undergo in the main two types of cleavage, (1) into the disubstituted acetic esters and simpler decomposition products and (2) into ethyl carbonate and the sodium enolate of the disubstituted acetic esters. The nature of the substituent groups determines the readiness and manner in which these malonic esters are cleaved.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY]

THE CONDENSATION OF CERTAIN PHENOLS WITH SOME ALIPHATIC ALDEHYDES[1]

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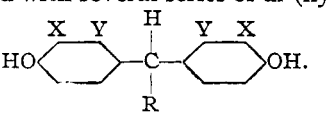
Recently there have been many studies of the bactericidal power of series of substituted phenols and phenol derivatives. Johnson and his co-workers.[2] Dohme, Cox and Miller[3] and Leonard[4] have studied the alkyl resorcinols. Other reports in this field have been made by Hampil,[5] Schaffer and Tilley,[6] Rettger and his co-workers,[7] and Klarmann.[8]

The bactericidal properties of the alkyl phenols have been studied by Schaffer and Tilley,[6] Rettger, Plastridge and Valley,[9] and the alkyl cresols by Coulthard, Marshall and Pyman.[10] Klarmann and his collaborators[11] have made an extensive investigation of the mono ethers of dihydric phenols, and recently Read and Miller[12] have reported on certain substituted phenols.

The present investigation is concerned with several series of di-(hydroxyphenyl)-alkyls of the general type  These were all prepared by the Baeyer reaction[13] which has been used by

[1] From the Ph.D. dissertation of Wilton C. Harden, Johns Hopkins University, 1932.

[2] Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913); Johnson and Lane, *ibid.*, **43**, 348 (1921).

[3] Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926).

[4] Leonard, *J. Am. Med. Assoc.*, **83**, 2205 (1924).

[5] Hampil, *J. Infectious Diseases*, **43**, 25 (1928).

[6] Schaffer and Tilley, *J. Bacteriology* **12**, 303 (1926); **14**, 259 (1927).

[7] Rettger, Valley and Plastridge, *Zentr. Bakt. Orig.*, **110**, 80 (1929).

[8] Klarmann, THIS JOURNAL, **48**, 791 (1926); **48**, 2358 (1926); Klarmann and Von Wowern, *ibid.*, **51**, 605 (1929).

[9] Rettger, Plastridge and Valley, *Zentr. Bakt. Orig.*, [I] **111**, 287 (1929).

[10] Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

[11] Klarmann, THIS JOURNAL, **53**, 3397 (1931); **54**, 298 (1932); **54**, 1204 (1932).

[12] Read and Miller, *ibid.*, **54**, 1195 (1932).

[13] Baeyer, *Ber.*, **5**, 280, 1096 (1872).

many investigators.[14] In the first four series, R varies from H to C_6H_{13}. Series I. Derivatives of phenol, X and Y = H: five of these have been previously reported. Series II. Derivatives of *o*-cresol, X = CH_3, Y = H: all except the first mentioned are new compounds. Series III. Derivative of *m*-cresol, X = H, Y = CH_3: all are new. Series IV. Derivatives of resorcinol, X = H, Y = OH: all of these except the first member are new. Series V. Condensation products of chloral with various phenols, R = CCl_3, X and Y = H or CH_3. Series VI. Miscellaneous: compounds made for purpose of comparison.

The bromo derivatives of the members of the first four series have been prepared for a better characterization of the compounds. These proved to be practically insoluble even in dilute alcohol and so could not be studied. The solubilities of the members of the first four series in water and 25% alcohol were determined. Their bactericidal power was tested against *Staphylococcus aureus*, strain no. 209. The compounds were, in general, dissolved in 25% alcohol, although in some cases stronger concentrations of alcohol were necessary. The technique employed consisted of the United States Department of Agriculture method, which is essentially as follows: 0.5 cc. of standard culture is added to 5 cc. of diluted antiseptic. Transfers are made with a 4-mm. platinum loop made from No. 23 B. and S. gage wire. The culture medium used was a sterile nutrient, beef extract broth, 10 cc. being used in each sub-culture tube. All dilutions were made with sterile distilled water.

The toxicities of the compounds of Series I, II and IV toward goldfish, *Carassius aureus*, and seedlings of *Lupinus albus* were determined.

Results

All the compounds of Series I, II, III and V are white crystalline solids which dissolve clear in the calculated amount of alkali solution to form the disodium salts. The compounds of Series IV and Compound No. 34 of Series VI could not be obtained colorless. Solutions of their sodium salts are dark red and oxidize to give tarry precipitates in the course of several hours.

The properties are shown in Tables I and II. In Figs. 1, 2 and 3 the solubilities, the melting points and bactericidal power of the compounds of Series I, II, III and IV are plotted against the number of carbon atoms in the side chain.

It will be noted that in all four series the solubilities in water decrease as the molecular weight of the side chain increases. In the case of 25% alcohol there are several exceptions. It will also be noted that in the case

[14] Lunjac, *Chem. Centr.*, **1**, 1650 (1904); II, 550 (1908); Zincke, *Ann.*, **302**, 237 (1898); Städel, *ibid.*, **194**, 329 (1878); **330**, 66 (1904); Claus and Trainer, *Ber.*, **19**, 3004 (1886); Auwers and Rietze, *Ann.*, **356**, 153 (1907); Fabinyl, *Ber.*, **11**, 283 (1878); Eberhardt, *ibid.*, **27**, 1804 (1824).

TABLE I

Comp. No.	R	M. p., °C.	Soly. in water, g./100 cc.	Soly. in 25% alcohol g./100 cc.	Maximum killing dilution, *S. aureus*	Ratio killing dilution to solubility	Toxicity to goldfish 1:30,000, killing time in minutes	Toxicity to *Lupinus albus* 1:30,000, % of normal growth
			Series I. Phenol					
1	H, *p-p'*	158	0.3950	0.780	300	2.34	100	70
2	H, *o-p'*	115	.2074	.937	450	4.24	100	70
3	CH_3	122	.0330	.671	1,200	8.05	65	70
4	C_2H_5	129	.0207	.1348	1,500	2.02	90	39
5	C_3H_7	137	.0165	.1744	3,500	6.10	50	14
6	C_4H_9	120	.0058	.0768	9,500	7.30	30	21
7	C_5H_{11}	110.5	.0037	.0388	12,500	4.86	25	14
8	C_6H_{13}	120[a]	.0005	.0120	14,000	1.68	20	39
			Series II. *o*-Cresol					
9	H	127	0.0560	0.0729	250	0.18	20	78
10	CH_3	100	.0489	.336	1,000	3.37	22	52
11	C_2H_5	94	.0259	.0784	3,500	1.99	38	40
12	C_3H_7	135	.0118	.0460	6,500	3.00	50	35
13	C_4H_9	97	.0022	.0226	7,500	1.70	60	46
14	C_5H_{11}	78	.0005	.0044	10,000	0.43	55	50
15	C_6H_{13}	85		.0035	24,500	0.86	55	43
			Series III. *m*-Cresol					
16	H	113	0.0445	0.0765	250	0.10		
17	CH_3	128	.0354	.1040	2,000	2.08		
18	C_2H_5	140	.0226	.0364	16,000	5.82		
19	C_3H_7	145	.0073	.0130	1,000	0.14		
20	C_4H_9	149	.0047	.0147	1,000	.14		
21	C_5H_{11}	152	.0018	.0112	20,000	2.23		
22	C_6H_{13}	156	.0007	.0071	20,000	1.42		
			Series IV. Resorcinol					
23	H	250	0.0534	0.0904	2,000	1.80	90	72
24	CH_3	do not	.0118	.0284	4,000	1.34	25	51
25	C_2H_5	melt	.0090	.0163	8,000	1.30	68	88
26	C_3H_7	at	.0091	.0101	10,000	1.00	50	86
27	C_4H_9	300° C.	.0081	.0091	2,000	0.19	75	93
28	C_5H_{11}		.0056	.0068	3,000	.20	300	85
29	C_6H_{13}		.0028	.0030	Satd. sol. does not kill	..	Alive after 24 hrs.	95

[a] Lunjac, *Chem. Centr.*, I, 1650 (1904), gives m. p. of 103°. The m. p. of 120° was checked after repeated crystallizations from different solvents.

of the derivatives of the lower aldehydes the order of solubility is as follows: phenol > *o*-cresol > *m*-cresol > resorcinol, while with the higher members this order is reversed. These curves serve to show the slight influence which the position and nature of such substituents as methyl and hydroxyl exert on the solubility of such compounds and the relatively large influence

TABLE II

Series V Condensations Using Chloral				Series VI Miscellaneous				
Comp. No.	Phenol used	M. p., °C.	Maximum killing dilution, *S. aureus*	Comp. No.	Aldehyde	Phenol	M. p., °C.	Maximum killing dilution, *S. aureus*
30	Phenol	199–200	1,350	33	Formaldehyde	Salicylic acid	239[a]	8000
31	*o*-Cresol	121–122	10,000	34	Formaldehyde	Pyrogallol	240[b]	2000
32	*m*-Cresol	162–163	10,000	35	Formaldehyde	Thymol	150	6000
36	Thymol	193.5	10,000					

[a] Methylene di-salicylic acid, German Patents 243,086, 499,070, also Madsen *Arch. Pharm.*, **245**, 44 (1907) and others.

[b] See Baeyer, *Ber.* **5**, 1096 (1872); Caro, *ibid.*, **25**, 947 (1892); Kahl, *ibid.*, **31**, 144 (1898).

of the length of the side chain. In Series I, II and III the melting points show an alternating effect; in Series I and II the net effect is a lowering of the melting point as the series advances; in Series III the opposite is the case. There seems to be no general relation between the melting point of the parent compound and the melting point of its bromine derivative, in some cases one is higher, in other cases the other.

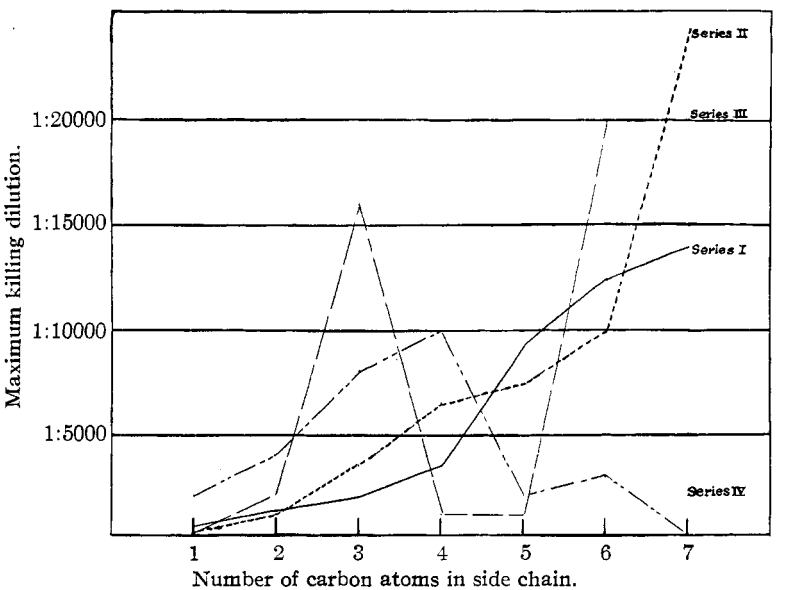


Fig. 1.—Germicidal power *in vitro:* test organism, *staphylococcus aureus.*

It will be seen that, in general, germicidal activity increases with increase in the length of the aliphatic chain. This is in accord with the results found by other investigators for similar series.[15] Since the degree of in-

[15] Walker and co-workers, *J. Chem. Soc.*, 514–520 (1931); Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926); Leonard, *J. Am. Med. Assoc.*, **83**, 2005 (1924); Schaef-

solubility is also directly proportional to the length of the side chain, it follows that the least soluble compounds are in general the *most* germicidal. This is rather to be expected for in such compounds the determining factor seems to be not the substituent groups themselves but their effect on the distribution coefficient. The germicidal activity is thus a function of the lipoid solubility and hence inversely proportional to the solubility in water.

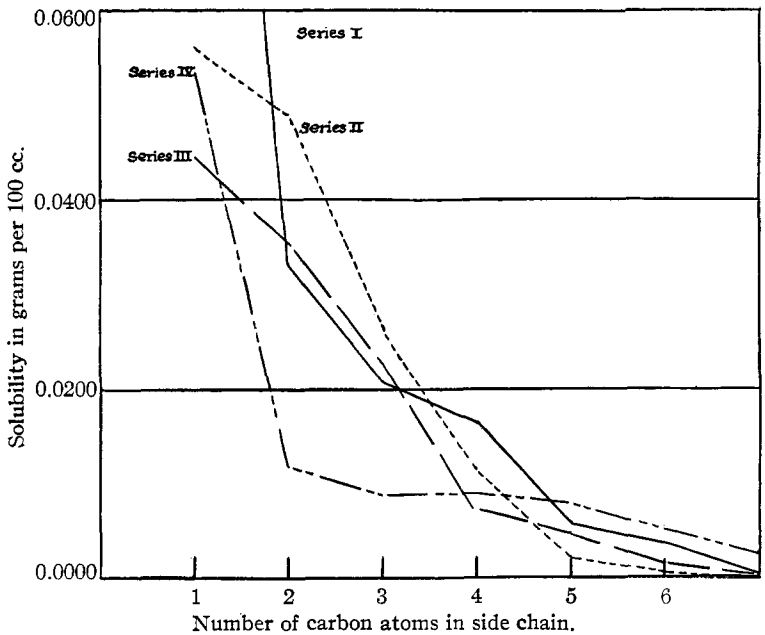


Fig. 2.—Solubilities in water at 25°.

Exceptions to these general statements are found in Compounds 19 and 20 of Series III and in the case of Series IV where germicidal activity reaches a maximum with the butyl compound and then falls off. No explanation is offered for this phenomenon.

To show that in these compounds, as in all phenolic germicides, germicidal activity is due in large part to the free hydroxyl groups, the dibenzoate of Compound No. 8 and the tetraacetate of Compound No. 26 were prepared. These compounds showed absolutely no germicidal action even in saturated solutions, while their parent compounds killed the test organism in dilutions of 1:14,000 and 1:10,000, respectively. This is in accord with the findings of other investigators in similar cases.[16]

fer and Tilley, *J. Bacteriology*, **14**, 259 (1927); Johnson, THIS JOURNAL, **35**, 1014 (1913), and others.

[16] Klarmann, Shternov and Von Wowern, *J. Bacteriology*, **17**, 440 (1929); Klarmann, Gatyas and Shternov, THIS JOURNAL, **53**, 3398 (1931).

Experimental

Materials Used.—The phenol used in preparing the compounds of Series I was Merck's "Reagent Grade," used without purification. The ortho and meta cresols in Series II and III were obtained from the Eastman Kodak Company and were redistilled before use. The resorcinol in Series IV was the ordinary resublimed resorcinol of commerce. All the aldehydes, with the exception of capron-aldehyde, were obtained from the Eastman Kodak Company. Considerable difficulty was experienced in finding a method to give satisfactory yields of capron-aldehyde. Finally hexyl alcohol was prepared by a Bouveault-Blanc[17] reduction of the ethyl ester of caproic acid using anhydrous butyl alcohol as the solvent. Some normal hexyl alcohol was also obtained from Kahlbaum. The alcohol was catalytically dehydrogenated, using a special catalyst. Single runs gave as high as 20% yields of capron-aldehyde and after repeated fractionations and redehydrogenations, an over-all yield of 80% was obtained.

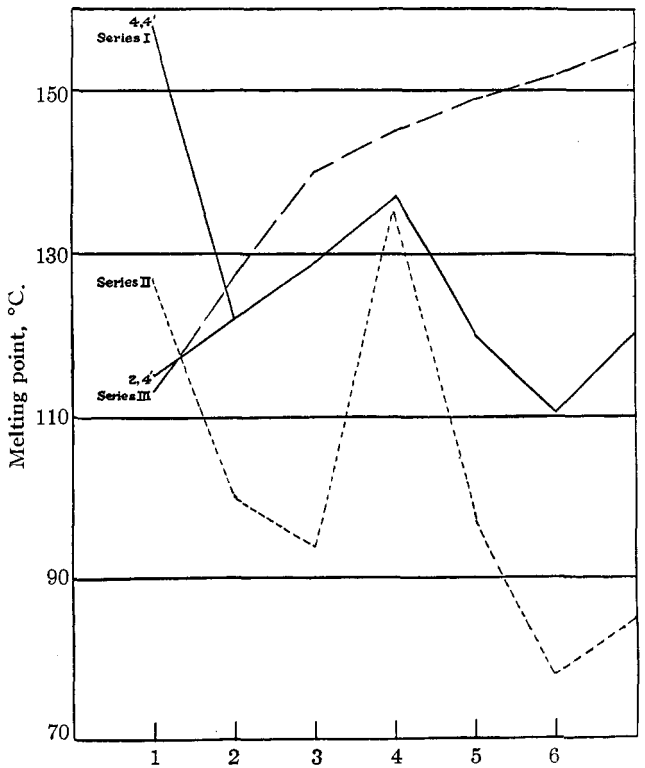


Fig. 3.—Melting points.

Preparation of Compounds of Series I.—The compounds of this series were prepared by two general methods. The first two members were prepared by one method and the remaining six by the other method. 2,4'- and 4,4'-dihydroxydiphenylmethane have been isolated as inter-

[17] Bouveault and Blanc, *Bull. soc. chim.*, [3] **31**, 666 (1904).

mediate steps in the formation of Bakelite and other phenolic resins and have also been prepared[18] from diaminodiphenylmethane.[19] They were prepared by us simultaneously according to the technique of Morgan.[20] Molecular quantities of phenol and para formaldehyde were dissolved in alcohol (200 cc. of alcohol per mole) and 1 to 2 cc. of concentrated hydrochloric acid added. The solution was allowed to stand at room temperature for several hours and finally warmed slightly for one hour. Alcohol and excess phenol were removed by steam distillation and the resulting resins repeatedly extracted with boiling water. These aqueous extracts upon concentration yielded first plates of the 4,4′-compound and on further concentration and cooling, needles of the 2,4′-isomer. These were repeatedly crystallized from water.

The remaining members of this series were all prepared by the second general method, namely, that used by Zincke and Lunjac.[21] A typical example is the preparation of Compound No. 3, dihydroxydiphenylethane.

Eighty-five grams of phenol was placed in a 500-cc. three-necked flask, equipped with mechanical stirrer, and well cooled in crushed ice; 10.0 g. of acetaldehyde was added slowly from a dropping funnel. When all the aldehyde had been added, 0.5 cc. of hydrochloric acid (sp. gr. 1.19) was added and stirring continued for three hours. The temperature was kept below 5°. At the end of three hours, the flask was stoppered and placed in the ice box overnight. The mass of fine, white crystals was then sucked dry on a Buchner funnel and washed with cold benzene. The crystals were then suspended in water and steam distilled until *all* phenol was removed. The resulting product was crystallized from a mixture of benzene and petroleum ether; yield 15.0 g., 28%; melting point 122°.

The compounds of Series II and III were prepared in a similar manner, except that in the case of Series III the time of condensation was shortened to about one-half hour. Much difficulty was experienced in obtaining them in the crystalline form. The lower members were crystallized from water, but the higher ones at first resisted all efforts. Finally they were dissolved in ether, after steam distillation had removed the residual cresol and aldehyde. The ether solution was then dried with sodium sulfate, filtered, and the ether removed by distillation. The resulting product was a heavy tar or resin which was dissolved in the least possible amount of hot xylene or toluene and poured into a Petri dish. This was placed in a vacuum desiccator for some weeks with occasional stirring. Eventually small groups of crystals began to form and finally the whole mass crystallized. These fine crystals were removed by filtration and washed with petroleum

[18] Baekeland, *J. Ind. Eng. Chem.*, **5**, 510 (1913).

[19] Haase, *Ann.*, **283**, 163 (1894).

[20] Morgan, *J. Soc. Chem. Ind.*, **49**, 245 (1930).

[21] Zincke, *Ann.*, **303**, 255 (1898); Lunjac, *Chem. Centr.* I, 1650 (1904).

ether. It was found that the crystals, once formed, could be recrystallized with comparative ease.

The first member of Series IV, like that of Series I and II, has been previously prepared.[22] The entire series was prepared using the technique devised by Caro,[23] who first condensed resorcinol and formaldehyde. Three parts of resorcinol and one part of aldehyde were dissolved in twenty parts of dilute hydrochloric acid and the solution stirred mechanically for several hours or until a precipitate had formed. With the lower aldehydes the solution was kept cool, but with the higher members the 1 to 5 hydrochloric acid was made by dilution with alcohol, and the solution was warmed, and in some cases even boiled on the water-bath. The precipitates thus formed were crystallized from suitable solvents. Repeated crystallizations were necessary to free the products from red dyes formed by side reactions. The tetrabromo compounds were prepared with some difficulty, apparently due to oxidation.

Series V. Condensations with Chloral.—In view of some of the interesting bacteriological and pharmacological properties exhibited by the compounds of the first four series, it was thought that condensations using trichloroacetaldehyde or chloral might also yield interesting products. Many workers[24] have studied various condensations of chloral and chloral hydrate but only two of these may be considered modified Baeyer reactions.

TABLE III

ANALYTICAL DATA

Series I. Phenol

Comp. No.	R	Formula	Bromine derivative	M. p., °C.	Bromine, % Found	Calculated
1	H, *p-p'*	$C_{13}H_{12}O_2$	$C_{13}H_8Br_4O_2$	226	62.00–61.98	61.98
2	H, *o-p'*	$C_{13}H_{12}O_2$	$C_{13}H_8Br_4O_2$	193	61.84–61.64	61.98
3	CH_3	$C_{14}H_{14}O_2$	$C_{14}H_{10}Br_4O_2$	140	60.30–60.12	60.34
4	C_2H_5	$C_{15}H_{16}O_2$	$C_{15}H_{12}Br_4O_2$	150	59.05–59.10	58.79
5	C_3H_7	$C_{16}H_{18}O_2$	$C_{16}H_{14}Br_4O_2$	152	57.05–57.20	57.31
6	C_4H_9	$C_{17}H_{20}O_2$	$C_{17}H_{16}Br_4O_2$	Tar	Tetrabromodiacetate m. p. 168°	
					48.55–48.87	48.75
7	C_5H_{11}	$C_{18}H_{22}O_2$	$C_{18}H_{18}Br_4O_2$	Tar	Tetrabromodiacetate m. p. 129°	
					47.73–47.42	47.73
8	C_6H_{13}	$C_{19}H_{24}O_2$	$C_{19}H_{20}Br_4O_2$	Tar	Tetrabromodiacetate m. p. 111°	
					46.78–47.02	46.75

[22] Morgan, *J. Soc. Chem. Ind.*, **49**, 236; Traubenberg, *Z. angew. Chem.*, **36**, 515 (1903).

[23] Caro, *Ber.*, **25**, 947 (1892).

[24] Chattaway and co-workers, *Chem. Abstracts*, **21**, 1980 (1927); **22**, 1965 (1928); **22**, 2946 (1928); **23**, 599 (1929); Prats, *Rev. Acad. Ciene Madrid*, **24**, 307 (1927); Chattaway and Farinholt, *J. Chem. Soc.*, 1737, 1828 (1931).

TABLE III (*Concluded*)

Comp. No.	R	Formula	Bromine derivative	M. p., °C.	Bromine, % Found	Calculated
			Series II. *o*-Cresol			
9	H	$C_{15}H_{16}O_2$	$C_{15}H_{14}Br_2O_2$	173.5		
10	CH_3	$C_{16}H_{18}O_2$	$C_{16}H_{16}Br_2O_2$	77		
11	C_2H_5	$C_{17}H_{20}O_2$	$C_{17}H_{18}Br_2O_2$	111		
12	C_3H_7	$C_{18}H_{22}O_2$	$C_{18}H_{20}Br_2O_2$	104		
13	C_4H_9	$C_{19}H_{24}O_2$	$C_{19}H_{22}Br_2O_2$	Oil	Dibromodiacetate m. p. 150°	
					30.34–30.40	30.39
14	C_5H_{11}	$C_{20}H_{26}O_2$	$C_{20}H_{24}Br_2O_2$	Oil	Dibromodiacetate m. p. 121°	
					29.41	29.02
15	C_6H_{13}	$C_{21}H_{28}O_2$	$C_{21}H_{26}Br_2O_2$	Oil[a]		
			Series III. *m*-Cresol			
16	H	$C_{15}H_{16}O_2$	$C_{15}H_{12}Br_4O_2$	185	58.70	58.80
17	CH_3	$C_{16}H_{18}O_2$	$C_{16}H_{14}Br_4O_2$[b]	207	57.29	57.12
18	C_2H_5	$C_{17}H_{20}O_2$	$C_{17}H_{16}Br_4O_2$[c]	121	55.39	55.91
19	C_3H_7	$C_{18}H_{22}O_2$	$C_{18}H_{18}Br_4O_2$	142	54.29	54.57
20	C_4H_9	$C_{19}H_{24}O_2$	$C_{19}H_{20}Br_4O_2$	Oil	Tetrabromodiacetate	
				m. p. 78°	46.56	46.75
21	C_5H_{11}	$C_{20}H_{26}O_2$	$C_{20}H_{22}Br_4O_2$[d]	119	52.19	52.09
22	C_6H_{13}	$C_{21}H_{28}O_2$	$C_{21}H_{24}Br_4O_2$	67	50.81	50.92
			Series IV. Resorcinol			
23	H	$C_{13}H_{12}O_4$	$C_{13}H_8O_4Br_4$	...	58.16	58.36
24	CH_3	$C_{14}H_{14}O_4$	$C_{14}H_{10}O_4Br_4$	...	56.80	56.90
25	C_2H_5	$C_{15}H_{16}O_4$	$C_{15}H_{12}O_4Br_4$	...	55.90	55.52
26[e]	C_3H_7	$C_{16}H_{18}O_4$	$C_{16}H_{14}O_4Br_4$	...	54.18	54.20
27	C_4H_9	$C_{17}H_{20}O_4$	$C_{17}H_{16}O_4Br_4$	...	52.94	52.90
28	C_5H_{11}	$C_{18}H_{22}O_4$	$C_{18}H_{18}O_4Br_4$	...	51.55	51.74
29	C_6H_{13}	$C_{19}H_{24}O_4$	$C_{19}H_{20}O_4Br_4$	...	50.10	50.60

[a] The dibromodiacetate and the dibromodibenzoate were both oils. The dibromodi(nitrobenzoate) was prepared, m. p. 215°, % bromine found, 20.69; calcd., 20.81; nitrogen found, 3.47%, calcd., 3.64.

[b] Dibromo derivative, m. p. 189°; % bromine found, 40.70; calcd., 40.22.

[c] Tetrabromodiacetate, m. p. 81°; % bromine found, 48.63; calcd., 48.74.

[d] Tetrabromodiacetate, m. p. 142°; % bromine found, 45.56; calcd., 45.81.

[e] Tetraacetate prepared, m. p. 250°.

Ter Meer[25] has reported dihydroxydiphenyltrichloroethane made by condensing phenol and chloral. This compound is also described by Elbs.[26] The method of Elbs has been used in the present investigation.

Table VI. Miscellaneous Condensations

The compounds of this series which are shown in Table VI were prepared in order to study particularly their germicidal activity. They were prepared by various modifications of the Baeyer reaction.

[25] Ter Meer, *Ber.* **7**, 1201 (1874).

[26] Elbs, *J. prakt. Chem.*, [2] **47**, 60 (1850).

TABLE IV

ANALYTICAL DATA

Series V. Condensations with Chloral

Comp. No.	Phenol	Formula	M. p., °C.	Chlorine, % Found	Calculated
30	Phenol	$C_{14}H_{11}Cl_3O_2$	199–200	33.35	33.57
31[a]	*o*-Cresol	$C_{16}H_{15}Cl_3O_2$	121–122	30.81	30.80
32	*m*-Cresol	$C_{16}H_{15}Cl_3O_2$	162–163	30.51	30.80
33	Thymol	$C_{22}H_{27}Cl_3O_2$	193.5	24.82	24.79

[a] Crystallizes from benzene with one mole of benzene of crystallization; m. p. 91°; % bromine found, 25.03, 24.97; chlorine calcd. for $C_{16}H_{15}Cl_3O_2 \cdot C_6H_6$, 25.12.

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Conclusions

Thirty-five compounds have been prepared by the Baeyer reaction. They are of the general type $R_1—\underset{R_2}{\overset{H}{C}}—R_1$ where R_1 is a phenol or substituted phenol and R_2 may be hydrogen or an alkyl from C_1 to C_6. Bromine derivatives of twenty-nine of them have been prepared. In all, sixty-seven compounds have been made and examined, fifty of which are not previously described in the literature.

These compounds have been tested bacteriologically and pharmacologically. Many of them show marked germicidal activity *in vitro*. The toxicity for animal and plant organisms has been tested and will be reported in more detail elsewhere.

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