Photochemical Formation of Hydrogen Peroxide in White Lotion U.S.P.

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White lotion U.S.P. produces hydrogen peroxide when it is irradiated with ultraviolet radiation or with natural sunlight. The amount of hydrogen peroxide formed during irradiation is sufficient to oxidize the sulfide ion to sulfate. When cholesterol is added and the product irradiated, the β-hydroxyl group on the cholesterol molecule is oxidized.

WHITE LOTION is a widely used external preparation in which insoluble compounds of zinc are present. It has been used for the topical treatment of a number of dermatologic diseases. The lotion was proposed for the American Recipe Book in 1912 (1). It became official in the U.S.P. XV and U.S.P. XVI with the following formula:

Zinc sulfate........................	40 Gm.
Sulfurated potash..................	40 Gm.
Purified water, a sufficient quantity to make........................	1000 ml.

"Dissolve the zinc sulfate and sulfurated potash separately, each in 450 ml. of purified water, and filter each solution. Add slowly the sulfurated solution with constant stirring. Then add the required amount of purified water, and mix.

"Note: Prepare the Lotion freshly and shake thoroughly before dispensing."

The mode of action of white lotion is attributed to be astringent and protective (2). The principal activity is associated with the sulfur content (3), and at one time the presence of residual hydrogen sulfide in the lotion was considered to be the important reason for preparing the lotion freshly.

DISCUSSION

A number of papers on the catalytic production of hydrogen peroxide by irradiation of zinc oxide in aqueous medium have appeared (4–13) since 1944. All these studies showed that zinc oxide catalyzed the production of hydrogen peroxide when exposed to light in the presence of water and air, the rate of production being influenced by the kind of light and temperature. Since this is a catalytic process, the production of peroxide would continue indefinitely as long as all components of the system were present. The source of ultraviolet light used in this study was a Dazor floating fixture ultraviolet lamp model No. U-58, equipped with a General Electric UA-3, 360-w. quartz photochemical lamp. The radiant energy is greatest at 2537 Å., 3131 Å., and 3564 Å. Irradiations were also done by exposing samples directly to sunlight.

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Samples for irradiation were placed in 600-ml. beakers. These were placed in a water bath situated on a six-plate magnetic stirrer. The U.V. lamp was suspended 30 cm. over the surface of the sample, and the entire assembly was enclosed in an aluminum box. Irradiation time was 30 min. in all cases unless otherwise noted.

Since sulfurated potash is a complex and variable mixture of potassium polysulfides and potassium thiosulfate depending on the particular batch and age of the product, and since zinc sulfate undergoes dissociation in water to give hydronium, sulfate, and zinc ions, a number of chemical reactions are possible. The extent of any one of these reactions can be affected by concentration and temperature of the system.

Possible reactions:

$$\text{sulfurated potash in water} \rightleftharpoons K^+, S^=, S_x^=, S_2O_3^=, OH^-$$

$$S_2O_3^= + 2H^+ \rightleftharpoons SO_2 + H_2O + S$$

$$SO_2 + 2H_2S \rightleftharpoons 3S + 2H_2O$$

$$S^= + Zn^{++} \rightleftharpoons ZnS$$

$$xS + Zn^{++} \rightleftharpoons ZnS_x \text{ (where } x \text{ is mostly 2 or 3)}$$

$$SO_4^= + 2K^+ \rightleftharpoons K_2SO_4$$

$$S_2O_3^= + Zn^{++} \rightleftharpoons ZnS_2O_3$$

The formation of zinc hydroxide in an acid medium of zinc sulfate solution occurs as follows:

$$[Zn(OH_2)_6]^{++} + H_2O \rightleftharpoons [Zn(OH_2)_5(OH)]^+ + H_3O^+$$
hexa-aquo zinc (II)

$$[Zn(OH_2)_5(OH)]^+ + H_2O \rightleftharpoons [Zn(OH_2)_4(OH)_2]^0 + H_3O^+$$
(zinc hydroxide)

The OH^- ions in the sulfated potash shift both reactions to the right forming zinc hydroxide.

In view of these considerations, white lotion was restudied to evaluate the following: (*a*) composition of the soluble phase of the lotion, (*b*) composition of the insoluble phase of the lotion, (*c*) the effect of order of mixing on the composition of the two phases, (*d*) the effect of temperature on the composition, (*e*) the production of hydrogen peroxide by catalytic action of zinc hydroxide, (*f*) the effect of hydrogen peroxide on the components of the lotion, (*g*) the effect of aging lotion, (*h*) the effect of hydrogen peroxide on additives such as cholesterol.

EXPERIMENTAL

Qualitative Analysis of the Fresh Lotion

Soluble Phase—*Potassium*—This was determined by cobaltinitrite solution: a finely divided yellow to orange-yellow precipitate was obtained.

Thiosulfate, Sulfate, Sulfite, and Zinc—The U.S.P. tests for these ions were applied. The presence of sulfate and thiosulfate ions was confirmed. No sulfite ion was detected.

Hydrogen Sulfide—Van Itallie reagent (14) (freshly prepared solution of *p*-diazobenezensulfonic acid) was added to the filtrate of the freshly prepared lotion (pH 7.3). No coloration occurred (reaction negative).

Insoluble Phase—*Sulfides*—This test depends on the ability of sulfides to facilitate the reaction between equal quantities of 0.2 *N* aqueous solution of iodine and 0.2 *N* sodium azide solution. A violent evolution of nitrogen occurs in this reaction. The washed precipitate obtained by filtration of white lotion gave a positive test for sulfides.

Zinc Hydroxide—The gelatinous precipitate of zinc hydroxide is amphoteric and dissolves in alkalies to form the complex ion $[Zn(OH)_4]^=$. The identification of zinc hydroxide was done by treating the insoluble phase with dilute ammonium hydroxide solution. The sample is filtered and the filtrate neutralized with acid. A white precipitate indicated zinc hydroxide (reaction positive).

Quantitative Analysis—A quantitative analysis was run on the washed and dried precipitate obtained from the lotion. The dried precipitate was extracted with carbon disulfide, filtered, and the solvent evaporated. The free sulfur was determined by a gravimetric or a volumetric procedure depending on the amount of the extracted sulfur obtained (15–17).

Sulfides were determined by Kolthoff's method (18) for insoluble sulfides as modified for polysulfides (19). Zinc was determined by the U.S.P. XVI method (20).

Table I gives percentage composition of dried precipitate from three differently prepared lotions. Each entry is the average of seven determinations.

Ultraviolet and sunlight irradiations were performed on suspensions made by resuspending the washed precipitate of the lotion in 40 ml. of water. The amounts of precipitate represented 25 and 5 ml. of lotion, respectively. After irradiation, both the filtrate and the precipitate were analyzed. Results are shown in Table II.

According to Goudah (9), increasing the zinc oxide irradiated in the aqueous system increases the peroxide formed but not in a linear relationship. In this work, irradiations were performed in identical containers, for the same period of time, stirred at the same speed, and placed in the same circulating water bath. The samples representing 25 ml. of lotion showed sulfite and zinc ions, free sulfur, zinc oxide, and no free hydrogen peroxide. The samples representing 5 ml. of lotion show the presence of sulfate and no zinc sulfides. It is concluded from these results that in the 25-ml. sample, the amount of hydrogen peroxide produced in the 30 min. of irradiation was insufficient to oxidize the larger amount of sulfides present in the 25-ml. samples. The 5-ml. sample, however, did produce sufficient peroxide in the 30 min. of irradiation to completely oxidize the sulfides to sulfates. This is probably due to the fact that in the irradiation of the sample under the conditions used, the exposure of zinc oxide to light in the 25-ml. samples was not proportionally greater than the zinc oxide in the 5-ml. samples. This is a reasonable conclusion since the area of the exposure was identical in all samples.

Table III lists the amount of peroxide present after irradiation of different amounts of washed precipitate resuspended in 40 ml. of water. The amount of residual peroxide detected showed an increase with the decrease of the amount of precipitate irradiation.

The iodometric method of Kolthoff (21), as modified by Chari and Qureshi (12), was utilized for the quantitative determination of hydrogen peroxide.

To the aqueous suspension made from the washed precipitate of 5 ml. of lotion, 200 mg. of cholesterol dissolved in 5 ml. of ethanol was added. The mixture was irradiated for 4 hr. in the sunlight, or

TABLE I—PERCENTAGE COMPOSITION (w/w) OF DRIED PRECIPITATE FROM THREE DIFFERENTLY PREPARED LOTIONS

	Contents, % w/w in the Dry Precipitate			
Lotion[a]	Free Sulfur	Zinc Oxide	Zinc Sulfides[b]	Sulfides' Sulfur
A	4.93	45.54	49.52	36.45
B	4.32	48.1	47.5	35.2
C	4.36	46.1	49.54	35.4

[a] *A*, freshly prepared U.S.P. lotion; *B*, lotion prepared by reverse order of mixing; *C*, lotion prepared according to the U.S.P. but using heated solutions at 80°. [b] Zinc sulfides are calculated values by subtracting free sulfur and zinc hydroxide content from 100% dry precipitate.

TABLE II—ANALYSIS OF SAMPLES AFTER 30 min. ULTRAVIOLET IRRADIATION

	Filtrate				Precipitate		
	$SO_4^=$	$SO_3^=$	H_2O_2	Zn^{++}	S	ZnO	ZnS
25-ml. lotion	−	+	−	+	+	+	+
5-ml. lotion	+	−	+	+	+	+	−

TABLE III—AMOUNT OF PEROXIDE PRESENT AFTER IRRADIATION OF WASHED PRECIPITATE RESUSPENDED IN 40 ml. WATER

Amt. of Precipitate	H_2O_2, mg.	Presence of ZnS_x
Ultraviolet Irradiation, 30 min.		
2 ml. original lotion	0.24	−
3 ml. original lotion	0.23	−
4 ml. original lotion	0.25	−
5 ml. original lotion	0.17	−
6 ml. original lotion	0.10	−
7 ml. original lotion	0.08	−
10 ml. original lotion	0.03	−
11 ml. original lotion	−	+
12 ml. original lotion	−	+
25 ml. original lotion	−	+
Sunlight Irradiation, 4 hr.		
2 ml. lotion	0.23	−
3 ml. lotion	0.19	−
5 ml. lotion	0.13	−
25 ml. lotion	−	+

30 min. under the ultraviolet light, with continuous stirring. The samples were then extracted with chloroform, the extract condensed under vacuum to 10 ml., dried in a desiccator, and analyzed by infrared spectroscopy. A sample of cholesterol, ethanol, and water was treated in the same manner. In addition, the precipitate suspension with cholesterol was placed in the dark. The entire process was repeated using samples made of 5 ml. of the entire lotion.

Infrared spectra are shown in Figs. 1, 2, 3, 4, and 5. Finally, the effect of aging white lotion was determined by storing the lotion in clean glass bottles at room temperature, and samples analyzed at intervals. Results are shown in Table IV.

RESULTS

The results of this study show that white lotion U.S.P. XVI is a mixture of several insoluble and soluble materials and that the percentage composition of each of these materials is not significantly affected by the order of mixing or alteration of the temperature of the reactants. The composition of the precipitate of freshly prepared lotion appears to contain approximately 4.5% of free sulfur, 45–48% of zinc oxide, and 47–49% of zinc sulfides. The zinc sulfides represent sulfur to the extent of 35 to 36% of the precipitate.

When the precipitate is separated and washed with distilled water, then resuspended in distilled water and subjected to irradiation by ultraviolet light, considerable alteration occurs. When 25 ml. of lotion is used the filtrate shows, after irradiation, sulfite and zinc ions. When 5 ml. of lotion is irradiated for the same time, the filtrate shows the presence of sulfate and zinc ions, and hydrogen peroxide, while the precipitate shows the absence of sulfide ions.

These changes show that the peroxide oxidizes the sulfide to sulfite and finally to sulfate and only after this reaction is completed is it possible to show the presence of hydrogen peroxide. Table III shows the results of peroxide formation from increasing amounts of resuspended precipitate when irradiated by ultraviolet light for 30 min., and by sunlight for 4 hr. These values show that the amounts of peroxide produced by the two light sources are approximately the same for the time periods used. This also indicates that these reactions may occur when white lotion is applied to the skin.

The existence of cholesterol on the skin, and the probability of its being a precursor of 7-dehydro-

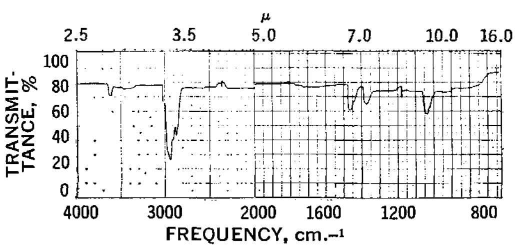

Fig. 1—Infrared spectrum of cholesterol.

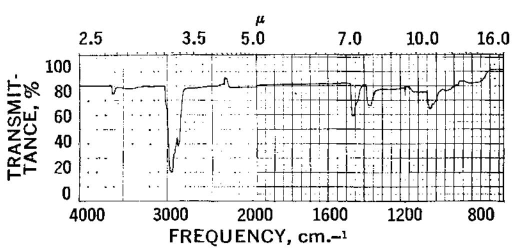

Fig. 2—Infrared spectrum of cholesterol extracted from precipitate (no irradiation).

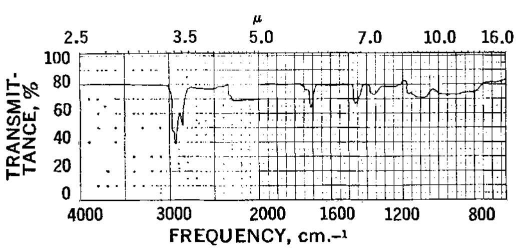

Fig. 3—Infrared spectrum of cholesterol extracted from precipitate after ultraviolet irradiation (30 min.).

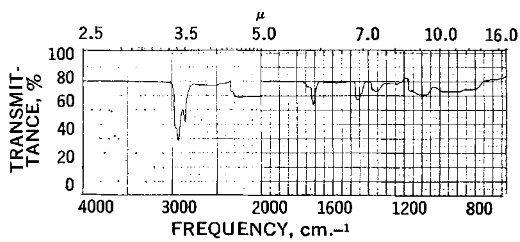

Fig. 4—Infrared spectrum of cholesterol extracted from precipitate after sunlight irradiation (4 hr.).

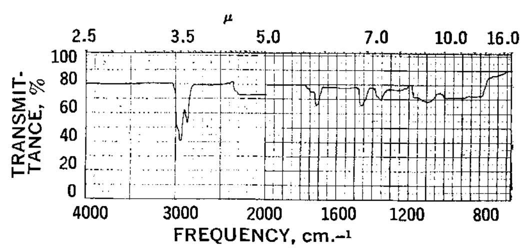

Fig. 5—Infrared spectrum of cholesterol extracted from white lotion after ultraviolet irradiation (30 min.).

TABLE IV—COMPOSITION OF WHITE LOTION STORED AT ROOM TEMPERATURE

	% w/w in the Dry Precipitate			
Time, Days	Free Sulfur	Zinc Oxide	Poly-sulfides	Sulfides' Sulfur
0	5	45.5	49.50	36.46
10	15.40	45.6	39.00	26.10
20	23.20	45.3	31.50	18.43
30	27.56	45.6	26.84	14.10
40	28.95	45.2	25.90	12.80
50	29.50	45.2	25.30	12.50
60	29.60	45.2	25.20	12.30

cholesterol (provitamin D_3) suggested the determination of the effect of irradiation of cholesterol in the presence of the white lotion. The results represented in the infrared spectra of cholesterol before and after irradiation show oxidation of cholesterol when irradiated in the presence of both the resuspended washed precipitate and in the entire white lotion.

The characteristic absorption band of the hydroxyl group of cholesterol is seen at 3600^{-1} or 2.75 μ wavelength in the infrared spectra of cholesterol and in that of cholesterol extracted from a nonirradiated sample. A band is noted at 1075 cm.$^{-1}$ due to the presence of a secondary alcohol (Figs. 2 and 3). These respective characteristic absorption bands disappear in the I.R. spectra of cholesterol extracted from the precipitate and from entire lotion samples after ultraviolet irradiation (30 min.) or sunlight irradiation (4 hr.) (Figs. 3, 4, and 5). A new absorption band appears in these spectra in the region of 6 μ or 1750 cm.$^{-1}$. This band is ascribed to the vibrations of carbonyl function C=O, and is found in about the same region as in ketones and aldehydes. The irradiation of cholesterol alone under the above condition does not produce any changes in the absorption peaks of the I. R. spectra. The results obtained are in agreement with previous work by Guth and Goudah (9).

The findings of this study suggest further investigation of the effect of the peroxide produced by white lotion on the sterols in the skin.

The results on the effect of aging on the white lotion showed an increase in the free sulfur content and a decrease in sulfides' sulfur as shown in Fig. 6. The physical stability of white lotion is affected only slightly on aging. Colloidal sulfur particles seem to aggregate and the components of the precipitate do not remain uniformly distributed, but since no caking or flocculation is noted, the lotion is readily redispersed into a uniform mixture when the container is shaken.

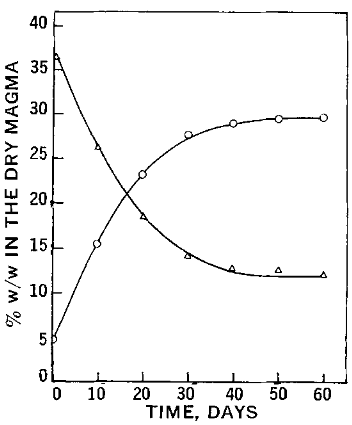

Fig. 6—Effect of aging on white lotion. Key: O, *free sulfur;* △, *sulfides' sulfur.*

It seems that the freshly prepared lotion was reported beneficial in acne and other dermatologic diseases due to its high content of insoluble sulfides. It appears from this study that there may be merit in requiring a freshly prepared lotion, since the effectiveness of white lotion could in part be associated with the gradual release of colloidal sulfur.

SUMMARY

1. White lotion U.S.P. contains zinc mono and polysulfides, zinc hydroxide, and free sulfur all suspended in an aqueous medium containing sulfate, thiosulfate, and potassium ions.
2. Zinc oxide catalyzed hydrogen peroxide is formed in white lotion when irradiated by ultraviolet and sunlight. The peroxide so formed is very active in oxidizing sulfides to sulfites and then to sulfates.
3. When cholesterol is present, β-hydroxyl group is oxidized.
4. On aging, there is a marked increase in free sulfur in the lotion.

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