[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.]

Aldehyde–Phenol Reaction Products and Derivatives

BY H. ELDRIDGE FAITH

In recent years discoveries of germicidal,[1,2] fungicidal[3] and teniacidal[4] action of various compounds of the methylenebisphenol type have been reported. The investigation reported here was undertaken for the purpose of providing more material for antibacterial and anthelmintic studies. The results are of chemical interest in showing the adaptation of known basic reactions[5,6] to a number of new combinations and in extending accumulated information as to reaction trends in specific cases, general applicability of standard methods, and exceptional behavior of scientific interest.

The experimental procedures, described in detail later, are of three general types as follows: (1) One-step condensation of one aldehyde[7] molecule, aldehyde hydrate, or polymer in an acid medium with two molecules of a phenol, linking the benzene rings of the phenols by a methylene or substituted methylene group to produce a methylene-, ethylidene- or benzalbisphenol. (2) Two-step condensations, wherein an intermediate phenol alcohol is first obtained by condensing the aldehyde molecule (formaldehyde) with one phenol molecule and then condensing this in an acid medium with more phenol. By employing different phenols in the two steps, so-called unsymmetrical or mixed methylenebisphenols are obtained. (3) Substitution by halogenation, methylation, sulfonation, etc., of products obtained by procedures of the type (1) or (2) to produce more complex compounds of the same type.

The structural assumptions regarding the crystalline products are based on long-established rules for such products. According to these, in condensations of aldehydes with phenols, the methylene bridge replaces hydrogen atoms of the benzene nucleus at positions para or ortho to the phenolic hydroxyl group, preferably in the order named. The designated structures of the products formed by direct chemical substitution are based on the demonstrated reactivity of the bisphenols in the positions ortho to the hydroxyl groups when the para positions are blocked.

With phenol analogs, such as aromatic amines, the hydrogen atom analogous to that of the phenolic hydroxyl has been found to be replaced, forming an acetal-type linkage. This appears to have been encountered in the present work in the condensation of *p*-chlorobenzenethiol with formaldehyde to form what is evidently a mercaptal.

Experimental[8]

One-step Condensation of Phenols with Aldehydes, 2:1 Ratio. Method A.[9]—One-tenth mole of the substituted phenol was dissolved in 20 ml. of glacial acetic acid, and a cold solution of 20 g. of concd. sulfuric acid in 40 ml. of glacial acetic acid was then added. Over a period of two and one-half hours, 4.2 ml. (*ca.* 0.055 mole) of 40% formaldehyde was introduced into the mixture at 0 to 5°. The reaction mixture was stirred cold for an additional three hours and was then stirred at room temperature until twenty-four hours after the beginning of the reaction. It was poured into cold water; the precipitate filtered off, and neutralized with sodium bicarbonate solution. The product was purified by crystallization.

B. Paraldehyde (18 g.) was added to *p*-chlorophenol (0.8 mole) in 400 g. of 75% sulfuric acid at 0 to 5° over a four-hour period. The cold mixture was stirred for three more hours and then diluted with water. Unreacted *p*-chlorophenol was removed by neutralizing an alkaline solution of the product to *p*H 8 and filtering off the precipitate.

C. Formaldehyde (40%) (0.116 mole) was added over a three-hour period to *p*-hydroxyphenylarsonic acid (0.209 mole) in 180 g. of 90% sulfuric acid at 0 to 5° and kept cold for twenty-one additional hours. Dilution of the mixture with water precipitated the product. It was washed with cold, dilute sulfuric acid, dissolved in sodium bicarbonate solution, precipitated by the addition of the solution to dilute hydrochloric acid and washed with dilute hydrochloric acid.

D. *p*-Chlorophenol (0.215 mole) and benzaldehyde (0.113 mole) were reacted in 135 g. of 90% sulfuric acid according to Method C. The gummy product which formed was washed with water, dissolved in ether and neutralized with sodium bicarbonate solution. The ether solution was concentrated and diluted with petroleum ether to precipitate the product.

E. The substituted phenol (0.1 mole) was dissolved in 15 ml. of glacial acetic acid. 1.58 g. of paraformaldehyde was added, and the mixture was saturated at 5° with dry hydrogen chloride. After four hours in an ice-bath, the reactants stood at room temperature for twenty hours. The mixture was diluted with petroleum ether, and the product was washed with petroleum ether. Additional material was sometimes obtained by concentrating the acid filtrate.[10]

Phenol Alcohols

Method F.—The Lederer–Manasse[6] reaction was used in making the three phenol alcohols listed below.

2,6-Bis-(hydroxymethyl)-4-chlorophenol.[11]—Equimolecular amounts of *p*-chlorophenol and formaldehyde

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[1] Klarmann, *et al.*, THIS JOURNAL, **51**, 605 (1929); **54**, 3315 (1932).

[2] The tuberculocidal activity of a number of the compounds described in this paper has been reported by H. J. Florestano, *J. Pharmacol.*, **96**, 238 (1949).

[3] Marsh and Butler, *Ind. Eng. Chem.*, **38**, 701 (1946).

[4] Craige and Kleckner, *N. Am. Veterinarian*, **27**, 26 (1946).

[5] Baeyer, *Ber.*, **5**, 280, 1094 (1872).

[6] Lederer, *J. prakt. Chem.*, **50** (II), 223 (1894); Manasse, *Ber.*, **27**, 2409 (1894).

[7] The usual aldehyde, because of its greater reactivity, is formaldehyde, in either its hydrated form (methylene glycol), known as formalin or 40% formaldehyde, or as the less reactive solid polymer known as paraformaldehyde.

[8] Most of the products produced by the following methods are tabulated in Table I.

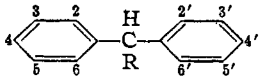
[9] *p-t*-Amyl-, o-phenyl-, *p-s*-butyl- and 2-chloro-4-*t*-butylphenol gave resinous, alcoholic-alkali-soluble products by this method. *p-t*-Butylphenol yielded a solid melting at 190-193°, but cryoscopic molecular weight determinations indicated a molecule larger than the methylenebisphenol.

[10] Niederl and McCoy have effected condensations of bis-(hydroxymethyl)-phenols with phenols in acetic acid-hydrogen chloride: THIS JOURNAL, **65**, 629 (1943).

[11] Weiler and Berres made a dimethylol-*p*-chlorophenol melting at 165°, *C. A.*, **25**, 974 (1931), German Patent 510,447.

TABLE I

GENERAL FORMULA



Substituents and their positions on the rings of the diphenylmethanes[a]	R	Yield,[r] %	M. p., °C., uncor.	Solvent[b]	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
One-step condensations									
X,X'-(OH)$_2$, X,X'-(OH)$_2$, X,X'-Cl$_2$[f]	H	A60[j]	150–151	11	$C_{13}H_{10}Cl_2O_4\cdot{}^1/_2H_2O$	50.33	50.41	3.58	3.72
X,X'-(OH)$_2$, X,X'-(CH$_3$)$_2$, X,X'-Cl$_2$[g]	H	A[k]	180–182	2	$C_{15}H_{14}Cl_2O_2$	60.62	60.49	4.75	4.51
2,2'-(OH)$_2$, 5,5'-Cl$_2$	CH$_3$	B65	170–171	1	$C_{14}H_{12}Cl_2O_2$	59.37	59.80	4.27	4.60
2,2'-(OH)$_2$, 5,5'-(AsO$_3$H$_2$)$_2$	H	C22	>300	5	$C_{13}H_{14}O_8As_2$	34.85	34.55	3.15	3.41
2,2'-(OH)$_2$, 5,5'-Cl$_2$	C$_6$H$_5$	D46	168–169.5[m]	6	$C_{19}H_{14}Cl_2O_2$	66.10	66.42	4.09	4.60
2,2'-(OH)$_2$, 3,3'-(*i*-C$_3$H$_7$)$_2$, 5,5'-Cl$_2$, 6,6'-(CH$_3$)$_2$	H	E44	128–129	3	$C_{21}H_{26}Cl_2O_2$	66.14	66.13	6.87	6.69
2,2'-(OH)$_2$, 3-CH$_2$OH, 5,5'-Cl$_2$[e]	H	F36	165–167	12	$C_{14}H_{12}Cl_2O_3$	56.22	56.17	4.02	4.18
Two-step condensations									
2,2'-(OH)$_2$, 3-*i*-C$_3$H$_7$, 5-Cl, 5'-*t*-C$_4$H$_9$, 6-CH$_3$	H	Ga64	158–159	2	$C_{21}H_{27}ClO_2$	72.71	72.70	7.85	7.86
2,2'-(OH)$_2$, 3-*i*-C$_3$H$_7$, 5,5'-Cl$_2$, 6-CH$_3$	H	Ga44	134.5–135.5	1	$C_{17}H_{18}Cl_2O_2$	62.78	62.72	5.58	5.74
2,4'-(OH)$_2$, 6,2'-(CH$_3$)$_2$, 3,5'-(*i*-C$_3$H$_7$)$_2$, 5-Cl[d]	H	Ga23	174–176	1	$C_{21}H_{27}ClO_2$	72.71	72.55	7.85	8.05
2,2'-(CH$_3$)$_2$, 4,4'-(OH)$_2$, 5,5'-(*i*-C$_3$H$_7$)$_2$[d,l]	H	Gb78[h]	162–164	4	$C_{21}H_{28}O_2$	80.73	80.20	9.03	10.8
Direct substitutions									
2,2'-(OCH$_3$)$_2$, 5,5'-Cl$_2$[n]	H	H70	95–97	7	$C_{15}H_{14}Cl_2O_2$	60.62	60.86	4.75	4.91
2,2'-(OCH$_2$COOH)$_2$, 5,5'-Cl$_2$	H	I51	242–245	8	$C_{17}H_{14}Cl_2O_6$	53.00	53.02	3.66	3.71
2,2'-(OH)$_2$, 3,3'-I$_2$, 5,5'-Cl$_2$[e,i]	H	J38	195–196	9	$C_{13}H_8Cl_2I_2O_2$	29.97	30.32	1.55	1.65
2,2'-(OH)$_2$, 3,3'-I$_2$, 5,5'-Cl$_2$[e,i]	C$_6$H$_5$	J66	193–194.5	9	$C_{19}H_{12}Cl_2I_2O_2$	38.22	38.62[p]	2.03	1.96
2,2'-(OH)$_2$, 3,3'-I$_2$, 5,5'-Cl$_2$,[e,i]	CH$_3$	J53	123–124.5	9	$C_{14}H_{10}Cl_2I_2O_2$	31.43	31.47[p]	1.88	2.08
2,2'-(OH)$_2$, 3-*i*-C$_3$H$_7$, 3'-I, 5-Cl, 5'-*t*-C$_4$H$_9$, 6-CH$_3$	H	J28[q]	126–127	3	$C_{21}H_{26}ClIO_2$	53.35	53.51[p]	5.54	5.72
2,2'-(OH)$_2$, 3-SO$_3$H, 5,5'-Cl$_2$[e]	H	Ka33		10	$C_{26}H_{22}Cl_4O_{12}S_2Ca$[o]	38.62	38.53	3.24	3.57
2,2'-(OH)$_2$, 3,3'-(SO$_3$H)$_2$, 5,5'-Cl$_2$[e]	H	Kb27		10	$C_{13}H_{12}Cl_2O_{10}S_2Ba$[o]	26.00	26.06	1.97	2.52
2,2'-(OH)$_2$, 3,3'-(NO$_2$)$_2$, 5,5'-Cl$_2$[e]	H	La63	181–182	9	$C_{13}H_8Cl_2N_2O_6$	43.47	43.33	2.25	2.62
2,2'-(OH)$_2$, 3,3'-(NH$_2$)$_2$, 5,5'-Cl$_2$	H	Lb83	230–232	8	$C_{13}H_{12}Cl_2N_2O_2$	52.19	52.27	4.04	4.60
2,2'-(OH)$_2$, 3,3'-(CH$_3$CONH)$_2$, 5,5'-Cl$_2$	H	Lc29	228–229	8	$C_{17}H_{16}Cl_2N_2O_4$	53.29	53.09	4.21	4.58

[a] Positions of the substituents are based on the normal condensation of an aldehyde or a phenol alcohol in the position ortho to the hydroxyl group of *p*-substituted phenols, unless otherwise indicated. All compounds are soluble in alcoholic sodium hydroxide. [b] Crystallization solvents: 1, heptane–benzene; 2, heptane; 3, naphtha; 4, benzene–pet. ether; 5, dilute hydrochloric acid; 6, xylene; 7, methanol; 8, ethanol; 9, acetic acid; 10, water; 11, ethylene dichloride; 12, benzene. [c] By Dr. C. Tiedcke. [d] Structure not determined conclusively. Derivatives[15,20,22] of thymol indicate that the position para to the hydroxyl group of thymol is the most reactive. See footnote (19). [e] See footnote (23). [f] X,X'-Methylenebis-(4-chlororesorcinol). [g] X,X'-Methylenebis-(3-methyl-4-chlorophenol). [h] 42% yield by Method E. [i] Made in collaboration with Mr. R. R. Smith. [j] Kept cold entire twenty-four hours. [k] Unreacted phenol was removed by steam. This isomer was extracted from the crude product with hot heptane, crystallized from toluene–heptane, and finally from heptane. [l] Previously made. See ref. 21. [m] Two runs gave a product with m. p. of 154.5–156°. *Anal.* C, 66.37; H, 4.50. [n] Fungicidal activity reported. See ref. 3. [o] Dihydrate. [p] Analyses by Oakwold Laboratories. [q] The reaction product was extracted with warm heptane and the fraction from the heptane was crystallized once from glacial acetic acid. [r] The prefix denotes method of preparation as described in the text.

(40%) gave a 54% yield (based on the amount of formaldehyde) of product that melted at 154–155° when crystallized from water. The product is evidently the dialcohol derivative,[12] although the molar proportions of the reactants were favorable for the formation of the mono alcohol.[13]

Anal. Calcd. for $C_8H_9ClO_3$: C, 50.94; H, 4.81. Found: C, 50.74; H, 4.86.

2-Hydroxymethyl-6-chlorothymol.[14]—6-Chlorothymol[15] was treated with formaldehyde by Method F. The product melted at 62–64° when crystallized from low-boiling petroleum ether; yield, 54%.

Anal. Calcd. for $C_{11}H_{15}ClO_2$: C, 61.54; H, 7.04. Found: C, 61.70; H, 7.23.

2,2'-Dihydroxy-3-hydroxymethyl-5,5'-dichlorodiphenylmethane.—This product was formed by the reaction (Method F) of 0.1 mole of 2,2'-methylenebis-(4-chlorophenol)[16] in the presence of an excess (0.2 mole) of formaldehyde over a four-day period.[17] For its properties and analyses see Table I.

Condensations of Phenol-Alcohols with Phenols. Method G.—(a) One-tenth mole of 2-hydroxymethyl-6-chlorothymol[18] reacted in 60 ml. of glacial acetic acid according to Method E with one-tenth mole of the appropriate phenol.[19] (b) 6-Hydroxymethylthymol[20] and thymol were condensed by procedure G (a) to produce 6,6'-methylenedithymol.[19,21] The preparations of 6,6'-ben-

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(12) One mole of this phenol dialcohol and two moles of *p*-chlorophenol reacted in acid to give a product which melted at 230–232°. Carbon and hydrogen analyses gave evidence that this was a dimethylene-tris-(*p*-chlorophenol), but cryoscopic mol. wt. determinations did not corroborate this. *Anal.* Calcd. for $C_{20}H_{15}Cl_3O_3$: C, 58.63; H, 3.69; mol. wt., 409.7. Found: C, 59.04; H, 3.69; mol. wt., 352.

(13) This is in accord with observations of F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932).

(14) Introduction of the hydroxymethyl group into the reactive 2 position ortho to the hydroxy group in 6-chlorothymol is favored, especially since the para and other ortho positions are blocked. No conclusive structure proof was made.

(15) Bocchi, *Gazz. chim. ital.*, **26**, (II) 403 (1896).

(16) This compound is described. I. G. Farbenindustrie Patent, *Chem. Zentr.*, **101**, II, 1453 (1930); Gump and Luthy, U. S. Patent 2,334,408 (1943).

(17) The bis-hydroxymethyl derivative has been reported, Zinke and Hanus, *Ber.*, **74B**, 211 (1941).

(18) Listed under Phenol Alcohols.

(19) The positions of the groups on one-half of the resultant diphenylmethane derivative are fixed by the structure of the phenol-alcohol. The configuration of the other half of the molecule is determined by the position of the condensation in the phenol.

(20) Manasse, *Ber.*, **27**, 2412 (1894); **35**, 3846 (1902).

(21) Probably identical with product reported by Euler and Holmberg, *Kunststofftech. u. Kunstoffanwend.*, **10**, 62 (1940); *C. A.*, **35**, 735 (1941).

zalbisthymol[22] and other derivatives[15,20] of thymol indicate that position 6 is more reactive than the 2 position.

Direct Substitution of Methylene-, Ethylidene- and Benzalbisphenols. Method H.—Methylation was accomplished in acetone solution by the use of dimethyl sulfate and potassium carbonate.

I. Chloroacetic acid was refluxed with a sodium hydroxide solution of the methylenebisphenol for two hours.

J. Iodination[23] was effected by utilizing the method of Burger, *et al.*[24] on the appropriate methylene-, ethylidene- and benzalbisphenols. The amount of methanol was varied.

K. (a) The methylenebisphenol (40 g.) was heated at 100° for four hours with 31 g. of concentrated sulfuric acid. It was then diluted with 500 ml. of water, filtered and neutralized to *p*H 5.6 with sodium hydroxide. The water-washed precipitate which contained sodium was soluble in ethyl acetate. The calcium salt was formed by adding calcium chloride solution to a solution of the sodium salt. (b) By concentration of the main filtrate from K (a), an ethyl acetate–insoluble sodium salt was obtained. Barium chloride produced the barium salt from a solution of the sodium salt.

L. (a) 2,2′-Methylenebis-(4-chlorophenol) (0.25 mole) was treated in 550 ml. of glacial acetic acid with 34 g. of fuming nitric acid (d. 1.5) for one and one-half hours at 25°. (b) The dinitro derivative from L (a) was reduced in alcoholic hydrogen chloride with stannous chloride at 80° for one hour. (c) The diamino compound from L (b) was selectively acetylated by a method similar to one described.[25]

Condensation of 4-Chlorobenzenethiol with Formaldehyde. Bis-(4-chlorophenylmercapto)-methane.—Method A was used in effecting this condensation. The product was insoluble in aqueous and alcoholic sodium hydroxide. Its alkali insolubility, its inertness to iodine in acetic acid, and its analysis indicated that the compound was a mercaptal.[26] It gave a positive sulfur test. When crystallized from methanol, it melted at 44–45°; yield, 75%.

Anal. Calcd. for $C_{13}H_{10}Cl_2S_2$: C, 51.83; H, 3.35. Found: C, 51.60; H, 3.89.

Acknowledgment.—The author takes pleasure in expressing appreciation to Mr. John W. Lee for his suggestions and interest concerning this investigation.

Summary

The Baeyer and Lederer–Manasse reactions have been applied successfully by different methods to a variety of phenols and aldehydes to produce a number of symmetrical and mixed methylenebisphenols, and phenol alcohols. Direct substitutions were made in several methylenebisphenol derivatives.

p-Chlorobenzenethiol and formaldehyde were found to react in an acid medium to form a mercaptal.

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[22] Bell and Henry, *J. Chem. Soc.*, 2215 (1928); Orndorf and Lacey, THIS JOURNAL, **49**, 818 (1927).

[23] The positions of the introduced substituents have not been proved conclusively. The chlorination of 2,2′-methylenebis-(4-chlorophenol) in this Laboratory to yield the known 2,2′-methylenebis-(4,6-dichlorophenol) indicates the reactivity of the positions ortho to the hydroxyl groups.

[24] Burger, Wilson, Brindley and Bernheim, THIS JOURNAL, **67**, 1416 (1945).

[25] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., Boston, Mass., 1935, p. 165.

[26] The formation of a mercaptal with benzenethiol and acetaldehyde has been reported: Escales and Bauman, *Ber.*, **19**, 2815 (1886).

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Preparation of Aryl Acrylates and Methacrylates by Pyrolysis of the Corresponding Acetoxy Esters

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In an earlier paper[2] we have shown that phenyl acrylate was obtained in good yield by pyrolysis of phenyl α-acetoxypropionate at 500–550°. The present paper reports the results of further study of this pyrolysis method for the preparation of various new aryl acrylates, namely, *p*-chlorophenyl, *m*-tolyl, *o*-allylphenyl, *p*-*t*-butylphenyl, *p*-*t*-amylphenyl and *p*-cyclohexylphenyl acrylate, and phenyl methacrylate. Phenyl methacrylate, both monomer and polymer have been briefly reported in the literature.[3]

The following series of reactions was used to obtain the acrylic ester: (1) acetylation of lactic acid with acetic acid to give acetoxypropionic acid[2,4]; (2) conversion of acetoxypropionic acid into its acid chloride by treatment with thionyl chloride; (3) interaction of the acid chloride with the phenol to produce the aryl acetoxypropionate, yields (see Table I) being 85–95% and (4) pyrolysis of the acetoxypropionate at 500 to 550° to form the aryl acrylate, generally in 70–80% yields (see Table II). Phenyl methacrylate was produced in 90% yield (Table II) by pyrolysis of phenyl acetoxyisobutyrate.

With a contact time of approximately ten seconds, pyrolysis at 550° consistently gave somewhat lower yields of the acrylate than did pyrolysis at 525 or 500°. The pyrolysis runs giving low yields of acrylate, *i. e.*, *m*-tolyl, *p*-*t*-amylphenyl, and *o*-allylphenyl acrylate, were characterized by formation of relatively large amounts of gaseous by-products, mainly carbon dioxide and carbon monoxide, as well as formation of polymer. This was overcome, in part at least, in the pyrolysis of *o*-allylphenyl acetoxypropionate, by thermal decomposition at lower temperature, *i. e.*, 500°. Polymer formation particularly during distilla-

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[2] Filachione, Lengel and Fisher, THIS JOURNAL, **66**, 494 (1944).

[3] Anonymous, *Ind. Eng. Chem.*, **28**, 1161 (1936).

[4] Filachione and Fisher, *ibid.*, **36**, 472 (1944).