

DECARBOXYLATION OF BENZOIC ACID DERIVATIVES

苯甲酸衍生物之脫二氧化碳反應

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Decarboxylation of carboxylic acids has been usually carried out by heating in quinoline in the presence of cupric oxide; some acids give good results but others fail to give clean reaction products. In still some other cases, decarboxylation does not occur; other reactions such as anhydride formation occur instead.

It has been reported that tetrachlorophthalic acid undergoes decarboxylation to form 2,3,4,5-tetrachlorobenzoic acid when heated in boiling dimethyl sulfoxide for 30 minutes.¹ This is the simplest procedure to decarboxylate the acid. Accordingly, the present study was undertaken to see what happens when substituted benzoic acids are heated in boiling dimethyl sulfoxide.

This study employed 24 carboxylic acids. Nitroterephthalic acid was prepared by nitration of terephthalic acid with a mixture of nitric acid and fuming sulfuric acid.² 3-Nitrophthalic acid was prepared by nitration of phthalic anhydride with a mixture of concentrated sulfuric acid and fuming nitric acid.³ 4-Nitrophthalic was also obtained as a by-product and was separated from 3-nitrophthalic acid through its diethyl ester.⁴ Tetrabromophthalic acid was synthesized from phthalic anhydride by bromination in fuming sulfuric acid.⁵ Tetraiodophthalic acid was prepared also from phthalic acid by the action of iodine in fuming sulfuric acid.⁶ Benzene-1,2,4-tricarboxylic acid was obtained by oxidation of pseudocumene(1,2,4-trimethylbenzene) with alkaline potassium permanganate.⁷ Benzene-

1, 2, 3-tricarboxylic acid was prepared from naphthalene-1, 8-dicarboxylic anhydride by oxidation with alkaline potassium permanganate.⁸ The latter anhydride was made by oxidation of acenaphthene with sodium dichromate in acetic acid.⁹ Benzene-1, 3, 5-tricarboxylic acid was synthesized from mesitylene by oxidation with potassium permanganate.¹⁰ Mesitylene was obtained by sulfuric acid induced condensation and dehydration of acetone.¹¹ 1, 8-Naphthalic acid was obtained by the alkaline hydrolysis of 1, 8-naphthalic anhydride.¹² 3-Nitro-1, 8-naphthalic acid was prepared by the nitration of 1, 8-naphthalic anhydride followed by hydrolysis.¹³ 2-Chloro-3, 5-dinitrobenzoic acid was obtained by nitration of 2-chlorobenzoic acid.¹⁴ 2-Nitroisophthalic acid was made starting from *m*-toluic acid by nitration to form 2-nitro-3-methylbenzoic acid¹⁵ followed by oxidation with potassium permanganate.¹⁶ 3-Chlorobenzoic acid was prepared from *m*-toluidine involving the Sandmeyer reaction to form *m*-chlorotoluene which was oxidized with potassium permanganate.¹⁷ *p*-Bromobenzoic acid was obtained from *p*-toluidine through *p*-bromotoluene¹⁸ which was oxidized with potassium dichromate.¹⁹ *m*-Nitrobenzoic acid was prepared by the nitration of benzoic acid.²⁰ 3, 5-Dinitrobenzoic acid was obtained by the action of fuming nitric acid and conc sulfuric acid on benzoic acid by heating.²¹

These acids together with *o*-, *m*-, and *p*-toluic acids, phthalic acid, isophthalic acid, terephthalic acid, and bromoterephthalic acid were individually heated in boiling dimethyl sulfoxide. The experiment with tetrachlorophthalic acid was also repeated to be sure that the experimental conditions used did lead to decarboxylation as reported.¹ The experiments were summarized in Table I.

Of the 26 compounds studied, only tetrabromophthalic, tetrachlorophthalic, and 3-nitrophthalic acids underwent decarboxylation to give, respectively, 2, 3, 4, 5-tetrabromobenzoic, 2, 3, 4, 5-tetrachlorobenzoic, and *m*-nitrobenzoic acids. Surprisingly, 4-nitro-

phthalic acid did not undergo decarboxylation. This fact would suggest the importance of a steric crowding as a requirement for decarboxylation to occur. This view was discouraged, however, by the fact that 2-nitroisophthalic acid failed to decarboxylate, although the nitro group is closely flanked by two carboxyl groups.

Looking at the rest of acids, it is evident that decarboxylation in boiling dimethyl sulfoxide is limited to suitably substituted phthalic acids. The substituents must be electron-withdrawing groups and appropriately situated so as to create a steric crowding. 1,2,3- and 1,2,4-Benzenetricarboxylic acids are also substituted phthalic acids, but the electron-withdrawing power of the only substituent (CO_2H) is not strong enough to cause decarboxylation.

Even in the presence of strongly electron-withdrawing nitro groups, 3,5-dinitrobenzoic acid failed to undergo decarboxylation. And with still another chlorosubstituent, 2-chloro-3,5-dinitrobenzoic acid did not undergo decarboxylation either. There was obtained, however, a yellow solid product which exhibits a carbonyl absorption in the infrared spectrum. Nitroterephthalic acid gave also a yellow solid product which could be recrystallized from water. This product, too, had a carbonyl absorption band in its infrared spectrum.

1,8-Naphthalic acid and 3-nitro-1,8-naphthalic acid formed the anhydrides in boiling dimethyl sulfoxide. These anhydride did not further react with dimethyl sulfoxide to form methylthiomethyl esters in the manner tetrachlorophthalic anhydride did.²²

In conclusion, decarboxylation in boiling dimethyl sulfoxide is characteristic of appropriately substituted phthalic acids. Some benzoic acids substituted with strongly electron-withdrawing groups could undergo reactions other than decarboxylation. The products from these reactions retain the carbonyl absorption in the infrared spectra.

Table I. Reactions of Aromatic Acids in Boiling Dimethyl Sulfoxide

<u>Carboxylic Acid</u>	<u>0</u>	<u>mmoles</u>	<u>Time</u>	<u>Product</u>
Phthalic	0.83	5	4 hr	no
Tetrachlorophthalic	1.52	5	0.5	tetrachloro- benzoic acid
Tetrabromophthalic	2.41	5	0.5	tetrabromo- benzoic acid
Tetraiodophthalic	1.34	2	0.5	complicated
3-Nitrophthalic	1.06	5	0.5	3-nitroben- zoic acid
4-Nitrophthalic	1.06	5	0.5	no
Isophthalic	0.83	5	4	no
2-Nitroisophthalic	0.63	3	2	no
Terephthalic	0.83	5	4	no
Bromoterephthalic	0.74	3	6	no
Nitroterephthalic	0.53	2.5	2	yes(a)
1,2,3-Benzenetricarboxylic	1.05	5	6	no
1,2,4-Benzenetricarboxylic	1.05	5	6	no
o-Toluic	0.68	5	4	no
m-Toluic	0.68	5	4	no
p-Toluic	0.68	5	4	no
m-Chlorobenzoic	0.47	3	2	no
p-Bromobenzoic	0.60	3	2	no
m-Nitrobenzoic	0.50	3	2	no
3,5-Dinitrobenzoic	0.63	3	2	no
2-Chloro-3,5-dinitrobenzoic	0.74	3	0.5	yes(b)
1,8-Naphthalic	0.22	1	2	anhydride
3-Nitro-1,8-naphthalic	0.52	2	1	anhydride
1,8-Naphthalic anhydride	0.60	3	2	no
3-Nitro-1,8-naphthalic anhydride	1.26	5	1	no

- (a) Dimethyl sulfoxide 5 ml. Addition of water precipitated a yellow crystalline product which was recrystallized from water, mp above 220; the infrared spectrum showed a carbonyl band.
- (b) Ether extraction gave a yellow solid product which shows a carbonyl absorption in the infrared spectrum. Purification is in progress.

EXPERIMENTAL

Nitroterephthalic Acid²

A mixture of 102 ml of nitric acid and 113 ml of fuming sulfuric acid was cooled to room temperature to which was added 20 g of terephthalic acid. The mixture was heated on a waterbath when a vigorous reaction took place. Heating was continued for 1.5 hours longer after the initial vigorous reaction subsided. Then, the reaction mixture was heated on a sand bath until it began to boil. After cooling, water was added to precipitate 22 g of a solid (88% yield) which was recrystallized from water to obtain nitroterephthalic acid, mp 262-263°.

3-Nitrophthalic Acid³

A mixture of 65 ml of conc sulfuric acid and 50 g of phthalic anhydride was heated to 80° on a water bath. Fuming nitric acid (21ml) was then added at such a rate as to maintain the temperature of the stirred mixture at 100-110. Conc nitric acid (90 ml) was then added as rapidly as possible without causing the temperature to rise above 110°. The mixture was then heated and stirred on the water bath for two hours longer.

The mixture was allowed to stand overnight and then poured into 150 ml of water. After cooling, the solid mixture of 3- and 4-nitrophthalic acids was filtered by suction through a glass filter. The wet cake was stirred thoroughly with 20 ml of water, which dissolved a large amount of the 4-nitro compound. The mixture was then filtered by suction, and the mother liquor was saved for the recovery of 4-nitrophthalic acid. The wet cake was dissolved by boiling with 30 ml of water. The solution was filtered hot and stirred until crystallization started. It is then allowed to stand overnight. The crystals were filtered off by suction and air-dried. The product had mp 205-210° and weighed 20 g (28% yield). It was recrystallized from 30 ml of water to obtain 3-nitrophthalic acid (17 g) which had mp 215-218°.

4-Nitrophthalic Acid⁴

The washings and mother liquor from the crystallization in the above preparation were carefully evaporated to obtain 37 g of air-dried solid material. This was heated at 100° for 2 hours and mixed with 50 ml of 98% ethanol. Conc hydrochloric acid (20 ml) was added and the mixture was heated in water bath for 3 hours. Water was then added and the precipitate was washed with sodium bicarbonate solution. The crude diethyl 4-nitrophthalate was recrystallized from ether-ethanol. The ester (30 g) in 80 ml of absolute ethanol was heated and a solution of 12 g of potassium hydroxide in 10 ml of water was added. The precipitate of potassium 4-nitrophthalate was collected by suction, washed with absolute ethanol, and dissolved in water. Conc hydrochloric acid was added to acidify the aqueous solution and the mixture was extracted with ether. The ethereal extracts were distilled off to obtain 10 g of 4-nitrophthalic acid (14%

yield) which was recrystallized from ether; mp 161° .

Tetrabromophthalic Acid⁵

Phthalic anhydride (50 g) was dissolved in 300 g of fuming sulfuric acid which contained 50% sulfur trioxide, to which was added 200 g of bromine in small portions so as to maintain the temperature at 60° . After the addition of bromine, the mixture was heated to 200° and water was added to precipitate the crude product, which was collected and boiled with sodium hydroxide solution. Conc sulfuric acid was added to acidify the basic solution when tetrabromophthalic acid precipitated; mp 266° (forming tetrabromophthalic anhydride). The yield was 78 g or 50%.

Tetraiodophthalic Acid⁶

A mixture of 5 g of phthalic acid and 40 g of fuming sulfuric acid was stirred and heated to 100° , to which was added 20 g of powdered iodine in small portions. Stirring was continued for 4 hours longer and the mixture was heated to 175° . After cooling, water was added and the precipitate was collected by suction and triturated with dilute sulfuric acid while being heated on a water bath. The crude product was recrystallized from acetic acid to obtain tetraiodophthalic anhydride, 8.8 g (40% yield), mp $320-325^{\circ}$. The anhydride was dissolved in the calculated amount of aqueous sodium hydroxide solution, enough water being added to effect complete solution when the mixture was brought to boiling. Then sulfuric acid was added to just acidify the solution and to precipitate tetraiodophthalic acid, which was recrystallized from nitrobenzene; 8.1 g, mp $324-327^{\circ}$.

1,2,4-Benzenetricarboxylic Acid⁷

A mixture of 10 g of pseudocumene (a sample from Aldrich Chemical Co.), 90 g of potassium permanganate, 1800 ml of water, and 50 ml of 10% sodium hydroxide was refluxed for 4 hours and acidified with sulfuric acid. The excess of the oxidizing agent was destroyed by the addition of methanol and the mixture was filtered. The filtrate was saturated with sodium sulfate and extracted with ether. The aqueous phase was then extracted with ethyl acetate from which 11g of 1,2,4-benzenetricarboxylic acid was obtained. It was recrystallized twice from acetone-benzene, mp 216° .

1,2,3-Benzenetricarboxylic Acid⁸

A mixture of 10 g of naphthalene-1,8-dicarboxylic anhydride, 4 g of potassium hydroxide, and 40 ml of water was heated in a water bath and 48 g of potassium permanganate in 1000 ml of water was added in small portions over a 2-hour period. After all the oxidizing agent had been added, the mixture was heated 3 hours longer on the water bath. Ethanol was added to destroy the excess of potassium permanganate and the mixture was filtered hot. The cake of manganese dioxide was washed with hot water and the filtrate was acidified with 19.8 g of sulfuric acid. The mixture was evaporated to 250 ml and cooled, and the potassium salt was collected (10 g). This was dissolved in a small volume of hot water and poured into hydrochloric acid. After cooling, 1,2,3-benzenetricarboxylic acid was collected by suction; 7.0 g, mp 190° (forming the anhydrids).

Naphthalene-1,8-dicarboxylic Anhydride⁹

A mixture of 25 g of acenaphthene (a sample from Wake Chemical Co.) and 300 ml of acetic acid was heated to 80° , to which was added 175 g of sodium dichromate in small portions over a 2-hour period.

The mixture was then refluxed for 2 hours (longer) and poured into water. The precipitate was collected by suction and dissolved in 400 ml of 10% sodium carbonate solution. The solution was acidified by the addition of sulfuric acid and cooled. The solid was filtered off and extracted with boiling ethanol. The ethanol extracts were evaporated and the residue was sublimed to obtain naphthalene-1,8-dicarboxylic anhydride, 9.0 g, 30% yield, mp 265°.

1,3,5-Benzenetricarboxylic Acid¹⁰

A mixture of 20 g of mesitylene and 2000 ml of water was heated to 95° and 158 g of potassium permanganate was added in small portions over a 5-hour period under stirring. The reaction mixture was left at this temperature under stirring for 25 hours longer. The excess of potassium permanganate was destroyed by the addition of methanol and the mixture was filtered. The filtrate was evaporated to about 300 ml, acidified with conc sulfuric acid, and cooled. The precipitate of 1,3,5-benzenetricarboxylic acid was collected by suction, 14 g, 40% yield, mp 345-350°.

Mesitylene¹¹

A flask containing 575 ml of acetone was cooled to 0-5° and 416 ml of conc sulfuric acid was added under stirring at such a rate that the temperature never exceeded 10°. The stirring continued for 3 hours longer and the reaction mixture was allowed to stand for 24 hours at this temperature.

The reaction mixture was placed in an all-glass apparatus and steam distilled. The organic layer in the distillate was separated from the water and shaken with sodium hydroxide solution until no more odor of sulfuric dioxide is noticeable., then washed twice with

water and distilled. The fraction which distilled up to 210° was collected. This was mixed with 1.5 g of sodium and heated just below the boiling point for 3 hours and then distilled to remove about two-thirds of the liquid. The residue is cooled, the liquid poured off from the solid material and distilled up to 210° . This was again fractionated to obtain a fraction having bp $163-167^{\circ}$ (40 g).

1,8-Naphthalic Acid¹²

1,8-Naphthalic anhydride (9.0 g) was dissolved in 400 ml of 10% sodium carbonate solution and acidified with conc hydrochloric acid to obtain 8.75 g (90% yield) of 1,8-naphthalic acid, which was recrystallized from ethanol. The acid changed to the anhydride at about 150° .

3-Nitro-1,8-naphthalic Acid¹³

1,8-Naphthalic anhydride (5 g) was dissolved in 20 ml of conc sulfuric acid and the solution was cooled to 5° . A mixture of 1.6 g of conc nitric acid and 5 ml of conc sulfuric acid was slowly added under stirring so that the temperature did not exceed 20° . The mixture was further stirred for 1 hour at 30° and then poured onto ice. The light yellow solid was collected by suction (4.3 g, 70% yield) and recrystallized from glacial acetic acid (charcoal) to obtain 3-nitro-1,8-naphthalic anhydride, mp 247° . This anhydride (2.5 g) was mixed with 25 ml of an aqueous solution containing 0.56 g (14 mmoles) of sodium hydroxide and boiled under stirring for 1 hour. Most of the solid did not dissolve and the mixture was filtered. The filtrate was acidified with dil sulfuric acid to obtain 1.2 g of 3-nitro-1,8-naphthalic acid.

2-Chloro-3,5-dinitrobenzoic Acid¹⁴

o-Chlorobenzoic acid (20 g) was mixed with 100 ml of conc sulfuric acid and 30 ml of fuming nitric acid and the mixture was heated at 130-140° for 6 hours. The reaction mixture was poured onto ice. The precipitate was collected by suction, washed with cold water, and recrystallized from water to obtain 16.8 g (70% yield) of 2-chloro-3,5-dinitrobenzoic acid, mp 199-200°.

2-Nitroisophthalic Acid^{15,16}

m-Toluic acid (3.0 g) was added in small portions to 30 ml of cold fuming nitric acid. After some time 1.2 g (24% yield) of crystals deposited which was recrystallized from ethanol to obtain 2-nitro-3-methylbenzoic acid, mp 223°.

The latter acid (10 g) was refluxed under stirring with 40 g of potassium permanganate and 5 g of magnesium sulfate in 1000 ml of water for 4 hours. The manganese dioxide was removed by suction and the filtrate was acidified with conc hydrochloric acid to obtain 8.1 g (70% yield) of 2-nitroisophthalic acid, which was recrystallized from water, mp 310-312°.¹⁶

m-Chlorobenzoic Acid¹⁷

m-Toluidine (14 g) was diazotized as below for p-toluidine. The solution was added into a cuprous chloride solution (40°) made from 30 g of cupric chloride, 70 ml of dil hydrochloric acid and 10 g of zinc. The mixture was steam distilled to obtain 12 g (80% yield) of m-chlorotoluene which was distilled, bp 162°.

The product (12 g) was refluxed with 20 g of potassium permanganate in 400 ml of water for 3 hours. The precipitate was collected

and the filtered solution was evaporated to 40 ml and acidified with conc hydrochloric acid. The precipitate was air-dried and recrystallized from benzene, 5.4 g (60% yield), mp 155°.

p-Bromobenzoic Acid^{18,19}

p-Toluidine (10.7 g) was dissolved in 10 ml of conc sulfuric acid in 100 ml of water and the solution was cooled to 20°. To this solution was added within 20 minutes 7.0 g of sodium nitrite in 13 ml of water.

A mixture of cupric sulfate (6.3 g), 2 g of copper powder, 15.4 g of sodium bromide, 3 g of conc sulfuric acid, and 100 ml of water was heated for 3 hours and cooled. The diaotized solution was added to this cuprous bromide solution and steam distilled to obtain crude (14 g) of p-bromotoluene. This product was washed with conc sulfuric acid and water, dried over calcium chloride, and distilled; b.p. 183-185°, yield 10 g.

p-Bromotoluene (15 g) was oxidized with 40 g of potassium dichromate and 50 g of sulfuric acid and poured into ice water. The precipitate was recrystallized from water to obtain 8.8 g (50% yield) of p-bromobenzoic acid, mp 251-253°.

m-Nitrobenzoic Acid²⁰

Benzoic acid which had been dried by melting (100 g) was mixed with 200 g of potassium nitrate, to which was added 15.0 g of conc sulfuric acid under stirring. The mixture was heated for 20 hours until nitrobenzoic acid formed as an oil layer over potassium sulfate. After cooling, the solidified nitrobenzoic acid was taken out of the salt, mixed with a small volume of water, and heated to melt. Then it was boiled with 100 ml of water to which was added conc barium

hydroxide solution to just precipitate the barium salt. The salt was acidified with conc hydrochloric acid to free the acid, which was dissolved in 10% sodium hydroxide solution and filtered. The filtrate was acidified with hydrochloric acid to obtain 100 g (70% yield) of m-nitrobenzoic acid, mp 140-141°.

3,5-Dinitrobenzoic Acid²¹

Benzoic acid (50 g) was warmed and 250 ml of conc sulfuric acid was added. The mixture was cooled and 85 ml of fuming nitric acid was added. The whole mixture was heated on a water bath for 2 hours and on a sand bath until no more red vapor came off. The reaction mixture was poured onto 4500 ml of ice water, the precipitate was collected, washed, air-dried, and recrystallized from ethanol to obtain 51 g (60% yield) of 3,5-dinitrobenzoic acid, mp 202°.

Heating Carboxylic Acids in Boiling Dimethyl Sulfoxide

The carboxylic acid was heated to reflux in boiling dimethyl sulfoxide (10 ml; see Table I) on a hot plate for the period of time specified. The reaction mixture was then poured into 100 ml of water. The precipitate if any was filtered off, dried in the air and then in a desiccator over calcium chloride, and infrared spectrum was recorded.

When the addition of water (100 ml) caused no precipitation, the whole mixture was then extracted with ether (100 ml), which was washed with water (50 ml), dried over magnesium sulfate, and distilled to dryness. Infrared spectrum was recorded for the residue.

The Product From Nitroterephthalic Acid

Addition of water (100 ml) caused precipitation of a yellow solid which was recrystallized three times from water, mp above 220°. Sodium fusion test indicated the absence of nitrogen and sulfur. The infrared spectrum showed a carbonyl band. This sample has been sent to elemental analysis.

The Product From 2-Chloro-3,5-dinitrobenzoic Acid

Addition of water (100 ml) caused no precipitation. The whole mixture was extracted with ether as mentioned above and evaporation of ether gave a yellow solid which had a carbonyl absorption band in the infrared spectrum. This product is being purified.

SUMMARY

Twenty-four aromatic acids were prepared or collected and they were individually heated in boiling dimethyl sulfoxide.

Phthalic acids carrying four chloro, four bromo, or one 3-nitro groups underwent decarboxylation to form, respectively, tetrachlorobenzoic acid, tetrabromobenzoic acid, or m-nitrobenzoic acid.

Nitroterephthalic acid gave a yellow solid product, mp above 220°. This product contains no nitrogen or sulfur and its infrared spectrum shows a carbonyl band.

2-Chloro-3,5-dinitrobenzoic acid also yielded a yellow crystalline product obtained by ether extraction. This also had a carbonyl band in the infrared spectrum.

Other carboxylic acids employed were stable to the treatment. Requirements for decarboxylation were discussed.

1,8-Naphthalic anhydride and 3-nitro-1,8-naphthalic anhydride

did not react with dimethyl sulfoxide to form the methylthionethyl esters in the manner tetrachlorophthalic anhydride did. The corresponding acids changed to the anhydrides in refluxing dimethyl sulfoxide.

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