SUMMARY.

1. In rats the acute Average Fatal Dose of propylene glycol was found to be 33.5 Gm. per Kg. orally, 22.5 Gm. subcutaneously, 14 Gm. intramuscularly and 6.8 Gm. intravenously. These figures are in agreement with those reported by other authors, with the exception of the intravenous fatal dose, which is somewhat less than half that reported by other authors. Reasons are given for believing the lower figure to be correct for the intravenous fatal dose.

2. In rabbits the acute Average Fatal Dose on intravenous administration was found to be 6.5 Gm. per Kg.

3. The chronic toxicity of propylene glycol was studied by the administration of the material to growing rats by way of their drinking water. Concentrations of 3% or less caused no appreciable change in rate of growth. A concentration of 10% caused a temporary slowing in rate of growth which lasted for about ten days. Rate of growth after this initial slowing became essentially normal. No significant changes were found on microscopic examination of organs of these animals sacrificed at the end of the experimental period of 100 days.

4. Hematuria was observed following the intravenous administration of sublethal doses of propylene glycol to rats. Hemolysis was produced *in vitro* by both diethylene glycol and propylene glycol in concentrations greater than 0.14 molar. This *in-vitro* action seems to be due to the dilution of isosmotic NaCl solution with the osmotically inactive glycol solution, rather than to a specific hemolytic action of these glycols in the dilutions used.

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LIQUOR ANTISEPTICUS.*

BY H. S. HOWELL,[1] LOUIS GOLDBERG,[1] R. K. SNYDER[1] AND E. N. GATHERCOAL.[1]

BORIC ACID IN LIQUOR ANTISEPTICUS.

The following statement in the N. F. VI monograph on Liquor Antisepticus has been criticized on the basis that the limits on these residues were not always attainable:

"Evaporate 10 cc. of the solution at 100° C.: not more than 0.184 Gm. of a white crystalline residue remains. Add 10 cc. of alcohol to this residue and ignite: the flame is enveloped with a green mantle and not less than 0.042 Gm. of residue remains."

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* National Formulary Research Project F7 at the University of Illinois College of Pharmacy. This is but an abstract of the original paper which is given in full in the National Formulary Bulletin, pages 2682-2689.

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Residue values were obtained by this test on nine lots of N. F. antiseptic solution prepared in the laboratory or obtained commercially. While the values in each case meet the official standards, yet the varying results, even on the same solution, are unsatisfactory. These variations are probably due to the effect of heat on boron compounds.

The following assay for boric acid has been developed in this laboratory.

Dilute Tumeric T.S. to fifteen times its volume with alcohol. Dissolve 2.5 Gm. (this could be made 2.4, 2.3 or even 2.2 Gm.) of boric acid, in a sufficient quantity of a 30 per cent alcohol-water mixture to make exactly 100 cc. of a boric acid standard solution. Mix 2.0 cc. of the tumeric dilution with 25 cc. of antiseptic solution, and another 2.0 cc. of the tumeric dilution with 25 cc. of the boric acid standard solution. Allow the mixtures to stand for ten minutes and then compare them in a colorimeter. The intensity of color developed in the mixture containing the antiseptic solution is not less than that developed in the mixture containing the boric acid standard solution.

NOTES.

(1) The color developed by the boric acid and tumeric is distinctive and considered to be a confirmative test for either item, and is frequently used as such.

(2) The test has shown that it is accurate to at least 96 per cent of the theoretical content of boric acid.

(3) The test is more accurate and more indicative of boric acid than the residue test now in the monograph. There is no interference from the other compounds in the antiseptic solution.

INCOMPATIBILITY OF THYMOL AND CHLORTHYMOL WITH EUCALYPTOL.

When the N. F. V monograph of Liquor Antisepticus was revised, 1.0 Gm. of chlorthymol was added to increase the antiseptic power of the solution. At the same time the amount of eucalyptol was reduced from 5 cc. to 2 cc. The N. F. VI formula has been criticized on the basis that chlorthymol is incompatible with eucalyptol.

Assay of Thymol and Chlorthymol.—An attempt to estimate thymol and chlorthymol in alcoholic solutions and in aqueous-alcoholic solutions, both in the absence of and the presence of eucalyptol, has been made by adapting the method tentatively adopted by the Association of Official Agricultural Chemists and developed by Leslie Hart, Associate Referee, U. S. Food and Drug Administration, St. Louis, Mo., to our purposes. Each cc. of tenth-normal bromine is equivalent to 0.003753 Gm. of thymol, 0.009228 Gm. of chlorthymol or 0.002667 Gm. of each in equal parts by weight.

1. The determination of the thymol or chlorthymol in simple alcoholic solutions by direct titration with tenth-normal bromine gave 100% results. In each of the other determinations the assay process was used and this gives consistently lower results, from 92.4% to 99.5%, mostly 96% and 97%.

2. Solutions in alcohol or in alcohol 1 vol.—water 3 vols., of thymol, of chlorthymol, or of thymol and chlorthymol are clear without filtration. When eucalyptol is added to these alcoholic solutions they still remain clear, but when water is then added, the clear solutions become very cloudy. It is evident that incompatibility, due to the eucalyptol, occurs when thymol or chlorthymol with eucalyptol is dissolved (?) in a mixture of alcohol 1 vol.—water 3 vols.

3. When the cloudy mixtures of No. 2 are well shaken and assayed, nearly 100% of the thymol or chlorthymol or both is determined.

4. When the cloudy mixtures of No. 2 are filtered until clear, the assay shows a loss of about one-third of the thymol and two-thirds of the chlorthymol. Probably the incompatibility is of a physical nature rather than chemical.

5. Liquor Antisepticus, *i. e.*, the product after filtration, has lost much of the thymol and chlorthymol used in its preparation.

6. L. Hart, who developed this assay method, obtained results varying from 90% to 103% of theory, while in this laboratory results vary from 82.2% to 99.8% of theory. The variation in results possibly lies in the difficulty in obtaining proper extraction with the solvents.

NEW FORMULA PROPOSED FOR LIQUOR ANTISEPTICUS.

From the experiments previously recorded it is evident that in the present official formula the flavoring ingredients cause precipitation of a considerable proportion of some of the active ingredients.

All of the ingredients in the present official formula are soluble, individually, in the solvent except eucalyptol. Experiments indicated that 0.8 cc. of eucalyptol was the maximum quantity that could be dissolved in a solvent composed of alcohol 300 cc. and water *q. s.* 1000 cc. When 1.0 Gm. of chlorthymol was introduced into this solution, immediately an oily globule formed on the surface and upon shaking the mixture became turbid.

Eucalyptol 0.1 to 0.2 cc. was the maximum amount that could be dissolved in a solution of 1.0 Gm. of chlorthymol in a mixture of alcohol 300 cc. and water *q. s.* 1000 cc.

When to the clear solution mentioned in the previous paragraph, 1.0 Gm. of menthol was added, an oily globule formed on the surface. These globules were tested for "chloride" by the Volhard method, but poor results were obtained.

If all of the thymol and chlorthymol be retained in the finished solution, the present official quantities could be reduced by one-half and the antiseptic power remain greater than at present.

Methyl salicylate does not affect precipitation; neither does menthol when reduced to 0.5 Gm. in the formula. The oil of thyme, however, requires careful adjustment, yet is important in developing the flavor.

After many combinations were tried, the following formula seemed to be most satisfactory:

Boric acid	25.0 Gm.
Thymol	0.5 Gm.
Chlorthymol	0.5 Gm.
Menthol	0.5 Gm.
Methyl salicylate	0.2 cc.
Eucalyptol	0.1 cc.
Oil of thyme	0.01 cc.
Alcohol	300.0 cc.
Water, a sufficient quantity, To make	1000.0 cc.

Dissolve the boric acid in 650 cc. of hot water and allow the solution to cool. Dissolve the other ingredients in 300 cc. of alcohol. Mix the two solutions and

add sufficient water to make 1000 cc. Allow to stand in a tightly closed container for 24 hours and filter.

This solution when first mixed is perfectly clear if a reagent grade of boric acid is used. Commercial U. S. P. boric acid frequently causes a slight cloudiness. However, upon standing for a day or so, a slight cloudiness always develops. Apparently this trace of turbidity has no effect on the thymol and chlorthymol, as assays on the filtered and unfiltered solutions show identical results. The aroma and taste of the new antiseptic solution differ slightly from the present official solution and the acridity and pungency is notably less. It is the concensus of opinion in this laboratory that the odor and taste are more pleasant than those of the official article.

The antiseptic power of the proposed preparation is higher than that of the official preparation. It kills the test organism, under the conditions of the test, in one minute instead of five minutes as allowed by the test. Even in half strength it will kill the test organism in one minute.

SUMMARY.

1. The limits on the residues from the boric acid obtained by the evaporation and the ignition tests of N. F. VI are not fully satisfactory.

2. An adaptation of the tumeric test for boric acid serves for the qualitative and quantitative determination of boric acid in Liquor Antisepticus.

3. An incompatibility that occurs during the preparation of Liquor Antisepticus is apparently physical in nature and occurs when eucalyptol above 0.02 per cent is added to the aqueous-alcoholic solution of thymol or chlorthymol or both.

4. The A. O. A. C. tentative assay for thymol has been used on solutions of thymol, and adapted to solutions of chlorthymol and Liquor Antisepticus.

5. A formula for Liquor Antisepticus which is unchanged from the official formula, except in the proportion of certain of the ingredients, is offered. It presents no incompatibilities, is more highly antiseptic than the present official solution, is not so acrid or pungent in taste, yet preserves the same aroma, is less difficult to compound and is less expensive.

A STUDY OF DATURA STRAMONIUM.*

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Datura Stramonium Linné is one of the two well-known species of Datura found in Pennsylvania. Within the limits of the city of Philadelphia it frequently thrives in impoverished soil and even where conditions are most unfavorable for the development of many uncultivated plants, Stramonium frequently grows to a height of two meters, produces large stems and rank foliage and otherwise exhibits most of the normal vegetative characteristics.

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