

CHEMICAL STRUCTURE AND ANTIMICROBIAL ACTIVITY OF BIS-PHENOLS. IV. BROAD SPECTRUM EVALUATION OF 2,2'-METHYLENEBIS (DICHLOROPHENOLS)

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ABSTRACT

Five symmetrical 2,2'-methylenebis (dichlorophenols) and the asymmetrical 3,4,4',5'-tetrachloro-2,2'-methylenediphenol were investigated for their antimicrobial activity against bacteria, molds and yeasts. The three isomers in which the 6- and 6'-positions adjacent to the hydroxyl groups are not substituted by chlorine were found to exhibit a broader spectrum of activity against the test organisms. The most potent compound was 2,2'-methylenebis (3,5-dichlorophenol); less active was 2,2'-methylenebis (4,6-dichlorophenol), G-5® (Sindar Corp.), a compound known for many years. It lacked activity against gram-negative bacteria (with the exception of *Proteus vulgaris*), yeasts and molds. None of the isomers was effective against gram-negative bacteria in presence of soap at a level of 20 µg. ml.

A previous study pertained to the bacteriostatic and fungistatic properties of hexachlorophene and its isomers (1). It was reported earlier (1,2) that 2,2'-methylenebis (3,4,5-trichlorophenol) exhibited the greatest activity against gram-positive and gram-negative bacteria. This compound is the only isomer of hexachlorophene which has no chlorine substituents adjacent to the hydroxyl groups. It seemed to be of interest to determine whether other bis-phenols with ring hydrogen atoms next to the hydroxyls are more active than those in which these hydrogen atoms are replaced by chlorine atoms. The series of 2,2'-methylenebis (dichlorophenols) was selected to be suitable for such a comparison. Of the six possible symmetrical isomers, five were synthesized and are listed in Table I with their melting points and chlorine contents. Omitted is 2,2'-methylenebis (4,5-dichlorophenol), as no satisfactory method for its preparation

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was found; the closely related asymmetrical compound 3,4,4',5'-tetrachloro-2,2'-methylenediphenol (No. VI) could, however, be readily prepared. It will be noted that in three isomers (I, IV and V) the hydrogen atoms in the 6,6'-positions are substituted by chlorine atoms, whereas in the other three (Nos. II, III and VI) this is not the case.

TABLE I—2,2'-METHYLENEBIS (DICHLOROPHENOL) ISOMERS

No.	Isomer	M.p., °C.	Analyses, % Chlorine* Found
I	2,2'-methylenebis (4,6-dichlorophenol), G-5®	168-170	41.7
II	2,2'-methylenebis (3,4-dichlorophenol)	221-223	41.9
III	2,2'-methylenebis (3,5-dichlorophenol)	186-187	41.6
IV	2,2'-methylenebis (3,6-dichlorophenol)	113-115	41.7
V	2,2'-methylenebis (5,6-dichlorophenol)	145-147	41.4
VI	3,4,4',5'-tetrachloro-2,2'-methylenediphenol	199-201	41.8

* Calculated for $C_{13}H_8O_2Cl_4$: Cl, 41.9%.

TABLE II—2,2'-METHYLENEBIS (BROMODICHLOROPHENOLS)

Nos. Corresponding to Those of Table I	Isomer	M.p., °C.
II A	6-bromo-3,4-dichloro	171-172
III A	4-bromo-3,5-dichloro	207-208
IV A	4-bromo-3,6-dichloro	162-164
V A	4-bromo-5,6-dichloro	213-214

TABLE III—BROMODICHLOROANILINES AND BROMODICHLOROPHENOLS

Compound (Anilines)	M.p., °C.	Compound (Phenols)	M.p., °C.
4-bromo-2,5-dichloro	91-92*	4-bromo-2,5-dichloro	71-73‡
4-bromo-3,5-dichloro	125-127†	4-bromo-3,5-dichloro	121-123
6-bromo-3,4-dichloro	91-93	6-bromo-3,4-dichloro	70-71
		4-bromo-2,3-dichloro	53-54
		6-bromo-2,3-dichloro	87-89

* m.p. 91-92, ref. 8. † m.p. 129°, ref. 7. ‡ m.p. 71-72°, ref. 8.

The bis-phenols II to V (Table I) were synthesized by condensation of the bromodichlorophenols (Table III) with formaldehyde in the presence of sulfuric acid, followed by debromination of the intermediate 2,2'-methylenebis (bromodichlorophenols) which are listed in Table II. Compounds I and VI were obtained from the reaction of 2,4-dichlorophenol and 3,4-dichlorophenol, respectively, with formaldehyde.

Of the 2,2'-methylenebis (dichlorophenols), only 2,2'-methylenebis (4,6-dichlorophenol) and a substance claimed to be 2,2'-methylenebis (4,5-dichlorophenol)* have been described previously (3,4). In the preceding papers (2, 5) we listed two compounds, 2,2'-methylenebis (5,6-dichlorophenol), No. 9, and 2,2'-methylenebis (4-bromo-5,6-dichlorophenol), No. 5. It has now been determined that these compounds are actually 4,4'-methylenebis (2,3-dichlorophenol) and 4,4'-methylenebis (6-bromo-2,3-dichlorophenol), respectively. The starting material had been 6-bromo-2,3-dichlorophenol and not, as we had assumed, 4-bromo-2,3-dichlorophenol. Bromination of 2,3-dichlorophenol leads to either compound, depending upon the solvent used.

EXPERIMENTAL

I. Chemical

2,3-Dichlorophenol and 3,4-dichlorophenol were purchased from Aldrich Chemical Co., Milwaukee, Wis. Of the various bromodichlorophenols (Table III) needed as starting materials, only the 4-bromo-2,3-dichlorophenol could be prepared by direct bromination of the dichlorophenol. Otherwise, this procedure results in mixtures of isomers which could not be separated. Bromination of 2,3-dichlorophenol led to 4-bromo-2,3-dichlorophenol when acetic acid was used as solvent; in the presence of methanol, 6-bromo-2,3-dichlorophenol† was predominantly formed. The other bromodichlorophenols were obtained from the corresponding bromodichloroanilines (Table III) through the diazonium salts as described by Tiessens (6).

Specific details for the preparation of the bromodichloroanilines and bromodichlorophenols are as follows:

6-Bromo-3,4-dichloroaniline. To a stirred slurry of 612 g. of 3,4-dichloroacetanilide and of 246 g. of anhydrous sodium acetate in 1500 ml. of acetic acid was added a solution of 480 g. of bromine in 600 ml. of acetic acid during six hours. The next day, the batch was heated at 50° for a

* The latter compound (4) was reportedly obtained by the condensation of 3,4-dichlorophenol with formaldehyde in the presence of 80% sulfuric acid. Recrystallization of the crude product yielded a substance melting at 194–196°. Further purification raised the m.p. to 201°. Following the cited procedure we isolated a bis-phenol with a m.p. of 199–201°. It is our belief that this bis-phenol is actually the asymmetrical 3,4,4',5'-tetrachloro-2,2'-methylene-diphenol and does not have the structure of 2,2'-methylenebis(4,5-dichlorophenol) assigned to it in Geigy Co.'s patents. The basis for this conclusion is presented under preparation of Compound No. VI in the Experimental part of this article.

† Its structure was proved by the following sequence of reactions: Condensation with formaldehyde gave 4,4'-methylenebis (6-bromo-2,3-dichlorophenol) which, on debromination, yielded 4,4'-methylenebis (2,3-dichlorophenol). When this compound was chlorinated, 4,4'-methylenebis (2,3,6-trichlorophenol) was obtained. It melted at 162–164°. The m.p. of a mixture with pure 4,4'-methylenebis (2,3,6-trichlorophenol), m.p. 166–167° (1), was 163–165° showing no depression.

period of five hours. After cooling, the solid was filtered, washed with water and crystallized from a mixture of 1000 ml. of isopropanol and 200 ml. of dimethylformamide. To the first filtrate a small amount of water was added, and the precipitate formed was crystallized from the isopropanol-dimethylformamide mother liquor. A total of 331 g. of 6-bromo-3,4-dichloroacetanilide, m.p. of 172–173°, was obtained. It was slowly heated to 120° with a mixture of 330 g. of a 50% (by weight) aqueous sodium hydroxide solution and 1000 g. of ethylene glycol and kept at this temperature for five hours. The batch was poured into a large amount of cold water, the precipitate filtered, washed with water and, while moist, crystallized from 450 ml. of isopropanol. First and second crops amounted to 258 g., m.p. 90.5–92°. Recrystallization from 450 ml. of petroleum naphtha (b.p. 120–135°), with the aid of Filtrol®*, yielded 210 g. of pure 6-bromo-3,4-dichloroaniline, m.p. 91–93°.

4-Bromo-2,5-dichloroaniline. It was prepared from 2,5-dichloroaniline by the following steps: 2,5-dichloroaniline → 2,5-dichlorobromobenzene → 4-bromo-2,5-dichloronitrobenzene → 4-bromo-2,5-dichloroaniline (8).

4-Bromo-3,5-dichloroaniline. Its preparation from 3,5-dichloroacetanilide was conducted as described for that of 6-bromo-3,4-dichloroaniline.

4-Bromo-2,3-dichlorophenol. In order to demonstrate that the bromination of 2,3-dichlorophenol in acetic acid solution results in the 4-bromo-derivative, a small amount of the bromination product was chlorinated in acetic acid. Crystallizations of the crude product from heptane and aqueous alcohol yielded a pure bromotrichlorophenol, m.p. 83–84°. 4-Bromo-2,3,6-trichlorophenol, obtained by bromination of 2,3,6-trichlorophenol (9), had the same m.p. and a mixture of both substances showed no depression.

4-Bromo-3,5-dichlorophenol. To 420 ml. of 96% sulfuric acid was added 42 g. of sodium nitrite with agitation and cooling, and then 144 g. of 4-bromo-3,5-dichloroaniline during 90 minutes at 25–30°. After addition of 410 ml. of 96% sulfuric acid, the mixture was slowly heated to 80–85°, held at this temperature for three hours, and overnight at room temperature. The diazonium salt solution was then dropped into a heated mixture of 1200 g. of cryst. cupric sulfate and 1200 ml. of water while steam passed through. Following a nine hour steam distillation, the distillates were extracted with isopropyl ether, the extract concentrated to dryness (101 g.) and the residue crystallized from 350 ml. of heptane, Filtrol being used for decolorization. Yield: 80.5 g.

In a similar manner, *4-bromo-2,5-dichlorophenol* (8) and *6-bromo-3,4-dichlorophenol* (10)† were obtained from the corresponding bromodichloroanilines.

* Filtrol Corp., Los Angeles, Calif.

† The compound was mentioned in the reference by name only. Its structure was established by chlorinating it to 6-bromo-2,3,4-trichlorophenol. The latter substance was identical with the one obtained by bromination of 2,3,4-trichlorophenol (8).

2,2'-Methylenebis (bromodichlorophenols) (Table II). IIA, IVA, and VA were prepared by condensing the appropriate bromodichlorophenols (50 g.) with paraformaldehyde in the presence of oleum and ethylene dichloride. The procedure was the same as the one employed (1) for the synthesis of 2,2'-methylenebis (4,5,6-trichlorophenol). The crude products (49 to 50 g.) were purified by crystallization from toluene with the aid of Filtrol. Yields: 29 to 31 g.

In the case of the more reactive 4-bromo-3,5-dichlorophenol, the method for the preparation of 2,2'-methylenebis (4-bromo-3,5-dichlorophenol), III A, was the same as the one described (1) for the preparation of 2,2'-methylenebis (3,4,5-trichlorophenol). From 72 g. of the bromodichlorophenol, 16.7 g. of an acetone-insoluble by-product and 49.7 g. of crude, III A, m.p. 201–202°, were obtained. Crystallization from 400 ml. of toluene, with the aid of Filtrol, yielded the pure substance (32.2 g.) in the form of a white, crystalline powder.

2,2'-Methylenebis (dichlorophenols) (compounds No. II to V, Table I). The 2,2'-methylenebis (bromodichlorophenols) were treated with zinc

TABLE IV

Crude Compounds (22–23 g.) No.	Solvents for Crystallization	Yields of Pure Compounds (g.)
II	mixture of 100 ml. of toluene 100 ml. of hexane 50 ml. of p-dioxane	16.7
III	mixture of 220 ml. of toluene 110 ml. of hexane	15.4
IV	1) 150 ml. of aqueous alcohol (60% by vol.) 2) 225 ml. of hexane	11.2
V	1) 75 ml. of toluene 2) 25 ml. of methanol	9.8

dust in potassium hydroxide solution to remove the bromines, following the procedure described previously (1). From 34 g. of the bromo compounds, yields of 22–23 g. of the crude 2,2'-methylenebis (dichlorophenols) were obtained. The purification was carried out by one or two crystallizations, Filtrol being used for decolorization. The solvents and the yields of the pure products are listed in Table IV. The chlorination of II led to 2,2'-methylenebis (3,4,6-trichlorophenol), hexachlorophene.

3,4,4',5'-Tetrachloro-2,2'-methylenediphenol (VI). Paraformaldehyde (7.6 g.) was added over a period of three hours to a mixture of 80 g. of 3,4-dichlorophenol, 160 g. of ethylene dichloride and 100 g. of 78% sulfuric acid which was stirred and kept at room temperature (25–28°). Agitation was continued for 18 hours. After steam distillation for the removal of unchanged 3,4-dichlorophenol (4.3 g.), a yellow solid (76 g.) remained which, after washing and drying, was crystallized from 280 ml. of toluene

with the aid of Filtrol. The product obtained (26.6 g., m.p. 190–195°) was recrystallized from 280 ml. of the ethylene dichloride yielding a white, crystalline powder (16.2 g.).

3,4,4',5',6,6'-Hexachloro-2,2'-methylenediphenol (VII). In order to prove the structure of compound No. VI, a solution of 2.3 g. in 30 ml. acetic acid was chlorinated by slowly adding a solution of 1 g. of chlorine in 50 ml. acetic acid. At the end of 4 hours, the solution was concentrated to about one-third volume and a small amount of water added. The precipitate was filtered, washed with water and dried; 2.8 g.; m.p. 148–151°. Recrystallization from ethylene dichloride gave fine, white needles, m.p. 162–163°; mixed m.p. with 2,2'-methylenebis (3,4,6-trichlorophenol), hexachlorophene 135–142°.

Anal. Calcd. for $C_{13}H_6O_2Cl_6$: C, 38.76; H, 1.5; Cl, 52.32. Found: C, 38.71; H, 1.6; Cl, 52.13.

As VII is not identical with hexachlorophene and could not be 2,2'-methylenebis (4,5,6-trichlorophenol) which melts at 220–222°, it was assumed that it is the asymmetrical 3,4,4',5',6,6'-hexachloro-2,2'-methylenediphenol. This substance was synthesized from 2-hydroxy-3,5,6-trichlorobenzyl alcohol (11) and 2,3,4-trichlorophenol, following the procedure of example 1 of a British patent (12). The crude product was recrystallized from a mixture of hexane and toluene (2:1) with the aid of Filtrol. It melted at 161–162° and showed no melting point depression when mixed with the substance melting at 162–163°. This proves that both compounds are 3,4,4',5',6,6'-hexachloro-2,2'-methylenediphenol and consequently, that VI is 3,4,4',5'-tetrachloro-2,2'-methylenediphenol, as the 6,6'-positions being ortho to the hydroxyl groups are most readily substituted by chlorine.

II. Microbiological.

The preparation of the stock solutions, the twofold serial dilutions and the solid and liquid media were described in a previous paper (1). The serial dilutions were made with the aid of an automatic apparatus (Dilumat[®], Fisher Scientific Co., Bloomfield, N.J.).

Where solid media were employed, 25 ml. aliquots (48°C) were dispensed into the appropriate sets of serial dilution tubes using a Brewer automatic pipette (Baltimore Biological Laboratories, Baltimore, Md.). The contents of the tubes were poured into sterile Petri plates; the hardened agar was then surface-inoculated with one drop (0.007 ml.) of a culture by means of an Accu-Drop dispenser (Scientific Products, Flushing, L. I., N. Y.). The liquid medium was inoculated in bulk at the rate of 0.5 ml. culture per l. of medium after which 25 ml. aliquots were aseptically dispensed with the Brewer pipette into the serial dilution tubes and the contents then transferred aseptically to 125 ml. Erlenmeyer flasks.

Inocula for the bacteria were prepared by diluting a 24 hour Tryptic Soy Broth (Difco) culture 1:100 in 0.1% peptone water; in the case of *Bacterium ammoniagenes* a 48 hour culture was used. Inocula for imperfect fungi and dermatophytes were obtained by harvesting conidia from 10 and 15 day slants, respectively, in 50 ml. of 0.1% peptone water. As with the bacteria, one drop of the conidial suspension was added to the agar plates. Yeast inocula were prepared from 24 hour Sabouraud Dextrose Broth (Difco) cultures diluted 1-100 in 0.1% peptone water.

Temperature of incubation of the cultures and of the test plates was 30°. Bacterial and yeast data were recorded at the end of five days; imperfect fungi and dermatophytes at the end of 10 days; *Chlorella* at the end of 30 days over continuous illumination.

Because of the magnitude of activity exhibited by some of the compounds against several gram negative organisms, it was considered of interest to ascertain levels of activity in the presence of soap. For this purpose, a 1 ml. aliquot of the alcoholic stock solution of each compound was added to 100 ml. 2.5% white soap stock (Lever Brothers Co. Lux base). Aqueous serial dilutions were made, agar added to the serial dilution tubes, plates poured and the hardened plates inoculated as previously stated. Incubation of plates was 72 hours at 30°. Soap controls were conducted to differentiate inhibition by the soap from the bacteriostatic activity of the compounds. The ratio of soap to test compound was held constant at 100-1 for gram-positive bacteria and at 50-1 for gram-negative bacteria.

All tests were conducted in triplicate and the bacteriostatic level of the compound calculated as the geometric mean of the three observations in $\mu\text{g}/\text{ml.}$, using a graphic technique for ease of calculation. Log_{10} concentrations of compound plotted against dilution tube number served as a rapid convenient plot for calculating geometric means. The highest level tested was 100 $\mu\text{g.}/\text{ml.}$, and no attempt was made to standardize inocula in any of the tests. The minimal inhibitory concentrations are reported in Tables V and VI.

DISCUSSION

Each of the compounds tested was found to be biologically active; however, as may be noted from Table V, the isomers with hydrogens in the 6- and 6'-positions (II, III and VI) showed a broader spectrum of activity than the ones where these positions are occupied by chlorine (I, IV and V). A similar pattern had been observed previously (1) in the series of hexachlorophene and its isomers; 2,2'-methylenebis (3,4,5-trichlorophenol) was superior to hexachlorophene and the 4,5,6-trichloro isomer. In the present series, 2,2'-methylenebis (4,6-dichlorophenol), also known as G-5[®], was found to exhibit the narrowest spectrum of activity; gram

TABLE V—ANTIMICROBIAL SPECTRA OF 2,2'-METHYLENE (DICHLOROPHENOL) ISOMERS (Minimal Inhibitory Concentration, $\mu\text{g./ml.}$)

Microorganism	Compound (by Number)					
	I	II	III	IV	V	VI
<i>S. aureus</i> 6538*	0.48	0.50	0.50	0.78	0.48	0.48
<i>S. epidermidis</i> 155	0.63	0.31	0.06	1.56	0.78	0.10
<i>B. subtilis</i> 9372	0.25	0.20	0.05	0.98	0.63	0.08
<i>B. ammoniagenes</i> 6871	0.62	0.15	0.04	0.98	1.56	0.05
<i>E. coli</i> 11229	X†	9.80	7.80	100.00	X	7.80
<i>S. choleraesuis</i> 10708	X	12.50	9.80	100.00	62.00	7.80
<i>S. typhosa</i> 6539	X	20.00	12.50	X	X	7.80
<i>P. vulgaris</i> 9920	3.12	3.12	1.28	5.20	0.78	1.95
<i>Ps. aeruginosa</i>	X	25.00	20.00	X	X	16.00
<i>C. albicans</i> 10231	X	6.25	6.25	31.50	16.00	6.25
<i>S. cerevisiae</i>	X	6.25	6.25	7.80	5.00	4.00
<i>P. funiculosum</i> 11797	X	12.50	4.00	31.20	6.25	6.25
<i>P. piscarium</i> 12109	X	3.12	1.95	62.50	25.00	2.46
<i>A. niger</i> 9642	X	4.90	1.95	16.00	9.80	6.25
<i>A. flavus</i> 9643	X	9.80	7.80	62.50	16.00	16.00
<i>T. mentagrophytes</i> 9129	0.96	0.96	0.39	0.78	0.62	0.78
<i>T. rubrum</i> 10218	0.50	1.00	0.78	0.62	0.30	1.00
<i>C. vulgaris</i> 9765	1.56	0.39	0.48	3.12	1.95	0.39

* American Type Culture Collection.

† X denotes growth at 100 $\mu\text{g./ml.}$

TABLE VI—BACTERIOSTATIC LEVELS OF 2,2'-METHYLENEBIS (DICHLOROPHENOL) ISOMERS IN THE PRESENCE OF SOAP*

Organism	Compounds (by Number)					
	I	II	III	IV	V	VI
<i>S. aureus</i>	0.98	1.25	0.63	1.25	0.98	0.98
<i>S. epidermidis</i>	1.25	0.63	0.16	1.95	1.25	0.20
<i>B. ammoniagenes</i>	1.55	0.31	0.16	1.55	1.95	0.16
<i>E. coli</i>	} growth at 20 $\mu\text{g./ml.}$					
<i>S. typhosa</i>						
<i>P. vulgaris</i>						

* Soap/compound ratio: 100/1 for gram-positive bacteria.
50/1 for gram-negative bacteria.

negative bacteria, with the exception of *Proteus vulgaris*, yeasts and molds grew at a level of 100 $\mu\text{g./ml.}$ of this chemical. The most potent compound appears to be the 3,5-dichloro isomer (III), followed by the asymmetrical (VI) and 3,4-dichloro (II) isomers. These three compounds show superior activity against gram negative bacteria, yeasts and molds. All isomers are alike in their behavior against *S. aureus*, the dermatophytes and *Chlorella vulgaris*.

In the presence of soap, no difference between the isomers could be observed; all are active against gram positive bacteria and inactive at a level of 20 $\mu\text{g./ml.}$ against gram-negative ones.

SUMMARY

The broad spectrum antimicrobial activity of five isomeric 2,2'-methylenebis (dichlorophenols) and of the asymmetrical 3,4,4',5'-tetrachloro-2,2'-methylenebiphenol was investigated. Greater over-all activity was shown by the three compounds in which the hydrogens adjacent to the hydroxyl groups are not substituted by chlorines, the most potent bis-phenol being the 3,5-dichloro isomer. On the other hand, less active was 2,2'-methylenebis (4,6-dichlorophenol), also referred to in the literature as G-5[®]. Against *S. aureus*, *C. vulgaris* and the dermatophytes, the activity of all isomers was found to be of the same magnitude. At a concentration of 20 $\mu\text{g./ml.}$, no activity against gram-negative bacteria was observed in presence of soap.

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