III. CONDENSATIONS WITH 5-HYDROXY-2-METHYLBENZOIC ACID¹

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ABSTRACT

The product obtained from the condensation of 5-hydroxy-2-methylbenzoic acid with aqueous formaldehyde and hydrochloric acid is dependent on the temperature. If the condensation is carried out at room temperature 3-hydroxy-6-methylphthalide results. This substance can also be obtained by the demethylation of 3-methoxy-6-methylphthalide. If the condensation is carried out at the boiling point the lactone of 8-hydroxymethyl-1,3-benzodioxane-6-methyl-7carboxylic acid results. Proof of the presence of the *m*-dioxane and phthalide rings in this latter substance has been established by opening these rings in succession. In both cases this has led by a series of degradative steps to 4methoxybenzene-1,2,3,5-tetracarboxylic acid. The structure of this acid has been confirmed by its synthesis in six unambiguous steps from mesitylene.

INTRODUCTION

When 5-hydroxy-2-methylbenzoic acid (I) is condensed with aqueous formaldehyde and hydrochloric acid at room temperature 3-hydroxy-6-methylphthalide (II) is obtained. However when the condensation is carried out at the boiling point the lactone of 8-hydroxymethyl-1,3-benzodioxane-6-methyl-7-carboxylic acid (III) is produced. The phthalide (II) has also been formed by demethylation with hydriodic acid or aluminum chloride of 3-methoxy-6methylphthalide (IV) prepared according to the directions of Charlesworth *et al.* (2).

The structure of the dioxanylphthalide (III) has been established from its preparation by further condensation of the phthalide (II) and also by the opening of the *m*-dioxane and phthalide rings in succession, with a study of the degradation products resulting therefrom. When the dioxanylphthalide (III) was oxidized with chromic oxide and acetic acid, the methylene ether – ester (V) was formed. On alkaline hydrolysis of V a molecule of formaldehyde split out and the hydroxy acid (VI) was produced. This could be readily methylated to VII. The free carboxyl groups of either VI or VII could be removed by heating with quinoline and copper chromite to yield the aforementioned phthalides II and IV respectively. By oxidation with alkaline permanganate at 60°C. the phthalide ring of VII was opened and the tricarboxylic acid (VIII) was formed. On more drastic oxidative treatment, the methyl side chain was attacked and the final tetracarboxylic acid (IX) was obtained.

If the dioxanylphthalide (III) was oxidized originally with alkaline permanganate, the dioxane ring is left intact and the phthalide ring was opened to produce the dioxanylphthalic acid (X). This acid readily formed the anhydride (XI) and the imide (XII). The acid (X) on treatment with chromic oxide and

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acetic acid gave the methylene ether – ester (XIII) which on alkaline hydrolysis lost formaldehyde and formed the hydroxytricarboxylic acid (XIV). Methylation of XIV gave the previously obtained acid (VIII).

The structure of the acid (IX) has been confirmed by its synthesis in six unambiguous steps from mesitylene. Bromomesitylene (XV) was methylated by treating its Grignard derivative with methyl sulphate to give isodurene (XVI). The sulphonic acid (XVII) of isodurene was oxidized with alkaline permangante to yield the tetracarboxylic sulphonic acid (XVIII). Fusion with



potash gave the phenolic tetracarboxylic acid (XIX) and methylation 4methoxybenzene-1,2,3,5-tetracarboxylic acid identical with the degradative acid (IX).

Since the publication of Part II (1) the hydrolysis of the lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxane-4-one-5-carboxylic acid has been accomplished to yield 5-hydroxy-4-methylphthalide-6-carboxylic acid, m.p. 195°C. This has been reported also in the meantime by Duncanson, Grove, and Zealley (3) in connection with their work on gladiolic acid.

EXPERIMENTAL

Most of the 2-methylbenzoic acid used in this research was prepared by the oxidation of o-xylene by dilute nitric acid as described by Zaugg and Rapala (9). 5-Hydroxy-2-methylbenzoic acid (I), 5-methoxy-2-methylbenzoic acid (II), and 3-methoxy-6-methylphthalide (IV) were made as described by Charlesworth *et al.* (2) in the first paper of this series.

3-Hydroxy-6-methylphthalide (II)

This product was formed by the demethylation of the corresponding methoxyphthalide (III). Two methods were employed:

(a) A mixture of 3-methoxy-6-methylphthalide (2.0 gm.), hydriodic acid (20 ml., sp. gr. 1.7) and red phosphorus (5.0 gm.) was refluxed gently under an atmosphere of nitrogen for three hours. The solid material was filtered off, washed with water, and dissolved in hot alcohol (charcoal). The hydroxy-phthalide was crystallized from the alcohol in fine colorless needles (0.8 gm.) which melted at 223-224°C.

(b) A mixture of 3-methoxy-6-methylphthalide (1.1 gm.) and anhydrous aluminum chloride (2.7 gm.) in dry benzene (40 ml.) was refluxed on a water bath for 10 hr. The solid was filtered off, washed with water, and dried. On crystallization from alcohol, needles (0.5 gm.) which melted at $223-224^{\circ}$ C.

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were obtained. The compound was very soluble in alcohol, acetone, ether, and hot sodium hydroxide solution. It was insoluble in water and 5% sodium bicarbonate solution. On warming this substance with resorcinol and concentrated sulphuric acid followed by sodium hydroxide solution, the greenish fluorescence characteristic of the phthalide ring developed. Found: C, 65.8; H, 4.98%; mol. wt., 168. Calc. for C₉H₈O₃: C, 65.8; H, 4.88%; mol. wt., 164.

The above hydroxyphthalide can also be obtained by allowing a well shaken mixture of 5-hydroxy-2-methylbenzoic acid, formaldehyde solution, and concentrated hydrochloric acid to stand overnight at room temperature. The solid then on top of the liquid layer was filtered off, washed, and crystallized from alcohol. It melted at 223-224°C. with no depression on mixing with the above samples.

If a sample of the hydroxyphthalide was refluxed with formaldchyde solution and concentrated hydrochloric acid it was converted to the dioxanylphthalide (III) m.p. 171–172°C.

The Lactone of 8-Hydroxymethyl-1,3,-benzodioxane-6-methyl-7-carboxylic Acid (III)

A mixture of 5-hydroxy-2-methylbenzoic acid (30 gm.) and formaldehyde solution (300 ml., 40%) was heated in a 2 liter flask over a wire gauze until the acid just dissolved. At this point concentrated hydrochloric acid (300 ml.) was added through the top of the reflux condenser and the mixture was boiled. In the first few minutes of heating after the addition of the hydrochloric acid, a flocculent white precipitate separated, a small sample of which was removed and found to be the above hydroxyphthalide (II) m.p. 223-224°C. As the boiling continued, the flocculent precipitate dissolved and then a second product separated in the form of light brown granules. After a total of one hour's boiling the mixture was cooled and the crude dioxanylphthalide (30 gm.) filtered off. It was dissolved in boiling alcohol (ca. 2 liters) and filtered from a little insoluble material. On cooling, the dioxanylphthalide separated as coarse, white needles which melted at 171-172°C. A small sample was recrystallized for analysis from acetone from which it separated in characteristic long needles. Found: C, 64.0; H, 4.91%; mol. wt., 204. Calc. for C₁₁H₁₀O₄: C, 64.1; H, 4.89%; mol. wt., 206. It gives the phthalide test with resorcinol and concentrated sulphuric acid. When the sample was warmed with phloroglucinol and strong sulphuric acid a reddish precipitate was formed which Mehta and Ayyar (6) have used to confirm the *m*-dioxane ring.

The Lactone of 8-Hydroxymethyl-6-methyl-1,3-benzodioxane-4-one- $\tilde{\gamma}$ -carboxylic Acid (V)

The dioxanylphthalide (III) (10 gm.) was dissolved in warm glacial acetic acid (250 ml.). The reaction flask was cooled externally with cold water, and finely ground chromium trioxide (15 gm.) was added with stirring at such a rate that the temperature was maintained at $65-70^{\circ}$ C. When the reaction appeared to be complete the mixture was diluted with water to a volume of 2 liters and allowed to stand overnight. White, fluffy needles (2.5 gm.) separated which were filtered off, dried, and recrystallized from acetone. The white

needles thus obtained melted at 184–185°C. Found: C, 60.4; H, 3.64%. Calc. for C₁₁H₈O₅: C, 60.0; H, 3.65%.

3-Hydroxy-6-methylphthalide-4-carboxylic Acid (VI)

A mixture of the above methylene ether – ester (V) (5.0 gm.) and sodium hydroxide solution (50 ml., 10%) was refluxed for one hour. A homogeneous solution gradually developed with the evolution of formaldehyde. The reaction mixture was cooled, filtered, and acidified with concentrated hydrochloric acid. The precipitate thus obtained was filtered off and dried. On recrystallization from water the acid was obtained as a white powder (4.0 gm.) which melted at 238°C. and which gave a dark violet color with 1% ferric chloride solution. Found: C, 57.6; H, 3.95%. Calc. for $C_{16}H_8O_5$: C, 57.7, H. 3.87%.

3-Methoxy-6-methylphthalide-4-carboxylic Acid (VII)

The hydroxy compound (VI) (7.5 gm.) was methylated in the usual manner with methyl sulphate and sodium hydroxide solution. After it was boiled with excess sodium hydroxide solution to hydrolyze any methyl ester, the mixture was acidified with hydrochloric acid. The crude acid (7.0 gm.) was twice recrystallized from water, from which it separated in white needles (6.0 gm.); these melted at 150–151°C. and gave no phenolic test with ferric chloride solution. Found: C, 59.6; H, 4.47%; neut. equiv., 218. Calc. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.54%; neut. equiv., 222.

3-Methoxy-6-methylphthalide (IV)

The above 4-carboxylic acid (VII) (1.0 gm.) was decarboxylated by heating at 180°C. for 15 min. with quinoline (15 ml.) and copper chromite (0.01 gm.). The mixture was cooled and poured into 10% hydrochloric acid (150 ml.). The phthalide separated as white needles which were crystallized from alcohol. They melted at 165–166°C. and showed no depression of melting point on being mixed with a sample of the phthalide produced by the method of Charlesworth *et al.* (2) from 5-methoxy-2-methylbenzoic acid.

If a similar decarboxylation with quinoline and copper chromite was carried out on the hydroxy acid (VI), the hydroxyphthalide was obtained, which melted at 223–224°C. and with no depression on being mixed with an authentic sample (II), described earlier in this section.

1-Methyl-4-methoxybenzene-2,3,5-tricarboxylic Acid (VIII)

A solution of the above methoxyphthalide (VII) (3.0 gm.) in 3.5% aqueous potassium hydroxide solution (200 ml.) was heated at 60°C. and stirred while potassium permanganate solution (105 ml., 0.27 *M*) was added over a period of one hour. Excess permanganate was decomposed with sodium bisulphite and the manganese dioxide removed by filtration. The filtrate was acidified with sulphuric acid and the resulting precipitate (2.0 gm.) collected. On crystallization from 50% acetic acid it melted at 238°C. Found: C, 52.0; H, 4.09%; neut. equiv., 83.3. Calc. for $C_{11}H_{10}O_7$: C, 52.0; H, 3.96%; neut. equiv., 84.7.

4-Methoxybenzene-1,2,3,4-tetracarboxylic Acid (IX)

The previous methyl tricarboxylic acid (VIII) (1.0 gm.) was dissolved in 5% aqueous potassium hydroxide solution (80 ml.). The solution was heated on a

steam bath and stirred while potassium permanganate solution (242 ml., 0.117 *M*) was added over a four hour period. The excess permanganate was decomposed with bisulphite and the manganese dioxide filtered off. The filtrate was evaporated to a small volume, refiltered, and acidified with concentrated sulphuric acid. The solution was extracted with three successive 50-ml. portions of ethyl acetate. The extract was evaporated to dryness and the residue recrystallized from 50% acetic acid. The tetracarboxylic acid (0.3 gm.) melted at 167–168° with effervescence. Found: C, 45.8; H, 3.00%; neut. equiv., 69. Calc. for $C_{11}H_8O_9$: C, 46.5; H, 2.83%; neut. equiv., 71.

There was no depression of melting point when the above acid was mixed with an authentic sample of 4-methoxybenzene-1,2,3,4-tetracarboxylic acid synthesized from mesitylene as described below.

Isodurene Sulphonic Acid (XVII)

Isodurene (XVI) was prepared by the Grignard methylation of bromomesitylene (XV) according to the directions of Smith (7). The isodurene was then sulphonated as described by Smith and Cass (8).

4-Hydroxybenzene-1,2,3,5-tetracarboxylic Acid (XIX)

The directions given below are a modification of methods outlined in French (4) and German (5) patents for the oxidation and fusion of pseudocumene-5-sulphonic acid.

Isodurene sulphonic acid (15 gm.) and potassium hydroxide solution (5.5 gm. in 250 ml. of water) were placed in a 1 liter three-necked flask equipped with a reflux condenser and stirrer. The flask was heated to 90°C. by a mantle and during vigorous stirring, powdered potassium permanganate (62.8 gm.) was added at such a rate that the temperature did not exceed 95°C. After the addition was complete the oxidation was continued at the stated temperature for a further 24 hr. Excess permanganate was decolorized with alcohol. The manganese dioxide was filtered and washed with two 150-ml. portions of boiling water. The resulting yellow solution was evaporated to dryness and the residue (15 gm.) pulverized. The bulk of the potassium salt was not purified further, but used in the next stage. A small portion of the potassium salt was acidified and extracted with ethyl acetate; the solvent was evaporated and the residue dissolved in a small quantity of hot water. On cooling, the sulphonic acid (XVIII) m.p. 238°C. was obtained, but it was not examined further.

The crude potassium salt of the sulphonic acid (14 gm.) was mixed with potassium hydroxide (40 gm.) and water (5 ml.) and fused at 200–220°C. for five hours in a nickel crucible. The melt was then cooled to a slush, mixed with water (60 ml.), and acidified with concentrated hydrochloric acid. Water (150 ml.) was added and the mixture heated to boiling and filtered. The filtrate was evaporated to dryness and the residue recrystallized from 5% hydrochloric acid (60 ml.). The hydroxy tetracarboxylic acid (6 gm.) melted at 281–282°C. Found: C, 44.4; H, 2.35%. Calc. for $C_{10}H_6O_9$: C, 44.0; H, 2.26%.

4-Methoxybenzene-1,2,3,5-tetracarboxylic Acid

The phenolic carboxylic acid (XIX) (4.0 gm.) was dissolved in sodium

hydroxide solution (25 ml., 10%) under an inert atmosphere (propane). Methyl sulphate (5 ml.) was added at such a rate that the temperature did not rise above 40°C. Three additional portions (5 ml.) of methyl sulphate were added under the same conditions, along with solid sodium hydroxide to always maintain an alkaline solution. The solution was allowed to stand overnight and finally boiled to destroy excess methyl sulphate and to saponify any ester. Precipitated sodium sulphate was filtered off and the acidified solution was extracted with three portions (15 ml.) of ethyl acetate. Purification of the crude acid obtained by evaporation of the solvent was difficult. It was dissolved in sodium bicarbonate solution, filtered to remove insoluble material, and decolorized with charcoal. The solution was acidified with hydrochloric acid and extracted with ethyl acetate as before. Repetition of this process gave a product (1.3 gm.) which melted at 164–166°C. and was identical with the product (IX) obtained previously by oxidative degradation. Found: C, 46.1; H, 2.98%. Calc. for C₁₁H₈O₉: C, 46.5; H, 2.83%.

The tetraphenacyl ester of this acid was made in the usual manner by treatment of its sodium salt with phenacyl bromide. On crystallization from alcohol it melted at 189–190°C. with previous softening and darkening. Found: C, 68.0; H, 4.27%. Calc. for $C_{43}H_{32}O_{13}$: C, 68.2; H, 4.25%.

6-Methyl-1,3-benzodioxane-7,8-dicarboxylic Acid (X)

The procedure followed was the cold oxidation method of Charlesworth, Anderson, and Thompson (1). If the oxidation is carried out at higher temperature, around 60°C., this phthalic acid could not be isolated.

The dioxanylphthalide (III) (6.0 gm.) was dissolved in warm potassium hydroxide solution (300 ml., 3.5%). The solution was filtered and cooled in an ice-water bath. The temperature was maintained at 5–10°C. while a solution of potassium permanganate (24 gm.) in water (700 ml.) was added over a period of one hour. The resulting solution was allowed to regain room temperature and to stand overnight. The manganese dioxide was filtered off, washed with water, and the combined filtrates made just acid with hydrochloric acid with litruus as indicator. The solution was evaporated at a temperature of 65°C. to a volume of about 100 ml. After the solution was cooled, the separated solid, a mixture of organic and inorganic material, was filtered off. The acidic organic material was dissolved in 5% aqueous sodium carbonate solution and filtered. On acidification a dark brown powder (1.5 gm.) precipitated, which was crystallized from dilute alcohol. The light yellow crystals melted at 223–224°C. with effervescence. Found: C, 55.3; H, 4.16%. Calc. for C₁₁H₁₆O₆: C, 55.4; H, 4.20%.

If at any time a solution of the phthalic acid became sufficiently acid to darken Congo red paper, only a dark brown tar was precipitated. Presumably the dioxane ring has opened under the influence of the strong acid and some sort of polymer has resulted. This tar could be converted to the phthalic acid by being boiled with 10 times its weight of 10% sodium hydroxide solution and then carefully acidified.

The Anhydride (XI) and Imide (XII) of 6-Methyl-1,3-benzodioxane-7,8dicarboxylic Acid

A mixture of the above phthalic acid (X) (2.0 gm.) and acetic anhydride (20 ml.) was heated on the water bath for one hour. The solution was filtered and allowed to stand in the refrigerator for 24 hr., when the anhydride separated as stout needles (1.3 gm.) of light brown color. These were crystallized from dry toluene and melted at 130°C.

An intimately powdered mixture of the anhydride (2.0 gm.) and urea (2.0 gm.) was heated in an oil bath at 160° until the evolution of ammonia ceased. The molten mixture was poured into boiling water (1 liter) in which it quickly dissolved. Upon cooling the phthalimide separated as orange plates (1.2 gm.) which were crystallized from 50% alcohol. The imide melted at 162°C. Found: C, 60.9; H, 4.13%. Calc. for C₁₁H₉O₄N: C, 60.3; H, 4.12%.

Degradation of 6-Methyl-1,3-benzodioxane-7,8-dicarboxylic Acid (X) to 1-Methyl-4-methoxybenzene-2,3,5-tricarboxylic Acid (VIII)

The dioxanylphthalic acid (X) (3.0 gm.) was dissolved in glacial acetic acid (80 ml.) and oxidized with chromic oxide at 65-70°C. by the method described above for the oxidation of the dioxanylphthalide (III). At the end of the oxidation water (600 ml.) was added and the solution evaporated in vacuo to dryness. Acidic organic material was dissolved by digestion with 5% sodium carbonate solution (50 ml.) and the resulting solution was then filtered off. Careful acidification of the filtrate gave the crude dioxanonephthalic acid (XIII) in the form of a brown tar. It was not possible to purify this further without hydrolysis of the dioxanone ring, so this was accomplished by boiling the tar for one hour with 10% aqueous sodium hydroxide (30 ml.). Acidification gave a small amount of light brown powder which gave a purplish color with ferric chloride solution and was the hydroxy acid (XIV). It was not purified further, but was methylated in alkaline solution in the usual manner. Upon acidification a small amount of light brown powder, m.p. 229°C. was obtained. It was recrystallized from 50% acetic acid and melted at 234°C. A mixed melting point with a sample of the methoxy tricarboxylic acid (VIII) previously described gave no depression.

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