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Disubstituted Dichlorobenzophenones, Isomeric Dichlorobenzhydrols and Related Compounds

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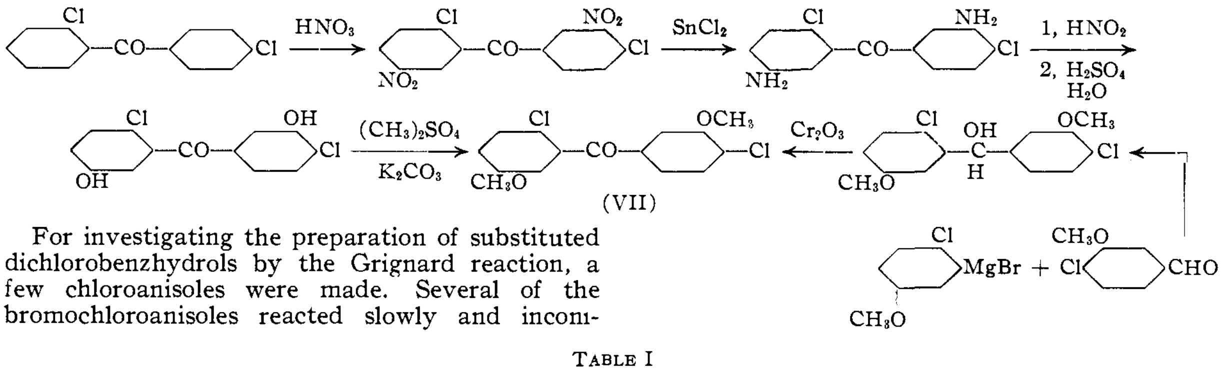
Dichlorobenzophenones disubstituted with nitro, amino, hydroxy, methoxy and acetoxy groups, dichlorobenzhydrols, and several related compounds have been prepared and tested microbiologically. Five chloroanisoles were made for use as chemical intermediates in Grignard reactions with substituted benzaldehydes.

A number of disubstituted dichlorobenzophenones, dichlorobenzhydrol isomers and derivatives of dichlorobenzhydrol have been made and tested in this Laboratory for their antimicrobial activity. Substituted benzophenones and benzhydrols have exhibited tuberculostatic,[1] antibacterial,[2] fungicidal,[3] and insecticidal[4] action.

Most of the present benzophenone derivatives have 2,4'-dichlorobenzophenone as the parent compound. Substitutions in the benzophenone nucleus by nitro, amino, hydroxy, methoxy or acetoxy groups were made by working directly with a suitable dichlorobenzophenone, or by oxidation of an intermediate benzhydrol formed from an appropriate aldehyde and Grignard reagent. By the latter method, only methoxy-substituted dichlorobenzophenones (II, VII and VIII) were made. One of these was demethylated to form the dihydroxy compound VI. Both methods were used in preparing compound VII as indicated by the diagram

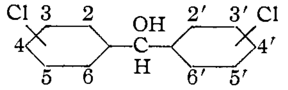


For investigating the preparation of substituted dichlorobenzhydrols by the Grignard reaction, a few chloroanisoles were made. Several of the bromochloroanisoles reacted slowly and incompletely with magnesium. 3-Bromo-4-chloroanisole in the diagrammed reaction gave a poor yield of the benzhydrol, but better success was had (33% yield) in the reaction between 4-chloro-3-methoxybenzaldehyde and the 3-bromo-2-chloroanisole Grignard reagent. However, only viscous sirups or waxy solids were obtained from this aldehyde and the magnesium compounds from 2-bromo-3-chloro-, 4-bromo-3-chloro- and 4-iodo-3-chloroanisoles. Oxidation products from the sirups could not be crystallized. From 4-iodo-3-chloroanisole and a simpler aldehyde, *p*-chlorobenzaldehyde, a crystalline ketone VIII was obtained in low yield *via* the intermediate benzhydrol.

In addition to the above derivatives we have prepared and described five unreported isomers of the six possible dichlorobenzhydrols or, more specifically, bis-(chlorophenyl)-carbinols (Table I). The 4,4'-dichloro isomer has been described in the literature.[5] Those reported herein were prepared in good yields from the condensation of the appropriate aldehyde and Grignard reagent. Three of these have an asymmetric carbon atom and are therefore racemic mixtures. Four of the dichlorobenzhydrols were oxidized to known benzophenones for comparative microbiological studies (Table II).

TABLE I

DICHLOROBENZHYDROLS



No.	Chlorine position	B.p. °C., uncor.	Mm.	M.p., °C. uncor.	Yield, %	Parent benzaldehyde	Analyses,[a] % C Found	H Found
IX	2,2'	175–180	4	90–91	43	*o*-Chloro	61.62	4.23
X	2,3'	183–185	4	48–49	67	*o*-Chloro	61.72	4.11
XI	2,4'	180–183	4	75–76	53	*o*-Chloro	61.62	3.80
XII	3,3'[b]	169–170	1–2	45.5–47	74	*m*-Chloro	61.65	4.34
XIII	3,4'	180–182	2–3	39–40	71	*p*-Chloro	61.84	4.27

[a] Calcd. for $C_{13}H_{10}Cl_2O$: C, 61.68; H, 3.98. [b] For additional antibacterial data see ref. 28.

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[1] B. L. Freedlander, *Am. Rev. Tuberc.*, **49**, 543 (1944); *Proc. Soc. Exptl. Biol. Med.*, **51**, 153 (1942).

[2] K. Okazaki, K. Matsui and H. Kotov, *J. Pharm. Soc. Japan*, **71**, 1337 (1951); R. Kuhn, *et al.*, *Ber.*, **75B**, 711 (1942); E. Fisher, *J. Pharm. and Pharmacol.*, **4**, 314 (1952); ref. 28 also.

[3] P. B. Marsh and M. L. Butler, *Ind. Eng. Chem.*, **38**, 701 (1946); F. J. Meyer, U. S. Patent 2,486,961.

[4] G. T. Bottger and C. Levin, *U. S. Dept. Agr., Agr. Research Admin., Bur. Entomol. Plant Quarantine* E-738, 14 pp. (1947); R. L. Metcalf, *J. Econ. Entomol.*, **41**, 875 (1948).

[5] P. J. Montagne, *Rec. trav. chim.*, **24**, 114 (1905).

TABLE II

ANTIMICROBIAL ACTIVITY OF DICHLOROBENZOPHENONES, DICHLOROBENZHYDROLS AND RELATED COMPOUNDS

Minimum microbicidal concn. in mg. per 100 cc.

Compd. no.	*Staph. aureus*	*Strep. agalactiae*	*E. coli*	*T. mentagrophytes*	*C. albicans*
			Dichlorobenzophenones		
II	>12.5		>12.5	>50.0	>50.0
IV			> 2.0	>25.0	
V	> 4.0	>4.0	> 4.0		
VI	> 4.0	>4.0	8.0		
VII	> 4.0	>4.0	> 4.0		
VIII	> 4.0	>4.0	> 4.0	6.25	
XVI	> 4.0	>4.0	> 4.0		
XVII	1.0	>1.0	2.0	0.78	
XVIII	0.5		2.0	0.78	25.0
238[a]	> 4.0	1.0	> 4.0		
203[b]	> 4.0	2.0	> 4.0		
237[c]	> 4.0	>4.0	> 4.0		
235[d]	> 4.0	>4.0	> 4.0		
			Dichlorobenzhydrols		
I				>25.0	>25.0
IX	8.0		>8.0	3.12	25.0
X	4.0		20.0	3.12	6.25
XI	4.0		>8.0	3.12	12.5
XII	4.0	2.0	10.0	0.78	12.5
XIII	2.0		5.0	1.56	6.25
XIX	4.0		8.0	12.5	
			Related compounds		
XIV	1.0	0.5	4.0	0.78	3.12
XV	> 4.0		> 4.0		

[a] 2,3′ - Dichlorobenzophenone. [b] 2,4′ - Dichlorobenzophenone. [c] 3,3′-Dichlorobenzophenone. [d] 3,4′-Dichlorobenzophenone.

Results of the microbiological studies summarized in Table II showed that several of the compounds had fair antibacterial activity against *Staphylococcus aureus*, *Streptococcus agalactiae* and *Escherichia coli*. On the other hand, relatively marked antifungal action against *Trichophyton mentagrophytes* was shown by the majority of the compounds tested. Several of the derivatives (X, XIII and XIV) also exhibited high activity against *Candida albicans*. The serial twofold dilution method was used in testing the compounds in appropriate liquid media.

Experimental[6]

3-Bromo-2-chloroanisole.—2-Chloro-3-nitrophenol[7,8] (24.7 g., 0.142 mole) was refluxed for two hours in 250 ml. of anhydrous acetone with 21 ml. of dimethyl sulfate and 15.6 g. of potassium carbonate to produce 21.75 g. (81%) of 2-chloro-3-nitroanisole.[7] Eighteen grams (0.096 mole) of this product in 87 ml. of concd. hydrochloric acid containing 65.2 g. of stannous chloride dihydrate was allowed to warm spontaneously to 95° under control of an ice-bath. The hot solution was stirred for 20 minutes without cooling, then chilled. The salts obtained were treated with sodium hydroxide solution to yield 2-chloro-*m*-anisidine[9,10] (14.5 g.). This, without further purification, was diazotized in 151.0 g. of 40% hydrogen bromide at 3 to 5°. Three hours were required. The diazotized solution was treated at 75° with cuprous bromide solution[11] made from 26.6 g. of cupric sulfate crystals and 12.7 g. of sodium bromide in a described manner.[11] After steam distillation, the oil was fractionally distilled; b.p. 136–139° (16–18 mm.), yield 13.6 g. (68%).

Anal. Calcd. for C_7H_6BrClO: C, 37.96; H, 2.73. Found: C, 38.17; H, 2.80.

2,4′-Dichloro-3,3′-dimethoxybenzhydrol (I).—A Grignard reagent was prepared by refluxing 11.35 g. (0.0513 mole) of 3-bromo-2-chloroanisole in 30 ml. of anhydrous ether (sodium dried) under nitrogen with 1.19 g. (0.049 g. atom) of magnesium turnings. To the solution was added 8.35 g. (0.049 mole) of 4-chloro-3-methoxybenzaldehyde in 24 ml. of ether over 10 minutes time. After 45 minutes of refluxing, the mixture was decomposed by stirring it with cold sulfuric acid. The oil was taken up in ether, washed with water until neutral, and dried over magnesium sulfate. The residue left from evaporation of the ether was washed with ligroin containing some ether and recrystallized from aqueous ethanol. It melted at 131–132°; yield 5.28 g. (32.8%).

Anal. Calcd. for $C_{15}H_{14}Cl_2O_3$: C, 57.52; H, 4.51. Found: C, 57.59; H, 4.48.

2,4′-Dichloro-3,3′-dimethoxybenzophenone (II).—A solution of chromium trioxide was prepared by dissolving 1.16 g. of the trioxide in 1.5 ml. of water and diluting to 7 ml. with glacial acetic acid. This was added in eight minutes to a refluxing solution of 2.73 g. (0.0087 mole) of the above benzhydrol (I) in 9.5 ml. of glacial acetic acid, and refluxing was continued for 25 minutes longer. The reaction mixture was poured into water, and ether extracted. The ether solution was shaken with sodium hydroxide solution, then with water, and dried with magnesium sulfate. Recrystallization from heptane gave 1.72 g. (63%) of product, m.p. 113–114°.

Anal. Calcd. for $C_{15}H_{12}Cl_2O_3$: C, 57.90; H, 3.89. Found: C, 57.75; H, 4.15.

2,4′-Dichloro-3,3′-dihydroxybenzophenone (III).—Compound II (3.28 g., 0.0106 mole) was demethylated by stirring it in 36 ml. of chlorobenzene with 41.4 g. of powdered aluminum chloride for 5.5 hours at 60°. The chilled mixture was added with cooling to 120 g. of ice and 20 ml. of concd. hydrochloric acid. Chlorobenzene was removed by steam distillation, the residue stirred with activated carbon in sodium hydroxide solution and precipitated by slowly acidifying with hydrochloric acid. When recrystallized from toluene containing some hexane, it melted at 157–158.5°; yield 2.65 g. (88%).

Anal. Calcd. for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 55.19; H, 2.87.

2,4′-Dichloro-5,3′-dinitrobenzophenone (IV).—Practical (Eastman) 2,4′-dichlorobenzophenone (100 g.) was heated with one liter of nitric acid (d. 1.5) at 50° for 1.5 hours. The solution was poured into water to give a cream-colored precipitate which was recrystallized from glacial acetic acid. One hundred grams of product melting at 153–159° (74%) was obtained and used without further purification in the preparation of the diamine (V) given below. A portion recrystallized from glacial acetic acid melted at 160–162°.

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_5$: C, 45.77; H, 1.77. Found: C, 45.79; H, 1.82.

2,4′-Dichloro-5,3′-diaminobenzophenone (V).—The dinitro compound IV (32.4 g., 0.095 mole) was reduced at 55–60° for one hour with 169.6 g. of stannous chloride dihydrate in 195 ml. of ethanol. The salts obtained after filtration were made alkaline with sodium hydroxide to dissolve the tin salts and to produce a precipitate. After solidifying, the precipitate was dissolved in warm dilute hydrochloric acid, treated with carbon, and poured into sodium hydroxide solution. Recrystallization from 250 ml. of 75% methanol gave 21.5 g. (80%) of yellow product, m.p. 113–115°.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: C, 55.53; H, 3.58. Found: C, 55.39; H, 3.61.

2,4′-Dichloro-5,3′-dihydroxybenzophenone (VI).—The diamine V (21.0 g., 0.0746 mole) was dissolved in 100 g.

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[6] Analyses have been determined by Dr. Carl Tiedcke, Laboratory of Microchemistry, Teaneck, N. J. Melting points are uncorrected.

[7] H. van Erp, *J. prakt. Chem.*, **127**, 20 (1930).

[8] It is interesting to note that in a preparation analogous to the one for this phenol, using *m*-nitrophenol, potassium bromate and hydrobromic acid (0–5°), we obtained not the 2-bromo derivative but probably 6-bromo-3-nitrophenol (26%): m.p. 116–118°, given m.p. 118–119°.

[9] F. W. Schlieper, *Ber.*, **26**, 2467 (1893).

[10] G. R. Clemo and A. F. Daglish, *J. Chem. Soc.*, 1481 (1950).

[11] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 130–133.

of warm 60% sulfuric acid, and diazotized at 0° within one hour with 10.3 g. of sodium nitrite in 25 ml. of water. The diazotized solution was poured gradually into 260 g. of 70% sulfuric acid at 160° (boiling). Upon stirring for 10 minutes after the addition, the mixture was diluted with an equal volume of water, cooled and filtered from the solution onto a sintered glass funnel. The solid was washed with water, stirred with activated carbon in sodium hydroxide solution and reprecipitated by acidification. Crystallization was slow. The product was recrystallized from water, slightly acidic with hydrochloric acid; then finally recrystallized from toluene to give 6.85 g. (32%) of white powder, m.p. 161°.

Anal. Calcd. for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.84. Found: C, 55.29; H, 3.06.

It formed a 2,4-dinitrophenylhydrazone, m.p. 283–284°.

The 2,4'-Dichloro-5,3'-dimethoxybenzophenone (VII). Method A.—The above dihydroxy compound VI (1.5 g.) was stirred in 15 ml. of dry, boiling acetone with 1.2 g. of potassium carbonate and 2.1 g. of dimethyl sulfate for 2 hours. The salts were removed by filtration, the acetone evaporated, then the residue stirred with dilute sodium hydroxide solution, and separated by filtration. It was recrystallized from heptane, activated alumina being used to decolorize; yield 1.4 g. (85%), m.p. 132–133.5°.

Anal. Calcd. for $C_{15}H_{12}Cl_2O_3$: C, 57.90; H, 3.89. Found: C, 57.77; H, 3.92.

Method B.—Compound VII was also made by means of the *Grignard reaction* as follows: 3-bromo-4-chloroanisole (5.35 g., 0.0241 mole) (see below) was stirred with 0.56 g. (0.023 g. atom) of magnesium turnings in 10 ml. of ether (dried over sodium). Several small iodine crystals were added and the mixture gently boiled for four hours without change, then the addition of two drops of ethyl iodide with a crystal of iodine initiated a reaction. After 3.5 hours of refluxing under nitrogen gas and standing at 30° overnight, the mixture still contained unreacted magnesium. 4-Chloro-3-methoxybenzaldehyde (3.5 g.) (see below) in 10 ml. of anhydrous ether was added to the solution and refluxed for 50 minutes. The solution was shaken with cold 28% sulfuric acid and then with dilute sodium hydroxide. Ether was removed and the residue steam distilled to remove volatile components, dissolved in benzene, and passed through an activated alumina adsorption column. The resultant benzhydrol (0.456 g.) which melted 123–128° was oxidized without further purification to the benzophenone by the method described above in producing II. When recrystallized from heptane it was found to be identical by mixed melting points with the product obtained by method A, that product having been obtained by several steps from the nitration of 2,4'-dichlorobenzophenone.

4-Chloro-3-methoxybenzaldehyde.[12]—*p*-Chlorobenzaldehyde[13] (26.5 g., 0.188 mole) was warmed at 30–35° with 55 g. of concd. sulfuric acid and 17 g. of sodium nitrate for 5.5 hours and finally at 48° for 10 minutes. The mixture was poured into a water–ice mixture, the oil ether extracted, washed with water, and dried with magnesium sulfate. After concentration of the extract, it was diluted with ligroin (b.p. 36–70°). A small amount of acid constituent was removed from the product by stirring it with sodium bicarbonate solution. Then the product was recrystallized from ether by diluting with ligroin and chilling. The yield of 4-chloro-3-nitrobenzaldehyde[14] was 17.2 g. (48%), m.p. 63–64°. The 3-nitro compound (30 g., 0.162 mole) was reduced to 3-amino-4-chlorobenzaldehyde with 110 g. (0.49 mole) of stannous chloride dihydrate in 150 ml. of hydrochloric acid by a standard method.[15] The stannic chloride salt, obtained by filtration, was diazotized at 3–5° in 165 ml. of 30% sulfuric acid with 11.5 g. of sodium nitrite in 37 ml. of water. This mixture was added over 15 min. to a boiling solution of 360 g. of 70% sulfuric acid,[16] the volume being kept constant by the addition of water while 4-chloro-3-hydroxybenzaldehyde[12] was distilling with steam. The first fraction (3.0 g.) obtained from the chilled distillate (m.p. 110–115°) was recrystallized from heptane. The main fraction (8.2 g.) melted at 119–121.5°; average yield, 40%. Methylation of the phenolic aldehyde (11.9 g.) was accomplished in 70–80% yield in dry acetone (60 ml.) with 8.5 g. of potassium carbonate and 15.3 g. of dimethyl sulfate by refluxing for 1.3 hours to yield 4-chloro-3-methoxybenzaldehyde[12] which melted at 52–53.5° when recrystallized from approximately 95% acetic acid.

3-Amino-4-chloroanisole Hydrochloride.—4-Chloro-3-nitroanisole[17] (m.p. 45°) was made in 88% yield from 4-amino-3-nitroanisole by the Sandmeyer reaction. This (31.6 g., 0.169 mole) was reduced with 114.0 g. (5.05 moles) of stannous chloride dihydrate in 152 ml. of concd. hydrochloric acid by allowing the mixture to warm spontaneously from 10 to 95° under control of an ice-bath. Then it was stirred without cooling as the temperature dropped from 95 to 40°. After chilling, the salts were removed by filtration and added to aqueous sodium hydroxide. The amine was dissolved in ether, washed with water, dried over magnesium sulfate and converted to the hydrochloride while in ether; then recrystallized from absolute ethanol. The salt melted at 203–205° dec. when heated 3° per minute from 198°; yield 20.2 g. (62%).

Anal. Calcd. for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67. Found: C, 43.49; H, 4.52.

The **picrate**, recrystallized from water, melted at 118° dec.

Anal. Calcd. for $C_{13}H_{11}N_4O_8Cl$: C, 40.37; H, 2.87. Found: C, 40.57; H, 2.69.

3-Bromo-4-chloroanisole.[18]—3-Amino-4-chloroanisole[19] made from 31.6 g. of 4-chloro-3-nitroanisole as described above was chilled and added to 200 ml. of 48% hydrobromic acid. The mixture was diazotized with 0.152 mole of sodium nitrite at 3–6° within 2.5 hours. The diazotized solution was added to warm (75°) cuprous bromide solution prepared from 47.6 g. of cupric sulfate crystals, and kept at 75° for one hour. Twenty-five ml. of 48% hydrobromic acid was added and the mixture was allowed to cool to 25°. Then it was diluted with 300 ml. of water and steam distilled. The oil was taken up in ether, washed with dilute sulfuric acid, then with dilute sodium hydroxide solution, and finally with water. After drying with magnesium sulfate, the solution was fractionally distilled, yielding 20.75 g. of the main fraction, b.p. 123–126° (13–14 mm.). The yield over the two steps was 64%, the diazotizable amine resulting from the first step being obtained in approximately 90% yield, and the bromination in about a 71% yield.

Anal. Calcd. for C_7H_6BrClO: C, 37.96; H, 2.73. Found: C, 37.99; H, 2.40.

4-Bromo-3-chlorophenol.—2-Chloro-4-nitroaniline[20] was prepared by treating 55.2 g. of *p*-nitroaniline in 1120 ml. of 10% hydrochloric acid at 0° with a 5% excess of chlorine over a 30-min. period. Repeated extraction of the product with hot water gave 18.66 g. of product (27%). This was diazotized, reacted with cuprous bromide–hydrobromic acid mixture, and steam distilled to yield 4-bromo-3-chloronitrobenzene[20] (69%). Reduction of the nitro compound (20.93 g., 0.0885 mole) was accomplished by warming it to 90–95° with 90 ml. of concd. hydrochloric acid, 59.9 g. of stannous chloride dihydrate and 55 ml. of ethanol saturated at 50° with hydrogen chloride. After 10 min. at 90°, the solution was stirred at 60–65° for one hour, chilled with a salt–ice bath and diluted with ethanol. The crystals were removed by filtration and added to cold sodium hydroxide solution to give crystalline 4-bromo-3-chloroaniline.[21,22] The yield was 16.2 g. (84%); m.p. 66–67°, without recrystallization. This amine was diazotized in concd. sulfuric acid with nitrosyl sulfuric acid and 90% phosphoric acid by a method[23] described for 2,4-dinitroaniline. The best yield was obtained when phosphoric acid was added at 0–2° over

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[12] Made by a different route: H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 147 (1926).

[13] Reference 11, 1941, p. 133.

[14] E. Erdman and H. Erdman, *Ann.*, **294**, 380 (1897).

[15] W. E. Bachmann, *Org. Syntheses*, **25**, 55 (1945).

[16] *Cf.* H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 404.

[17] Made by different routes. See reference 7. Also H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, **135**, 1812 (1932).

[18] Also made by the debromination of 2,3,6-tribromo-4-chlorophenol. No yields given; M. Kohn and S. Reichmann, *J. Org. Chem.*, **12**, 213 (1947).

[19] No purification other than washing the tin salts with absolute ethanol before converting to the base with sodium hydroxide.

[20] G. Korner and A. Contardi, *Atti accad. Lincei*, **22**, I, 823 (1914); *C.A.*, **8**, 73 (1914).

[21] H. L. Wheeler and W. Valentine, *Am. Chem. J.*, **22**, 270 (1899).

[22] F. D. Chattaway and K. J. P. Orton, *J. Chem. Soc.*, **79**, 466 (1901).

[23] H. A. J. Schoutissen, THIS JOURNAL, **55**, 4531 (1933).

a 45-minute period, the solution stirred 45 minutes longer, and then stirred with urea for 10 minutes. To form the phenol, the cold diazotized solution, made from 0.077 mole of the amine, was added in a stream with stirring to 310 g. of boiling 35% sulfuric acid. The distillate was chilled and filtered to remove 4-bromo-3-chlorophenol, m.p. 66–68°; from ligroin, m.p. 67.5–69°[24]; yield 77%.

Anal. Calcd. for C_6H_4BrClO: C, 34.73; H, 1.94. Found: C, 34.92; H, 2.29.

4-Bromo-3-chloroanisole.—The above phenol (10.38 g., 0.05 mole) was refluxed for 2.25 hours in 80 ml. of dry acetone with 5.93 g. of potassium carbonate and 8.0 ml. of dimethyl sulfate. After filtration, the solution was concentrated *in vacuo*, the residue made alkaline with dilute sodium hydroxide and extracted with ether. The ether solution was washed with water, dried with magnesium sulfate, and fractionated twice; yield 8.9 g. (81%), b.p. 129–132° (16–17 mm.).

Anal. Calcd. for C_7H_6BrClO: C, 37.96; H, 2.73. Found: C, 38.37; H, 2.84.

3-Chloro-4-iodoanisole.—3-Chloro-4-aminoanisole hydrochloride was obtained in a 22% yield from the stannous chloride reduction of *p*-nitroanisole as described.[25] The amine hydrochloride (29.3 g., 0.151 mole) was diazotized in 120 ml. of 20% hydrochloric acid at 0–2° with 10.6 g. of sodium nitrite in 24 ml. of water. The cold diazotized solution was poured into cold potassium iodide (27.6 g.) solution. In order to lessen decrepitation, the cold mixture was allowed to warm to room temperature in portions with good stirring, and then finally warmed to 50° to complete the reaction. The dark oil was extracted with chloroform, treated with sodium bisulfite solution, and washed with water. It was steam distilled from dilute sodium hydroxide solution and from dilute sulfuric acid. After drying in ether with magnesium sulfate, it was fractionally distilled twice, b.p. 127–130° (6–7 mm.); yield 22.9 g. (57%).

Anal. Calcd. for C_7H_6ClIO: C, 31.31; H, 2.25. Found: C, 31.76; H, 2.44.

2,4′-Dichloro-4-methoxybenzophenone (VIII).[26]—4-Iodo-3-chloroanisole (8.0 g.) readily reacted with 0.695 g. of magnesium turnings in anhydrous ether. *p*-Chlorobenzaldehyde (4.0 g.) in 10 ml. of ether was added to the solution causing it to reflux. After 50 minutes of refluxing, the solution was shaken with cold 30% sulfuric acid. The ether layer was washed with aqueous sodium hydroxide, with water, and the volatile components removed by steam distillation. The non-crystallizable residue was dissolved in dry benzene and passed through an activated alumina column. Five sirupy fractions were collected. The last three were combined (5.7 g.) and oxidized with chromium trioxide by the method used above in preparing II. The viscous product was dissolved in benzene and passed through activated alumina. The residual fractions crystallized in about 24 hours. Further purification was accomplished by recrystallization from methanol containing some water; yield 0.45 g., m.p. 73–74.5° (lit.[26] 68–70°).

Anal. Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 59.58; H, 3.70.

It gave a 2,4-dinitrophenylhydrazone, m.p. 213–217°.

The first two sirupy fractions when oxidized gave an unidentified product which melted at 89.5–90°.

Anal. Found: C, 58.22; H, 3.89.

Its 2,4-dinitrophenylhydrazone melted at 208–211°.

Dichlorobenzhydrols (IX to XIII). General Method.—An appropriate bromochlorobenzene (14.32 g., 0.075 mole) in 20 ml. of anhydrous ether was treated with 1.82 g. (0.075 g. atom) of magnesium in 10 ml. of ether and refluxed for 30 minutes after the initial reaction had subsided. Then 10.53 g. of a suitable chlorobenzaldehyde (as indicated in Table I), dissolved in 30 ml. of ether, was added and refluxed for one hour. The magnesium compound was hydrolyzed by stirring and extracting with portions of 10% sulfuric acid (100 g. total). After extraction of the ether solution with 10% sodium hydroxide solution and with water, it was subjected to steam distillation. The residual benzhydrol, dried in ether with magnesium sulfate, was fractionally distilled and then recrystallized from ligroin or hexane. Oxidation of the dichlorobenzhydrols (IX to XIII) in good yields to **dichlorobenzophenones**[27] with chromium trioxide in acetic acid was accomplished by the method described for II, except refluxing was continued for 35 minutes after a 10-minute addition period.

2,4′-Dichloro-5,3′-dihydroxydiphenylmethane (XIV).[28]—The benzophenone VI (4.0 g.) was reduced by a modified Clemmensen reduction.[29] The crude product was treated with decolorizing carbon in dilute sodium hydroxide solution. After precipitation by acidification, it was extracted with hot water, filtered, acidified, and cooled to crystallize. Then it was recrystallized from 500 ml. of aqueous acetic acid, activated carbon being used. Three ml. of 10% hydrochloric acid was added to facilitate crystallization; yield 1.0 g., m.p. 119–120°.

Anal. Calcd. for $C_{13}H_{10}Cl_2O_2$: C, 58.01; H, 3.75. Found: C, 57.56; H, 3.72.

4,4′-Dichloro-3,3′-dimethoxybenzil (XV).—By refluxing 9.5 g. (0.0557 mole) of 4-chloro-3-methoxybenzaldehyde for 3.5 hours with 1.25 g. of 95% potassium cyanide in 60 ml. of 60% ethanol, the benzoin was obtained. Without recrystallization, it was oxidized to the benzil by stirring for two hours at 100° in a solution of 14.5 ml. of pyridine and 5 ml. of water containing 13.0 g. of cupric sulfate crystals.[30] Addition of water gave a precipitate which was recrystallized from acetic acid diluted with some water, and then from benzene–hexane; yield 3.3 g. (35%), m.p. 206°; yellow needles.

Anal. Calcd. for $C_{16}H_{12}Cl_2O_4$: C, 56.66; H, 3.57. Found: C, 56.72; H, 3.79.

Demethylation of this benzil with aluminum chloride by the method used[31] to demethylate an isomeric compound gave no well defined product.

2,2′-Dimethoxy-5,5′-dichlorobenzophenone (XVI).—2,2′-Methylenebis-(4-chloroanisole)[32] (20.0 g.) was oxidized with chromium trioxide by the procedure used in producing II. The benzophenone was recrystallized from aqueous methanol using activated carbon, and finally from ligroin; yield 14.0 g. (67%), m.p. 110°.

Anal. Calcd. for $C_{15}H_{12}Cl_2O_3$: C, 57.89; H, 3.89. Found: C, 57.75; H, 3.91.

2,2′-Dihydroxy-5,5′-dichlorobenzophenone (XVII).[33]—The dimethoxy compound XVI (22.0 g., 0.071 mole) was demethylated at 60° in 150 ml. of chlorobenzene for 5.5 hours with aluminum chloride (278.0 g.) by a described method,[31] yield 18.3 g. (92%). The yellow product was recrystallized from ligroin, m.p. 151–152°.

Anal. Calcd. for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 54.74; H, 3.18.

Its 2,4-dinitrophenylhydrazone decomposed above 300°. XVII formed a white alkali-insoluble product when autoclaved at 125° for 15 min. in a buffered solution (*p*H 7) of sodium dihydrogenphosphate and sodium hydroxide. This is probably 2,7-dichloroxanthone.[34] The melting point, 226° (from ethanol), is in close agreement with that (225°) recorded for dichloroxanthone[35] made by the chlorination of xanthone.

Anal. Calcd. for $C_{13}H_6Cl_2O_2$: C, 58.90; H, 2.28. Found: C, 58.98; H, 2.38.

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[24] At the time this work was finished the preparation of this phenol from 4-nitroso-3-chlorophenol was reported. Reported m.p. 63°. No yield given; H. H. Hodgson and W. H. H. Norris, *J. Chem. Soc.*, Suppl. Issue No. I, S 181 (1949).

[25] W. G. Hurst and J. F. Thorpe, *ibid.*, **107**, 934 (1915).

[26] After the completion of this work, the preparation of VIII by a different route was reported: R. Baltzly, *et al.*, *J. Org. Chem.*, **14**, 775 (1949).

[27] H. L. Haller, *et al.*, This Journal, **67**, 1591 (1945).

[28] For additional antibacterial data see H. J. Florestano and M. E. Bahler, *J. Am. Pharm. Assoc., Sci. Ed.*, Vol. XLII, 576 (1953).

[29] Method B of H. L. Bradlow and C. A. VanderWerf, This Journal, **69**, 1254 (1947).

[30] Method described by H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 87.

[31] H. Shapiro and K. A. Smith, *J. Chem. Soc.*, 143 (1946).

[32] H. E. Faith, This Journal, **72**, 837 (1950).

[33] For fungicidal activity see P. B. Marsh and M. L. Butler, *Ind. Eng. Chem.*, **38**, 704 (1946).

[34] 2-Ethoxy-2′-hydroxy-5,5′-dibromobenzophenone in potassium hydroxide at 100° gave 2,7-dibromoxanthone: O. Diels and K. Rosenmund, *Ber.*, **39**, 2361 (1906).

[35] S. N. Dhar, *J. Chem. Soc.*, **117**, 1053 (1920).

No 2,4-dinitrophenylhydrazone was obtained after warming the xanthone for eight hours at 60° with an ethanolic solution of 2,4-dinitrophenylhydrazine and sulfuric acid.

2,2′-Diacetoxy-5,5′-dichlorobenzophenone (XVIII).[36]—The dihydroxy compound XVII (5.0 g.) was acetylated by refluxing with 11.0 ml. of acetic anhydride for 80 minutes. Then the solution was stirred with water, filtered, and the white precipitate recrystallized from ethanol; yield 6.1 g. (94%), m.p. 99–100°.

Anal. Calcd. for $C_{17}H_{12}Cl_2O_5$: C, 55.60; H, 3.30. Found: C, 55.10; H, 3.29.

2,2′-Dihydroxy-5,5′-dichlorobenzhydrol (XIX).[36]—Pulverized lithium aluminum hydride (3.57 g., 0.094 mole) was refluxed one hour in 60 ml. of anhydrous ether. 2,2′-Diacetoxy-5,5′-dichlorobenzophenone (XVIII) (15.0 g., 0.041 mole) was dissolved for the most part in 200 ml. of anhydrous ether and added fast enough to the stirred suspension to maintain gentle refluxing (50 min.). After an additional two hours of refluxing, 8.0 ml. of water was added slowly. When hydrogen had ceased evolving, the mixture was shaken with dilute sulfuric acid, the ether layer separated, washed with water, and dried with magnesium sulfate. After removal of the ether, the residual oil was dissolved in dilute sodium hydroxide solution and treated with activated carbon. Precipitation with acid gave a white solid which was recrystallized from benzene. When heated 3° per minute from 140° it melted at 149°; yield 8.3 g. (70%). A test with 2,4-dinitrophenylhydrazine was negative for a keto group.

Anal. Calcd. for $C_{13}H_{10}Cl_2O_3$: C, 54.76; H, 3.54. Found: C, 55.07; H, 3.57.

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[36] Prepared in the Pitman-Moore Research Department by Robert R. Smith.

[CONTRIBUTION FROM THE CORNING GLASS WORKS AND DOW-CORNING CORPORATION MULTIPLE FELLOWSHIP AT MELLON INSTITUTE, AND THE UNIVERSITY OF PITTSBURGH]

Methyl-Silicon Cleavage of Certain Substituted Carboxylic Acids in Sulfuric Acid. Kinetics and Mechanism

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The kinetics of the reactions of β-trimethylsilylpropionic and γ-trimethylsilylbutyric acids with sulfuric acid to cleave one methyl group from silicon as methane has been studied. A mechanism involving both nucleophilic attack on silicon and electrophilic attack on carbon is proposed.

Certain organosilicon compounds containing a trimethylsilyl group, $(CH_3)_3Si$, linked to a carbon atom undergo displacement of one methyl group by the bisulfate group in the presence of sulfuric acid.[2-6] Swain contends that simple polar displacement reactions in solution involve a concerted attack of a nucleophilic reagent upon a central atom and of an electrophilic agent upon the group to be displaced.[7] Depending upon the reagent, the reaction with a given compound may be initiated by an electrophilic or nucleophilic attack. The nature of the attack is influenced also by the requirements of the central atom. Displacement of groups from a silicon atom may be favored by an initial attack of a nucleophilic reagent on silicon because silicon can accept the electrons of such a reagent by expanding its valence shell to form pentavalent intermediates.[8,9] Thus a given nucleophilic reagent can be expected to attack a silicon atom more readily than a carbon atom in a comparable compound because carbon cannot expand its valence shell. By the careful selection of reagent, reacting species and/or reaction conditions a twofold attack by the reagent may be clearly revealed. This appears to be the case in the cleavage of a methyl group from β-trimethylsilylpropionic and γ-trimethylsilylbutyric acids in aqueous sulfuric acid solutions.

Determination of Reactants and Products

The kinetics were studied for the reaction discovered by Sommer, *et al.*,[5,6] as described nearly quantitatively by the equation (where $n = 2$ and 3)

$$(CH_3)_3Si(CH_2)_nCOOH + H_2SO_4 \longrightarrow HOSO_2OSi(CH_3)_2(CH_2)_nCOOH + CH_4$$

The formation of methane has been proved by infrared absorption analysis.[5,6] The other reaction products, 4,4,6,6-tetramethyl-4,6-disila-5-oxa-nonanedioic and 5,5,7,7-tetramethyl-5,7-disila-6-oxa-undecanedioic acids, were isolated in yields of 95 and 82%, respectively.[6] *n*-Butyric acid also was identified as a product in the latter reaction.

Although Sommer and co-workers[10] extracted di-(trimethylsilyl) sulfate from the solution that resulted when allyltrimethylsilane was treated with concentrated sulfuric acid, later cryoscopic work[11,12] would indicate that the primary product in this acid medium was the acid sulfate. It is likely that in all such cleavage reactions the product is the acid sulfate, though this has not been proven conclusively. Sommer[4] also believed this to be true.

Kinetic Results

The observed kinetics for the cleavage of a methyl group from β-trimethylsilylpropionic acid in aqueous sulfuric acid solutions was found to be first or-

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