

A structural analogy between these compounds and cysteine or cystine has been pointed out, and some of the reasons have been given for considering the action of alkali on the two classes of compounds as analogous. From these considerations, a mechanism for the alkaline decomposition of cysteine has been developed and reasons have been indicated for the anticipation of greatly increased reactivity in certain specified types of cysteine and cystine derivatives.

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[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

### ROTENONE. XIII. OXIDATION OF METHYLDERRITOLIC ACID AND THE SYNTHESIS OF 2,3,5- AND 2,3,6-TRIMETHOXYBENZOIC ACIDS AND THEIR DERIVATIVES

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As reported in previous articles,<sup>1</sup> derritol methyl ether is converted by catalytic hydrogenation into methyl derritolic acid, which is oxidized by hydrogen peroxide in alkaline solution to a compound of the formula of a trimethoxyphenylacetic acid. We have also reported that this trimethoxyphenylacetic acid is oxidized by permanganate to a trimethoxybenzoic acid melting at 78–80°.

Four of the six trimethoxybenzoic acids have been definitely described in the literature, but since the properties of none of the known acids agree with those of the oxidation product of the trimethoxyphenylacetic acid from derritol methyl ether, it seemed necessary to prepare the two missing members, that is, the 2,3,5- and 2,3,6-trimethoxybenzoic acids.

Orthovanillin was used as the starting material, the methylation of which was carried out according to the method of Späth and Mosettig.<sup>2</sup> The methyl ether was nitrated by the method of Perkin and Robinson<sup>3</sup> and the isomeric 2,3-dimethoxy-5-nitro and 2,3-dimethoxy-6-nitrobenzaldehydes were separated by means of their *p*-toluidides.<sup>4</sup>

The first-mentioned compound was converted into 2,3-dimethoxy-5-hydroxybenzaldehyde, which was then methylated and oxidized to the 2,3,5-trimethoxybenzoic acid, which melted at 105°.

The 2,3,5-trimethoxyphenylacetic acid was prepared from the corresponding aldehyde by the Mauthner synthesis.

The 2,3,6-trimethoxybenzoic acid was prepared by first oxidizing the 2,3-dimethoxy-6-nitrobenzaldehyde and then replacing the nitro group

<sup>1</sup> LaForge and Smith, *THIS JOURNAL*, **52**, 1088, 4597 (1930).

<sup>2</sup> Späth and Mosettig, *Ann.*, **433**, 144 (1923).

<sup>3</sup> Perkin and Robinson, *J. Chem. Soc.*, **105**, 2389 (1914).

<sup>4</sup> Perkin, Robinson and Stoye, *ibid.*, **125**, 235 (1924).

by the hydroxyl group with subsequent methylation to the trimethoxy derivative.

The melting points of the six theoretically possible trimethoxybenzoic acids are given in the following table:

Trimethoxybenzoic acid	Melting point, °C.	Trimethoxybenzoic acid	Melting point, °C.
2,3,4	97-99	2,4,5	144
2,3,5	105 <sup>a</sup>	2,4,6	142-144 (decomposition)
2,3,6	145-146	3,4,5	168-170

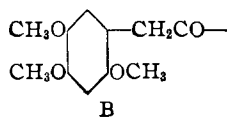
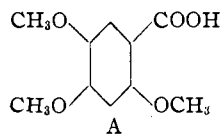
<sup>a</sup> For a compound which they assume to have this formula, Faltis and Neumann, *Monatsh.*, **42**, 372 (1921), report a melting point of 141-143°.

As the properties of none of these acids agreed with those of the oxidation product of the trimethoxyphenylacetic acid from derritol methyl ether, it seemed probable that our supposed trimethoxybenzoic acid was an impure substance. Therefore, we have repeated our oxidation experiments and found that the product obtained under the conditions employed was in fact a mixture containing considerable quantities of unchanged starting material from which we were unable to isolate the oxidation product.

We have now, by an indirect method, obtained the trimethoxybenzoic acid corresponding to the natural trimethoxyphenylacetic acid in a pure condition and found it to melt at 145°.

The procedure followed was to convert the trimethoxyphenylacetic acid into its ethyl ester, from which the trimethoxybenzylidiphenylcarbinol was prepared by the Grignard reaction. The carbinol was then dehydrated to the corresponding alkene, which yielded the trimethoxybenzoic acid by permanganate oxidation.

This acid is identical with the trimethoxybenzoic acid recently prepared by Clark<sup>5</sup> by the methylation of the dimethoxyhydroxybenzoic acid obtained by the oxidation of dehydrodeguelin and identified as asaronic acid of formula (A), melting at 145°. When mixed with this acid the trimethoxybenzoic acid from derritol methyl ether showed no depression of the melting point, but it showed a very marked depression when mixed with 2,3,6-trimethoxybenzoic acid, which also melts at 145°. Dihydroderritol methyl ether also gave asaronic acid when oxidized in acetone solution with permanganate and from derritol a small yield of the dimethoxyhydroxybenzoic acid was obtained which was identical with the oxidation product of dehydrodeguelin.<sup>5</sup>



It is established, therefore, that the three methoxyl groups in derritol methyl ether occupy the 2,4,5-positions, and that this compound contains the grouping (B).

<sup>5</sup> E. P. Clark, *THIS JOURNAL*, **53**, 2007 (1931).

### Experimental

**2,3-Dimethoxy-5-hydroxybenzaldehyde.**<sup>6</sup>—Three grams of 5-nitro-*o*-vanillin methyl ether was dissolved in 5.25 cc. of 30% sodium bisulfite and the solution diluted with 25 cc. of water. This solution was slowly added to a boiling mixture of 22.5 g. of calcium carbonate (from 23.5 g. of calcium chloride and 37.5 g. of potassium carbonate) and 60 g. of ferrous sulfate in 150 cc. of water. The mixture froths considerably especially in the early stages of the reaction. The boiling was continued for one and one-half hours, after which the dissolved amino aldehyde, which proved to be unstable in the free state, was filtered into 12 cc. of concentrated hydrochloric acid diluted with two or three parts of water. This solution was cooled to 3° and 0.93 g. of sodium nitrite in 75 cc. of water was added. The solution of the diazo compound was warmed to room temperature and then left on the steam-bath for two hours. After boiling for ten minutes with decolorizing carbon the solution was filtered and extracted with ether. The ether extracts after drying over anhydrous sodium sulfate were evaporated. The crystalline residue of 2,3-methoxy-5-hydroxybenzaldehyde was recrystallized from water; m. p. 152°. The yield varied somewhat but was usually about 0.5 g.

*Anal.* Subs., 0.0569: CO<sub>2</sub>, 0.1240; H<sub>2</sub>O, 0.0283. Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>4</sub>: C, 59.34; H, 5.49. Found: C, 59.43; H, 5.52.

**Methylation of 2,3-Methoxy-5-hydroxybenzaldehyde.**—Two grams of the aldehyde was dissolved in 4 cc. of 33% sodium hydroxide and 12 cc. of water in a three-necked flask fitted with a mechanical stirrer. Four cc. of methyl sulfate was slowly added, followed by 2 cc. of 33% sodium hydroxide. After stirring for three hours on a water-bath, the mixture was filtered, and the separated crystals were washed with water. The 2,3,5-trimethoxybenzaldehyde was recrystallized from 50% ethyl alcohol; m. p. 71°; yield, 1.2 g.

*Anal.* Subs., 0.0209: AgI, 0.0753. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub>: 3CH<sub>3</sub>O, 47.44. Found: CH<sub>3</sub>O, 47.58.

**Oxidation of 2,3,5-Trimethoxybenzaldehyde.**—Thirty-five hundredths gram of the aldehyde was suspended in 50 cc. of water containing 0.1 g. of potassium hydroxide. The mixture was oxidized on the steam-bath with 8 cc. of 3% potassium permanganate. The solution was filtered from the manganese dioxide, acidified with dilute hydrochloric acid and extracted with ether. The ether extracts after drying over anhydrous sodium sulfate were evaporated, leaving the crystalline 2,3,5-trimethoxybenzoic acid, which was then recrystallized from water; m. p. 105°; yield, 0.15 g.

*Anal.* Subs., 0.0735: CO<sub>2</sub>, 0.1521; H<sub>2</sub>O, 0.0367. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>6</sub>: C, 56.6; H, 5.66. Found: C, 56.43; H, 5.54.

**Azactone of 2,3,5-Trimethoxybenzaldehyde.**—One and two-tenths grams of the aldehyde, 1.5 g. of hippuric acid and 0.6 g. of anhydrous sodium acetate were intimately mixed in a mortar. The mixture was placed in a 50-cc. Erlenmeyer flask, 3.5 cc. of acetic anhydride added, and the mixture heated on the steam-bath for two hours. After cooling, 5 cc. of water was added, the mixture allowed to stand for an hour, filtered and the product washed with water and then with ethyl alcohol. The azactone was recrystallized from ethyl alcohol; m. p. 181–183°. The yield was nearly quantitative.

*Anal.*<sup>7</sup> Subs., 3.892 mg.: CO<sub>2</sub>, 9.625 mg.; H<sub>2</sub>O, 1.737 mg. Subs., 7.099 mg.; N, 0.260 cc. Calcd. for C<sub>10</sub>H<sub>17</sub>O<sub>6</sub>N: C, 67.25; H, 5.01; N, 4.13. Found: C, 67.56; H, 4.96; N, 4.16.

<sup>6</sup> German Patent 62,950.

<sup>7</sup> We are indebted to Mr. J. R. Spies of this division for carrying out the micro analyses reported in this paper.

**2,3,5-Trimethoxyphenylacetic Acid.**—One and eight-tenths grams of the azlactone was boiled for one and one-half hours with 14 cc. of water containing 2.8 g. of potassium hydroxide. After cooling, 1.3 cc. of 30% hydrogen peroxide was added, the solution was allowed to stand for one and one-fourth hours and then warmed for fifteen minutes on the steam-bath. After acidifying with hydrochloric acid, the solution was extracted with ether. The ether extracts after drying over anhydrous sodium sulfate were evaporated, and the products were kept in an oven at 105° overnight to remove benzoic acid. The remaining substance was recrystallized from water, m. p. 83°. When mixed with the trimethoxyphenylacetic acid from methyl derritolic acid, the melting point was depressed to 60–65°.

*Anal.* Subs., 4.130 mg.: CO<sub>2</sub>, 8.873 mg.; H<sub>2</sub>O, 2.296 mg. Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>6</sub>: C, 58.40; H, 6.15. Found: C, 58.46; H, 6.13.

**Reduction of 2,3-Dimethoxy-6-nitrobenzoic Acid.**—Nine grams of ferrous sulfate was dissolved in 25 cc. of water and an excess of concentrated ammonium hydroxide was added. The mixture was heated to 92° and 1 g. of the acid dissolved in ammonium hydroxide was added in small portions. The solution was boiled for one hour, then filtered and cooled. As the resulting amino acid proved to be unstable, the solution was cooled to 5°, made acid with an 8 cc. excess of concentrated hydrochloric acid, and 0.66 g. of sodium nitrite dissolved in 25 cc. of water was added in small portions with constant stirring. The solution was allowed to warm to room temperature and then boiled for ten minutes with decolorizing carbon. After filtering, the solution was cooled and extracted with ether. The ether extract, after drying over anhydrous sodium sulfate, was evaporated and the resulting 2,3-methoxy-6-hydroxybenzoic acid was recrystallized from water. It consists of long needles of m. p. 82°; yield, 0.25 g.

*Anal.* Subs., 0.0683: CO<sub>2</sub>, 0.1365; H<sub>2</sub>O, 0.0311. Subs., 0.0206: AgI, 0.0487. Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>5</sub>: C, 54.54; H, 5.05; 2CH<sub>3</sub>O, 31.31. Found: C, 54.49; H, 5.06; CH<sub>3</sub>O, 31.23.

**Methylation of 2,3-Methoxy-6-hydroxybenzoic Acid.**—One gram of the acid was dissolved in 40 cc. of 5% potassium hydroxide and to this solution 2 cc. of methyl sulfate was added with mechanical stirring. The stirring was continued for three hours, after which the solution was made acid with hydrochloric acid and extracted with ether. After drying over anhydrous sodium sulfate, the ether extracts were evaporated. The 2,3,6-trimethoxybenzoic acid was recrystallized from water, m. p. 145–146°.

*Anal.* Subs., 0.0580: CO<sub>2</sub>, 0.1208; H<sub>2</sub>O, 0.0297. Subs., 0.0194: AgI, 0.0647. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>6</sub>: C, 56.6; H, 5.66; 3CH<sub>3</sub>O, 43.86. Found: C, 56.78; H, 5.69; CH<sub>3</sub>O, 44.05.

**Amide of 2,4,5-Trimethoxyphenylacetic Acid from Methyl derritolic Acid.**—Five-tenths gram of the acid was dissolved in 10 cc. of benzene and to this solution 0.5 g. of phosphorus pentachloride was added. After boiling off the hydrogen chloride, the solution was cooled in an ice-bath and saturated with dry ammonia. Water was then added and the benzene removed by boiling. The amide was recrystallized from water; m. p. 169°; yield, 0.4 g.

*Anal.* Subs., 3.481 mg.; CO<sub>2</sub> 7.498 mg.; H<sub>2</sub>O, 2.050 mg. Subs., 3.396 mg.; N, 0.186 cc. Calcd. for C<sub>11</sub>H<sub>15</sub>O<sub>4</sub>N: C, 58.67; H, 6.67; N, 6.22. Found: C, 58.74; H, 6.54; N, 6.22.

**Ethyl Ester of the 2,4,5-Trimethoxyphenylacetic Acid from Methyl derritolic Acid.**—Two and two-tenths grams of the acid, 5 cc. of absolute ethyl alcohol and 0.5 cc. of concentrated sulfuric acid was refluxed for three hours. After dilution with two volumes of water, the solution was made alkaline with solid potassium carbonate and extracted with ether. The ether solution was extracted with water and after drying over an-

hydrous sodium sulfate was evaporated. The crude ester was not purified further but was treated directly with the Grignard reagent.

**2,4,5-Trimethoxybenzylidiphenylcarbinol.**—The phenylmagnesium bromide was prepared in the usual manner, with 1.34 g. of magnesium turnings and 8.34 g. of bromobenzene. Four and one-half grams of the crude trimethoxyphenylacetic ester in ether solution was added to the Grignard reagent over a period of forty-five minutes, with constant stirring. The mixture was then refluxed for an hour and, after cooling, hydrolyzed with dilute sulfuric acid with slight warming to complete the reaction. The ether layer was separated and after drying over anhydrous sodium sulfate was evaporated. The resulting carbinol was recrystallized from ethyl alcohol, m. p. 130–131°.

*Anal.* Subs., 0.0700: CO<sub>2</sub>, 0.1942; H<sub>2</sub>O, 0.0419. Calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>4</sub>: C, 75.82; H, 6.59. Found: C, 75.65; H, 6.65.

**$\alpha$ -2,4,5-Trimethoxyphenyl- $\beta$ -diphenylethylene.**—One-half gram of 2,4,5-trimethoxybenzylidiphenylcarbinol was heated with a trace of iodine in an Abderhalden drier at 138° until the evolution of water ceased. On cooling, the oily residue became crystalline and was recrystallized from dilute ethyl alcohol; m. p. 101–103°; yield, 0.35 g.

*Anal.* Subs., 0.0667: CO<sub>2</sub>, 0.1951; H<sub>2</sub>O, 0.0386. Calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>3</sub>: C, 79.76; H, 6.35. Found: C, 79.77; H, 6.43.

**2,4,5-Trimethoxybenzoic Acid.**—Three-tenths gram of  $\alpha$ -2,4,5-trimethoxyphenyl- $\beta$ -diphenylethylene was dissolved in 25 cc. of acetone and small amounts of finely ground potassium permanganate were added over a period of several days until a permanent purple color was obtained. The solution was filtered, the precipitate washed with acetone and after drying digested with boiling water. After filtering from the manganese dioxide, the solution was made acid with dilute hydrochloric acid and extracted with ether. The ether extracts after drying over anhydrous sodium sulfate were evaporated. The resulting 2,4,5-trimethoxybenzoic acid was recrystallized from water, m. p. 145–146°. A mixed melting point with 2,4,5-trimethoxybenzoic acid prepared by Dr. E. P. Clark of this Laboratory gave no depression.

*Anal.*<sup>7</sup> Subs., 3.356, 4.572 mg.: CO<sub>2</sub>, 6.959, 9.447 mg.; H<sub>2</sub>O, 1.658, 2.252 mg. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>5</sub>: C, 56.6; H, 5.66. Found: C, 56.55, 56.35; H, 5.49, 5.47.

**Oxidation of Dihydroderritol Methyl Ether.**—Five grams of dihydroderritol methyl ether was dissolved in 200 cc. of anhydrous acetone neutral to permanganate. The solution was cooled in an ice-bath, and 16 g. of finely powdered potassium permanganate was added in small portions with mechanical stirring. Several days were required to complete the reaction. The mixture was filtered and the precipitate digested with 300 cc. of water and filtered from manganese dioxide. The filtrate, after concentrating to a small volume under reduced pressure, was made acid and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from water, m. p. 145°. The yield was 0.4 g. A mixed melting point with asaronic acid showed no depression.

**Oxidation of Derritol.**—Five grams of derritol was oxidized and the reaction product isolated in the manner described above. The reaction was complete in about five hours. The product was washed with a small amount of dilute methyl alcohol and then recrystallized from water, m. p. 211–212° with decomposition. When mixed with the hydroxydimethoxybenzoic acid, which Clark obtained from dehydrodeguelin, the melting point showed no depression.

### Summary

The preparation and properties of 2,3,5 and 2,3,6-trimethoxybenzoic acids are described. The addition of these two missing members completes the series of six possible acids of this type.

The 2,3,5-trimethoxyphenylacetic acid was prepared from the corresponding 2,3,5-trimethoxybenzaldehyde.

The trimethoxyphenylacetic acid obtained from derritol methyl ether was converted into its ethyl ester, which yielded the diphenylcarbinol by the Grignard reaction. This carbinol was dehydrated to the corresponding trimethoxyphenyldiphenylethylene, which was oxidized to a trimethoxybenzoic acid. This acid proved to be identical with 2,4,5-trimethoxybenzoic acid (asaronic acid).

The same acid was obtained by direct oxidation of derritol methyl ether and derritol itself yielded a dimethoxyhydroxybenzoic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

## THE NUMBER OF ISOMERIC HYDROCARBONS OF THE METHANE SERIES

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At various times attempts have been made by both mathematicians and chemists to derive a formula by which the number of isomeric hydrocarbons of the methane series could be calculated.

Apparently the first attempt to derive such a formula was made by the English mathematician Cayley<sup>1</sup> in 1875. He recognized that the number of isomers for a given carbon content was dependent upon the number of those of lesser carbon contents, and thus he obtained successively for every magnitude an expression for the fundamental chains common to all of magnitude  $N$ . This function led to the building of "centric and bicentric trees," and with the help of the same he predicted the number of isomeric hydrocarbons inclusive of a carbon content of thirteen. However, his predictions of the number of isomers for the carbon contents of twelve and thirteen were in error.

Almost simultaneously with this attempt of Cayley was that of Schiff.<sup>2</sup> Using a method involving combinations and permutations, he calculated the number of isomeric hydrocarbons through the dodecanes, obtaining for the dodecanes, however, the same erroneous value as that of Cayley.

This error, along with that of Cayley as to the number of tridecanes, was first corrected by Hermann<sup>3</sup> about five years later. The latter divided the structural formulas of the isomers into types, according to the number of branches attached to the fundamental chain of each, and attempted to relate the number of isomers of each type to the total number

<sup>1</sup> Cayley, *Ber.*, **8**, 1056 (1875).

<sup>2</sup> Schiff, *ibid.*, **8**, 1542 (1875).

<sup>3</sup> Hermann, *ibid.*, **13**, 792 (1880); **30**, 2423 (1897); **31**, 91 (1898).