

THE PERSULFATE OXIDATION OF SALICYLIC ACID. 2,3,5-
TRIHYDROXYBENZOIC ACID¹

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The oxidation of salicylic acid to gentisic acid by persulfate ion has been described (1, 2, 3). Recently a more complete study of the products of the reaction has revealed in addition to gentisic acid the presence of 2,3-dihydroxybenzoic acid to the extent of 15% of the total product (4). This is apparently the first published report of *ortho* attack even though the *para* position was unsubstituted. Prior to this communication *ortho* substitution was reported only when the *para* position was blocked (5).

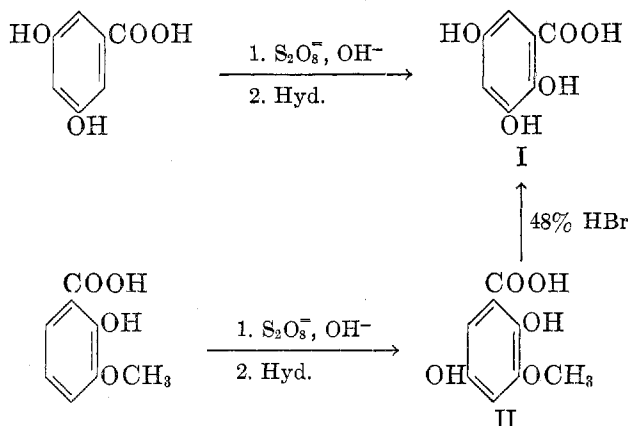
Invariably, published procedures employ equimolecular quantities of a monohydric phenol and persulfate ion, even though unreacted starting material can usually be recovered from the reaction-mixture. In these Laboratories a study of this reaction was undertaken to determine conditions for optimum yield of gentisic acid from salicylic acid. Since the effect of excess oxidizing agent has not been reported, this was undertaken first. With a moderate excess of persulfate ion, somewhat improved yields of gentisic acid were obtained but a second product melting at 225° (d.) was also formed and, indeed, predominated if large excesses of oxidizing agent were employed. This second compound was ultimately separated and identified as 2,3,5-trihydroxybenzoic acid² (6). Purification was extremely difficult, for mixtures with gentisic acid were formed from which it could not be separated by recrystallization. In experiments carried out with 300% excess persulfate ion, two mixtures were encountered which melted constantly and did not change in composition after several recrystallizations. In one, m.p. 227° (d.), the composition was approximately 80% 2,3,5-trihydroxybenzoic acid and 20% gentisic acid while the other, m.p. 209–210°, contained only 15% of the trihydroxybenzoic acid. Each mixture melted sharply and had the characteristics of a pure compound but carbon-hydrogen analyses revealed the presence of two components. A mixture of the two pure components prepared to correspond to the 15%–85% combination was found to have the same melting point and composition as that isolated from the reaction mixture. The presence of the trihydroxybenzoic acid was not indicated when equimolecular quantities of oxidizing agents were employed.

The crude acid was purified by conversion to the tripropionate followed by an acid hydrolysis of this derivative back to the acid. It formed pale yellow needles and melted with decomposition at 230–232°. Its synthesis has been ef-

¹ Presented before the Division of Medicinal Chemistry at the Cleveland Meeting of the American Chemical Society, April 1951.

² The synthesis of this compound was reported after this work was completed. The procedure reported is analogous to that given in the Experimental part.

ected from either 3,5-dihydroxybenzoic acid or 2-hydroxy-3-methoxybenzoic acid as summarized in the diagram.



EXPERIMENTAL³

Reaction of salicylic acid with varying quantities of ammonium persulfate. Variability in yields was experienced both with ammonium and potassium persulfate (4). Since the ammonium salt had a far greater solubility it was preferred in the following experiments.

A. *With three moles of ammonium persulfate.* To a solution of 138 g. of salicylic acid (1 mole) and 560 g. of sodium hydroxide (14 moles) in 2 liters of water was added a solution of 684 g. of ammonium persulfate (3 moles) in 2 liters of water. The temperature was maintained at 20–25° by occasional cooling; the addition was made over a period of five hours. The mixture was then allowed to stand for 15 hours, and was acidified by the gradual addition of 750 ml. of conc'd sulfuric acid (foaming!). The dark solution was boiled for 1 hour, treated with 20 g. of decolorizing carbon and filtered through a bed of filter cell. The cooled filtrate was extracted with five 600-ml. portions of butyl acetate. The combined extracts were dried over magnesium sulfate and concentrated at reduced pressure to a crystalline mush. Further precipitation was effected by the addition of 1 l. of Skellysolve B. The yield of product was 77.0 g., m.p. 201°(d.). After three recrystallizations from hot water, there was obtained 32.1 g. of pale yellow product, m.p. 227°(d.). A carbon-hydrogen analysis indicated a mixture of gentisic acid and 2,3,5-trihydroxybenzoic acid containing 80% of the latter.

Anal. Calc'd for $\text{C}_7\text{H}_6\text{O}_4$: C, 54.55; H, 3.92. Calc'd for $\text{C}_7\text{H}_6\text{O}_5$: C, 49.46; H, 3.56.

Found: C, 50.38; H, 3.93.

In another experiment carried out in essentially the same manner a like yield of product was obtained which melted at 207°(d.). Although this product was recrystallized from hot water five times, the melting point of 209–210° and the composition by carbon-hydrogen combustion remained unchanged. In this mixture the amount of trihydroxybenzoic acid is approximately 15%.

Anal. Calc'd for $\text{C}_7\text{H}_6\text{O}_4$: C, 54.55; H, 3.92. Calc'd for $\text{C}_7\text{H}_6\text{O}_5$: C, 49.46; H, 3.56.

Found: C, 53.73; H, 4.00.

A mixture of pure components in the ratio of 4 parts of gentisic acid to 1 part of the pure trihydroxybenzoic acid was prepared and recrystallized from water. The melting point was 209–210° and unchanged on admixture with the above product.

Anal. C, 53.99; H, 4.11.

³ Microanalyses by E. F. Shelberg and staff. All melting points are uncorrected.

B. *With two moles of ammonium persulfate.* The procedure was carried out as in A using 340 g. of sodium hydroxide (8.5 moles) and 465 g. of ammonium persulfate (2 moles). In the work-up, 35.2 g. of salicylic acid was recovered, and from the butyl acetate extract after recrystallization from water, there was obtained 45.2 g. of gentisic acid, m.p. 203-204°.

C. *With 20% excess of one mole of ammonium persulfate.* Using 160 g. of sodium hydroxide (4 moles) and 274 g. of ammonium persulfate (1.2 moles) crude yields of gentisic acid varied between 60 and 78 g. From these reactions 40-50 g. of salicylic acid could be recovered after acidification. Recrystallization raised the melting point to 202-204° indicating that any 2,3-dihydroxybenzoic acid, reported by Forrest and Petrow (4), was removed in the purification.

For the separation of the trihydroxybenzoic acid, the crude product from three such experiments was dissolved in 1000 ml. of ether and extracted with first a 150-ml. portion of a saturated sodium bisulfite solution. This was repeated with a 75-ml. portion. The aqueous extract was extracted continuously for 24 hours with ether, which removed some dissolved gentisic acid. Conc'd hydrochloric acid was added to pH 1-2 and the solution again continuously extracted with ether for 24 hours. The dark extract was dried over magnesium sulfate, treated with decolorizing carbon and filtered. The ether left 8.8 g. of a light tan solid, m.p. 224°(d.). Three recrystallizations from hot water yielded pale yellow needles decomposing at 227-228°. The analysis showed that the product was approximately 85% pure and is apparently the same mixture as in A.

Anal. Calc'd for $C_7H_6O_5$: C, 49.46; H, 3.56.

Found: C, 50.20; H, 3.88.

2,3,5-Trihydroxybenzoic acid (I). A. *From salicylic acid.* The product from part A in the preceding section, m.p. 227°(d.), was converted to the propionate by the following procedure. To a suspension of 3.0 g. of the mixture in 15 ml. of propionic anhydride was added 2 drops of conc'd sulfuric acid and it was heated on the steam bath for 15 minutes. Excess anhydride was hydrolyzed by pouring into water. The crystalline solid was recrystallized three times from dilute ethanol, at which time the m.p. was constant at 146-147°.

Anal. Calc'd for $C_{16}H_{18}O_8$: C, 56.85; H, 5.36.

Found: C, 56.81; H, 5.65.

Hydrolysis was effected by refluxing for 3 hours a mixture of 1.5 g. of this material and 30 ml. of a 1:1 mixture of methanol and conc'd hydrochloric acid. Then 50 ml. of water was added and the solution concentrated under reduced pressure to about 35 ml. The pale yellow solution was chilled and the product was recrystallized from hot water; yellow needles, m.p. 233°(d.); the yield was 0.76 g.

Anal. Calc'd for $C_7H_6O_5$: C, 49.42; H, 3.56.

Found: C, 49.73; H, 3.73.

B. *From 2-hydroxy-3-methoxybenzoic acid.* The starting material was prepared from 2-hydroxy-3-methoxybenzaldehyde according to the directions for the oxidation of vanillin to vanillic acid (7).

The usual procedure was carried out using molar quantities of 2-hydroxy-3-methoxybenzoic acid, m.p. 147-148°, and ammonium persulfate in the presence of 6 moles of alkali. In working up this reaction a great deal of resinous material was obtained. The crude product (II) weighed 25.1 g. and melted at 229°(d.). Two recrystallizations from hot water raised the m.p. to 238°(d.).

Anal. Calc'd for $C_9H_8O_6$: C, 52.20; H, 4.37.

Found: C, 51.94; H, 4.27.

A solution of 8.0 g. of the above product was boiled under reflux in 50 cc. of 48% hydrobromic acid for 3 hours. Then 50 ml. of water was added and the dark solution continuously extracted with ether for 15 hours. The extract was dried over magnesium sulfate, treated at the boiling point with decolorizing carbon and filtered. Concentration of the ether yielded 4.9 g. of solid, m.p. 224°(d.). On recrystallization from hot water the melting point was 232°(d.). For identification a small sample was converted to the tripropionate as be-

fore; m.p. 146–147°, unchanged in mixture with the corresponding product from the oxidation of salicylic acid.

C. *From 3,5-dihydroxybenzoic acid.* The usual procedure was employed with 30.8 g. of 3,5-dihydroxybenzoic acid (0.2 mole), 48 g. of sodium hydroxide (1.2 moles) and 46.5 g. of ammonium persulfate (0.2 mole). There was obtained 6.2 g. of crude product which melted at 214°(d.). This material was acetylated by heating 1 hour on the steam bath with 20 ml. of acetic anhydride and 2 drops of conc'd sulfuric acid. After pouring into water the dark crystalline solid was filtered. The crude triacetate weighed 4.5 g. and was recrystallized once from ethyl acetate-Skellysolve B and once from benzene. The m.p. was 143–144° unchanged in mixture with the acetate of the trihydroxybenzoic acid prepared from salicylic acid.

Anal. Calc'd for $C_{13}H_{12}O_9$: C, 52.44; H, 4.08.

Found: C, 52.83; H, 4.44.

SUMMARY

Oxidation of salicylic acid with persulfate ion leads to the formation of gentisic acid in fair yield. If excess persulfate is employed, 2,3,5-trihydroxybenzoic acid is formed in addition to the gentisic acid. The trihydroxybenzoic acid may predominate if sufficient oxidizing agent is present.

Two constant-melting mixtures of gentisic acid and 2,3,5-trihydroxybenzoic acid were encountered from which the components could not be separated by recrystallization.

The structure of the trihydroxybenzoic acid was confirmed by two independent syntheses.

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