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Preparation and Bacteriostatic Properties of Substituted Trisphenols

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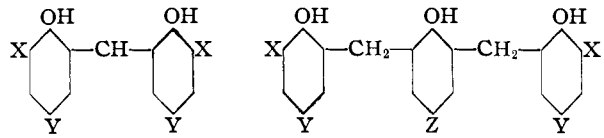
The preparation of 17 new trisphenols by three procedures is described and their physical properties and bacteriostatic activity against two types of bacteria and one fungus are shown.

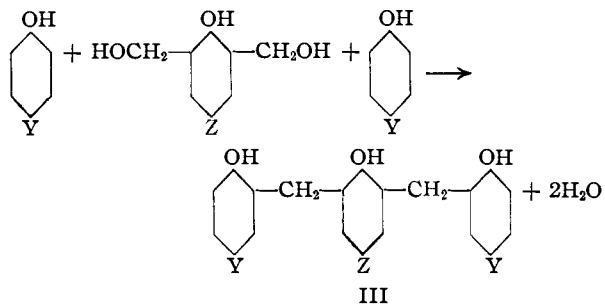
The evaluation of several bisphenols, prepared and described in a previous paper[1] from this Laboratory, has shown these compounds exhibit sufficient fungicidal and bacteriostatic properties to warrant the investigation of the analogous trisphenol derivatives. Conforming to the use of bisphenol for compounds of type I, the name "trisphenol" is suggested for compounds of type II



I II

in which X, Y and Z represent substitutions by hydrogen, alkyl, aryl or halogen, and which may be the same or different.

Notwithstanding the tremendous volume of reported work on phenol–formaldehyde plastics in which trisphenols appear as intermediates, apparently little attempt has been made to widen the scope of the reaction to prepare analogs. The first trinuclear product mentioned in the literature[2] was formed by condensing *p*-cresol dialcohol and *p*-cresol according to the reaction



III

in which Y and Z are methyl.

Megson and co-workers[3] and later Koebner[4] confirmed the reaction and established the structure as a trinuclear phenol. Since then, scattered references have appeared in the literature, trisphenols having been prepared and described in defending a disputed structure as reported[5] previously. Several others were isolated as intermediates formed in phenol–formaldehyde condensations.[4,6] Claims are made for the trinuclear compounds prepared from *p*-*t*-octylphenol dialcohol and several phenols.[7] Two compounds have been evaluated as fungicides[8] but neither the methods of preparation nor the properties of the compounds are given.

A study of this reaction showed that it was applicable to a large variety of substituted phenols subject only to the limitations imposed by steric hindrance and the strong deactivating influence of electronegative groups in the phenol adduct. Essentially, the reaction is an acid-catalyzed condensation of one mole of a 2,6-dimethylolphenol and two moles of a substituted phenol, using a large excess of the latter to restrict side reactions to a minimum. As seen in the structural formula III, X and Y must of necessity be other than hydrogen to prevent formation of long chain polymers, unless the above noted excess of phenol is used.

This report covers 17 trisphenols previously unreported in the literature. All of the compounds described were prepared by condensing the indicated 2,6-*p*-substituted phenol dialcohol with the specific substituted phenol noted in the table. The intermediate dialcohols were prepared *via* the reaction of Lederer–Manasse[9] as modified by Auwers.[10] Preparatory methods for phenol di-

TABLE I

BACTERIOSTATIC ACTIVITY OF TRISPHENOLS

Compound no.	Maximum dilution inhibiting *micrococcus pyogenes var. aureus*	Inhibition distance in mm. *Aspergillus niger*
1	<1/100,000	0.0
2	<1/100,000	.0
3	<1/100,000	.0
4	1/800,000	.0
5	<1/100,000	.0
6	1/800,000	8.0
7	1/3,200,000	0.0
8	1/800,000	.0
9	1/1,600,000	.0
10	<1/100,000	Not tested
11	<1/100,000	0.0
12	<1/100,000	.0
13	<1/100,000	.0
14	<1/100,000	18.0
15	1/100,000	0.0
16	<1/100,000	0.0
17	1/400,000	Not tested
18	1/800,000	0.0
19	Not tested	Not tested
20	<1/100,000	Not tested
21	1/100,000	0.0

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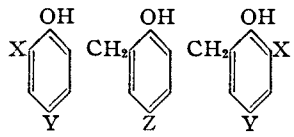
TABLE II

TRISPHENOLS



	X	Y	Z	Procedure	Reaction time, hr.	Yield, %	Form[a]	Crystallizing solvent	M.p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
1	Hydrogen	Methyl	Methyl	A	0.2	89.9	W.N.	Et. acetate	216.3–216.9[c]	$C_{23}H_{24}O_3$	79.28	79.11	6.94	7.25	...	...
2	Methyl	Methyl	Methyl	A	0.2	41.2	W.Pl	Toluene	187.4–187.8[d]	$C_{25}H_{28}O_3$	79.75	79.75	7.50	7.39	...	...
3	Hydrogen	Chloro	Methyl	A	2.0	77.0	W.G.	Toluene	237.2–237.7[e]	$C_{21}H_{18}Cl_2O_3$	64.80	65.13	4.66	4.91	...	...
4	Methyl	Chloro	Methyl	A	2.0	67.3	W.Pr	Et. acetate	231.8–232.4	$C_{23}H_{22}Cl_2O_3$	66.20	66.39	5.32	5.40	16.99	16.93
5	Hydrogen[f]	Methyl[f]	Hydrogen[f]	A	0.2	51.0	W.N.	Toluene	191.8–192.4	$C_{24}H_{26}O_3$	79.50	79.87	7.23	7.29	...	...
6	Hydrogen	Chloro	Chloro	A	.5	73.5	W.G.	Toluene	233.9–234.4[g]	$C_{20}H_{15}Cl_3O_3$	58.64	58.59	3.69	3.74	25.97	25.46
7	Methyl	Chloro	Chloro	A	.4	62.4	W.Pr	Et. acetate	194.8–195.3	$C_{22}H_{19}Cl_3O_3$	60.36	60.55	4.37	4.36	24.31	24.06
8	Hydrogen	Bromo	Chloro	A	.2	49.6	W.Pr	75% acetic	236.7–237.2	$C_{20}H_{15}Br_2ClO_3$	48.18	48.13	3.03	3.23	21.3[h]	20.7[h]
9	Methyl[i]	Chloro[i]	Chloro[i]	A	.5	65.1	W.N.	50% ethanol	168.1–168.6	$C_{23}H_{21}Cl_3O_3$	61.12	60.97	4.69	4.82	...	...
10	Hydrogen[j]	Chloro[j]	Chloro[j]	A	.2	8.5	W.N.	Toluene	236.0–237.0	$C_{22}H_{19}Cl_3O_3$	60.36	60.32	4.37	4.21	24.31	24.30
11	Hydrogen	Methyl	Butyl	A	.3	61.3	W.Pl	Heptane	137.6–138.1	$C_{26}H_{30}O_3$	79.95	80.21	7.75	8.02	...	...
12	Chloro	Butyl	Chloro	B	3.0	42.4	W.Pr	75% ethanol	166.5–167.0	$C_{28}H_{31}Cl_3O_3$	64.45	64.47	5.99	6.22	20.39	20.00
13	Chloro[k]	Methyl[k]	Chloro[k]	B	2.0	51.0	W.Pl	50% ethanol	172.0–172.6	$C_{22}H_{19}Cl_3O_3$	60.36	60.15	4.37	4.57	24.31	24.00
14	Methyl	Butyl	Methyl	A	0.5	71.5	W.Pl	Toluene	195.8–196.4	$C_{31}H_{40}O_3$	80.79	80.73	8.75	8.64	...	...
15	Chloro	Methyl	Chloro	B	.5	36.1	W.G.	Et. acetate	150.1–150.8	$C_{22}H_{19}Cl_3O_3$	60.36	...	4.37	..	24.31	23.96
16	Methyl[l]	Butyl[l]	Methyl[l]	A	.2	18.0	W.Pr	Heptane	138.8–139.5	$C_{31}H_{40}O_3$	80.79	80.98	8.75	8.44	...	...
17	Benzyl	Chloro	Chloro	B	3.0	2.0	W.Pr	Toluene	181.5–182.1	$C_{34}H_{27}Cl_3O_3$	69.23	68.94	4.61	4.99	18.04	18.07
18	Hydrogen	Nitro	Chloro	C	0.5	11.0	W.G.	Toluene	273–274	$C_{20}H_{15}ClN_2O_7$	55.76	55.82	3.51	3.51	8.23	8.48
19	Hydrogen	α-Cumyl	Methyl	A	0.2	9.8	W.N.	Toluene	219.5–220.2	$C_{39}H_{40}O_3$	84.14	84.34	7.24	7.23	...	...
20	Methyl	Chloro	Nonyl	A	0.2	33.2	W.Pl	Heptane	139.4–139.8	$C_{31}H_{33}Cl_2O_3$	70.28	70.32	7.23	7.35	13.39	13.92
21	Chloro	Chloro	Chloro	C	16.0	40.0	W.Pr	Gl. acetic	185.8–186.2	$C_{20}H_{12}Cl_6O_3$	50.19	50.14	2.74	2.76	37.05	36.90

[a] W., white; N., needles; Pl., plates; G., granules; Pr., prisms. [b] All melting points are corrected when given to tenths of degree—otherwise uncorrected. [c] Ref. 4 gives m.p. 215°. [d] E. Ziegler, *et al.*, *Monatsh.*, **78**, 334 (1948), reported m.p. 183–184°. [e] Ref. 5 gives m.p. 239–240°. [f] Contains methyl groups ortho to Z. [g] Ref. 13 lists compound but gives no description. [h] Computed for total halogen as chlorine. [i] Contains one methyl group ortho to Z. [j] Contains methyl groups ortho to X. [k,l] The hydroxy group occupies the 4-position, between X and Y.

alcohols in which Z is alkyl[11] and halogen[12] are reported. Although a limited number of trisphenols have been reported[8,13] as having a low order of fungicidal activity, a study of these compounds has shown some fungistatic activity in two instances and a high order of bacteriostatic activity against representative species of Gram-positive cocci in several instances.

Experimental

The compounds described in this paper were prepared by the following procedures. The yield figures given were obtained frequently in one experiment only and do not represent the maximum yields obtainable. The substituted phenols used were commercial grade products and no attempt was made at further purification. The properties of 21 trisphenols are shown in Table II.

-Intermediate Dialcohols. 2-Hydroxy-α^1,α^3-mesitylenediol. Experiments 1, 2, 3, 4, 14, 16 and 19.—The procedure as described by Ullmann and Brittner[14] was followed.

A solution of 50.0 g. of NaOH in 200 ml. of water was added with stirring to a solution of 108.0 g. (1.0 mole) of *p*-cresol in 215 ml. of 40% formaldehyde. When the initial rise in temperature had subsided, the mixture was stoppered in a 600-ml. erlenmeyer flask and held for 3 days at 30–40°. The yellow crystalline sodium salt was filtered, washed with six 50-ml. portions of saturated sodium chloride solution, and dissolved in 1 liter of hot water. On acidification with 1:1 acetic acid and cooling to 30°, the product precipitated in white lustrous plates. Recrystallization from ethyl acetate gave large colorless prisms, m.p. 130.4–131.1°, yield 94.0%.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.21; H, 7.20. Found: C, 64.30; H, 7.28.

5-Chloro-2-hydroxy-*m*-xylene-α^1,α^3-diol. Experiments 6, 7, 8, 10, 12, 13, 15, 17, 18 and 21.—A 90.5% yield was obtained following the procedure of Openshaw and Robinson[12]; fine white plates, m.p. 160.4° dec.

Anal. Calcd. for $C_8H_9ClO_3$: C, 50.94; H, 4.81; Cl, 18.80. Found: C, 51.03; H, 4.69; Cl, 18.91.

5-Chloro-2-hydroxy-4-methyl-*m*-xylene-α^1,α^3-diol. Experiment 9.—A 49.7% yield was obtained from 142.5 g. (1.0 mole) of 4-chloro-*m*-cresol following the procedure of Openshaw described above; fine white prisms from ethyl acetate, m.p. 135.1–136.0°.

5-*t*-Butyl-2-hydroxy-*m*-xylene-α^1,α^3-diol. Experiment 11.—The product was obtained as fine needle clusters from heptane in 37.2% yield following the procedure of Strating and Backer,[15] except that 600 ml. of methanol per mole of *p*-*t*-butylphenol was added to aid solution.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.53; H, 8.63. Found: C, 68.71; H, 8.70.

5-Nonyl-2-hydroxy-*m*-xylene-α^1,α^3-diol. Experiment 20.—The product was prepared essentially as the 5-*t*-butyl derivative. On acidification, a yellowish oil separated. It was taken up in ether, washed with four 100-ml. portions of water, separated and the ether removed. Product was a yellow oil, $n^{25}D$ 1.4963, yield 70.0%.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 9.98. Found: C, 73.17; H, 10.06.

Condensation Procedures. Procedure A. α^2,α^6-Bis-(6-hydroxy-*m*-tolyl)-mesitol (No. 1).—Approximately 4 ml. of concd. HCl was added to a well-stirred solution of 16.8 g. (0.1 mole) of 2-hydroxy-α^1,α^3-mesitylenediol in 64.9 g. (0.6 mole) of *p*-cresol. The strongly exothermic reaction caused a rapid rise of temperature to 95° at which point a heavy slurry was precipitated. When the temperature had dropped to 40–50°, 100 ml. of heptane was added and stirring continued for 1 hour. The crude product was filtered, washed with two 25-ml. portions of heptane and dried at 80°, yield 89.9%, m.p. 210–215°. Two recrystallizations from ethyl acetate gave large colorless prisms, m.p. 216.3–216.9°.

Procedure B. 4-Chloro-α^2,α^6-bis-(5-chloro-4-hydroxy-*m*-tolyl)-2,6-xylenol (No. 13).—Approximately 5 ml. of concd. H_2SO_4 was added to a well-stirred solution of 9.4 g. (0.05 mole) of 5-chloro-2-hydroxy-*m*-xylene-α^1,α^3-diol and 42.8 g. (0.3 mole) of 6-chloro-*o*-cresol in 35 ml. of glacial acetic acid and held at 80° over 2 hours. The oily reaction product solidified on standing overnight. The product was filtered, slurried into 25 ml. of benzene, refiltered and dried at 80°. Two recrystallizations from 50% ethanol gave fine white plates, m.p. 172.0–172.6°, yield 65%.

Procedure C. 4-Chloro-α^2,α^6-bis-(3,5-dichloro-2-hydroxyphenyl)-2,6-xylenol (No. 21).—The solution of 65.2 g. (0.5 mole) of 2,4-dichlorophenol in 49.0 g. (0.5 mole) of concd. H_2SO_4 and 75.0 g. of glacial acetic acid was held at 85–90° over 2 hours while adding portionwise 18.8 g. (0.1 mole) of 5-chloro-2-hydroxy-*m*-xylene-α^1,α^3-diol. The solution was held at 90° for 8 hours, then at 70–80° over 2 hours while neutralizing with 53.0 g. (0.5 mole) of solid Na_2CO_3 added portionwise. The solution was filtered hot, cooled to 20°, which crystallized the contents as fine white needles. The contents were added into 1 liter of water, dissolving the inorganic salts, leaving a pink amorphous powder. Four recrystallizations from glacial acetic acid gave fine white prisms, m.p. 185.8–186.2°, yield 16.0%.

Bacteriostatic Test Procedures.—In testing the antimicrobial activity of this series of compounds, it was desired that one be found which retained its activity in the presence of soap. A stock solution of each compound was prepared by dissolving 0.1 g. of the compound in 100 ml. of a 5% solution of "Ivory Snow." These stock solutions provided 0.1% concentrations of the test compounds in media with the test compounds–soap ratio of 1:50. Further dilutions were made in water at 10 times the desired final concentration so that 2.5 ml. of each dilution and 22.5 ml. of molten nutrient agar would give the desired final concentration. In this manner dilution of each compound in doubling concentrations from 1/100,000 to 1/12,800,000 were prepared in nutrient agar and distributed in petri plates.

Inocula were prepared from 24-hour broth cultures of the standard test organisms *Micrococcus pyogenes* var. *aureus* and *Salmonella typhosa*. Two standard loopfuls from each culture were transferred into separate 5-ml. water blanks. One loopful of the diluted culture of each organism was streaked on each test plate. After 48 hours incubation at 37° the test plates were examined for inhibition of bacterial growth.

In order to evaluate the antifungal activity of this series of compounds an agar-cup-plate technique was used. Petri dishes were prepared which contained 20 to 25 ml. of Trommer's Malt Agar. After hardening, a hole was cut in the center with a No. 8 cork borer and the agar plug was removed with a sterile spatula. Enough of the test compound was placed in this hole to make solid contact with the agar at all points.

Spore suspensions of *Aspergillus niger*, obtained from a culture approximately two weeks old, were sprayed through an atomizer onto the surface of the agar medium. All such test plates were inoculated for 5 days at 27° and at 65 to 75% relative humidity. At the end of the incubation period, the degree of antifungal activity was measured in terms of the distance between the edge of the agar cup and the edge of the fungus growth.

None of the compounds tested inhibited the growth of *Salmonella typhosa* in the lowest dilution tested, *i.e.*, 1/100,000. A number of the compounds exhibited exceptionally good bacteriostatic activity against the Gram positive organism *Micrococcus pyogenes* var. *aureus* and fungistatic activity was noted in only two compounds. The results of these antimicrobial investigations are recorded in Table I.

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