

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HYNSON, WESTCOTT & DUNNING, INC., AND WASHINGTON AND LEE UNIVERSITY]

## The Halogenation of Ortho-Sulfobenzoic Anhydride

BY DANIEL TWISS AND LARKIN HUNDLEY FARINHOLT

The preparation of polyhalogenated *o*-sulfobenzoic anhydrides seemed interesting in several respects. In the first place, as starting materials for the preparation of new sulfonphthaleins, in view of their possible use as indicators, certain of these compounds have since been described by Harden and Drake.<sup>1</sup> Second, with regard to the possibility that the neutral sodium salts of some of these halogenated *o*-sulfobenzoic acids, in particular the tetraiodo derivative, might be useful as radiographic mediums: this phase of the investigation has been discussed by Macht and Twiss,<sup>2</sup> and by Keller.<sup>3</sup>

To date little is known concerning the halogenated *o*-sulfobenzoic acids. The 4-chloro acid was prepared by Roode<sup>4</sup> and the 4-bromo acid by Hübner, Post and Weiss<sup>5</sup> and by Remsen and Bayley,<sup>6</sup> by oxidizing the corresponding toluene sulfonic acid or sulfonamide.

In the present investigation, halogenated *o*-sulfobenzoic anhydrides were prepared by the halogenation of *o*-sulfobenzoic acid or its anhydride dissolved in fuming sulfuric acid, with or without the presence of some iodine as a catalyst.<sup>7</sup> This method of halogenation has also been used by Juvalta<sup>8</sup> in the preparation of di- and tetrahalogenated phthalic anhydride.

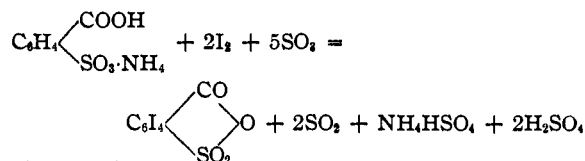
Without impairing the yield, it proved to be more convenient to use the acid ammonium salt of *o*-sulfobenzoic acid as the starting material since it is more readily available than the acid or anhydride. The acid ammonium salt may be obtained by the hydrolysis of saccharin with dilute hydrochloric acid.

By the method described above, di-, tri-, tetraiodo-; mono-, di-, tri-, tetrabromo-; and di- and tetrachloro-*o*-sulfobenzoic anhydrides were prepared.

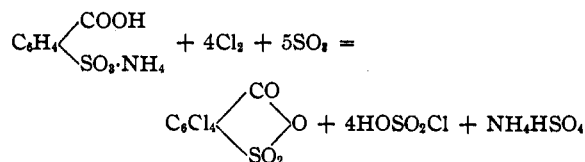
Concerning the mechanism of this halogenation

- (1) Harden and Drake, *THIS JOURNAL*, **51**, 562, 2278 (1929).
- (2) Macht and Twiss, *Proc. Soc. Exptl. Biol. Med.*, **27**, 850 (1930).
- (3) Keller, *Int. J. Med. Surg.*, **44**, 78 (1931); **45**, 258 (1932); *Med. Record*, **141**, 76 (1935); also editorial, *J. Am. Med. Assn.*, **95**, 1749 (1930).
- (4) Roode, *Am. Chem. J.*, **13**, 227, 231 (1891).
- (5) Hübner, Post and Weiss, *Ann.*, **169**, 26 (1873).
- (6) Remsen and Bayley, *Am. Chem. J.*, **8**, 230 (1886).
- (7) U. S. Patent 1,760,328 (1930).
- (8) German Patent 50,177 (1889), *Frdl.*, **2**, 93 (1889).

nothing is known, but it is probable that *o*-sulfobenzoic anhydride forms an unstable addition complex with sulfuric acid or sulfur trioxide, which facilitates the substitution of halogen. The bromination and iodination take place according to analogous equations. The hydrogen iodide and bromide produced in the reactions are oxidized by sulfur trioxide, and the halogen thus made available again for further substitution. The formation of tetraiodo-*o*-sulfobenzoic anhydride, for example, may be represented by the equation



The chlorination differs from the bromination and iodination only by the fact that the hydrogen chloride, generated in the chlorination process, is not oxidized by sulfur trioxide, but combines with it to form chlorosulfonic acid

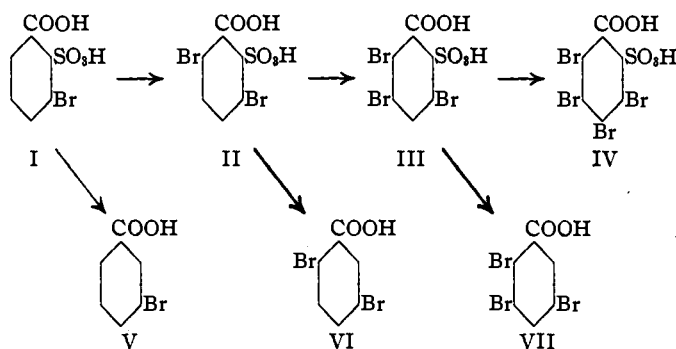


The anhydrides of the halogenated *o*-sulfobenzoic acids are crystalline substances. With the exception of the tetraiodo derivative, they react very readily with water and are converted, even by moisture in the air, into the corresponding acids.

From a theoretical point of view, it seemed important to determine in what order the halogen atoms enter the available positions. The general procedure which was followed in order to settle this question consisted in eliminating the sulfonic acid group by hydrolysis and identifying the resulting halogenated benzoic acid. The removal of the sulfonic acid group was accomplished by heating the halogenated *o*-sulfobenzoic acid with sulfuric acid containing enough water to cause the mixture to boil between 200 and 210°. This procedure could not be applied to the iodinated acids,

owing to the fact that iodine was split off and the compound destroyed. The positions assigned to the iodine atoms have therefore been based on the analogy between these compounds and the corresponding chlorinated and brominated acids.

The elimination of the sulfonic acid group from monobromo-*o*-sulfobenzoic acid yielded 3-bromobenzoic acid (V), while the dibrominated acid produced 2,5-dibromobenzoic acid (VI). From this it may be concluded that the sulfonic acids were 3-bromo- (I) and 3,6-dibromo-2-sulfobenzoic acid (II). Tribromo-*o*-sulfobenzoic acid yielded 2,3,5-tribromobenzoic acid (VII), so that the sulfonic acid was 3,5,6-tribromo-2-sulfobenzoic acid (III). Tetrabromo-*o*-sulfobenzoic acid should naturally be represented by formula IV.



By the same method dichloro-*o*-sulfobenzoic acid yielded 2,5-dichlorobenzoic acid, besides a small quantity of *p*-dichlorobenzene. The formation of the latter compound is due to the fact that not only is the sulfonic acid group removed, but in addition the carboxyl group is also partly split off.

The above facts show that the first halogen atom substitutes in the position meta to the carboxyl and ortho to the sulfonic acid group, and the second halogen atom in the position meta to the sulfonic acid and ortho to the carboxyl group. The third halogen atom enters in the second position meta to the carboxyl group, and the fourth in the remaining second meta position with regard to the sulfonic acid group. In the preparation of the mono-, di- and tri-halogenated *o*-sulfobenzoic anhydrides by direct halogenation, no evidence of the formation of isomers has been found.

It was noted that when an aqueous 10% solution of the neutral sodium salt of tetraiodo-*o*-sulfobenzoic acid was exposed to sunlight, a slow decomposition took place with liberation of iodine and formation of some sodium iodide. A small

deposit of crystals consisted of the acid sodium salt of tetraiodo-*o*-sulfobenzoic acid, while the supernatant liquid contained a mixture of the sodium salts of tri- and tetraiodo-*o*-sulfobenzoic acids. The salt of the triiodo acid was converted into the anhydride, which was shown to be identical with 3,5,6-triiodo-*o*-sulfobenzoic anhydride, obtained by direct iodination of *o*-sulfobenzoic acid.

The neutral ammonium salt of the same triiodo acid was precipitated when a concentrated ammoniacal solution of tetraiodo-*o*-sulfobenzoic acid was treated with hydrogen sulfide. The filtrate contained, besides some sulfur and ammonium iodide, the neutral ammonium salt of a diiodo-*o*-sulfobenzoic acid. Its anhydride, obtained by the action of thionyl chloride, forms colorless crystals which are different from the 3,6-diiodo-*o*-sulfobenzoic anhydride prepared by direct iodination of *o*-sulfobenzoic acid. The position of the iodine atoms has not been determined.

## Experimental

### Halogenation of *o*-Sulfobenzoic Acid

The preparation of each of the following *o*-sulfobenzoic anhydrides was carried out in a three-necked flask provided with a monel metal stirrer and a reflux condenser. The latter was connected with an absorption tower through which circulated water, in order to remove escaping sulfur dioxide and trioxide as well as small quantities of halogen.

**3,4,5,6-Tetraiodo-*o*-sulfobenzoic Anhydride.**—In 1000 g. of 60% fuming sulfuric acid, 160 g. of *o*-sulfobenzoic acid was dissolved by heating in an oil-bath kept at 60–70°. To this solution, while stirring vigorously, 400 g. of iodine was gradually added. This caused foaming, especially during the latter part of the reaction. After the addition of the iodine, the temperature of the oil-bath was raised slowly to 110–120° and the heating continued for twenty-four hours. The reaction was finished by raising the temperature to 170–175° for one hour. By this time the reaction mass had become too thick for further stirring. After cooling, the reaction mass was mixed with 600 cc. of glacial acetic acid and, after cooling again, filtered by suction on a glass wool pad and washed with glacial acetic acid.

3,4,5,6-Tetraiodo-*o*-sulfobenzoic anhydride was thus obtained as a yellow substance, having no melting point but gradually decomposing in the neighborhood of 300°. The yield of the crude product was 400 g., or 75%.

In a similar manner, the anhydride of *o*-sulfobenzoic acid and its acid ammonium salt were both iodinated with the same results, the yield being approximately 70% in each case.

Free *o*-sulfobenzoic acid may be obtained from the anhydride by boiling with water, which slowly hydrolyzes it. The acid is very soluble in water. Its mono- and disodium salts are prepared by adding the calculated quantities of sodium hydroxide solution to the aqueous solution of the

acid. The acid sodium salt is pale yellow and fairly insoluble in water, while the neutral sodium salt is dark yellow and quite soluble. Both are obtained in crystalline form. The acid salt precipitates when the aqueous solution of the neutral salt is acidified with hydrochloric acid.

A good method for preparing pure tetraiodo-*o*-sulfobenzoic anhydride from the sodium salts is to heat either the mono- or disodium salt of the acid with an excess of concentrated sulfuric acid in an oil-bath at 150–165° for one hour. The mixture is then poured on cracked ice and the anhydride filtered off. It is first washed thoroughly with water to free the anhydride of sulfuric acid, then with glacial acetic acid, and finally with a mixture of equal volumes of acetic anhydride and glacial acetic acid, and dried in an oven. It may also be obtained readily from the free acid by treating with acetic anhydride.

The anhydride is very insoluble in most solvents. It can, however, be crystallized from acetic anhydride, in which it is very sparingly soluble.

*Anal.* Calcd. for  $C_7I_4SO_4$ : I, 73.81; S, 4.66. Found: I, 73.78; S, 4.58.

**3,4,5,6-Tetrabromo-*o*-sulfobenzoic Anhydride.**—In the same manner as described above, 165 g. of *o*-sulfobenzoic acid was dissolved in 1000 g. of 60% fuming sulfuric acid. The bromination was carried out by heating the oil-bath to 80–100° and slowly adding 100 cc. of bromine below the surface while stirring. In order to avoid loss of bromine, the rate of addition was regulated according to the rate of absorption. The absorption of bromine went very slowly so that the reaction required a long period of time, between two or three days. In several experiments 10 g. of iodine was added as a catalyst. It has not definitely been established whether this increases the rate of reaction, but it is certain that good results were also obtained when the catalyst was omitted. After all the bromine had been added, the temperature of the oil-bath was slowly raised to 160–170°. On cooling, tetrabromo-*o*-sulfobenzoic anhydride crystallized out and was separated from the sulfuric acid by filtration on a glass wool pad. It was washed free of sulfuric acid with glacial acetic acid containing 25% acetic anhydride. The yield of crude anhydride thus obtained was about 75%. It was crystallized from glacial acetic acid containing 25% acetic anhydride.

3,4,5,6-Tetrabromo-*o*-sulfobenzoic anhydride forms colorless crystals melting at 216–217°.

*Anal.* Calcd. for  $C_7Br_4SO_4$ : Br, 63.97; S, 6.42. Found: Br, 63.44; S, 6.42.

It is much less stable toward water than the tetraiodo derivative and even takes up moisture from the air to change into tetrabromo-*o*-sulfobenzoic acid with considerable evolution of heat. The latter substance is extremely soluble in water. The addition of acetic anhydride will convert the acid back into the anhydride.

Instead of using *o*-sulfobenzoic acid as the starting material in the above preparation, the acid ammonium salt of *o*-sulfobenzoic acid and *o*-sulfobenzoic anhydride were used in several experiments with the same results.

**3,5,6-Tribromo-*o*-sulfobenzoic Anhydride.**—As a by-product in the preparation of the tetrabromo derivative, some 3,5,6-tribromo-*o*-sulfobenzoic anhydride was obtained. It is less soluble in the acetic acid-acetic anhydride mixture than the tetrabromo derivative and was

separated from the latter by fractional crystallization. It forms colorless crystals melting at 224°.

*Anal.* Calcd. for  $C_7HBr_3SO_4$ : Br, 56.97; S, 7.62. Found: Br, 56.87; S, 7.57.

**3,4,5,6-Tetrachloro-*o*-sulfobenzoic Anhydride.**—To a solution of 51 g. of *o*-sulfobenzoic acid in 300 g. of 60% fuming sulfuric acid, 2 g. of iodine was added as a catalyst and a slow current of chlorine was passed through the solution, the oil-bath being kept at a temperature of 70–90°. After no more chlorine was absorbed, the reaction was completed by raising the temperature of the oil-bath to 150–160°. Tetrachloro-*o*-sulfobenzoic anhydride crystallized from the ice-cooled solution and was separated from the mother liquor by filtration. The crude anhydride was washed with an acetic acid-acetic anhydride mixture and was crystallized from a mixture of the same composition. Concentration of the liquids used for washing and crystallization gave a second crop of crystals. The total yield was 67%.

The anhydride was also obtained in about the same yield when the preparation was carried out with *o*-sulfobenzoic anhydride or the acid ammonium salt of *o*-sulfobenzoic acid.

3,4,5,6-Tetrachloro-*o*-sulfobenzoic anhydride forms colorless crystals, melting at 158–159°. It is even more sensitive toward the action of water than the tetrabromo derivative.

*Anal.* Calcd. for  $C_7Cl_4SO_4$ : Cl, 44.06; S, 9.96. Found: Cl, 43.83; S, 9.75.

**3,5,6-Triiodo-*o*-sulfobenzoic Anhydride.**—Using the same procedure as described above, 191 g. of iodine was added to a solution of 92 g. of *o*-sulfobenzoic anhydride in 500 g. of 60% fuming sulfuric acid while the oil-bath was kept at a temperature of 60–70°. The reaction was terminated by raising the temperature to approximately 170° for one hour. The yield of the crude triiodo-*o*-sulfobenzoic anhydride, thus obtained, was about 65%. This product contained a small amount of tetraiodo-*o*-sulfobenzoic anhydride.

A pure sample of triiodo-*o*-sulfobenzoic anhydride was obtained by boiling some of the crude anhydride with acetic acid to which a small amount of water had been added. It dissolved to form the free acid and the anhydride was then precipitated by adding an excess of acetic anhydride. The triiodo-*o*-sulfobenzoic anhydride was crystallized from a glacial acetic acid-acetic anhydride mixture, the relatively insoluble tetraiodo derivative remaining behind.

3,5,6-Triiodo-*o*-sulfobenzoic anhydride is obtained as yellow crystals melting at 287–288°.

*Anal.* Calcd. for  $C_7HI_3SO_4$ : I, 67.77; S, 5.71. Found: I, 67.75; S, 5.67.

**3,6-Diiodo-*o*-sulfobenzoic Anhydride.**—In a mixture of 400 g. of 60% fuming sulfuric acid and 200 g. of 95% sulfuric acid (which gives about a 40% fuming sulfuric acid), 109.5 g. of the dry acid ammonium salt of *o*-sulfobenzoic acid was dissolved. In the course of three days, at an oil-bath temperature of about 80°, 127 g. of iodine was added. The temperature was then raised to 105–110° and stirring continued for forty-eight hours in order to ensure complete reaction of the iodine. Finally, the temperature was gradually raised to 180° to eliminate part of the excess

sulfur trioxide. The cooled reaction mixture was poured on cracked ice and the anhydride allowed to hydrolyze to the acid form. The amount of sulfate ions was determined quantitatively in a small sample, and the calculated amount of barium hydroxide, dissolved in hot water, added to the main solution. The filtrate from this then contained the acid ammonium salt of diiodo-*o*-sulfobenzoic acid. By evaporating to dryness in the presence of an excess of ammonia, the neutral ammonium salt was obtained in a yield of about 85%.

In order to convert the neutral ammonium salt into the anhydride, it was refluxed for four hours with a solution of an excess of thionyl chloride in benzene. The precipitate of ammonium chloride was extracted several times with hot benzene containing some thionyl chloride. The combined filtrates yielded mainly 3,6-diiodo-*o*-sulfobenzoic anhydride along with small amounts of the triiodo derivative as well as a product of lower iodine content which could not be purified. The 3,6-diiodo compound was obtained by fractional crystallization in a 55% yield. No isomeric diiodo-*o*-sulfobenzoic anhydride could be isolated.

Crystallized from dry benzene, or a mixture of glacial acetic acid and acetic anhydride, 3,6-diiodo-*o*-sulfobenzoic anhydride forms faintly yellow crystals melting at 243–245°.

*Anal.* Calcd. for  $C_7H_2I_2SO_4$ : I, 58.23; S, 7.35. Found: I, 58.19; S, 7.29.

The anhydride may also be prepared from the neutral as well as from the acid ammonium salt by heating with concentrated sulfuric acid at 150° for one hour. It is isolated by pouring the cooled solution on cracked ice, filtering off the anhydride rapidly, dissolving the moist product in glacial acetic acid and precipitating it by addition of acetic anhydride.

**3,6-Dibromo-*o*-sulfobenzoic Anhydride.**—At an oil-bath temperature of 50–60°, 109.5 g. of the acid ammonium salt of *o*-sulfobenzoic acid dissolved in 600 g. of 60% fuming sulfuric acid was brominated by adding 80 g. of bromine in the course of fifty hours. The reaction was finished by raising the temperature to 170–180° for one hour. The cooled reaction mass was poured on ice and the neutral ammonium salt isolated by the same procedure as that described for the 3,6-diiodo anhydride. It was obtained in a yield of 80%. The anhydride was prepared by the action of thionyl chloride in benzene solution in the same manner as above. 3,6-Dibromo-*o*-sulfobenzoic anhydride hydrolyzes readily, even in moist air.

3,6-Dibromo-*o*-sulfobenzoic anhydride crystallizes from benzene containing a little thionyl chloride as colorless crystals. Calcd. at 167–168°.

*Anal.* Calcd. for  $C_7H_2Br_2SO_4$ : Br, 46.75; S, 9.38. Found: Br, 46.93; S, 9.05.

3,6-Dibromo-*o*-sulfobenzoic acid is not changed back into its anhydride under the influence of acetic anhydride, unlike most of the other halogenated *o*-sulfobenzoic acids, but the conversion may be accomplished by the action of thionyl chloride.

**3,6-Dichloro-*o*-sulfobenzoic Anhydride.**—A slow current of chlorine was passed into a solution of 109.5 g. of the acid ammonium salt of *o*-sulfobenzoic acid dissolved in 400 g. of 60% fuming sulfuric acid at an oil-bath temperature of 60–65°. The reaction was completed when the increase

in weight of the reaction mass had reached 70 g. The excess of sulfur trioxide was converted into chlorosulfonic acid by passing dry hydrogen chloride gas into the solution and was eliminated by distillation from a retort. On cooling, 3,6-dichloro-*o*-sulfobenzoic anhydride crystallized from the remaining solution. Recrystallized from a glacial acetic acid-acetic anhydride mixture, it forms colorless crystals melting at 121–122°. It may also be purified by adding ligroin to the solution of the crude product in dry toluene. The compound was obtained in a yield of 40–45%. It hydrolyzes very readily when exposed to moist air.

*Anal.* Calcd. for  $C_7H_2Cl_2SO_4$ : Cl, 28.03; S, 12.67. Found: Cl, 27.80; S, 12.59.

**3-Bromo-*o*-sulfobenzoic Anhydride.**—In the course of fifty hours, 40 g. of bromine was added to a solution of 109.5 g. of the dry acid ammonium salt of *o*-sulfobenzoic acid in 600 g. of 60% fuming sulfuric acid at an oil-bath temperature of 50–60°. The temperature was then gradually raised to 180°, and then allowed to cool. After standing for one week, 17 g. of 3,6-dibromo-*o*-sulfobenzoic anhydride had separated. The remaining solution was poured on cracked ice and the neutral ammonium salt isolated in the same manner already described for the diiodo derivative. The reaction yielded 130 g. of neutral ammonium salt from which 34 g. of 3-bromo-*o*-sulfobenzoic anhydride was obtained. In view of the low yield, the possibility that an isomeric monobromo derivative is formed in the reaction should be taken into account. None was isolated, however.

3-Bromo-*o*-sulfobenzoic anhydride crystallizes from benzene containing some thionyl chloride to form colorless needles, melting at 175–176°. It is very sensitive toward moisture.

*Anal.* Calcd. for  $C_7H_2BrSO_4$ : Br, 30.39; S, 12.19. Found: Br, 30.16; S, 12.04.

#### Determination of the Positions of the Halogen Atoms

The method of determining the positions of the halogen atoms in the halogenated *o*-sulfobenzoic acids consisted in the elimination of the sulfonic acid groups to form halogenated benzoic acids of known constitution. These reactions were carried out in the following manner.

The halogenated *o*-sulfobenzoic anhydride was converted into the corresponding acid by heating with some water, an equal volume of concentrated sulfuric acid was then added and water distilled off until the boiling point of the mixture had reached a temperature of 200–210°. It was then refluxed for several hours at this temperature and again distilled, this time collecting the distillate. The halogenated benzoic acid was carried over with the water.

By the above method, tribromo-*o*-sulfobenzoic acid yielded 2,3,5-tribromobenzoic acid, m. p. 185–187°. The methyl ester of the latter was prepared and gave a melting point of 77°. Dibromo-*o*-sulfobenzoic acid gave 2,5-dibromobenzoic acid, m. p. 151–152°, and monobromo-*o*-sulfobenzoic acid gave 3-bromobenzoic acid, m. p. 155°. Dichloro-*o*-sulfobenzoic acid yielded 2,5-dichlorobenzoic acid, m. p. 151–152°, along with a small quantity of *p*-dichlorobenzene, m. p. 53°.

Attempts to convert the iodinated *o*-sulfobenzoic acids into the corresponding iodobenzoic acids were unsuccessful

since the acids were destroyed completely under the conditions of the reaction.

#### Action of Ammonium Sulfide on Tetraiodo-*o*-sulfobenzoic Acid

A concentrated solution of tetraiodo-*o*-sulfobenzoic acid was prepared by boiling 22.4 g. of the corresponding anhydride with 50 cc. of water. Fifty cc. of concentrated aqueous ammonia was then added (causing the neutral ammonium salt to precipitate partially), the solution was saturated with hydrogen sulfide and allowed to stand for twenty-four hours. The white precipitate thus obtained in a yield of 11.5 g. was the neutral ammonium salt of triiodo-*o*-sulfobenzoic acid. It was crystallized from water.

*Anal.* Calcd. for  $C_7H_5O_6I_3N_2S$ : I, 62.02; S, 5.22; N, 4.56. Found: I, 61.98; S, 5.26; N, 4.80.

When heated with concentrated sulfuric acid at 160° for one hour, the neutral ammonium salt was converted into the anhydride of triiodo-*o*-sulfobenzoic acid. The cooled sulfuric acid mixture was poured on cracked ice and, after washing with water, the moist yellow solid was dissolved in hot glacial acetic acid. The anhydride was precipitated again by adding acetic anhydride. It is a pale yellow substance, melting at 287–288°, and identical with the 3,5,6-triiodo-*o*-sulfobenzoic anhydride obtained by direct iodination. A mixed melting point with the latter substance did not show a depression.

After the white crystals of the neutral ammonium salt of 3,5,6-triiodo-*o*-sulfobenzoic acid were filtered off, a yellow solution remained. It was evaporated to dryness and extracted with water. The residue consisted of 1.3 g. of sulfur. The evaporated extract yielded 6.4 g. of an alcohol-soluble portion, which was shown to be ammonium iodide. The analysis of the alcohol-insoluble fraction, consisting of 5.7 g. of a white substance, showed it to be the diammonium salt of a diiodo-*o*-sulfobenzoic acid.

*Anal.* Calcd. for  $C_7H_9O_6I_2N_2S$ : I, 52.02; S, 6.57; N, 5.74. Found: I, 51.78; S, 6.79; N, 5.9.

Treatment with concentrated sulfuric acid at 150° did not produce an anhydride as in the case of the 3,6-diiodo derivative, but a diiodo-*o*-sulfobenzoic anhydride was apparently obtained by refluxing the diammonium salt with thionyl chloride for several hours. It dissolved in the excess of thionyl chloride and was isolated by separating the solution from the precipitate of ammonium chloride and evaporating the thionyl chloride. It was dissolved in water, the solution decolorized with charcoal, and again evaporated to dryness. The residue was treated with acetic anhydride and recrystallized several times from that solvent. In this manner, a diiodo-*o*-sulfobenzoic anhydride was isolated, different from the one obtained by direct iodination. The compound melted at 221–223°. The position of the iodine atoms was not determined.

*Anal.* Calcd. for  $C_7H_7I_2SO_4$ : I, 58.23; S, 7.35. Found: I, 57.97; S, 7.27.

Our thanks are due to Mr. Grant Spurrier for carrying out much of the analytical work.

#### Summary

1. Mono-, di-, tri- and tetrahalogeno substitution products of *o*-sulfobenzoic anhydride were prepared by halogenation in fuming sulfuric acid.

2. The positions of the halogen atoms were determined by eliminating the sulfonic acid group by hydrolysis and identifying the resulting halogenated benzoic acids.

BALTIMORE, MARYLAND  
LEXINGTON, VIRGINIA

RECEIVED JUNE 1, 1936

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY]

## A Study of Some Substituted Hydroxybenzyl Alcohols<sup>1</sup>

BY BROWN DUNNING, JR., FITZGERALD DUNNING AND E. EMMET REID

As saligenin (*o*-hydroxybenzyl alcohol) has three distinct types of physiological action, anesthetic, antispasmodic, and antiseptic, it seemed desirable to prepare a number of its derivatives in which one or more of these might be accentuated and to study these in connection with the derivatives, homologs and analogs already known to see how these properties are altered by changes of structure and composition. It was also of interest to find out how far the physiological activities of these compounds can be correlated with their physical properties, particularly their solu-

bilities and partition coefficients. Eight new compounds have been prepared and studied along with ten that were already known. These include halogen and alkyl substituted saligenins and halogen substituted *m*- and *p*-hydroxybenzyl alcohols.

The unsubstituted hydroxybenzyl alcohols were made by the reduction of the corresponding hydroxybenzaldehydes through the use of the Adams platinum catalyst.<sup>2</sup> The halogen derivatives of these were prepared by direct halogenation. The alkyl derivatives were synthesized from various

(1) From the Ph.D. dissertation of Brown Dunning, Johns Hopkins University, 1934. Original manuscript received November 26, 1935.

(2) Adams, "Organic Syntheses," Vol. VIII, Wiley and Sons, Inc., New York, 1928.