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

HYDROQUINOLSULFONEPHTHALEIN AND SOME OF ITS DERIVATIVES

BY W. R. ORNDORFF AND C. V. SHAPIRO[1]

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The preparation of hydroquinolsulfonephthalein was first attempted by Sohon[2] but it is questionable whether he actually isolated it, as his description of its properties accords, not with that of the pure compound which has now been obtained in a crystalline state, but rather with that of an amorphous by-product whose constitution has not been established.

Hydroquinolsulfonephthalein is the sulfonic acid analog of hydroquinolphthalein. The constitution of the salts of the latter compound has been the subject of considerable debate,[3] due to the fact that it does not lend itself to normal para- or ortho-quinoid formulation. Two configurations, the meta-quinoid of Meyer[3a] and the ortho-quinoid of Green,[3b] have received the most attention, but both are subject to criticism, the former from stereochemical considerations and on account of its uniqueness, since no other admittedly meta-quinoid compound is as yet known. Green's formula, on the other hand, does not account for all of the chemical properties of hydroquinolphthalein. A study of the chemical properties of hydroquinolsulfonephthalein and of the absorption spectra of these two compounds has led us to regard the meta-quinoid constitution as representing their behavior most consistently. Hydroquinolsulfonephthalein is quinoid in the free state and exists as an inner salt, since it does not form a hydrochloride, either in solution or in the solid state when exposed to hydrogen chloride. The basic properties of the phthaleins are assumed to reside in the quinoid oxygen and in the present instance it is neutralized by the sulfonic acid group. On the other hand, hydroquinolphthalein reacts with hydrogen chloride to form a colored salt and, as will be shown later, the absorption spectrum of this salt is identical in its general features with that of a neutral solution of hydroquinolsulfonephthalein. These facts cannot be accounted for either by the ortho-quinoid structure or by any other configuration which simultaneously

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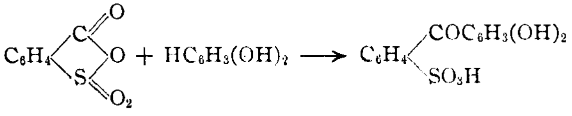
[1] This article is based on a portion of a thesis submitted to the Faculty of the Graduate School of Cornell University by C. V. Shapiro in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Sohon, *Am. Chem. J.*, **20**, 257 (1898).

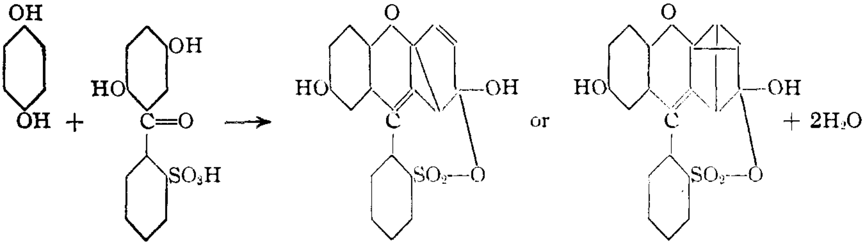
[3] (a) Meyer and co-workers, *Ber.*, **36**, 2949 (1903); **38**, 1318, 3958 (1905); **40**, 1437 (1907); **41**, 2437 (1908); **42**, 2814 (1909); **44**, 1954 (1911). (b) Green and co-workers, *J. Chem. Soc.*, **85**, 398 (1904); *Ber.*, **39**, 2365 (1906); **40**, 3724 (1907); *Proc. Chem. Soc.*, **24**, 206 (1908); *J. Soc. Chem. Ind.*, **27**, 4 (1908). (c) Baeyer, *Ann.*, **372**, 80 (1910); *Ber.*, **46**, 70 (1913). (d) Kehrmann, *Ann.*, **372**, 287 (1910). (e) H. Liebig, *J. prakt. Chem.*, **85**, 97 (1912). (f) Dominikiewicz, *Roczniki Chem.*, **3**, 350 (1923); *J. Chem. Soc. Abstracts*, **128**, 53 (1925).

satisfies the condition that only dibasic and not tri- or tetrabasic metallic salts can be obtained from either of these phthaleins.

By analogy with the other phthaleins and sulfonephthaleins which have been studied in this Laboratory, it is probable that the formation of hydroquinolsulfonephthalein occurs in two steps, although no success attended efforts to isolate the intermediate acid.



o-Sulfobenzoic acid Anhydride Hydroquinol Intermediate acid



Hydroquinolsulfonephthalein

Hydroquinolsulfonephthalein, as indicated above, contains the pyrone ring and analysis shows it to have the empirical formula $C_{19}H_{12}O_6S$, not $C_{19}H_{14}O_7S$ as suggested by Sohon.[4] It is, therefore, isomeric with sulfonefluorescein[5] but unlike that compound shows no trace of fluorescence in alkaline solution. Hydroquinolphthalein bears a similar relation in structure and fluorescence properties to fluorescein.

Hydroquinolsulfonephthalein does not appear to behave as a tautomeric compound, since no colorless, lactoid derivatives could be obtained from it. It forms a cream-colored dibenzoate which yields a bright yellow alcoholic solution. The absorption spectrum of this solution confirms the quinoid nature of this compound, since it fails to show certain bands the presence of which has served as an excellent criterion for benzenoid derivatives of the triphenylmethane series.[6]

Experimental Part[7]

Preparation of Hydroquinolsulfonephthalein. 1. From the Anhydride of *o*-Sulfobenzoic Acid and Hydroquinol.—Fifty g. each of hydroquinol and of the anhydride of *o*-sulfobenzoic acid were heated together at 150°, but as soon as the mixture had be-

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[4] Ref. 2. Evidently due to a typographical error, this formula is given in Sohon's article as $C_{19}H_{14}O_8S$.

[5] Orndorff and Vose, This Journal, **46**, 1896 (1924).

[6] Gibbs and Shapiro, *Proc. Nat. Acad. Sci.*, **14**, 251 (1928).

[7] We are indebted to the Monsanto Chemical Works of St. Louis for the saccharin used in this investigation.

come fluid the temperature was quickly lowered to 130°. The fusion was continued for eighteen to twenty-four hours, although even after longer periods of heating the mixture did not become hard. An air condenser was provided for the flask to avoid loss of hydroquinol by sublimation; the crystals of hydroquinol were occasionally pushed down and the mixture stirred. At the end of the condensation 200 cc. of water was added to the hot melt, the solution was allowed to stand for several hours and the hydroquinolsulfonephthalein was filtered off. The precipitate was washed with small portions of distilled water to remove excess mother liquor, but large volumes of water must be avoided in handling the crude sulfonephthalein as the impure material is fairly soluble. The washed sulfonephthalein was dissolved in 100 cc. of 5% sodium bicarbonate solution by boiling, the solution filtered, diluted with one liter of distilled water and again brought to a boil. Small amounts of 5% hydrochloric acid were added and the liberated tarry matter was filtered off as it appeared until neutralization was effected, when the hydroquinolsulfonephthalein separated in small, dark brown crystals. An alternative method for the preliminary purification was to suspend the dried, crude sulfonephthalein in 100 cc. of cold, absolute alcohol for one hour with frequent stirring, filter and wash with several 10cc. portions of alcohol. Further purification was necessary in both cases by one or two reprecipitations from a boiling bicarbonate solution, after which the compound was obtained in the form of shining red plates. The average yield was 20%. The material was dried at 110° prior to analysis.

Anal. Subs. (dry), 0.3025, 0.4930: $BaSO_4$, 0.1945, 0.3152. Calcd. for $C_{19}H_{12}O_6S$: S, 8.71. Found: 8.83, 8.78. Calcd. for $C_{19}H_{14}O_7S$: S, 8.29.

2. **From the Anhydride of *o*-Sulfobenzoic Acid and Hydroquinol in the Presence of Dehydrating Agents.**—Numerous attempts were made to improve the yield and quality of hydroquinolsulfonephthalein by carrying out the condensations in the presence of dehydrating agents such as zinc chloride, sulfuric acid, boric acid and stannous chloride. With the exception of the first mentioned compound, excessive tar formation occurred which rendered the purification a prolonged and difficult process. With zinc chloride the best yield obtained was 5% with very little tarry contamination, but when a higher temperature or more prolonged heating was employed to raise the yield, the production of tar again increased.

A condensation of saccharin with hydroquinol in the presence of concd. sulfuric acid resulted in the recovery of a small amount of amorphous material which dissolved in alkali with a yellow-brown color, recalling Sohon's description[2] of the behavior of the substance he thought to be hydroquinolsulfonephthalein. As the material could not be obtained in a crystalline state no attempt was made to analyze it.

Properties of Hydroquinolsulfonephthalein.—Hydroquinolsulfonephthalein crystallizes from a hot, aqueous solution, slightly acidified with hydrochloric acid, in the form of dark red, thin plates which grind up to a bright red powder. It is practically insoluble in most organic solvents. In methyl and ethyl alcohol and in water it dissolves sparingly to give an orange-red solution, but the solubility is greatly increased by the presence of traces of impurity. An exact solubility determination for a highly purified sample yielded 0.0117 g. per 100 cc. at 22° in distilled water and 0.0120 g. per 100 cc. in absolute ethyl alcohol. Sodium hydroxide solutions dissolve it readily, sodium carbonate more slowly, to give a deep blue-purple solution. The color of both solutions changes very rapidly to a tan or brown. A 5% solution of sodium bicarbonate dissolves it slowly, even at the boiling point, but the solution is relatively stable as no change of the purple color was observed after standing for several days.

Dr. Barnett Cohen of the Hygienic Laboratory, U. S. Public Health Service, Washington, D. C., has kindly determined the indicator properties of hydroquinolphthalein and hydroquinolsulfonephthalein and an excerpt from his report follows.

"Hydroquinolphthalein.—This beautifully crystallized compound dissolved readily in alcohol and behaved very much like phenolphthalein, except that the color range lies between *P*H 8.6 and *P*H 10.

"Hydroquinolsulfonephthalein.—When tested in buffers of different *P*H, the indicator gave a brownish-yellow coloration from *P*H 1 down to *P*H 5. Between *P*H 5.0 and 6.0 the color became a purer yellow. Between PH 6.4 and 8.0 there was a definite stepwise change in coloration from yellow through greenish-yellow to dark olive. At *P*H 8.0 the color was dark olive with a violet tinge. From *P*H 8 to 10 there was also a definite stepwise color change to deeper shades of purple. Apparently there are two dissociations which overlap near *P*H 8. From my preliminary measurements, I should say that one dissociation constant is at P_K 7.2 and the other at 8.8."

Hydroquinolsulfonephthalein does not melt below 300°. It dissolves in concentrated sulfuric acid, forming an orange solution, and is partially precipitated when the solution is poured into a large volume of water. It does not absorb hydrogen chloride when exposed to the dry gas, which indicates that it possesses an inner salt structure. This agrees with the subsequent observation, in a study of the absorption spectra of hydroquinolsulfonephthalein, that the addition of dry hydrogen chloride gas to an alcoholic solution produces no change in its absorption, even in ratios as high as 10,000 molecules of acid to one of the sulfonephthalein.

Action of Ammonia Gas.—When dry hydroquinolsulfonephthalein was exposed to ammonia gas, previously dried over sodium, it absorbed about three molecules of ammonia and became blue-black in color.

Anal. Subs., 0.1076; gain, 0.0125. Calcd. for $C_{19}H_{12}O_6S + 3NH_3$: NH_3, 12.19. Found: 10.39.

When allowed to stand in a desiccator over concentrated sulfuric acid until it reached constant weight, the sample retained one molecule of ammonia.

Anal. Subs., 0.1076; gain, 0.0050. Calcd. for $C_{19}H_{12}O_6S + NH_3$: NH_3, 4.41. Found: 4.44.

The mono-ammonium salt dissolves in water with a murky green color; this is due to hydrolysis, since the true color of the salt is blue-purple and that of the neutral sulfonephthalein, orange-red. A similar effect has been obtained in the study of the absorption spectra of alkaline solutions of hydroquinolsulfonephthalein, where even with four molecules of potassium hydroxide to one of the sulfonephthalein it is found that the characteristic bands of the neutral substance and its salt are simultaneously present.

Salts of Hydroquinolsulfonephthalein.—The disodium salt of hydroquinolsulfonephthalein was obtained by treating the latter with an alcoholic solution of sodium ethoxide. The air dried product contained a molecule of alcohol of crystallization ($C_{19}H_{10}O_6SNa_2 + C_2H_5OH$).

The barium salt ($(C_{19}H_{11}O_6S)_2Ba$) was obtained by boiling a suspension of hydroquinolsulfonephthalein and barium hydroxide in water, filtering and concentrating. After several recrystallizations from water it was separated entirely free from barium hydroxide in the form of brown, flaky plates.

Hydroquinolsulfonephthalein Dibenzoate.—Three g. of hydroquinolsulfonephthalein was boiled with 100 cc. of benzoyl chloride for one hour. The solution was filtered and the excess benzoyl chloride evaporated off in a water oven. The residue was extracted several times with warm benzene to remove tarry matter, after which it was dissolved in boiling benzene and recrystallized from that solvent several times. Two g. of pale, cream-colored crystals was obtained, but when heated at 110° to remove benzene they changed to a bright yellow color.

Anal. Subs. (dry), 0.2098, 0.3551: $BaSO_4$, 0.0844, 0.1411. Calcd. for $C_{19}H_{10}O_6S(C_6H_5CO)_2$: S, 5.56. Found: 5.53, 5.46.

The maximum solubility of the dibenzoate in absolute ethanol was determined at 22° as 0.0150 g. per 100 cc. It is also very difficultly soluble in methanol, benzene, toluene and acetone. It is slowly saponified by boiling with dilute sodium hydroxide solution, when the characteristic blue color of the sulfonephthalein in alkaline solution appears.

Summary

1. The preparation of pure, crystalline hydroquinolsulfonephthalein has been described. It gives evidence of being an inner salt and on the basis of its chemical and physical behavior it is accorded a meta-quinoid structure.

2. Hydroquinolsulfonephthalein gives colored metallic salts and a colored dibenzoate, but unlike the other phthaleins and sulfonephthaleins, it does not yield any colorless, lactoid derivatives.

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