

UNITED STATES PATENT OFFICE

2,287,724

ANTISEPTIC

Milton T. Bush, Nashville, Tenn., assignor to
Mallinckrodt Chemical Works, St. Louis, Mo., a
corporation of Missouri

No Drawing. Application April 5, 1939,
Serial No. 266,127

14 Claims. (Cl. 167—71)

This invention relates to antiseptics, and with regard to certain more specific features, to antiseptics particularly adapted for skin sterilization, as in preoperative surgical technique.

Among the several objects of the invention may be noted the provision of antiseptics of the class described which possess an extraordinarily high ability to sterilize in vivo; the provision of antiseptics of the class described which utilize, as their chief active ingredient, an alkyl mercuric salt; the provision of antiseptics of the class described which are free of harmful effects; and the provision of a method of antiseptics using new compositions of matter for this purpose. Other objects will be in part obvious and in part pointed out hereinafter.

The invention accordingly comprises the elements and combinations of elements, the proportions thereof, steps and sequence of steps, and features of composition and manipulation, which will be exemplified in the substances, products, and methods hereinafter described, and the scope of the application of which will be indicated in the following claims.

The present invention is bottomed upon the discovery, by the applicant, of the capability of alkyl mercuric salts, particularly alkyl mercuric halides, to effect an extraordinarily high degree of antiseptics, or sterilization, particularly in connection with preoperative procedures in surgery.

Alkyl mercuric salts have long been known to exist. In fact, it has long been known that such substances find valuable use as seed disinfecting media. Furthermore, the toxicities of several alkyl mercuric salts with respect to microorganisms generally have been reported in the literature.

However, so far as I have been able to determine, no one has ever investigated the antiseptic activity of such salts, particularly under conditions in vivo. I have made such an investigation, as will appear more fully hereinafter, and have, by comparative tests, ascertained the wholly unexpected fact that the antiseptic activity of alkyl mercuric salts is far greater than substantially any other antiseptic in current use. The antiseptic or sterilizing activity of the alkyl mercuric salts is particularly well demonstrated in the case of skin sterilization, which is a procedure customarily followed in surgery as a prelude to operative measures. Surprisingly, I have found that solutions of these alkyl mercuric salts are outstandingly useful for such preoperative technique, and are substantially totally free from any objectionable effects.

The problem of skin sterilization, it will be understood, is one involving a peculiarly high and reliable antiseptic activity on the part of the sterilizing agent. This is in part because the antiseptic is obliged to exert its action not only at the surface of the skin to which it is applied, but also for a short distance into the skin; for the deleterious or pathogenic microorganisms encountered in the skin are frequently by no means all at the surface thereof.

Furthermore, for preoperative technique, it is desirable, and almost essential, that the antiseptic be of the bactericidal, rather than the bacteriostatic class. The alkyl mercuric salts are bactericidal, and not merely bacteriostatic.

For a purpose so critical as a preoperative skin sterilizing agent, mere in vitro tests of antiseptic activity afford no good criteria. This is because antiseptics is frequently easily demonstrable in vitro, but turns out, in vivo, to be either impossible, or at least impracticable, for one reason or another. Hence, in determining the suitability of the alkyl mercuric salts as preoperative skin sterilizing agents, my tests were based upon in vivo methods rather than in vitro methods.

In order fully to explain the highly satisfactory antiseptic properties deduced, the precise method for the in vivo testing of the alkyl mercuric salts herein claimed is set forth below. My method of testing is a variation, or improvement, upon the method described by Birkhaug, in the Journal of Infectious Diseases, vol. 53, page 250 et seq. (1933). My method of testing is as follows:

Normal young adult rabbits were strapped firmly to animal boards. The hair on the belly was quickly and completely removed by first clipping it close to the skin, followed by the application of a thin barium sulphide-flour (1:1) paste. The depilated skin was then washed, taking especial care to remove all the barium sulphide. The animal was anesthetized with "Nembutal" administered intraperitoneally. When the belly was thoroughly dry, it was marked off into squares of approximately one square inch each. With aseptic technique, the animal was draped in such a manner as to expose only the depilated area. Organisms were not added to the skin, since in no case was it ever sterilized by depilation. The antiseptic to be used was placed in sterile test tubes, each of which contained a sterile swab. The swab, soaked in antiseptic, was rubbed vigorously over the desired skin square for 25 seconds. This process of rubbing was adopted because I had been able to demon-

strate that it enhanced the antiseptic activity of a compound. At the end of 3 minutes, a piece of skin approximately 15 mm. in diameter was removed from the medicated square with sterilized forceps and Stille steel scissors. It was immediately dropped into 100 cc. of infusion broth and incubated at 37° C. As a standard of comparison, from six to twelve squares were treated in an identical manner with 70 per cent ethyl alcohol. A total of no less than 18 squares was obtained on each rabbit. Three pieces of untreated skin were taken from each animal to be certain that barium sulphide had not itself sterilized the skin. The presence of organisms was determined at intervals by the development of a cloudiness in the media.

Following the observations made at 48 hours, the growth was in most cases confirmed by the staining of the organisms according to Gram's method. The morphology of the organisms present was observed and recorded. Any flasks which remained clear after 48 hours incubation were inoculated with from 50 to 1000 organisms obtained from an unmedicated skin culture. All these inoculated flasks developed a good growth of organisms, eliminating the possibility of bacteriostasis. Growth, however, did not always appear at a uniform rate. No attempt was made to culture anaerobic organisms.

To obviate the possibility of misleading conclusions because of animal variation, a minimum of twelve animals was used in testing each antiseptic preparation.

Using the technique described above, I tested the antiseptic activity of methyl, ethyl, propyl, n-butyl, n-amyl, and n-heptyl mercuric chlorides. In each instance, I made up a solution of the desired alkyl mercuric salt in aqueous ethyl alcohol. For each animal, in order to get a direct comparison, certain of the skin squares were rubbed not with the solution of the alkyl mercuric salt, but with aqueous alcohol in the same concentration as the solvent for the particular alkyl mercuric salt under test. The following table sets forth the results obtained:

Antiseptic	Solvent (percent ethyl alcohol in water)	Concen- tration (molar)	No. of rabbits	Medicated skin snips		Standard of comparison		Differ- ence
				Total number	Percent sterile	Total number	Percent sterile	
	<i>Percent</i>							
Methyl-mercuric-chloride.....	25	0.0018	5	60	31.6	60	1.6	30.0
Do.....	70	0.0036	6	72	91.7	72	50.0	41.7
Ethyl-mercuric-chloride.....	25	0.0018	5	60	33.0	60	1.6	31.4
Do.....	70	0.0036	6	72	83.3	72	47.2	36.1
Propyl-mercuric-chloride.....	25	0.0018	4	48	41.7	48	0.0	41.7
Do.....	25	0.0036	7	84	84.5	84	1.2	83.3
Do.....	70	0.0036	4	48	81.3	48	27.1	54.2
n-Butyl-mercuric-chloride.....	70	0.0036	4	48	93.7	48	47.9	45.8
n-Amyl-mercuric-chloride.....	70	0.0036	7	84	97.6	84	46.4	51.2
n-Heptyl-mercuric-chloride.....	70	0.0036	4	47	87.2	47	34.2	53.0

In the above table, the right-hand column, headed "Difference," shows the numerical difference between the per cent. of sterile snips for the medicated skin snips, on the one hand, and for the unmedicated control skin snips, on the other, and this "difference" thus comprises a numerical evaluation of the relative antiseptic activities of the compounds investigated. By way of comparison, it may be stated that the identical technique applied to 3% picric acid in 70% ethyl alcohol shows a "difference" figure of 18.0; 0.1% mercury oxycyanide in 70% ethyl alcohol shows a "difference" figure of 3.2; N. N. R. surgical tincture of mercurochrome (2%) shows a "differ-

ence" figure of 24.1; and a 7% U. S. P. tincture of iodine shows a "difference" figure of 33.6. The superiority of the alkyl mercuric salts investigated is thus evident.

In addition to the alkyl mercuric chloride indicated in the above table, I have also tested and found to be possessed of relatively high antiseptic activity, the following alkyl mercuric salts:

1. 0.018 molar solution of methyl mercuric bromide in 80% ethyl alcohol.
2. 0.018 molar solution of ethyl mercuric bromide in 80% ethyl alcohol.
3. 0.2% solution of hexyl mercuric bromide in 80% ethyl alcohol.
4. 1% solution of secondary butyl mercuric chloride in 75% ethyl alcohol.
5. 0.16% solution of heptyl mercuric bromide in 80% ethyl alcohol.

Salts other than the chlorides and bromides also appear to have the desired antiseptic property. For example, the iodides, the sulfates, the nitrates, and the hydroxides likewise appear to present this activity. I intend, for purposes of the present application, to include the hydroxides in the term "salts."

The antiseptic activity appears to reside in the cation $R-Hg^+$, where R is an alkyl, and accordingly any substance which in water solution will present such a cation is within the scope of the present invention.

It is to be noted that the propyl mercuric salts, among the several alkyls investigated, appear for some reason to have much the greatest antiseptic activity of all of the salts. Note the "difference" value of 83.3 for the 0.0036 molar solution in 25% ethyl alcohol as given in the above table. It will accordingly be understood that propyl mercuric chloride is apparently the preferred embodiment of the present invention, although this is not intended to exclude the other salts as useful.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As many changes could be made in the above methods and substances and products without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

I claim:

1. An antiseptic containing, as an active ingredient thereof, a substance which, in aqueous solution, provides a cation having the type-formula $R-Hg^+$, where R is an alkyl.

2. A preoperative skin sterilizing agent containing, as an active ingredient thereof, a substance which, in aqueous solution, provides a

cation having the type-formula $R-Hg^+$, where R is an alkyl.

3. An antiseptic containing, as an active ingredient thereof, an alkyl mercuric salt.

4. An antiseptic containing, as an active ingredient thereof, an alkyl mercuric halide.

5. A preoperative skin sterilizing agent containing, as an active ingredient thereof, an alkyl mercuric salt.

6. An antiseptic containing, as an active ingredient thereof, propyl mercuric chloride.

7. A preoperative skin sterilizing agent containing, as an active ingredient thereof, propyl mercuric chloride.

8. The method of producing antiseptics which comprises applying to the region to be treated a substance which, in aqueous solution, provides a cation having the type-formula $R-Hg^+$, where R is an alkyl.

9. The method of sterilizing living skin which

comprises applying to the skin a substance which, in aqueous solution, provides a cation having the type-formula $R-Hg^+$, where R is an alkyl.

10. The method of producing antiseptics which comprises applying propyl mercuric chloride to the region to be treated.

11. The method of sterilizing living skin which comprises applying propyl mercuric chloride to the skin.

12. An antiseptic containing as an active ingredient thereof an alkyl mercuric chloride.

13. As a sterilizing agent an alkyl mercuric compound which provides in solution a cation having the type formula $R-Hg^+$ where R is an alkyl group.

14. As a sterilizing agent propyl mercuric chloride.

MILTON T. BUSH.