

UNITED STATES PATENT OFFICE

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ANTISEPTIC AND PREPARATION THEREOF

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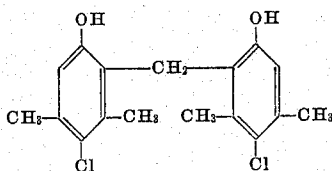
1

This invention relates to a new, hydroxylated, chlorinated diphenylmethane having valuable uses as a bactericidal agent and antiseptic. More specifically, this invention relates to 2,2'-methylene-bis-(4-chloro-3,5-xenol).

This application is a continuation in part of our prior, pending application of Serial Number 244,729, filed August 31, 1951, now abandoned.

The use of the class of substances often called methylene-bis-phenols as germicides, antiseptics and topical antibacterial agents has become generally recognized in the art. A principal problem has been to obtain a high degree of antibacterial efficacy without concomitant high toxicity toward the animal or human body. Consequently, much effort has been expended in the search for compounds of increased efficacy and suitably low toxicity.

We have now discovered, according to the present invention, the new compound which has the following formula



and is named 2,2'-methylene-bis-(4-chloro-3,5-xenol), according to the practice of Chemical Abstracts, which may be designated properly also as bis-(5-chloro-4,6-dimethyl-2-hydroxyphenyl) methane.

We have also discovered that the product of the present invention is safe and highly effective as a bactericidal agent and antiseptic, particularly for topical use.

A typical example of the activity of the new hydroxylated diphenylmethane derivative in comparison with one of the best of the previous members of the class of methylene-bis-phenols is obtained by tests against the standard pathogen *Staphylococcus aureus*, as measured in the serial dilution procedure. The results of this test are given in Table I. The compound used for comparison has usually been designated in commerce as G-11 or hexachlorophene and was originally prepared by Gump (U. S. Patent 2,250,480).

2

TABLE I

In vitro antibacterial activity

Compound	Minimum Effective Concentration in Micrograms per Milliliter
I. 2,2'-methylene-bis(4-chloro-3,5-xenol) ----- II. Bis-(3,5,6-Trichloro-2-hydroxyphenyl) methane (G-11) -----	* 0.5 b 0.5-2.0

* Minimum concentration required to inhibit completely the growth of the test organism, *Staphylococcus aureus*.

b Range of minimum concentration through which this compound exhibits partial to complete inhibition of the growth of the test organism, *Staphylococcus aureus*.

The greater potency of the compound (I) of the present invention is indicated by inspection of this data. This superiority may be extended to many other compounds by the use of the prior art, since the activity of compound II relative to other bis-phenols has been disclosed.

However, the significance of the higher potency of this new hydroxylated diphenylmethane as an advance in the art becomes most apparent when considered in conjunction with its very low toxicity. A typical example of the low toxicity of the compound of the present invention as compared to one of the most useful of the present members of the methylene-bis-phenol class is obtained by the measurement of the minimum lethal dose required to kill fifty percent of a group of mice upon intraperitoneal injection, commonly designated LD₅₀. The compound used for comparison is G-11 and the results are shown in Table II.

TABLE II

Toxicity

Compound	LD ₅₀ mouse, I. P., mgms./kg.
I. 2,2'-Methylene-bis(4-chloro-3,5-xenol). II. Bis-(3,5,6-Trichloro-2-hydroxyphenyl) methane (G-11).	greater than 1,000±200. 84±15.

As determined by these particular tests, the product of the present invention is about one to four times as potent and about one-eleventh as toxic as one of the leading products of the prior art. Other tests give different numerical values

for this comparison but continue to indicate the improvement in terms of increased potency and decreased toxicity which has been achieved in the compound of the present invention.

2,2'-methylene-bis-(4-chloro-3,5-xylene) is a white, crystalline, practically odorless solid. It is readily soluble in alcohol, acetone, many organic solvents and in alkaline aqueous solutions. It may be emulsified using the common surface-active agents or diethanolamine and its homologues. Its bacteriostatic activity is of sufficiently high an order that effective concentrations are readily attainable in virtually all types of product media; for example, an aqueous solution containing 0.06 milligram per milliliter completely inhibits the gram-negative organism *E. coli*.

A more comprehensive understanding of this invention is obtained by reference to the following example, which is given by way of illustration and not of limitation.

EXAMPLE 1

A solution of 156 grams 4-chloro-3,5-xylene in 300 milliliters methanol is placed in a flask equipped with a mechanical stirrer, and heated to 50-70° C. A stream of hydrogen chloride is bubbled through, and after saturation is attained, the slow addition of 35 milliliters aqueous formaldehyde (37%) is begun at a rate requiring 2 hours for total addition. An additional 40 milliliters of formaldehyde solution is now added over an hour's duration. The white precipitate which separates is filtered, washed with water, and pressed as dry as practical.

The filter cake is digested with a boiling mixture of 900 ml. 15% aqueous sodium hydroxide and 900 ml. methanol, and the hot suspension, containing alkali-insoluble material, is diluted with stirring by the addition of 4 liters cold water. After cooling and filtering, the clear filtrate is slowly acidified with concentrated aque-

ous hydrochloric acid until pH 11 is reached. The precipitate of 2,2'-methylene-bis-(4-chloro-3,5-xylene) is collected by filtration, washed well with water, and dried in the oven. Yield: 30 grams. The compound may be recrystallized from 40 milliliters hot toluene per gram. Under these conditions it forms colorless needles which melt at about 231-232° C.

Molecular Weight.—Calculated for $C_{17}H_{12}O_2Cl_2$: 325. Found: (Rast camphor procedure): 322.

Analysis.—Calculated for $C_{17}H_{12}O_2Cl_2$: C. 62.8; H. 5.58. Found: C. 62.9; H. 5.06.

We claim:

1. The compound 2,2'-methylene-bis-(4-chloro-3,5-xylene).

2. The process of making 2,2'-methylene-bis-(4-chloro-3,5-xylene) comprising reacting 4-chloro-3,5-xylene with formaldehyde in the presence of an acidic condensing agent and purifying the product.

3. The process of making 2,2'-methylene-bis-(4-chloro-3,5-xylene) comprising reacting 4-chloro-3,5-xylene with formaldehyde in the presence of hydrochloric acid and purifying the product.

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REFERENCES CITED

The following references are of record in the file of this patent:

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Number	Name	Date
2,353,725	Gump	July 18, 1944

OTHER REFERENCES

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