PHTHALIDE FORMATION

IV. CONDENSATIONS WITH 5-METHOXY-3-METHYLBENZOIC ACID[1]

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ABSTRACT

The products of the condensation of 5-methoxy-3-methylbenzoic acid with aqueous formaldehyde and hydrochloric acid in the presence of glacial acetic acid are dependent on the length of the heating period. A very short period of heating (2 minutes) yields 6-methoxy-4-methylphthalide and the two chloromethylphthalides of m.p. 135° and 154° C, related to the unisolated 4-methoxy-6-methylphthalide. If the period of heating is 20 minutes or longer, the above chloromethylphthalide melting at 135° is formed and in addition some of the 6-methoxy-4-methylphthalide is chloromethylated to 6-methoxy-7-chloromethyl-4-methylphthalide, melting at 179°. The orientation of all three chloromethylphthalides has been established.

INTRODUCTION

In 1945, Charlesworth *et al.* (1) reported the isolation of two products from the condensation of 5-methoxy-3-methylbenzoic acid (I) with formaldehyde and concentrated hydrochloric and acetic acids. Of these, the compound which melted at 176–178° C was established as a chloromethylphthalide, but its orientation was not proved. The present paper establishes the orientation of this and other products isolated in this reaction.

The phthalide ring may form in two ways to produce the simple phthalides II and III. On further reaction a chloromethyl group may enter positions 5 or 7 in II or 5 or 7 in III. Thus, four chloromethylphthalides (IV–VII) are theoretically possible. All condensations were carried out using the Edwards, Perkin, and Stoyle (2) method as modified by Rây and Robinson (3) by the addition of glacial acetic acid to the formaldehyde – hydrochloric acid mixture. The length of the heating period determined the number and nature of the products isolated.

When the mixture was heated for 2 minutes or less, that is, just for the length of time to put everything into solution, only the simple phthalide II and the chloromethylphthalides VI and VII were formed. The chloromethylphthalide IV, m.p. 178–179° C, of the earlier paper was not formed under these conditions. It was formed along with II and VI if the condensation time was extended to 20 minutes or more. It (IV) can also be formed alone from phthalide II in continued condensation of 20 minutes or more. Phthalide III was not isolated from any of the condensations and apparently is chloromethylated as fast as produced.

The orientation of phthalide II was established by mixed melting point and infrared spectra comparison with this phthalide produced by the Fritsch reaction. Meldrum (4) synthesized and established the orientation of both the simple phthalides by this method. When phthalide III formed by the Meldrum method was subjected to further chloromethylation VI and VII are produced, but not IV. Thus, chloromethylphthalides VI and VII have been proved to be related to phthalide III, and IV, as previously, to phthalide II. In establishing the orientation of the three isolated chloromethylphthalides it was thus necessary to determine the orientation of IV (or V) as derived from the simple phthalide II and one of the two chloromethylphthalides VI or VII as formed from simple phthalide III. Once a definite orientation could be affixed to either VI or VII the other was also known.

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[1] *For Part III of this series, see Can. J. Chem.,* ***32****, 941 (1954).*

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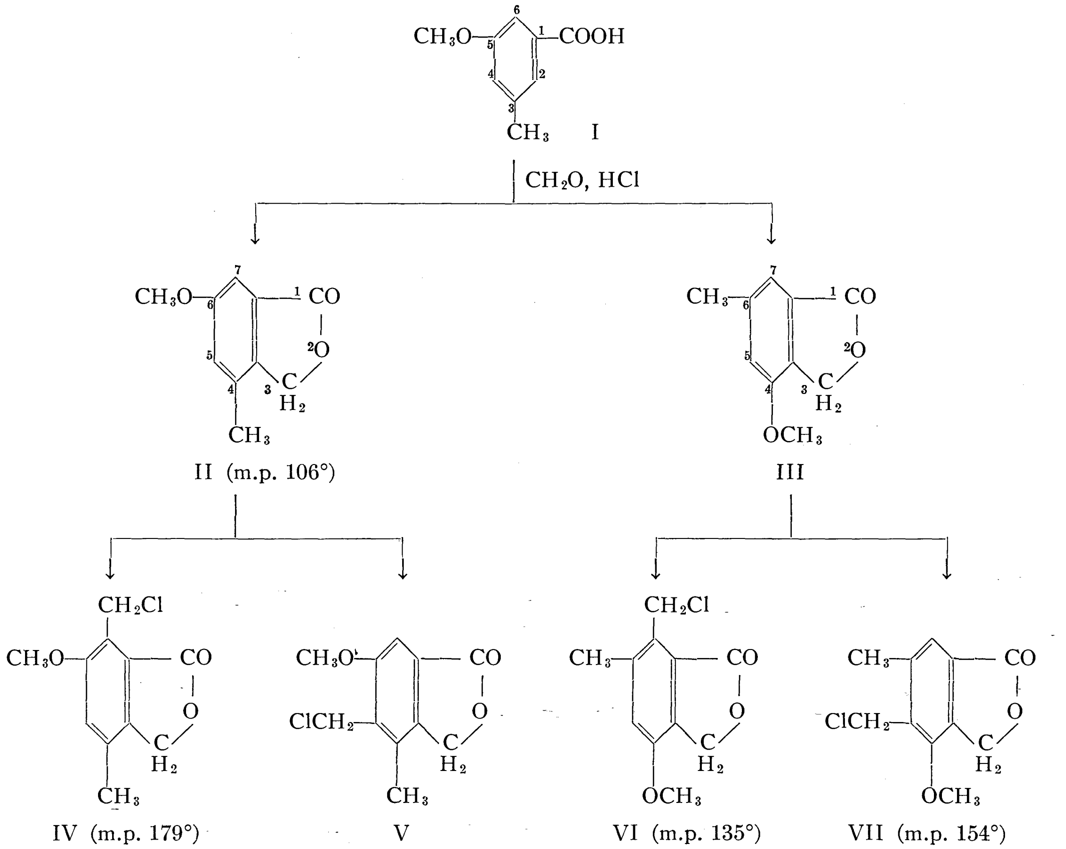


I

II (m.p. 106°)

III

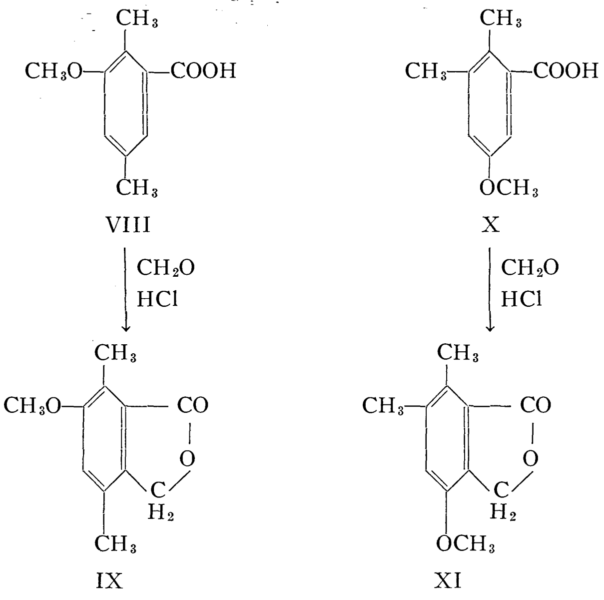
IV (m.p. 179°)

V

VI (m.p. 135°)

VII (m.p. 154°)

A successful attack on this problem involved a synthesis of the two substituted aromatic acids VIII and X. Once these acids were available they were subjected to the normal condensation reaction to produce the corresponding phthalides IX and XI.



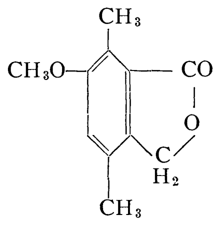
VIII

X

IX

XI

Reduction of the four theoretically possible chloromethylphthalides, IV, V, VI, and VII, derived from 5-methoxy-3-methylbenzoic acid with zinc and hydrochloric acid would yield the corresponding chlorine-free phthalides A, B, C, and D.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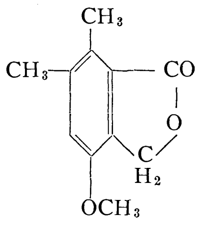
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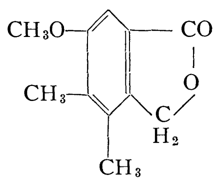
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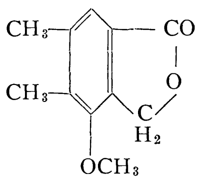
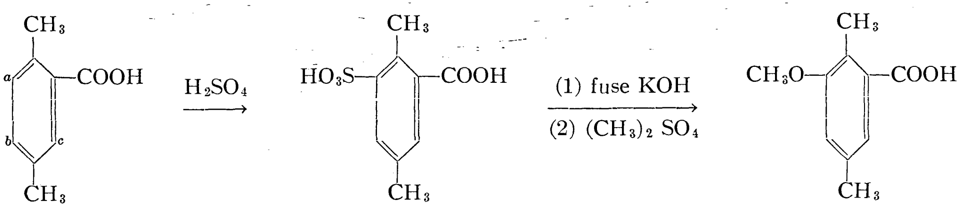

D

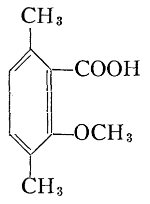
The phthalide IX prepared synthetically from 2,5-dimethyl-3-methoxybenzoic acid (VIII), whose orientation is proved below, was found to be identical with phthalide A, in turn derived from the chloromethylphthalide IV of melting point 178–179° C. In this way the orientation of IV was definitely established. Similarly, phthalide XI formed from 2,3-dimethyl-5-methoxybenzoic acid (X) was shown to be identical with phthalide C, thus definitely establishing the orientation of chloromethylphthalide (VI) of melting point 134–135° C. The remaining chloromethylphthalide melting at 152.5–154° C must by elimination have the structure VII.

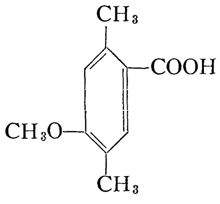
The synthesis of 2,5-dimethyl-3-methoxybenzoic acid (VIII) was carried out as follows:



XII VIII

There are three possible positions of sulphonation in the starting molecule of 2,5-dimethyl-benzoic acid (XII). If the sulphonic acid group had entered position *c* it would yield, after alkali fusion and methylation, the acid of structure XIII. It would be impossible for this acid to form a phthalide because there is no position ortho to the carboxyl group

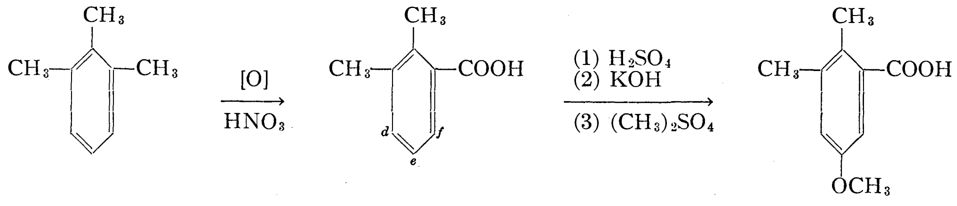

XIII


XIV

unsubstituted. The phenol corresponding to XIII would be expected to yield a color with ferric chloride solution. The actual acid obtained did not give a ferric chloride reaction, but does form a phthalide. Thus structure XIII can be ruled out.

If the sulphonic acid group had entered position *b* the final methyl ether would be identical with 4-methoxy-2,5-dimethylbenzoic acid (XIV), first produced by Gattermann (5) from 2,5-dimethylphenol by a Gattermann reaction, followed by methylation of the phenolic aldehyde and oxidation of the aldehyde to the corresponding acid. We have synthesized this acid by a modification of the original procedure and it is not identical with our acid (VIII), which thus must have the structure indicated.

The synthesis of 5-methoxy-2,3-dimethylbenzoic acid (X) was carried out in a similar manner from hemimellitene (XV). This was oxidized by dilute nitric acid to the acid XVI first reported by Jacobsen (6), which was then sulphonated and subjected to alkali fusion and methylation. As in the previous case, the sulphonic acid substituent can enter three possible positions. Our phenol did not give a ferric chloride reaction, but its methyl ether did form a phthalide. Position *f* is thus ruled out on both counts. It was now a relatively simple matter to establish whether carbon *d* or *e* was sulphonated. 3,4-Dimethylphenol and 2,3-dimethylphenol are solids and commercially available. Decarboxylation of our phenol formed a product identical with 3,4-dimethylphenol. Thus position *e* has been established for the sulphonation of acid XVI.



XV XVI X

An earlier plan of attack to establish the orientation of the three isolated chloromethylphthalides (IV, VI, and VII) was oxidative attack on the reduced phthalides A, C, and D to obtain the corresponding dicarboxylic acids. These were then to have been decarboxylated and the resulting methyl ethers demethylated and compared with the commercially available solid phenols. Two of these dicarboxylic acids were isolated in the form of their anhydrides, but attempts at decarboxylation were unsuccessful.

EXPERIMENTAL

Condensation of 5-Methoxy-3-methylbenzoic Acid

The general method followed was that of Edwards, Perkin, and Stoyle (2) as modified by Rây and Robinson (3). This procedure was employed in all condensations carried out, with modifications in the period of heating, the proportion of formaldehyde, and the method of isolation of the resultants. The 5-methoxy-3-methylbenzoic acid was made from *m*-toluic acid as described in the first paper of this series (1).

Condensation Time Two Minutes or Less

5-Methoxy-3-methylbenzoic acid (4.0 g), concentrated hydrochloric acid (25.0 ml), aqueous formaldehyde (10 ml, 37%), and glacial acetic acid (25 ml) were mixed in a small flask fitted with a reflux condenser and heated on a steam bath just long enough to permit the 5-methoxy-3-methylbenzoic acid to dissolve. This usually took about 2 minutes. The flask was then cooled in ice to prevent further reaction. On standing overnight in the refrigerator a yellowish precipitate formed, which was filtered off and washed.

Isolation of 6-Methoxy-4-methylphthalide (II)

Cold water was added to the filtrate obtained above, when a white precipitate settled out. After standing the solution overnight in the cold this precipitate was filtered off and washed with water. Repeated crystallization from ethyl alcohol (95%) gave the 6-methoxy-4-methylphthalide (0.7–0.9 g), which melted at 105–106° C. Found: C, 66.9; H, 5.64%. Calc. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.62%.

A small amount of material insoluble in ethyl alcohol and with a melting point above 275° C was found. It was considered to be a diphenylmethane type of material and was not examined further.

Isolation of the Two Chloromethylphthalides VI and VII

The yellowish precipitate, mentioned above, obtained directly from the reaction mixture, was crystallized from alcohol (charcoal). The dry colorless crystals were washed on the filter funnel with four or five portions (5.0 ml) of boiling alcohol. This treatment dissolved the more soluble chloromethylphthalide and left the less soluble on the funnel. The latter was recrystallized from glacial acetic acid and finally from alcohol. This chloromethylphthalide, VII (0.6 g), melted at 153–154° C. Found: C, 58.2; H, 5.06; Cl, 15.4%. Calc. for $C_{11}H_{11}O_3Cl$: C, 58.3; H, 4.86; Cl, 15.7%.

The more soluble chloromethylphthalide, VI (1.0 g), was also purified by recrystallization from acetic acid and from alcohol. It melted at 134–135° C. Found: C, 58.3; H, 5.21; Cl, 15.4%. Calc. for $C_{11}H_{11}O_3Cl$: C, 58.3; H, 4.86; Cl, 15.7%.

Condensation Time Twenty Minutes or Longer

The Chloromethylphthalide IV

The procedure was as above except that the time of heating was increased to 20 minutes. The 6-methoxy-4-methylphthalide (II) was isolated as before. Two chloromethylphthalides were separated by portions of hot alcohol, the more soluble being the previously mentioned VI of melting point 134–135° C and the less soluble, IV (2.1 g) of melting point 178–179° C. Found: C, 58.4; H, 5.07; Cl, 15.6%. Calc. for $C_{11}H_{11}O_3Cl$: C, 58.3; H, 4.86; Cl 15.7%. The infrared spectrum of IV differs from that of VI and VII by not possessing characteristic peaks at 6.91 and 8.90 μ.

6-Methoxy-4-methylphthalide (II) and 4-Methoxy-6-methylphthalide (III)

These two simple phthalides were produced by the Fritsch method as reported by Meldrum (4), who also established their orientation. Mixed melting point determination and infrared spectra comparison of the simple phthalide obtained from the condensation above proved its identity with 6-methoxy-4-methylphthalide (II), m.p. 104–105° C, produced by Meldrum's directions.

Condensation of the Meldrum Phthalides II and III with Formaldehyde and Hydrochloric Acid

When 6-methoxy-4-methylphthalide II (0.85 g) was condensed with formaldehyde solution, hydrochloric acid, and glacial acetic acid for $1\frac{1}{2}$ hours in the standard manner, a chloromethylphthalide (0.6 g) which melted at 178–179° C was isolated. This proved identical with the product of the same melting point isolated from the main reaction. None of the other chloromethylphthalides were found in the reaction mixture. Thus chloromethylphthalide IV must be related to simple phthalide II. If the condensation time was only 2 minutes the chloromethylphthalide was not formed, but the unchanged simple phthalide (II) could be recovered.

When the simple Meldrum phthalide III (2.0 g) was subjected to further chloromethylation for 2 minutes, a solid separated on cooling, which on crystallization from alcohol in the manner previously described gave a product (0.4 g) which melted at 153–154° C. Dilution of the reaction mixture with water and repeated crystallization of the separated product from alcohol gave the second chloromethylpthalide (0.32 g), which melted at 133–134°. These two substances were identical with the products VII and VI of the same melting points isolated from the main condensation. Thus VI and VII must be related to the simple phthalide III.

Formation of the Three Chlorine-free Phthalides (A, C, and D)

6-Methoxy-4-methyl-7-chloromethylphthalide (3.5 g) of melting point 178–179° C, zinc dust (3.7 g), concentrated hydrochloric acid (10 ml), and ethyl alcohol (75 ml, 95%) were refluxed for 15 hours. Excess hydrochloric acid was added until the zinc had completely dissolved. The solution was cooled and cold water (75 ml) added, when a thick white paste was formed. The solid was collected, washed well with water, and dried. Crystallization from ethyl alcohol produced colorless crystals (3.2 g) of 6-methoxy-4,7-dimethylphthalide (A) which melted at 169–170° C. Found: C, 68.3; H, 6.15%. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.26%.

Reduction of 4-methoxy-6-methyl-7-chloromethylphthalide (VI) of melting point 134–135° C by the same method gave 4-methoxy-6,7-dimethylphthalide (C) which melted at 179–180° C. Found: C, 68.5; H, 6.29%. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.26%.

Reduction of 4-methoxy-6-methyl-5-chloromethylphthalide (VII) of melting point 153–154° C gave 4-methoxy-5,6-dimethylphthalide (D) which melted at 174–175° C. Found: C, 68.5; H, 6.19%. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.26%.

Formation of the Three Phthalic Acids (Anhydrides) from the Phthalides A, C, and D

6-Methoxy-4,7-dimethylphthalide (3.0 g) was dissolved in warm potassium hydroxide solution (100 ml, 6 *N*). After cooling, finely powdered potassium permanganate (3.8 g) was added slowly over a 10-minute period. The dark solution was allowed to stand at room temperature for 36 hours. The brown manganese dioxide was filtered off, leaving a green filtrate. On acidification with dilute sulphuric acid a white precipitate of 4-methoxy-3,6-dimethylphthalic acid was formed. This relatively pure product (2.1 g) was collected, washed with water, and allowed to dry. It melted at 181–182° C and effervesced vigorously with sodium bicarbonate solution. Found: C, 58.4; H, 5.41%. Calc. for $C_{11}H_{12}O_5$: C, 58.9; H, 5.36%. Crystallization from either ethyl alcohol or glacial acetic acid converted the acid into the corresponding anhydride, which melted at 185–186° C and no longer effervesced with bicarbonate solution. Found: C, 63.9; H, 5.10%. Calc. for the anhydride $C_{11}H_{10}O_4$: C, 64.1; H, 4.85%.

6-Methoxy-3,4-dimethylphthalic anhydride (1.2 g) was prepared in a similar manner from phthalide C (3.0 g). On crystallization from acetic acid it melted at 230–231° C. Found: C, 63.8; H, 4.98%. Calc. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.85%.

3-Methoxy-4,5-dimethylphthalic anhydride was prepared from 4-methoxy-5,6-dimethylphthalide (D) as in the two previous cases. It melted at 174–175° C. Found: C, 63.8; H, 4.75%. Calc. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.85%.

Attempts to decarboxylate the 4-methoxy-3,6-dimethylphthalic acid with copper chromite and quinoline were unsuccessful. Solid material recovered from this attempt proved to be the corresponding 4-methoxy-3,6-dimethylphthalic anhydride.

Preparation of 3-Methoxy-2,5-dimethylbenzoic Acid (VIII)

(a) Sulphonation of 2,5-Dimethylbenzoic Acid

2,5-Dimethylbenzoic acid (11.0 g, Eastman No. 7270) was heated at 110° with stirring for 2 hours with a mixture of concentrated sulphuric acid (15 ml) and fuming sulphuric acid (35 ml, 20% SO_3). After cooling, the solution was poured cautiously into ice-cold water (200 ml). After further cooling the acid was partially neutralized by the slow, careful addition of sodium bicarbonate (10 g). Sodium chloride (25 g) was added and the mixture warmed until solution was complete. The clear liquid was cooled in an ice bath, when a brown solid began to separate. This sodium salt of 2,5-dimethyl-3-sulphobenzoic acid (15 g) was collected on a sintered-glass funnel, washed well with a small quantity of saturated sodium chloride solution, and dried in an oven.

(b) 3-Hydroxy-2,5-dimethylbenzoic Acid

The above sodium salt (14 g) was fused with potassium hydroxide (80 g) in the conventional manner. The melt was dissolved in water (300 ml) and neutralized with dilute sulphuric acid. The solution was made slightly alkaline, cooled, and the precipitated potassium sulphate removed. The mother liquor was concentrated (charcoal) to about one third the original volume, filtered, cooled, and a second crop of potassium sulphate removed. On acidification with concentrated hydrochloric acid the required 3-hydroxy-2,5-dimethylbenzoic acid (5.8 g) separated. It was recrystallized from water and melted at 163–165° C. It did not give a color with ferric chloride solution. Found: C, 65.0; H, 5.99%; neut. equiv., 163. Calc. for $C_9H_{10}O_3$: C, 65.1; H, 6.03%; neut. equiv., 166.

(c) 3-Methoxy-2,5-dimethylbenzoic Acid (VIII)

3-Hydroxy-2,5-dimethylbenzoic acid (5.2 g) was methylated in the conventional manner with sodium hydroxide solution and dimethyl sulphate (10 g). The 3-methoxy-2,5-dimethylbenzoic acid (2.3 g) was crystallized from aqueous alcohol, and melted at 143–144° C. Found: C, 67.0; H, 6.74%. Calc. for $C_{10}H_{12}O_3$: C, 66.8; H, 6.68%.

6-Methoxy-4,7-dimethylphthalide (IX)

3-Methoxy-2,5-dimethylbenzoic acid (1.5 g), concentrated hydrochloric acid (11.0 ml), glacial acetic acid (11 ml), and formaldehyde solution (9 ml, 35%) were heated on a steam cone for 45 minutes. Complete solution did not take place. The flask was then cooled and the solid collected and washed with water. On crystallization from alcohol, the 6-methoxy-4,7-dimethylphthalide (1.3 g) was obtained, and melted at 169–170° C. Found: C, 68.4; H, 6.24%. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.25%.

A mixed melting point of this material and the chlorine-free phthalide A of the same melting point formed by the reduction of the chloromethylphthalide IV of m.p. 179° C showed no depression. Thus the orientation of chloromethylphthalide IV has been established.

Preparation of 5-Methoxy-2,3-dimethylbenzoic Acid (X)

(a) Oxidation of 1,2,3-Trimethylbenzene

The oxidation of 1,2,3-trimethylbenzene (hemimellitene) (XV) with dilute nitric acid was first reported by Jacobsen (6). His experimental details are scanty, but the following procedure was satisfactory. It appeared impossible, however, to stop at the required monocarboxylic stage without the production of some dicarboxylic acid.

1,2,3-Trimethylbenzene (60 ml, Aldrich Chemical Co.) was refluxed with a mixture of nitric acid (50 ml, 70%) and water (140 ml) for about 20 hours, a magnetic stirrer operating throughout the heating period. The mixture was poured into cold water (400 ml). On standing in the refrigerator, the crude acid, which separated as an oil, solidified. It was separated and dissolved in sodium hydroxide solution (200 ml, 10%). The cold dark red alkaline solution was extracted with ether to remove unoxidized hemimellitene, warmed with decolorizing carbon, and filtered. The warm filtrate was acidified with dilute hydrochloric acid, when the acid separates as a brown solid. On recrystallization from ethyl alcohol (charcoal) the required 2,3-dimethylbenzoic acid (8.0 g) was obtained. It melted at 139–141° C. Jacobsen gives a value of 144° C for the melting point, but it was considered sufficiently pure for sulphonation purposes.

(b) 5-Hydroxy-2,3-dimethylbenzoic Acid

The sulphonation of 2,3-dimethylbenzoic acid (12 g) was carried out exactly as described above for 2,5-dimethylbenzoic acid, and the sodium salt of the required 1,2-dimethyl-5-sulphobenzoic acid was isolated. This salt was fused with alkali as described above and the 5-hydroxy-2,3-dimethylbenzoic acid obtained. It was crystallized from water and melted at 179.0–179.5° C. Found: C, 64.6; H, 6.04%; neut. equiv., 161. Calc. for $C_9H_{10}O_3$: C, 65.1; H, 6.03%; neut. equiv., 166. This phenolic acid did not yield a color with ferric chloride solution.

(c) Decarboxylation of 5-Hydroxy-2,3-dimethylbenzoic Acid

Attempts to decarboxylate this acid by refluxing with quinoline and copper chromite were unsuccessful. However, when the acid was heated with soda lime a product was obtained which melted at 62–63° C. This did not effervesce with sodium bicarbonate solution nor give a color with ferric chloride solution. A mixed melting point with commercial 3,4-dimethylphenol gave no depression.

(d) 5-Methoxy-2,3-dimethylbenzoic Acid (X)

Methylation of 5-hydroxy-2,3-dimethylbenzoic acid (0.6 g) in the conventional manner gave 5-methoxy-2,3-dimethylbenzoic acid (0.47 g). On crystallization from aqueous ethyl alcohol it melted at 102–103° C. Found: C, 66.7; H, 6.68%. Calc. for $C_{10}H_{12}O_3$: C, 66.8; H, 6.68%.

4-Methoxy-6,7-dimethylphthalide (XI)

The above 5-methoxy-2,3-dimethylbenzoic acid, X (0.4 g), was condensed as described above for the preparation of 6-methoxy-4,7-dimethylphthalide. After crystallization from ethyl alcohol the 4-methoxy-6,7-dimethylphthalide (0.3 g) melted at 179–180° C. Found: C, 68.5; H, 6.38%. Calc. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.25%. A mixed melting point of this material and the chlorine-free phthalide C, formed by the reduction of the chloromethylphthalide VI of m.p. 135° C, showed no depression. Thus the orientation of the chloromethylphthalide VI has been established.

Synthesis of 4-Methoxy-2,5-Dimethylbenzoic Acid

(a) 4-Hydroxy-2,5-dimethylbenzaldehyde

This aldehyde, m.p. 130–132° C, was synthesized from 2,5-dimethylphenol by a Gattermann reaction as modified by Adams and Montgomery (7) employing zinc cyanide and anhydrous aluminum chloride as the condensing agent.

(b) 4-Methoxy-2,5-dimethylbenzaldehyde

The aldehyde of the previous paragraph was methylated as described by Clemo *et al.* (8). It boiled at 147–179° at 12 mm and melted at 32–33° C.

(c) 4-Methoxy-2,5-dimethylbenzoic Acid

The methoxyaldehyde (23.5 g) of the previous paragraph was oxidized by boiling for 40 minutes with acetone (300 ml) containing finely powdered potassium permanganate (35 g). The hot solution was filtered and the dark solid suspended in water and treated with sulphur dioxide gas to dissolve the manganese dioxide, leaving a thick white precipitate of the 4-methoxy-2,5-dimethylbenzoic acid. A further quantity of the acid could be obtained by concentration of the acetone filtrate and dilution with water. On crystallization from aqueous acetic acid the purified acid (14.6 g) melted at 164–165° C, in agreement with the figure reported by Clemo (8). This acid is not identical with the acid VIII described above.

ACKNOWLEDGMENT

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