prepared by mixing 10 cc. of N acetic acid and 10 cc. of N sodium acetate and diluting to 100 cc.

Solution C was identical with Solution A except that 15 drops of 0.1 N sodium hydroxide solution were used instead of the 0.1 N hydrochloric acid; and Solution D was identical with Solution B except that 15 drops of 0.1 N sodium hydroxide solution replaced the 0.1 N hydrochloric acid. The results are given below.

	P_H	L
Solution A—HCl added, not buffered	3.57	103
Solution B—HCl added, buffered	4.68	135
Solution C—NaOH added, not buffered	7.15	117
Solution D—NaOH added, buffered	4.77	135

Thus the acetate solution changed the Sörensen value of the solutions to within the range required.

Summary

The diastase in an infusion of malt was as sensitive to changes in hydrogen-ion concentration as the highly purified diastase used by Sherman, Thomas and Baldwin. The optimum P_H range was 4.5 to 5.5. It is shown that for correct results by the polarimetric Lintner method, the mixture of soluble starch and diastase infusion must be held within the above range.

The Fleischmann Company,
New York, N. Y.

[Contribution from the Chemical Laboratory of the University of Illinois]

TRIHYDROXY-METHYLANTHRAQUINONES. V. SYNTHESIS OF MORINDONE[1]

By R. A. Jacobson[2] with Roger Adams

Received October 24, 1924 Published January 8, 1925

Morindone, chiefly in the form of its glucoside, morindin, is the main constituent of *Morinda citrifolia* and M. *umbellata*.[3] It is an anthraquinone derivative which before the advent of synthetic dyes was rather extensively used in India for dying cloth. Both morindin and morindone were discovered as early as 1849,[4] and the similarity of the latter compound

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[1] Previous papers in this field are (a) Graves and Adams, This Journal, **45,** 2439 (1923); (b) Gardner and Adams, *ibid.*, **45,** 2455 (1923); (c) Jacobson and Adams, *ibid.*, **46,** 1312 (1924); (d) *ibid.*, **46,** 2788 (1924).

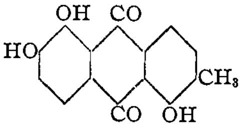
[2] This communication is an abstract of a portion of a thesis submitted by R. A. Jacobson in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] (a) Oesterle and Tisza, *Arch. Pharm.*, **245,** 534 (1907). (b) Perkin, *Proc. Chem. Soc.*, **24,** 150 (1908). (c) Simonsen, *J. Chem. Soc.*, 113, 766 (1918).

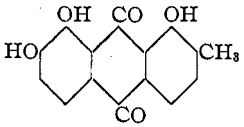
[4] Anderson, *Ann.*, **71,** 216 (1849).

to alizarin was noted. It remained for Thorpe and Greenall[5] and Thorpe and Smith[6] to prove conclusively that morindone had the formula $C_{15}H_{10}O_5$ and was in all probability a trihydroxy-methylanthraquinone, a view that was confirmed by Perkin and Hummel[7] who obtained 2-methylanthracene by distillation of morindone with zinc dust.

Simonsen made a careful study of the reactions of morindone, the detailed results of which have been reviewed in one of his communications.[3c] Little doubt was left that morindone was either hydroxy-methylanthrarufin (1,2,5-trihydroxy-6-methylanthraquinone, I) or hydroxy-methylchrysazin (1,2,8-trihydroxy-7-methylanthraquinone, II) and a study of the color reactions with concd. sulfuric acid indicated that Formula I was the more likely.



I



II

Simonsen[8] was unsuccessful in his attempts to prepare 1,2,5-trihydroxy-6-methylanthraquinone (I), but recently[9] he has prepared the trimethyl ether of 1,2,8-trihydroxy-7-methylanthraquinone (II), and shown it not to be identical with morindone trimethyl ether. The same conclusion was reached during this investigation[10] in which 1,2,8-trihydroxy-7-methylanthraquinone was synthesized and shown not to be identical with morindone.

This communication describes an investigation which had as its object the confirmation of Simonsen's structure (I) for morindone by its synthesis. This has been accomplished and natural morindone and its derivatives have been shown to be identical with synthetic 1,2,5-trihydroxy-6-methylanthraquinone and its corresponding derivatives.

This synthesis was made possible through the application of a general method[1d] recently described for synthesizing polysubstituted anthraquinones of this type. The preparation consists in the condensation of opianic acid (3,4-dimethoxy-2-carboxy benzaldehyde) with *p*-bromo-*o*-cresol. The phthalide (III) produced was readily reduced with zinc and sodium hydroxide yielding a substituted benzyl-benzoic acid (IV), and at the

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[5] Thorpe and Greenall, *J. Chem. Soc.*, **51**, 52 (1887).

[6] Thorpe and Smith, *ibid.*, **53**, 171 (1888).

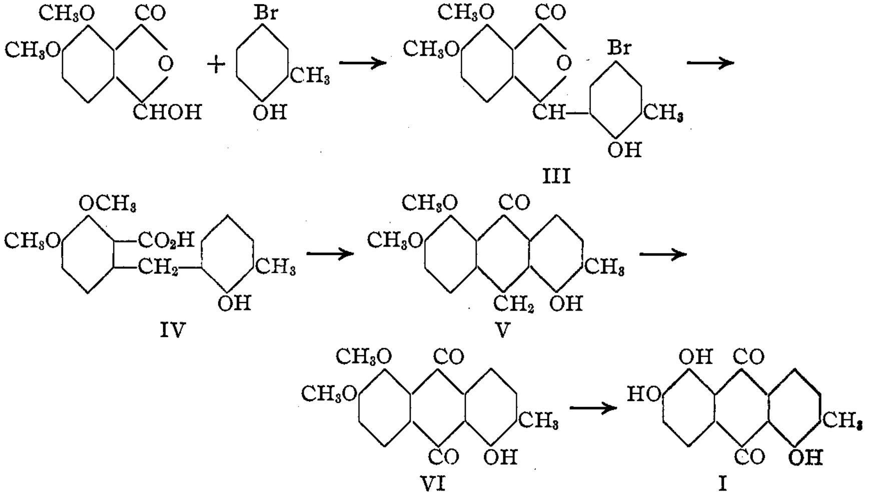
[7] Perkin and Hummel, *ibid.*, **65**, 851 (1894).

[8] Simonsen and Rau, *J. Chem. Soc.*, **119**, 1339 (1921).

[9] Simonsen, *ibid.*, **125**, 721 (1924).

[10] The preparation of 1,2,8-trihydroxy-7-methylanthraquinone was completed before the appearance of the article of Simonsen describing the trimethyl ether of this compound. As the details for synthesis are considerably different from those of Simonsen, they are given in the experimental part.

same time the halogen was replaced by hydrogen. Although the usual method for condensing *o*-benzyl-benzoic acids to anthrones is by means of concd. sulfuric acid, this procedure was unsuccessful in this case, due probably to the fact that the *para* position to the hydroxyl group is unfilled and therefore is readily sulfonated. Substitution of 85% sulfuric acid for the concentrated acid, however, accomplished the result admirably, the conversion of 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic acid (IV) to 1,2-dimethoxy-5-hydroxy-6-methyl-9,10-dihydro-9-keto anthracene (V) being almost quantitative. It was a simple matter to oxidize the anthrone in the usual way with chromic acid, in order to obtain the corresponding anthraquinone, namely, 1,2-dimethoxy-5-hydroxy-6-methylanthraquinone (morindone dimethyl ether, VI). By demethylation with hydrobromic acid, the reagent previously found very suitable for demethylations of this type,[1a] 1,2,5-trihydroxy-6-methylanthraquinone (synthetic morindone) was obtained.

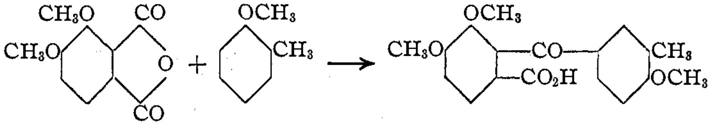


III IV V VI I

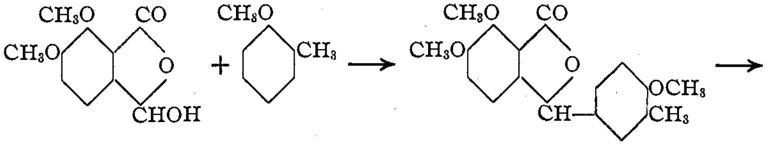
The melting point of 1,2,5-trihydroxy-6-methylanthraquinone was 281–282° (corr.), the same as that found for a highly purified sample of the natural morindone (the literature reports 275°). A mixture with the natural product showed no change in melting point and the color tests and other physical properties agreed in all respects. Moreover, the synthetic triacetyl derivative (m. p., 255–256.5°) and tribenzoyl derivative (m. p., 233–234°) were identical in every way, as determined by melting point, mixed melting point and other physical properties, with the corresponding derivatives of the natural product.

The samples of natural morindone and a number of its derivatives were very kindly furnished by Dr. John Lionel Simonsen of the Forest Research Institute, Dehra Dun, India. The authors desire to express their deep indebtedness to Dr. Simonsen for these samples as with their aid the absolute proof of the constitution of morindone has been made certain.

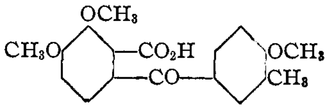
The evidence is fairly conclusive that when hemipinic anhydride condenses with phenols or phenol ethers, the carbonyl group adjacent to the methoxyl group forms the ketone group in the benzoyl-benzoic acid. Nevertheless, occasion has been again taken in this research to substantiate this orientation. The benzoyl-benzoic acid [3,4-dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic acid] (VII) from hemipinic anhydride and *o*-cresol methyl ether is not identical with the benzoyl-benzoic acid [5,6-dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic acid, IX] formed from opianic acid and *o*-cresol methyl ether, then subsequent oxidation. Since *o*-aldehyde acids are known always to condense as indicated, the non-identity of the two benzoyl-benzoic acids shows that the carbonyl adjacent to the methoxyl in the hemipinic anhydride is the ketone group in the corresponding benzoyl-benzoic acid.



VII



VIII



IX

Experimental Part

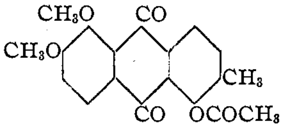
5,6-Dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic Acid. IV.—The preparation of this acid is described in a previous paper.[1d]

1,2-Dimethoxy-5-hydroxy-6-methyl-9,10-dihydro-9-keto Anthracene (V).—A suspension of 13.9 g. of finely divided 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl) benzoic acid in 265 cc. of 85% sulfuric acid was allowed to stand at room temperature and occasionally stirred until solution was complete. This required 3.5 hours. The anthrone was precipitated by slowly pouring the solution over ice. The yellow precipitate was filtered off and washed free from sulfuric acid; yield, 13 g. (quantitative).

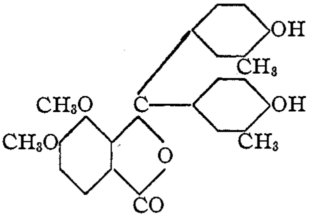
The anthrone was not purified but was oxidized directly to the corresponding anthraquinone.

1,2-Dimethoxy-5-hydroxy-6-methylanthraquinone (Dimethyl Morindone). VI.—To a solution of 10 g. of crude 1,2-dimethoxy-5-hydroxy-6-methyl-9,10-dihydro-9-keto-anthracene in 100 cc. of glacial acetic acid was added a solution of 4.7 g. of chromium trioxide in 20 cc. of 50% acetic acid. Oxidation took place at once, the temperature of the solution rising from 40° to 70°. The acetic acid was removed by evaporation on the steam bath in a current of air. The residue was extracted several times with boiling toluene from which the anthraquinone crystallized on cooling. The yield was 4.7 g. (44.8%) of yellow needles which after purification from toluene melted at 138.5–139° (corr.). Acetic acid is also an excellent solvent for recrystallization.

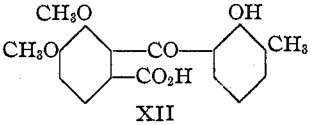
Anal. Subs., 0.1919: CO_2, 0.4816; H_2O, 0.0752. Calcd. for $C_{17}H_{14}O_5$: C, 68.44; H, 4.73. Found: C, 68.46; H, 4.38.



X



XI



XII

1,2-Dimethoxy-5-acetoxy-6-methylanthraquinone. X.—A mixture of 1.77 g. of 1,2-dimethoxy-5-hydroxy-6-methylanthraquinone, 2 g. of freshly fused sodium acetate and 50 cc. of acetic anhydride was refluxed for four hours. The acetic anhydride was removed by evaporation on the steam-bath in a current of air; yield, 1.31 g., or 64%. After purification from glacial acetic acid, yellow needles were obtained which melted at 185–185.5° (corr.).

Anal. Subs., 0.1836: CO_2, 0.4496; H_2O, 0.0744. Calcd. for $C_{19}H_{16}O_6$: C, 67.04; H, 4.74. Found: C, 66.80; H, 4.53.

1,2,5-Trihydroxy-6-methylanthraquinone (Morindone). I.—To a solution of 5.2 g. of 1,2-dimethoxy-5-hydroxy-6-methylanthraquinone in 775 cc. of glacial acetic acid was added 175 cc. of hydrobromic acid (d., 1.48). The addition of the hydrobromic acid caused precipitation of a portion of the dimethyl-morindone. The mixture was refluxed for 12 hours at the end of which time solution was complete. Upon cooling, 3.6 g. (75%) of crystalline 1,2,5-trihydroxy-6-methylanthraquinone separated. The product was purified by crystallization from toluene from which orange-red needles were obtained; m. p., 281–282° (corr.). A sample of crude, natural morindone, m. p., 165–170°, was recrystallized six times from toluene to a constant melting point of 281–282° (corr.).

Anal. Subs., 0.1989: CO_2, 0.4862; H_2O, 0.0676. Calcd. for $C_{15}H_{10}O_5$: C, 66.65; H, 3.73. Found: C, 66.68; H, 3.80.

The identity of the synthetic product with natural morindone was shown by a mixed-melting-point determination, and further by preparing the tribenzoate,[30] m. p., 233–234° (corr.), and the triacetate,[30] m. p. 255–256.5° (corr.).

The sample of natural morindone tribenzoate furnished by Dr. Simonsen also melted, in the apparatus used in this Laboratory, at 233–234° (corr.), although the melting point reported in the literature is 218–219°. The sample of natural morindone triacetate after four recrystallizations from glacial acetic acid melted at 255–256° (corr.).

The experimental work on the preparation of 1,2,8-trihydroxy-7-methylanthraquinone and on the condensation of opianic acid with *o*-cresol methyl ether and subsequent oxidation of the product was carried out by J. H. Gardner.

Condensation of Hemipinic Anhydride with *o*-Cresol.[9]—A solution of 5 g. of hemipinic anhydride in 20 cc. of *o*-cresol was treated with 8 g. of anhydrous aluminum chloride. The mixture was heated to 70° during a period of two hours and maintained at 68–70° for four hours. It was decomposed with 100 cc. of hydrochloric acid and the excess of *o*-cresol was driven off with steam.

The residue was cooled and the solid material filtered off. The solid mass was dissolved in boiling 10% sodium hydroxide solution, and the red alkaline liquid saturated with carbon dioxide, precipitating 2.5 g. (26%) of 3,4-dimethoxy-2,2-di-(4-hydroxy-3-methylphenyl)phthalide which was filtered off. The filtrate was acidified with hydrochloric acid, precipitating 3.3 g. (45%) of 3,4-dimethoxy-2-(2-hydroxy-3-methylbenzoyl)-benzoic acid.

3,4-Dimethoxy-2,2-di-(4-hydroxy-3-methylphenyl)phthalide, XI.—The phthalein was recrystallized several times from dil. acetic acid, finally being obtained as faintly yellow needles melting at 238–239.5° (corr.) (the melting point in the literature is 237–238°). It is soluble in alkalies giving an intensely blue-red solution, and may serve as an indicator, the color changing at *P*H 8.7. For the determination of this value, the writers are indebted to Mr. W. R. Brode, of this Laboratory.

Anal. Subs., 0.0816: CO_2, 0.2104; H_2O, 0.0408. Calcd. for $C_{24}H_{22}O_6$: C, 70.94; H, 5.42. Found: C, 70.32; H, 5.56.

3,4-Dimethoxy-2-(2-hydroxy-3-methylbenzoyl) benzoic Acid. XII.—The benzoylbenzoic acid was recrystallized several times from methyl alcohol, using Norite as a decolorizer the first time. It was thus obtained in the form of a finely crystalline, white powder, melting at 253–254° (corr.) (the melting point in the literature is 250–251°).

Anal. Subs., 0.0828: CO_2, 0.1976; H_2O, 0.0378. Calcd. for $C_{17}H_{16}O_6$: C, 64.56; H, 5.07. Found: C, 65.09; H, 5.07.

1,2,8-Trihydroxy-7-methylanthraquinone. II.—A mixture of 5 g. of 3,4-dimethoxy-2-(2-hydroxy-3-methylbenzoyl)benzoic acid and 5 g. of boric acid was dissolved in 50 cc. of concd. sulfuric acid. The solution was heated rapidly to 140°, and maintained at 135–140° for half an hour. It was then poured onto ice and the dark brown precipitate which separated, filtered off. The residue on the filter was dissolved in 10% sodium hydroxide solution, the alkaline liquid filtered, and the 1,2,8-trihydroxy-7-methylanthraquinone reprecipitated with hydrochloric acid; yield, 3.5 g., or 82%. It was purified by crystallization from dil. acetic acid giving fine brownish-yellow needles; m. p., 287–288° (corr.).

Anal. Subs., 0.0760: CO_2, 0.1483; H_2O, 0.0260. Calcd. for $C_{15}H_{10}O_5$: C, 66.65; H, 3.73. Found: C, 66.14; H, 3.80.

It is characterized by the following colors of its solutions: aqueous sodium hydroxide—red, with faint bluish cast; concd. sulfuric acid—bluish-red; alcohol—yellow; alcoholic sodium hydroxide—red; alcoholic hydrochloric acid—greenish-yellow.

3,4-Dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic Acid. VII.—To a solution of 5 g. of hemipinic anhydride in 20 cc. of *o*-cresol methyl ether, was added 8 g. of anhydrous aluminum chloride. The mixture was heated to 70° during the course of four hours, and was maintained at that temperature for two and one-half hours. To it was then added 50 cc. of 1:1 hydrochloric acid and the excess of cresol ether removed by steam distillation. The residue was cooled and filtered, and the solid material extracted with 10% sodium hydroxide solution. The alkali-insoluble material was filtered off and discarded. The filtrate was saturated with carbon dioxide, the aluminum hydroxide filtered off, and the second filtrate acidified with hydrochloric acid. A precipitate of 4.5

g. (57%) of 3,4-dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic acid resulted. The acid crystallized from methyl alcohol in the form of a coarse, white powder, melting at 223.5–224° (corr.) (the melting point in the literature is 218–219.5°).[11]

Anal. Subs., 0.1038, 0.1220; CO_2, 0.2472, 0.2906; H_2O, 0.0494, 0.0600. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 64.95, 64.96; H, 5.29, 5.46.

5,6-Dimethoxy-2-(4-methoxy-3-methylphenyl)phthalide. VIII.—A mixture of 5 g. of opianic acid and 3 cc. of *o*-cresol methyl ether was rubbed in a mortar and 13.5 cc. of 73% sulfuric acid added drop by drop. After the acid had been introduced the mixture was allowed to stand for ten hours. It was then stirred with water, the mixture filtered, and the residue washed free from sulfuric acid. There was obtained in this way 6.5 g. (87%) of 5,6-dimethoxy-2-(4-methoxy-3-methylphenyl)phthalide. It was purified from dil. acetone, crystallizing in colorless flakes; m. p., 119–119.5° (corr.) (Bistrzycki and Zen-Ruffinen give 117.5–119°).[12]

Anal. Subs., 0.0904: CO_2, 0.2284; H_2O, 0.0480. Calcd. for $C_{18}H_{18}O_5$: C, 68.79; H, 5.73. Found: C, 68.91; H, 5.90.

5,6-Dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic Acid. IX.—A solution of 1 g. of the phthalide (VIII) in 50 cc. of methyl alcohol was treated with a solution of 0.3 g. of potassium hydroxide in 2 cc. of water. The mixture was evaporated almost to dryness on the steam-bath, then diluted to 50 cc. with water, and the evaporation and dilution repeated several times in order that all of the alcohol might be driven off. Finally, the alcohol-free solution was heated to boiling and 3% potassium permanganate solution was added slowly until a permanent purple color appeared. A little alcohol was then introduced to reduce the excess of permanganate and the manganese dioxide formed was filtered off. The filtrate was cooled and acidified with hydrochloric acid, precipitating the 5,6-dimethoxy-2-(4-methoxy-3-methylbenzoyl)benzoic acid. It was purified by recrystallization from methyl alcohol and then from glacial acetic acid. It was then dried at 100° for 24 hours, and allowed to stand in an evacuated desiccator over sodium hydroxide for 24 hours; m. p., 206–206.5° (corr.).

Anal. Subs., 0.0700: CO_2, 0.1674; H_2O, 0.0356. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.23; H, 5.62.

A sample mixed with an equal amount of the acid obtained from hemipinic anhydride and *o*-cresol methyl ether melted over a range of 15°, from 170° to 185°, proving that the compounds were not identical. From this it follows that the structures assigned to the products from hemipinic anhydride with *o*-cresol, and with *o*-cresol methyl ether must be correct.

Summary

1. A method is described for the synthesis of 1,2,5-trihydroxy-6-methylanthraquinone. This substance and its derivatives proved to be identical with natural morindone and its corresponding derivatives.

2. The procedure consisted in condensing opianic acid with *p*-bromo-*o*-cresol. The resulting phthalide was reduced to 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic acid. This in turn was condensed to the corresponding anthrone, the anthrone oxidized to the anthraquinone and finally demethylated to yield mroindone.

3. The synthesis of 1,2,8-trihydroxy-7-methylanthraquinone was completed and the substance shown not to be identical with morindone.

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[11] Bistrzycki and Krauer, *Helvetica Chim. Acta*, **6**, 754 (1923).

[12] Bistrzycki and Zen-Ruffinen, *ibid.*, **3**, 387 (1920).

4. The benzoyl-benzoic acid formed by the condensation of hemipinic anhydride with *o*-cresol methyl ether proved not to be identical with the benzoyl-benzoic acid produced by condensing opianic acid with *o*-cresol methyl ether and oxidation of the product. This is further evidence that in hemipinic anhydride the carbonyl adjacent to the methoxyl group forms the ketone group in the benzoyl-benzoic acids.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

PYROGALLOLBENZEIN AND ITS HYDROCHLORIDE

Preliminary Paper

BY W. R. ORNDORFF AND C. WANG

RECEIVED NOVEMBER 24, 1924 PUBLISHED JANUARY 8, 1925

Pyrogallolbenzein was first made by Doebner and Förster[1] by heating pyrogallol with benzotrichloride. They give it the formula, $C_{38}H_{24}O_{11} + 5H_2O$. As it seemed probable from the work done in this Laboratory on gallein and on pyrogallol-sulfonephthalein that this formula was not correct, the work of these chemists has been repeated and it has been shown that the formula of pyrogallolbenzein is $C_{19}H_{12}O_5$.

Preparation of Pyrogallolbenzein.—A mixture of pyrogallol (2 molecular equivalents) and benzotrichloride (1 equivalent) was heated in a 1-liter distilling flask in a boiling water-bath until the evolution of hydrogen chloride stopped. The flask was then connected with a vacuum pump and the heating at the boiling point of water continued for about four hours longer. Water was then added and the mixture boiled to decompose the hydrochloride formed and remove the pyrogallol and benzotrichloride left. After repeatedly extracting the benzein with water until free from hydrochloric acid, it was filtered off, dried and purified by crystallization of its hydrochloride (see below). The dark red crystals of the *pure* hydrochloride were repeatedly boiled with water until all of the hydrochloric acid was removed. The benzein thus obtained was *crystalline.* It was recrystallized from a mixture of equal parts of 95% ethyl alcohol and benzene and the dark green crystals, which lost no weight when heated, were analyzed.

Anal. Subs., 0.1808, 0.1832, 0.1838: CO_2, 0.4723, 0.4778, 0.4799; H_2O, 0.0627, 0.0646, 0.0651. Calcd. for $C_{19}H_{12}O_5$: C, 71.24; H, 3.78. Found: C, 71.26, 71.15, 71.23; H, 3.88, 3.95, 3.96.

Pyrogallolbenzein does not melt, but begins to decompose at about 200°.

The benzein, purified by means of its hydrochloride as above described, was also recrystallized from methyl alcohol a number of times until the crystals were uniform. These crystals contained 3 molecules of water of

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[1] Doebner and Förster, *Ann.*, **257**, 61 (1890).