[CONTRIBUTION FROM THE LABORATORIES OF HYNSON, WESTCOTT AND DUNNING AND THE UNIVERSITY OF MARYLAND]

A NEW SERIES OF SULFONEPHTHALEINS

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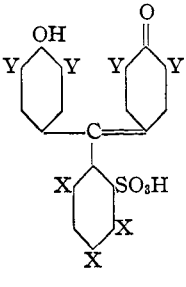
The sulfonephthaleins together with the phthaleins constitute a group of compounds that has long been of much interest. Since the synthesis of the first members of the former class by Remsen and his co-workers,[1] they have been extensively used both as indicators and as diagnostic aids in clinical and experimental medicine. Orndorff and his students,[2] Clark and Lubs,[3] Cohen[4] and others have made important contributions to this field of chemistry.

The sulfonephthaleins, in general, and phenolsulfonephthaleins in particular, have been much used as a means of testing the renal function, since they are eliminated from the blood stream after intravenous injection almost quantitatively through the kidneys.[5] Those phenolphthaleins, on the other hand, which contain four halogens in the phthalic acid residue are eliminated from the blood stream through the liver and hence are used as tests of hepatic function.[6]

Having these facts in mind, it was thought that a study of the chemical behavior and pharmacological action of those sulfonephthaleins having four halogens in the *o*-sulfobenzoic acid part of the molecule would be of interest. The recent synthesis of the di- and tetra-halogenated *o*-sulfobenzoic acids and their anhydrides by Twiss[7] has made possible the preparation of such a series of compounds. The purpose of the present paper is to describe a limited number of compounds of this class. Their general formula may be represented as shown in the accompanying diagram, where X is any halogen and Y may be hydrogen or halogen.



No attempt has been made to prepare all the possible members of this class, the authors having been content to limit themselves to the following compounds: phenoltetrachlorosulfonephthalein, phenoltetrabromosulfonephthalein, *o*-cresoltetrachlorosulfonephthalein, *o*-cresoltetrabromosulfone-

[1] (a) Remsen, *Am. Chem. J.*, **6**, 180 (1884); (b) Remsen and Saunders, *ibid.*, **17**, 352 (1895); (c) Sohon, *ibid.*, **20**, 257 (1898).

[2] (a) Orndorff and Sherwood, THIS JOURNAL, **45**, 486 (1923); (b) Orndorff and Shapiro, *ibid.*, **46**, 2856 (1924), and others.

[3] (a) Clark and Lubs, *J. Wash. Acad. Sci.*, **5**, 609 (1915); (b) **6**, 481, 483 (1916).

[4] (a) Cohen, *U. S. Pub. Health Reports*, **38**, 199 (1923); **41**, (b) 53, (c) 3015 (1926).

[5] Rowntree and Geraghty, *J. Pharmacol.*, **1**, 579 (1910).

[6] (a) S. M. Rosenthal, *J. Pharmacol.*, **24**, 385 (1922); (b) Rosenthal and White, *J. Am. Med. Assocn.*, **84**, 1112 (1925).

[7] Twiss, U. S. Patent Application No. 267,473, filed April 4, 1928.

phthalein, tetrabromophenoltetrabromosulfonephthalein, tetrabromophenoltetrachlorosulfonephthalein, dibromo-*o*-cresoltetrabromosulfonephthalein, dibromo-*o*-cresoltetrachlorosulfonephthalein, dibromophenoltetrabromosulfonephthalein and *o*-cresoltetra-iodosulfonephthalein. Phenoltetra-iodosulfonephthalein has also been prepared but is not included in the present investigation. In naming these compounds the author has adopted the usual custom, that is, halogen preceding the phenol indicating its presence in the phenolic part of the molecule and halogen following the phenol indicating its presence in the *o*-sulfobenzoic acid part.

Experimental Part

Preparation of Phenoltetrachlorosulfonephthalein.—Eleven g. of phenol was heated to 110° in a small three-necked flask; 16.1 g. of tetrachloro-*o*-sulfobenzoic acid anhydride was then added and the mixture stirred until all had dissolved. Eight cc. of fuming stannic chloride was then added and the temperature raised to 120–130°. Heating was continued at this temperature for eight hours, with mechanical stirring. The melt was then poured into water and steam distilled to remove excess phenol. After distillation the dye solution was made alkaline with sodium carbonate and allowed to stand overnight. It was then filtered to remove the precipitated tin and poured into 1:1 hydrochloric acid with rapid mechanical stirring. The crude dye was thus precipitated as a red or pink amorphous powder. It was filtered off, redissolved in sodium carbonate, filtered and again precipitated with hydrochloric acid; yield, 11 grams (45%). A small portion was then crystallized from hot benzene, in which it is difficultly soluble, dried and analyzed.

Anal. Calcd. for $C_{19}H_{10}O_5Cl_4S$: Cl, 28.85; S, 6.50. Found: Cl, 28.64; S, 6.58.

Preparation of Tetrabromophenoltetrachlorosulfonephthalein.—Four and nine-tenths g. of crude phenoltetrachlorosulfonephthalein prepared as described above was suspended in 50 cc. of glacial acetic acid. A slight excess over the calculated amount of bromine dissolved in glacial acetic acid was introduced through a dropping funnel while the suspension was stirred mechanically. The suspended dye slowly dissolved upon addition of the bromine and when all had been added the flask was allowed to stand uncorked at room temperature overnight. A small crop of crystals settled out; these were filtered off, the solution wsa warmed on a water-bath and the hydrobromic and some of the acetic acid removed by passing a current of air through the solution. When the solution had been reduced to about half its original volume, the flask was stoppered and allowed to cool in the ice box. The brominated dye crystallizes as salmon-colored crystals; yield 6.5 (81%). After two recrystallizations from acetic acid a sample analyzed as follows.

Anal. Calcd. for $C_{19}H_6O_5Cl_4Br_4S$: Cl, 17.56; Br, 39.58; S, 3.96. Found: Cl, 17.10; Br, 39.90; S, 3.61.

Preparation of Phenoltetrabromosulfonephthalein.—Fifteen g. of phenol was heated in an oil-bath for half an hour at 110°, 25.85 g. of the anhydride of tetrabromo-*o*-sulfobenzoic acid was added, the mixture well stirred, 8 cc. of fuming stannic chloride added and the mixture heated to 130–140° for seven hours. The solid melt thus obtained was subjected to steam distillation, treated with sodium carbonate and hydrochloric acid as in the case of the tetrachloro compound, dried and weighed; yield, 20 g. (60%). A small portion was repeatedly recrystallized from hot benzene as before.

Anal. Calcd. for $C_{19}H_{10}O_5Br_4S$: Br, 47.70; S, 4.70. Found: Br, 47.56; S, 4.55, 4.71.

Preparation of Tetrabromophenoltetrabromosulfonephthalein.—Six and seven-tenths g. of the phenoltetrabromosulfonephthalein prepared as above was suspended in 50 cc. of glacial acetic acid, and 7 g. of bromine in 20 cc. of glacial acetic acid was added slowly with constant stirring. The solution was allowed to stand at room temperature overnight; hydrobromic acid was then removed by a current of air, the solution cooled, filtered, the cream-colored crystals recrystallized twice from acetic acid, dried at 80° and analyzed.

Anal. Calcd. for $C_{19}H_6O_5Br_8S$: Br, 64.77; S, 3.23. Found: Br, 64.68, 64.48; S, 3.41, 3.40.

Preparation of *o*-Cresoltetrachlorosulfonephthalein.—Twelve g. of *o*-cresol was heated just as in the previous condensations, and 16.1 g. of the anhydride of tetrachloro-*o*-sulfobenzoic acid added. No condensing agent was used, previous experience having shown it to be unnecessary in most condensations with *o*-cresol. The mixture was heated for two hours at 120–130° and then the temperature was slowly raised (one hour) to 160° and maintained at this point for an additional two hours. Purification was carried out as in previous condensations, the crude dye being crystallized from hot benzene in greenish-red iridescent plates; yield, 19 g. (73%). After one recrystallization, analysis gave the following results.

Anal. Calcd. for $C_{21}H_{14}O_5Cl_4S$: Cl, 27.27; S, 6.15. Found: Cl, 27.16; S, 6.14.

Preparation of Dibromo-*o*-cresoltetrachlorosulfonephthalein.—Six g. of *o*-cresoltetrachlorosulfonephthalein prepared as above was suspended in 50 cc. of glacial acetic acid and the calculated amount of bromine in glacial acetic acid added as before. In several minutes a large crop of white crystals had formed. On standing overnight in the ice box another portion crystallized out. The portions were united and recrystallized three times from acetic acid.

Anal. Calcd. for $C_{21}H_{12}O_5Br_2Cl_4S$: Br, 23.57; Cl, 20.92; S, 4.72. Found: Br, 23.92; Cl, 20.61; S, 4.74.

Preparation of *o*-cresoltetrabromosulfonephthalein.—The condensation was carried out as in the case of the *o*-cresoltetrachloro compound, using 14 g. of *o*-cresol and 25 g. of the anhydride of tetrabromo-*o*-sulfobenzoic acid; yield, 28 g. (82%). Repeated crystallization from benzene gave a product which analyzed as follows.

Anal. Calcd. for $C_{21}H_{14}O_5Br_4S$: Br, 45.80; S, 4.58. Found: Br, 45.48; S, 4.56.

Preparation of Dibromo-*o*-cresoltetrabromosulfonephthalein.—Fourteen g. of the material just described was suspended in 100 cc. of glacial acetic acid, the calculated amount of bromine in glacial acetic acid added and the mixture treated as in previous brominations. In this case, however, crystallization from acetic acid did not give a pure product, so the crystals were dissolved in a small amount of hot acetone, 5 g. of "Norite" and 2 cc. of acetic acid added and the mixture boiled for one hour under a reflux condenser. The solution was then filtered while hot and concentrated by evaporation on the water-bath. The dye came out as a pink amorphous powder, which was dried and again crystallized from acetic acid. By this method a product giving the following analysis was obtained.

Anal. Calcd. for $C_{21}H_{12}O_5Br_6S$: Br, 56.03; S, 3.73. Found: Br, 56.12; S, 3.65.

Preparation of *o*-Cresoltetra-iodosulfonephthalein.—Eighteen g. of *o*-cresol was heated in an oil-bath to 110–120° and 20 g. of tetra-iodo-*o*-sulfobenzoic acid anhydride was added and the mixture well stirred. Ten cc. of stannic chloride and 0.5 cc. of sulfuric acid were then added and the mixture heated at 120–130° for five hours, being stirred mechanically. The melt was then poured into water and steam distilled to remove excess cresol. The crude dye was then repeatedly dissolved in dilute sodium

hydroxide and precipitated by hydrochloric acid. A small fraction was recrystallized several times from acetic acid, in which it is only slightly soluble.

Anal. Calcd. for $C_{21}H_{14}O_5I_4S$: I, 57.32; S, 3.61. Found: I, 57.25; S, 3.61.

Preparation of Dibromophenoltetrabromosulfonephthalein.—Twenty g. of *o*-bromophenol (Eastman) was heated at 110° and 26 g. of tetrabromo-*o*-sulfobenzoic acid anhydride was added. When the anhydride had completely dissolved, 5 cc. of stannic chloride was added and the temperature raised to 120–130° and kept at this point for twelve hours. Excess bromophenol was removed by steam distillation and the dye partially purified by repeated solution in sodium carbonate and precipitation by means of hydrochloric acid. The dye is very soluble in water and appreciably soluble in dilute hydrochloric acid. A small sample was crystallized from acetic acid and analyzed.

Anal. Calcd. for $C_{19}H_8O_5Br_6S$: Br, 58.90; S, 3.86. Found: Br, 58.69; S, 3.91.

Discussion

Since the unhalogenated analogs of all these compounds are useful indicators for the determination of hydrogen-ion concentration, it was thought that a study of the useful P_H range of these compounds would be of value. The method employed in each case was as follows: 0.1 g. of the dye was thoroughly ground in a small glass mortar with sufficient $N/20$ sodium hydroxide to form the monosodium salt. The resulting solution was diluted to 250 cc. to give a 0.04% aqueous solution of the sodium salt.[3] One-half cc. of this solution was then added to 10 cc. of various buffers from P_H 1.0 to 9.6 and the color ranges carefully observed. The indicators were found to have the ranges and colors shown in the accompanying table (Table I).

TABLE I

COLOR CHANGE AND USEFUL P_H RANGE OF TETRAHALOGENATED SULFONEPHTHALEINS

Name	P_H interval	Color change
Phenoltetrabromosulfonephthalein	6.6 to 8.2	Yellow to purple
Phenoltetrachlorosulfonephthalein	6.6 to 8.2	Yellow to purple[a]
o-Cresoltetrabromosulfonephthalein	7.2 to 8.8	Yellow–violet–purple
o-Cresoltetrachlorosulfonephthalein	7.2 to 8.8	Yellow–violet–purple
Tetrabromophenoltetrabromosulfonephthalein	3.0 to 4.6	Yellow–green–blue
Tetrabromophenoltetrachlorosulfonephthalein	3.0 to 4.6	Yellow–green–blue[a]
Dibromo-*o*-cresoltetrabromosulfonephthalein	5.2 to 6.8	Yellow–green–violet
Dibromo-*o*-cresoltetrachlorosulfonephthalein	5.2 to 6.8	Yellow–green–violet[a]
Phenoltetra-iodosulfonephthalein (crude)	6.4 to 8.0	Yellow to red
o-Cresoltetra-iodosulfonephthalein	7.0 to 8.6	Yellow to purple
Dibromophenoltetrabromosulfonephthalein	5.6 to 7.2	Yellow to purple

[a] Lighter shades.

Table II shows the useful P_H interval of their unhalogenated analogs. A study of the two tables brings out some very interesting facts. The nature of the halogen in the *o*-sulfobenzoic acid part seems to affect the color only very slightly. The only difference is that in the case of the chlorine compounds the shades are somewhat lighter. A more important

[3] Clark and Lubs, "Determination of Hydrogen Ions," Williams and Wilkins Company, Baltimore, Maryland, **1922**, 2nd ed.

observation, however, is that the replacement of four hydrogens in the *o*-sulfobenzoic acid part of the molecule by halogens does not materially change the useful *P*H range of the compounds. In each case the useful range is practically the same for the two series, although the colors are somewhat different. The halogenated compounds show an additional extremely acid range not measurable by the ordinary buffers. This range might possibly prove useful since in strong acid (*N* HCl) they are red shading to yellow at *P*H's in the vicinity of 2.0.

TABLE II[a]

COLOR CHANGE AND *P*H RANGE OF THE UNHALOGENATED ANALOGS OF THOSE COMPOUNDS SHOWN IN TABLE I

Name of indicator	Trade name	Concn., %	Interval in *P*H	Color Acid	Color Alkaline
Phenolsulfonephthalein	Phenol red	0.02	6.8–8.6	Yellow	Red
Tetrabromophenolsulfonephthalein	Brom phenol blue	.04	3.0–4.6	Yellow	Blue
o-Cresolsulfonephthalein	Cresol red	.02	7.2–8.8	Yellow	Red
Dibromo-*o*-cresolsulfonephthalein	Brom cresol purple	.04	5.2–6.8	Yellow	Purple

[a] Adapted from Kolthoff and Furman, "Indicators," John Wiley and Sons, Inc., New York, 1928.

The effect of halogen and alkyl substitution in the phenolic part of the molecule as shown in Table I is identical with that observed by other investigators.[3a,4c] in the unhalogenated series.

The new compounds show the usual dichromatism found in so many of the sulfonephthaleins and possess no apparent advantage as indicators over those now in general use. No attempt has been made to determine the apparent dissociation constants of these compounds nor any spectrophotometric data regarding them.

The author wishes to express his thanks to Mr. Grant Spurrier of the Research Laboratories of Hynson, Westcott and Dunning for his technical assistance.

Summary

1. The following compounds have been prepared: phenoltetrabromosulfonephthalein, phenoltetrachlorosulfonephthalein, *o*-cresoltetrabromosulfonephthalein, *o*-cresoltetrachlorosulfonephthalein, *o*-cresoltetra-iodosulfonephthalein, tetrabromophenoltetrabromosulfonephthalein, dibromophenoltetrabromosulfonephthalein, tetrabromophenoltetrachlorosulfonephthalein, dibromo-*o*-cresoltetrabromosulfonephthalein and dibromo-*o*-cresoltetrachlorosulfonephthalein.

2. Their color change with changing hydrogen-ion concentration has been determined.

3. Their pharmacological and bacteriological action is being investigated and will be reported elsewhere.

4. Further investigation of compounds of this series is in progress.

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