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The Bis-chloromethylation of Aromatic Compounds

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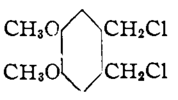
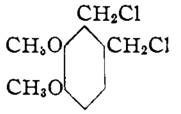
The need for a variety of bis-chloromethyl benzenes prompted us to undertake a study of the direct introduction of two chloromethyl groups into phenolic ethers and alkyl benzenes. While there has been an occasional interest in the direct introduction of two chloromethyl groups by the action of formaldehyde and hydrogen chloride, most bis-chloromethyl compounds so obtained have resulted as low yield by-products.[3]

Table I summarizes the portion of this work which is new. The choice of starting compounds was determined by the positions desired for the entering chloromethyl groups. Thus, in order to obtain satisfactory yields of compounds with the chloromethyl groups in a *para* relationship, *p*-xylene and *p*-dimethoxybenzene[4] were chosen. Similarly, properly chosen starting compounds led to the *ortho* and the *meta* bis-chloromethyl compounds. No efforts were made to characterize the other products beyond determining that no appreciable amounts of isomeric bis-chloromethyl compounds had formed.

Proof of the structure of the bis-chloromethyl compound (I) obtained by the chloromethylation of veratrole proved to be tedious because the melting point of metahemipinic acid, the known compound that would result by the oxidation of I, is within three degrees of that of hemipinic acid, the compound which would result if the structure corresponded to II. In order to make the proper choice between these two acids and hence between structures I and II, the first chloromethyl group was introduced into an unequivocal position by starting with 2,3-dimethoxybenzaldehyde, reducing to the alcohol and then replacing the alcohol function with chlorine. Chloromethylation with formalin and hydrogen chloride then gave a bis-chloromethyl product (II) which was not identical with the one obtained by bis-chloromethylation of veratrole. Thus, structure II was indicated for the one obtained in a stepwise fashion and structure I for the other. Verification of these structures was then obtained by oxidation of II to the known pseudomeconin (III) which was in turn oxidized to a dicarboxylic acid which had the correct melting point of hemipinic acid, and by the oxidation of I to the known metameconin (IV) which was then oxidized to a dicarboxylic acid having a melting point corresponding to that of metahemipinic acid. The dicarboxylic acid obtained from I depressed the melting point of the acid obtained from II by about eleven degrees. Both acids gave the phthalide test and neutral equivalents corresponding to two acid groups. Also, both chloromethyl compounds gave the phthalide test, and, in addition, would not undergo the normal Sommelet reaction to give aldehydes. These facts are additional evidence of an ortho relationship between the two chloromethyl groups.



I



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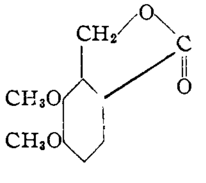

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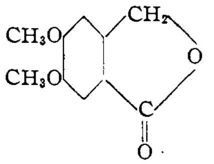

IV

All efforts to isolate chloromethyl derivatives from the chloromethylation of resorcinol dimethyl ether failed. The reaction was violent, unless carried out at low temperatures, and proceeded to the formation of high molecular weight polymers. A method was worked out for obtaining a small portion of the desired compound by chloromethylating in chloroform at low temperatures for about three minutes and then precipitating the chloromethyl compounds existing at the time by adding hexamethylenetetramine. Upon hydrolyzing the resulting salt, a 10% yield of the 4,6-dialdehyde was obtained. The dialdehyde was characterized by conversion to the known dicarboxylic acid and by analysis of the dinitrophenylhydrazone.

Although 2,4-bis-(chloromethyl)-thiophenol methyl ether had been reported,[5] no proof of

TABLE I

Starting compound	Bis-chloromethyl derivative	Yield, %	M. p., °C.
p-Xylene	2,5-[a]	57	134
Methylthiophenol	2,4-	62.5	46
Resorcinol dimethyl ether	4,6-[b]	..	....
Veratrole	4,5-	35	85.5
3-Chloromethylveratrole	3,4-	40	Liquid[c]

[a] Previously reported in 7% yield by V. Braun and Nelles, *Ber.*, **67**, 1094 (1933). The melting point reported was 133°. [b] Isolated only as the hexamethylenetetramine salt. [c] Boiling point 152–153° (3 mm.).

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[1] Tennessee Eastman Corporation Fellow, 1948–1949.

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[3] For a survey of work done see Adams, "Organic Reactions," John Wiley & Sons, New York, N. Y., Vol. I, p. 63–90.

[4] Reported in a previous paper: Wood and Gibson, THIS JOURNAL, **71**, 393 (1949).

[5] Brunner, U. S. Patent 1,887,396 (1933).

structure was offered. Therefore, the structure was established by replacement of the $-SCH_3$ group with chlorine and oxidation to the known chloroisophthalic acid.

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Experimental

2,5-Bis-(chloromethyl)-*p*-xylene.—Hydrogen chloride was introduced with vigorous stirring into a mixture of 106 g. (1 mole) of *p*-xylene, 530 ml. of concd. hydrochloric acid and 212 g. of 35% (2.6 moles) formalin at 60–70° for a period of fifteen hours. A white crystalline material separated and was removed (yield 50 g.). An additional 212 g. of formalin was added to the mother liquor and the reaction was continued a second fifteen-hour period under the same conditions as above. After cooling and filtering, 41 g. of additional material was obtained. The process was repeated a third time to yield 24 g. A fourth repetition gave no appreciable amount of precipitate. A vacuum distillation of the mother liquor gave 35 g. of a material which came over between 103° and 145° at 14 mm. and consisted mostly of chloromethyl-*p*-xylene, and a second fraction of 10 g. which came over between 150° and 160° at 14 mm., and which was mostly the bis-chloromethyl derivative. The crude precipitates and the higher boiling distillate were combined and recrystallized twice from petroleum ether. The yield was 111 g. (55%) of 2,5-bis-(chloromethyl)-*p*-xylene, m. p. 134° (cor.), see note (a).

4,5-Bis-(chloromethyl)-veratrole.—The following is a modification of Brunner's[5] general method for the chloromethylation of aromatic compounds.

A solution of 42 g. (0.3 mole) of veratrole in 250 ml. of 1,4-dioxane was placed in a three-necked, one-liter flask equipped with a mechanical stirrer and surrounded by an ice–water-bath. To this mixture was added, with stirring, 40 ml. of concd. hydrochloric acid and the flask was connected to a cylinder of hydrogen chloride. After initiation of flow of the gas, 30 ml. of 35% formalin was added, followed by a second equal portion of formalin after an interval of forty-five minutes. Stirring and introduction of hydrogen chloride were continued for six hours, the ice–water-bath being removed at the end of two hours. During this time the solution changed from colorless to a dark green. On cooling, white crystals were deposited and were filtered off by suction. The filtrate was poured into an equal volume of concd. hydrochloric acid. On standing, more crystals formed along with a green oil. The crystals were removed and dried as much as possible by suction filtration. Both crops of crystals were dissolved as completely as possible in boiling ligroin (70–90°); the insoluble portion was removed by filtration. On cooling, the filtrate deposited a yellow oil which was separated by decantation of the ligroin upper layer, the decanted layer depositing fine white crystals on further cooling. These crystals on air drying melted at 76–78° and amounted to 30 g. Two recrystallizations from ligroin failed to change the melting point but recrystallization from acetone gave 25 g. (35%) of pure 4,5-bis-chloromethylveratrole, m. p. 85.5–86.0° (cor.). Isolation of other products was not attempted. *Anal.* Calcd. for $C_{10}H_{12}O_2Cl_2$: Cl, 30.16; mol. wt., 235. Found: Cl, 29.96; mol. wt. (Menzies and Wright[6]), 235, 238.

Direct oxidation of the bis-chloromethyl compound to the known metahemipinic acid was not achieved. Rather, it was converted through the diacetate to the alcohol and this was oxidized to the known metameconin and metahemipinic acid, thus establishing the position of the chloromethyl groups.

4,5-Dimethoxy-o-xylylene Diacetate.—Five grams (0.02 mole) of 4,5-bis-(chloromethyl)-veratrole, dissolved in 75 ml. of glacial acetic acid, was added to 3.5 g. of anhydrous sodium acetate in 100 ml. of glacial acetic acid. The mixture was refluxed with stirring for two hours. After removal of the precipitated sodium chloride, the solution was distilled under reduced pressure to a volume of about 30 ml. to remove most of the solvent. It was then poured into water. Upon extracting with ether, washing with sodium carbonate and then water, drying over calcium chloride and evaporating the ether, a white solid formed. This was recrystallized from water to give a white crystalline material, m. p. 94–95°. The yield was 5.8 g. (93%). *Anal.* Calcd. for $C_{14}H_{18}O_6$: sapn. equiv., 141.14. Found: sapn. equiv., 139.6.

4,5-Dimethoxyphthalyl Alcohol.—Five grams of 4,5-dimethoxyxylylene diacetate was refluxed for three hours with 100 ml. of 20% sodium hydroxide. During this period the solution became completely homogeneous. After cooling, the reaction mixture was extracted with two 25-ml. portions of acetone. Filtration followed by evaporation of the acetone at room temperature gave a slightly yellow solid. Three recrystallizations of this solid from benzene gave 2.8 g. (78%) of the alcohol, a white, crystalline solid, m. p. 114–115° (cor.). The alcohol was very soluble in water as well as the more polar organic solvents and gave a positive phthalide test.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 61.39; H, 7.15.

Oxidation of 4,5-Dimethoxyphthalyl Alcohol.—To one gram of the alcohol in 50 ml. of water was added a saturated solution of potassium permanganate until the pink permanganate color persisted after warming to 50°. The mixture was then filtered and the filtrate treated with just sufficient sodium bisulfite to decolorize it. Acidification and cooling caused the formation of crystals which on recrystallization from water melted at 156–157° (0.5 g., 51%). The reported melting point of metameconin[7] is 155–156°. The product gave a positive phthalide test. *Anal.* Calcd. for $C_{10}H_{10}O_4$: sapn. equiv., 194. Found: sapn. equiv., 191.

Oxidation of Metameconin.—Three-tenths gram of metameconin was dissolved in 30 ml. of 10% aqueous alkali and heated to 75°. A concentrated solution of potassium permanganate was added dropwise until the color just persisted after heating the solution to boiling. Decolorization with sodium bisulfite and acidification of the reaction mixture, followed by cooling in the ice-chest, gave a crystalline product which was recrystallized from water to give white crystals melting at 174–175°, the reported melting point of metahemipinic acid.[8] It gave a positive phthalide test. The yield was almost quantitative. *Anal.* Calcd. for $(CH_3O)_2C_6H_2(CO_2H)_2$: neut. equiv., 113. Found: neut. equiv., 115.

2,3-Dimethoxybenzyl Alcohol.—This and the following compound were necessary in the synthesis of 3,4-bis-(chloromethyl)-veratrole. Their preparations, briefly indicated here, represent improved yields over those described previously. A crossed Cannizzaro reaction was employed starting with 2,3-dimethoxybenzaldehyde and following the procedure described for the preparation of *p*-tolylcarbinol.[9] However, the purification was achieved by recrystallization from ligroin and then ether rather than distillation. The product was obtained in an 80% yield and melted at 48–49°. The reported melting point[10] is 50°.

2,3-Dimethoxybenzyl Chloride.—This compound was obtained by treating 2,3-dimethoxybenzyl alcohol with thionyl chloride in chloroform. Distillation of the reaction mixture gave a sufficiently pure fraction boiling at 108.5–110° at 11 mm. (71% yield).

3,4-Bis-(chloromethyl)-veratrole.—To a solution of 62 g. (0.28 mole) of 2,3-dimethoxybenzyl chloride and 250 ml. of dioxane in a three-necked flask, equipped with a mechanical stirrer, were added 45 ml. of concd. hydrochloric acid and 50 ml. of 35% formalin. Hydrogen chlo-

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(6) Menzies and Wright, This Journal, **43**, 2314 (1921).

(7) Perkin, *J. Chem. Soc.*, **81**, 1027 (1902).

(8) Goldschmidt, *Monatsh.*, **9**, 772 (1888).

(9) Davidson and Weiss, "Organic Syntheses," Coll. Vol. II, p. 590.

(10) Kaufmann and Muller, *Ber.*, **51**, 123 (1918).

ride was then introduced with stirring for four and one-half hours at room temperature. The temperature rose and the solution became deep red. It was then poured into 500 ml. of concd. hydrochloric acid and allowed to stand for an hour. Separation into an oil and a water layer occurred. The mixture was extracted with ether. The extract was washed twice with water, once with sodium carbonate solution and again with water, then dried over magnesium sulfate for four hours. The solvent was then evaporated and the residue submitted to vacuum distillation. A fraction was obtained boiling at 153–158° at 5–8 mm. and amounting to 35 g. Distillation of this gave 33 g. (40%) of 3,4-bis-(chloromethyl)-veratrole, a viscous liquid boiling at 152–153° at 5 mm. It had a strong tendency to polymerize on standing. *Anal.* Calcd. for $C_{10}H_{12}O_2Cl_2$: Cl, 30.16. Found: Cl, 30.22.

Oxidation of 3,4-Bis-(chloromethyl)-veratrole.—No identifiable oxidation product was obtained by the action of potassium permanganate in neutral, acid or alkali media. However, upon treating 3 g. of the chloromethyl compound dissolved in 50 ml. of acetic acid with an acetic acid solution of sodium acetate in the manner described above for the formation of 4,5-dimethoxyxylylene diacetate, approximately 3 g. of an oil was obtained which was assumed to be the 3,4-dimethoxyxylylene diacetate. The oil was refluxed for five hours with 25 ml. of 10% potassium hydroxide to effect saponification to the alcohol. After cooling to room temperature, 6.25 g. of potassium permanganate dissolved in just sufficient water was added slowly. The mixture was then warmed to 70° to complete the oxidation. After decolorizing with sodium bisulfite and making acid with sulfuric acid, a crystalline material separated upon cooling. After washing with cold, dilute sodium hydroxide, the residue was recrystallized from hot water to give 0.5 g. (20%) of pseudomeconin, m. p. 122.5°. The reported melting point[11] is 123–124°. *Anal.* Calcd.: sapn. equiv., 194. Found: sapn. equiv., 197.

To 100 mg. of the pseudomeconin in 30 ml. of 5% sodium hyroxide at the boiling point was added saturated potassium permanganate until the color persisted. The mixture was boiled thirty minutes longer. Upon cooling and decolorizing and acidifying as above, hemipinic acid precipitated. Recrystallization from water gave a quantitative yield, m. p. 174–175°. The reported melting point[12] is 175°. A mixed melting point with the acid obtained by the oxidation of 4,5-dimethoxyphthalyl alcohol gave a depression of eleven degrees. Both pseudomeconin and hemipinic acid gave a positive phthalide test.

4,6-Bis-(chloromethyl)-resorcinol Dimethyl Ether.—All efforts to isolate chloromethyl compounds as such by the action of formalin or chloromethyl ether on resorcinol dimethyl ether failed. High molecular weight compounds resulted. The following is a method for stopping the reaction with a low yield as the hexamethylenetetramine salt.

To 5 g. (0.036 mole) of resorcinol dimethyl ether was added 10 g. (0.124 mole) of chloromethyl ether. After the reaction mixture had been stirred for three minutes at room temperature, 40 ml. of dry chloroform containing 17.4 g. (0.124 mole) of hexamine was added slowly. The salt began to appear after a few minutes. The mixture was stirred for three hours and then filtered. The salt of course was a mixture of several chloromethyl compounds with hexamine. That the 4,6-bis-chloromethyl compound was present was shown by the isolation of 0.5 g. (20%) of 4,6-dimethoxyisophthalaldehyde[13] from the hydrolysis products of the hexamine salts.

2,4-Bis-(chloromethyl)-thiophenol Methyl Ether.—Although this compound has been reported by Brunner,[5] specific details for its preparation and structural proof were not included. The following is an adaptation of Brunner's method. Into a mixture of 10 g. (0.08 mole) of methyl phenyl thioether, 40 g. (0.47 mole) of 35% formalin and 30 g. of concd. hydrochloric acid was introduced a stream of hydrogen chloride for a period of thirty-two hours at room temperature. Upon cooling, filtering, washing the residue with ice water, and drying, there was obtained 11 g. (62.5%) of crude bis-chloromethyl derivative, m. p. 44–45°. One recrystallization from cyclohexane gave white crystals, m. p. 46°.

Oxidation of 2,4-Bis-(chloromethyl)-thiophenol Methyl Ether.—To a suspension of 1 g. (0.005 mole) of the thiophenol ether in 15 ml. of 25% sodium hydroxide was added saturated potassium permanganate solution until the color persisted. During this operation the temperature was maintained at about 80°. The manganese dioxide was removed by filtration of the hot mixture. After making acid, sodium bisulfite was added to remove unreacted permanganate. Upon cooling, the crude acid separated. Purification by recrystallization from water gave 0.7 g. (63%) of **4-methylsulfonylisophthalic acid**, m. p. 192–193°. *Anal.* Calcd. for $C_9H_8O_6S$: S, 13.12. Found: S, 13.67.

Cleavage of the sulfone gave the known 4-chloroisophthalic acid: A mixture of 1 g. (0.004 mole) of the sulfone and 7 g. (0.034 mole) of phosphorus pentachloride was heated in a sealed glass tube inside a steel bomb at 210–220° for five hours. The addition of ice water to the reaction mixture gave an oil. The oil was hydrolyzed by boiling water or dilute alkali to an acid which was purified by recrystallization from water (17% yield), m. p. 294°. This corresponded to the reported melting point of 294.5° for 4-chloroisophthalic acid.[14] Calcd. for $C_8H_5O_4Cl$: neut. equiv., 100.2. Found: neut. equiv., 101.0.

Summary

The introduction of two chloromethyl groups in *p*-xylene, methylthiophenol, resorcinol dimethyl ether, and veratrole in satisfactory yields was achieved except in the case of resorcinol dimethyl ether. The new bis-chloromethyl derivatives were characterized by conversion to known dicarboxylic acids.

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[11] Solomon, *Ber.*, **20**, 889 (1887).

[12] Pschorr and Sumuleanu, *ibid.*, **32**, 3411 (1899).

[13] Wood, Tung, Perry and Gibson, THIS JOURNAL, **72**, 2992 (1950).

[14] Ullmann and Uzbachian, *Ber.*, **36**, 1799 (1903).