydroxyl ions and it even acts as a reducing solution. As the bactericidal power of Chloramine-T is due probably to the oxidizing action (Cl^+), the question of the reaction of the medium is very important. The statement that Chloramine-T is fifty times more active as a germicide than phenol may be entirely wrong in certain media. There is great need for bacteriologic work to determine whether or not in an alkaline solution Chloramine-T has marked antiseptic value such as exists in an aromatic powder containing sodium bicarbonate. In fact from these experiments, it would not be surprising to find that the hydrogen ion concentration (C_H), the oxidation potential and the bactericidal coefficient would be in direct ratio and that Chloramine-T is weakly antiseptic in alkaline solutions. It is hoped that some investigators will take up work along this line.

PURITY OF MARKET SUPPLY OF CHLORAMINE-T AND PREPARATIONS.

The essential standards of purity for Chloramine-T (sodium para-toluene sulphochloramid $CH_3C_6H_4SO_2NaN—Cl^+ + 3H_2O$, 1:4) are described in "New and Nonofficial Remedies." The determinations reported in this paper are (1) loss in weight at 100–102° C., (2) decomposition (melting point), and (3) chlorine content (active chlorine).[4,5] The specimens were purchased on the open market

[1] This sample of Chloramine-T contained no free alkali and its solution reacted neutral to phenolphthalein and to methyl red.

[2] The Wendt Electro-Titration Apparatus was used.

[3] Using normal potassium chloride solution.

[4] It is not uncommon to find chemists using the term "available" chlorine, irrespective of what factor is employed. In these determinations, the actual content of positively charged chlorine is determined, that is, the amount of the active form of chlorine. Available chlorine is calculated on the assumption that the positive chlorine (Cl^+) takes up an atom of negative chlorine (Cl^-) forming a molecule of chlorine, Cl_2 ($Cl^- - Cl^+$). This terminology probably is a hangover from the archaic method of determining the strength of hypochlorites by measuring the amount of chlorine evolved under appropriate treatment in the presence of chlorides. It would seem that the time has come for the Pharmacopœia and books of reference to give analytical figures on the actual amount of the reactive substance and to discard the term "available." Whenever the

in original containers. They were received during the latter part of November and the first of December 1921, and kept in the dark until the analysis was made in June 1922.

Chloramine-T Powder.—All the recent specimens of Chloramine-T contain some free alkali. Of the specimens examined, one of the Squibb samples was considerably below the standard in both chlorine and water, while the other two Squibb samples and the Calco product did not contain the correct amount of moisture. The remaining products more closely approximate the "N. N. R." standards.[1] As may be seen from Table I, the products as found on the market are evidently quite stable.

TABLE I.—CHLORAMINE-T POWDER.

Brand.	Loss in weight at 100° C.	Melting point.	Chlorine (Cl^+) content.
Chloramine-T—Calco (Manufacturers).....	11.4	158	12.2
			12.2
Chloramine-T—Monsanto (Baltimore).....	17.8	163	12.50
			12.50
Chloramine-T—Monsanto (Chicago).....	17.8	162	12.50
			12.50
Chloramine-T—Squibb (Baltimore).....	13.4	169	12.2
			12.2
Chloramine-T—Squibb (Chicago).....	8.4	166	10.9
			10.9
Chloramine-T—Squibb (New York).....	13.9	163	12.7
			12.7
Chlorazene—Abbott (Baltimore).....	18.5	160	11.94
			12.00
Chlorazene—Abbott (Chicago).....	17.3	159	11.66
			11.84
Chlorazene—Abbott (New York).....	17.6	159	12.48
			12.47
"N. N. R.".....	18–20	160–185	12–13

Chloramine-T Tablets.—There are two brands described in "N. N. R.:" Chloramine-T Tablets—Squibb and Chlorazene Tablets—Abbott; each is claimed to contain 4.6 grains of Chloramine-T. The tablets were weighed and then assayed, the results appearing in Table II. The tablets as found on the market are quite satisfactory.

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figures for "available chlorine" are given, the mathematical value is just twice the actual amount of positively charged chlorine present (Cl^+).

[5] The assay methods are as follows:

If 1 gram of Chloramine-T is dried at from 100–102° C. for two hours, it loses not less than 18 per cent. nor more than 20 per cent. (water of hydration).

If about 0.5 gram of Chloramine-T (accurately weighed) is dissolved in 50 cc of water, 10 cc of potassium iodide (10 per cent.) and 5 cc of acetic acid (36 per cent.) added and titrated with tenth-normal sodium thiosulphate, the chlorine content should not be higher than 13 per cent. or lower than 12 per cent. Each cubic centimeter of tenth-normal thiosulphate solution is equivalent to 0.00177 grams of chlorine.

[1] In previous editions of "N.N.R.," the limits of water were 17 to 20 per cent. and of chlorine (Cl^+) from 11.5 to 13.0. On the recommendation of the manufacturers and after consultation the standards were made more stringent: the lower water limit raised to 18 per cent. and the lower chlorine limit raised to 12.0 per cent. The market supply is more in keeping with the old standards than with the revised standards.

TABLE II.—ANALYSIS OF "CHLORAMINE-T TABLETS, 4.6 GRAINS."

Brand.	Weight of tablet. Grams.	Weight of tablet. Grains.	Amount of Chloramine-T found. Grams.	Amount of Chloramine-T found. Grains.
Chloramine-T—Squibb (Baltimore)	0.2995	4.62	0.2911	4.49
	0.2951	4.55	0.2863	4.41
	0.3176	4.89	0.3060	4.72
	0.2901	4.47	0.2850	4.30
Chloramine-T—Squibb (Chicago)	0.2935	4.53	0.3034	4.67
	0.2937	4.53	0.2934	4.53
Chloramine-T—Squibb (New York)	0.2998	4.62	0.3006	4.63
	0.2871	4.43	0.2839	4.38
	0.2826	4.40	0.2818	4.35
Chlorazene—Abbott (Baltimore)	0.3496	5.38	0.2977	4.58
	0.3612	5.57	0.3027	4.65
	0.3477	5.35	0.2906	4.47
	0.3546	5.46	0.2956	4.54
Chlorazene—Abbott (Chicago)	0.3498	5.40	0.2927	4.51
	0.3324	5.12	0.2785	4.28
	0.3348	5.15	0.2816	4.33
	0.3468	5.34	0.2961	4.56
Chlorazene—Abbott (New York)	0.3472	5.35	0.2991	4.61
	0.3484	5.37	0.2991	4.61
	0.3450	5.32	0.2977	4.58
	0.3462	5.33	0.2991	4.61

Chloramine-T Surgical Paste (or Cream).—Chloramine-T Surgical Paste is claimed to consist essentially of 1 gram of Chloramine-T in 100 grams of a base composed approximately of sodium stearate 15 per cent. and water 85 per cent. Three market specimens each of "Chlorazene Surgical Cream" and "Chloramine-T Surgical Paste" were analyzed as follows:

Chloramine-T Paste—Squibb (Baltimore)	0.83% Chloramine-T[1]
	0.81% Chloramine-T
Chloramine-T Paste—Squibb (Chicago)	1.05% Chloramine-T
	1.06% Chloramine-T
Chloramine-T Paste—Squibb (New York)	1.01% Chloramine-T
	1.00% Chloramine-T
Chlorazene Surgical Cream (Baltimore)	1.19% Chloramine-T
	1.18% Chloramine-T
Chlorazene Surgical Cream (Chicago)	1.12% Chloramine-T
	1.17% Chloramine-T
Chlorazene Surgical Cream (New York)	1.14% Chloramine-T
	1.19% Chloramine-T

The variations are not as much as might be expected from a product containing so much water and organic matter. This fact illustrates how a slight alkalinity preserves the Chloramine-T.

Aromatic Chlorazene Powder—Abbott.—According to "New and Nonofficial Remedies," "Aromatic Chlorazene Powder—Abbott" is composed of "chlorazene 5 per cent., sodium bicarbonate 5 per cent., eucalyptol 2 per cent., saccharin 1

[1] Five to ten grams of the paste were transferred to a glass-stoppered Erlenmeyer flask and accurately weighed. Twenty cc of chloroform, 20 cc of potassium iodide solution (10 per cent.), 70 cc of water and 30 cc of acetic acid U. S. P. were added in the order named. The mixture was shaken until the paste had been entirely broken up, then titrated with tenth-normal sodium thiosulphate, using starch solution as indicator.

per cent. and sodium chloride 87 per cent." Three market specimens were analyzed the amount of Chloramine-T present being calculated from the reactive chlorine (Cl^+).

ANALYSES OF AROMATIC CHLORAZENE POWDER.

	Wt. of sample.	Wt. of Chloramine-T.	Per cent.
(Baltimore).....	7.6579	0.3511	4.59
	10.5332	0.4923	4.65
(Chicago).....	5.7615	0.2706	4.69
	7.3941	0.3476	4.70
(New York).....	8.0189	0.3070	3.83
	7.6588	0.2935	3.83

Thus in case of Samples 1 and 2, the amount of Chloramine-T found is only eight per cent. below the amount claimed whereas in Sample 3, the amount is 25 per cent. less than claimed. This result is probably due to poor mixing since the product is quite stable as will be shown later.

Chlorazene Surgical Powder.—This substance is composed of "Chlorazene (Chloramine-T) 1 per cent., zinc stearate 10 per cent. and sodium stearate 89 per cent." Three specimens were analyzed.

ANALYSES OF CHLORAZENE SURGICAL POWDER.

	Wt. of sample.	Wt. of Chloramine-T.	Per cent.
(Baltimore).....	8.6154	0.0803	0.93
	8.7700	0.0811	0.92
(Chicago).....	9.2089	0.1182	1.28
	9.8076	0.1296	1.31
(New York).....	10.6416	0.0098	0.08
	9.8875	0.0084	0.08

This product shows considerable variation—from thirty per cent. over the claimed amount to 92 per cent. below. (A sample, previously unopened, received in 1917 contained no Chloramine-T.) It is evident that certain conditions arise which cause the Chloramine-T to decompose. The product cannot be considered satisfactory from a standpoint of stability.

PURITY OF MARKET SUPPLY OF DICHLORAMINE-T.

As in the case of Chloramine-T, the essential standards for the purity of Dichloramine-T, para-toluene sulphone dichloramid $\left(CH_3C_6H_4SO_2N\langle^{Cl^+}_{Cl^+}\right)$, are described in "New and Nonofficial Remedies." The determinations reported in this paper are (1) melting (decomposition) point and (2) chlorine content ("active chlorin").[1] The specimens were bought at the same time and in the same method as described under Chloramine-T.

Dichloramine-T Powder.—Of the eight specimens examined (the melting points and the chlorine determinations are given in Table III), all of them came well

[1] The chlorine (Cl^+) determination is carried out according to the "N. N. R." method: About 0.1 gram of Dichloramine-T, accurately weighed, is dissolved in 5 cc of glacial acetic acid, 10 cc of 10 per cent. aqueous solution of potassium iodide added and the mixture titrated with tenth-normal sodium thiosulphate. (If the reagents used liberate iodine, the number of cubic centimeters of tenth-normal sodium thiosulphate volumetric required for their decoloration, as determined by a control, should be deducted from the total volume used.) The chlorine content should not be higher than 29.53 per cent. or lower than 28 per cent. Each cubic centimeter of thiosulphate solution is equivalent to 0.00177 gram of chlorine.

within the standards prescribed in "New and Nonofficial Remedies" except one sample of the Squibb product purchased in Chicago; in the latter case the melting point was quite low indicating decomposition, and the chlorine content was substandard; as might have been expected free hydrogen chloride was very perceptible; the other Squibb specimens were of good order. Except for this one instance, the products are all quite satisfactory.

TABLE III.—DICHLORAMINE-T (POWDER).[1]

Brand.	Melting point.	Chlorine (Cl^+) content.
Dichloramine-T—Abbott (Baltimore)	79–80	28.96%
		29.08
Dichloramine-T—Abbott (Chicago)	81–82	29.28
		29.33
Dichloramine-T—Abbott (New York)	81–82	29.24
		29.41
Dichloramine-T—Monsanto (Baltimore)	80–82	29.27
		29.29
Dichloramine-T—Monsanto (Sargents)	79–81	29.18
		29.18
Dichloramine-T—Squibb (Baltimore)	78–80	28.80
		28.78
Dichloramine-T—Squibb (Chicago)	68–69	25.52
		25.70
Dichloramine-T—Squibb (New York)	77–79	28.85
		28.86
"N. N. R." requirement	78–83	28–29.5

Dichloramine-T Tablets.—Only one firms's tablets have been described in "New and Nonofficial Remedies," namely, the Abbott brand. Three original specimens were examined. (See results in Table IV.) The tablets (claimed to contain 4.6 grains Dichloramine-T) are uniform in weight and are within the variations accepted in this form of medication.

TABLE IV.—"TABLETS DICHLORAMINE-T—ABBOTT, 4.6 GRAMS."

	Weight of tablets.		Dichloramine-T.	
	Grams.	Grains.	Grams.	Grains.
1. Baltimore	0.2950	4.55	0.2916	4.49
	0.3006	4.63	0.2976	4.58
	0.3014	4.65	0.2976	4.58
	0.2975	4.59	0.2934	4.50
	0.2953	4.55	0.2922	4.50
2. Chicago	0.3047	4.69	0.3012	4.64
	0.3025	4.66	0.3000	4.63
	0.2983	4.59	0.2928	4.50
	0.3000	4.63	0.2970	4.58
3. New York	0.2920	4.50	0.2895	4.47
	0.2958	4.56	0.2916	4.49

PURITY OF THE MARKET SUPPLY OF HALAZONE.

Halazone is used almost exclusively in the form of tablets, containing a mild alkaline substance in which the halazone dissolves when water is treated with the tablet. The powder is, therefore, not carried by some firms in regular stock.

[1] The McNeil brand is also described in "New and Nonofficial Remedies." However, our buyers were not able to supply the product. On inquiry, the firm gave the information that their product was sold almost entirely to dispensing physicians, hence, it was not found in the regular drug trade channels.

The specimens received by us from the drug house bore only typewritten labels; in case of one firm no specimen was obtained. The essential standards of purity are the melting point or rather decomposition point and the chlorine (Cl^+) content.[1] Halazone is para-dichloramidosulphone benzoic acid

$$\left(\begin{matrix}Cl^+\\Cl^+\end{matrix}\!\!>\!\!NSO_2C_6H_4COOH\right).$$

Halazone Powder.—The products of two firms were examined:

Brand.	Decomposition point.	Chlorine (Cl^+) content.
Halazone—Abbott (Chicago)	195	22.96
		23.14
Halazone—Abbott (New York)	194	22.92
		23.11
Halazone—Monsanto	190	24.08
		24.08
"N. N. R." requirement	—	24.00 to 26.2

The Abbott products are slightly low in chlorine content; the one specimen of Monsanto product is just inside the chlorine (Cl^+) limits.

Halazone Tablets.—The tablets of two firms are listed in "New and Non-official Remedies"—"Abbott" and "Squibbs." Each tablet is claimed to contain 0.004 gram ($^1/_{16}$ grain) of halazone, 0.004 gram of sodium carbonate, and approximately 0.1 gram of sodium chloride. Chlorine (Cl^+) determinations yielded the following results, calculated to halazone:

	Amount of halazone in each tablet.
Halazone Tablets—Abbott (Chicago)	0.0030 gram
	0.0030 gram
Halazone Tablets—Abbott (New York)	0.0035 gram
	0.0035 gram
Halazone Tablets—Squibb (Baltimore)	0.0033 gram
	0.0032 gram
Halazone Tablets—Squibb (Chicago)	0.0030 gram
	0.0030 gram
Halazone Tablets—Squibb (New York)	0.0034 gram
	0.0033 gram

The five specimens reported above are 12.5 to 25 per cent. below the amount of halazone claimed; considering how the compound is used, however, the variations are not therapeutically serious.

[1] The following method for chlorine (Cl^+) determination is detailed in "New and Non-official Remedies:" About 0.150 gram of halazone (or in the case of halazone tablets, 30 tablets), accurately weighed, is dissolved in from 50 to 100 cc of water and 10 cc of a 10 per cent. sodium hydroxide solution. Fifteen cubic centimeters of a 10 per cent. potassium iodide solution are added, and the mixture titrated with tenth-normal sodium thiosulphate volumetric solution. (If the reagents used liberate iodine, the number of cubic centimeters of tenth-normal sodium thiosulphate volumetric solution requires for their decolorization should be deducted from the total volume used.) The available chlorine content of halazone should not be higher than 26.26 per cent. or lower than 24 per cent. Each cubic centimeter of tenth-normal thiosulphate volumetric solution is equivalent to 0.00177 grams of chlorine. The theoretical chlorine content of pure halazone is 26.26 per cent.

TABLE V.—STABILITY OF "CHLORAMINES."

		Decomposition point.	Moisture.	Chlorine (Cl^+).
Chloramine-T—Monsanto	Feb. 1918	164–166	18.46	11.94
	Sept. 1918	*163–164*	*16.61*	*11.9*
	July 1922	152	18.05	11.81
Chloramine-T—Calco	Oct. 1917	168–170	16.82	11.67
	Sept. 1918	*158–159*	*15.69*	11.8
	July 1922	(See footnote 1)		....
Chloramine-T—Squibb	June 1918	181	9.0	11.40
	Sept. 1918	*181*	*9.1*	*11.2*
	July 1922	173	9.2	11.1
Chlorazene—Abbott[2]	July 1916	Notes	misfiled	....
(Received July 5, 1916)	Sept. 1918	163		*11.07*
	July 1922	163		11.00
Chlorazene Surgical Powder				0.00
(Received Dec., 1917)	.....	.....		(July 1922)
Aromatic Chlorazene Powder				4.72
(Received August, 1919)	.....	.....		(July 1922)
Dichloramine-T—Abbott	Sept. 1918	*76–78*		*27.62*
(Received Oct., 1917)	July 1922	69–72		26.51
Dichloramine-T—Calco	Nov. 1917	81–82		28.6
	Sept. 1918	*75–77*		*27.9*
	July 1922	71–73		26.4
Dichloramine-T—Monsanto	Feb. 1918	80–82		29.2
	Sept. 1918	*77–79*		*28.6*
	July 1922	72–74		27.6
Dichloramine-T—Squibb	June 1918	77–79		29.00
	Sept. 1918	*76–79*		*28.3*
	July 1922	68–69		25.0
Halazone—Abbott	Aug. 1917	196		25.9
	July 1922	192		24.4
Halazone—Calco	Dec. 1917	195		25.9
	Sept. 1918	200		*25.8*
	July 1922	204		25.0
Halazone—Monsanto	Dec. 1917			24.9
	Sept. 1918	*198*		*24.2*
	July 1922	204		24.1
Halazone—Squibb	July 1918	204		24.0
	Sept. 1918	...		*23.8*
	July 1922	202		23.2

STABILITY OF THE CHLORAMINES.

From the foregoing discussion, it is evident that Chloramine-T, Dichloramine-T and Halazone, as now found on the market, do not show serious deterioration in

[1] The Calco specimen of Chloramine-T—Calco was sent in a colorless glass container, and kept as the other specimens. On reëxamination at this time, it was found to be entirely decomposed, containing *no* reactive chlorine and melting at 122–123°. All the other specimens were in dark glass as are the market specimens of Calco. This does not reflect at all against the Calco product, but the observation is of academic interest.

[2] Chlorazene was the first product on the American market. Several specimens were examined, at the request of the Committee on Synthetic Drugs, while the product was in the experimental stage. Then when the market specimen was submitted to the Council, it likewise was examined and found to be satisfactory. The exact figures on this latter specimen have been misfiled, but a chlorine determination on the sample was made by Mr. Rabak in 1918, as well as the recent one reported in this paper.

spite of the presence of the relatively unstable form in which the chlorine exists. This does not dispose of the question of stability over a period of years; so, it was opportune to reëxamine samples analyzed when the products were first submitted to the Council and again examined during 1918 by Mr. Wm. Rabak, at that time connected with the A. M. A. laboratory. In the foregoing table (Table V) are given the dates of the analyses and the figures found in the order in which they were made. Those in italics were by Mr. Rabak to whom credit is due. The specimens were kept in the dark, in their original containers, and at room temperature.

It will thus be seen from Table V that samples of Chloramine-T, kept for about five years, show little deterioration. Dichloramine-T deteriorates somewhat, but the decomposition is not of a spontaneous nature. Halazone undergoes little change on standing. Chlorazene Surgical Powder probably does not keep over a long period, the sample (which had not previously been opened) having no Chloramine-T present; possibly the excipient had a slightly acid reaction hastening decomposition. On the other hand, aromatic Chlorazene Powder is stable; this is to be expected in view of the fact that it is an alkaline substance and hence the oxidizing power of Chloramine-T is lessened. Even solutions of Aromatic Chlorazene Powder deteriorate slowly when kept at room temperature exposed to indirect light over a period of weeks.

DECOMPOSITION OF SOLUTION OF AROMATIC CHLORAZENE POWDER.

(Based on Chlorine (Cl^+) Determination.)

Time.	Per cent.
1 hour	0.0
3 hours	0.7
1 day	2.7
3 days	5.0
8 days	7.0
23 days	14.0
4 months	37.0

CONCLUSIONS.

1. The oxidizing power of Chloramine-T is greatly lessened by slight increase in alkalinity of the solution. It is suggested that the bactericidal power may likewise be lessened in alkaline fluids and investigation is needed.

2. The market supply of Chloramine-T was examined. One Squibb specimen was below standard in both water and chlorine, and two Squibb specimens the Calco Chloramine-T did not contain a sufficient amount of water of crystallization. The Monsanto and Abbott products were satisfactory.

3. Chloramine-T Tablets of all firms described in "New and Nonofficial Remedies" were satisfactory.

4. Aromatic Chlorazene powder is stable.

5. Two samples of Chlorazene Surgical Powder (one recent and one old) were very poor; two others were satisfactory.

6. The market specimen of Chloramine-T pastes are satisfactory.

7. On the whole, the market specimens of Dichloramine-T—"N. N. R." are satisfactory, as are the tablets.

8. The market specimens of Halazone examined were slightly substandard.

9. Halazone tablets over 12.5 per cent. to under 25 per cent. of the professed content were found.

10. Chloramine-T and Halazone are sufficiently stable to be kept over a period of five years. Dichloramine-T, on the other hand, decomposes slowly.

CHICAGO, ILLINOIS

SYNTHETIC HYPNOTICS IN THE BARBITURIC ACID SERIES.

BY ARTHUR W. DOX.

The increasing demand for sleep-producing drugs is perhaps one of the characteristics of the restless age in which we now live. Not a year passes but half a dozen new synthetic hypnotics appear in the patent literature and a few of these find their way into the drug market. Most of these fail to meet the claims made by the manufacturers and are soon discarded, and the physicians continue to prescribe the eight or ten more or less familiar drugs that have survived several decades of clinical experience. Meanwhile, the chemical and pharmaceutical laboratories continue their search for the ideal hypnotic, for it must be admitted that none of the hypnotics in present-day use are entirely free from certain objectionable qualities.

Long before our era of chemical and pharmaceutical research the sleep-producing properties of opium and alcohol were widely known. In oriental countries hashish, or cannabis indica, has been used for centuries, but this has never become popular in our western civilization. Among the natural drugs, hyocyamus is perhaps the only other hypnotic of any importance. The first three, opium, alcohol and cannabis, are decidedly habit-forming. As a matter of fact, only a very small percentage of the total consumption of these drugs can be considered legitimate in the sense of being used under circumstances where a physician would feel justified in prescribing them.

Opium, including its chief constituent, morphine and the morphine derivatives —codeine, heroine, etc.—has been both a blessing and a curse to humanity. For the relief of acute pain, especially in post-operative surgery, no satisfactory substitute has yet been discovered. On the other hand, the morphine habit has fastened itself upon thousands of otherwise useful citizens and left them physical and moral wrecks. The discovery of synthethic hypnotics which are now used in a great many cases where morphine was formerly prescribed, represents, therefore, a distinct advance in medical science. It may be said in general that for the relief of insomnia or sleeplessness due to other causes than acute pain, the use of morphine or its derivatives is no longer necessary.

Curiously enough, none of the synthetic hypnotics bears the slightest chemical resemblance to morphine. The exact structure of the morphine molecule is still unknown, but we know that it is far more complex than any synthetic hypnotic thus far used. The presence of a phenanthrene nucleus, an oxygen bridge forming a furane ring, two hydroxyls one of which is phenolic and the other alcoholic, and a nitrogen ring bearing a methyl group, is about all that has been definitely proved of the morphine structure. On the other hand, some of our common sleep-producing drugs are extremely simple and easily synthesized. The difference is not so much in the size as in the compactness of the molecule. For example, morphine has a molecular weight of 285, and luminal, one of the most powerful of our synthetic