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# THE SULFONATION OF SALICYLANILIDES AND RELATED SUBSTANCES

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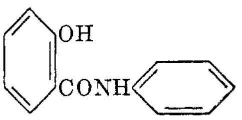
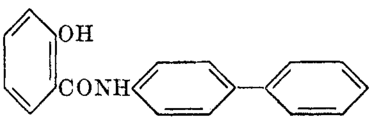
A review of the literature reveals that there has been very little information published regarding the sulfonation of *ortho*-hydroxy amides of type I. The only information available is published in a German report (1) in which a procedure is described for sulfonating this type of compound; no analytical results or properties are given. The present study was therefore undertaken to provide a better knowledge of the sulfonation process.

To study this reaction, salicylanilide (I), 4′-phenylsalicylanilide (II), disalicylbenzidide (III), 4′-chloro-1-hydroxy-2-naphthanilide (IV), and 1-hydroxy-3′-trifluoromethyl-2-naphthanilide (V) were used. When sulfonated by heating at 90–100° for five hours with concentrated sulfuric acid, compounds I, II, and III were disulfonated, while compounds IV and V were monosulfonated. The products are assigned structures VI, VII, VIII, IX, and X, respectively.



I



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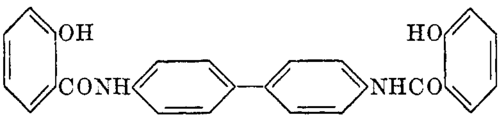

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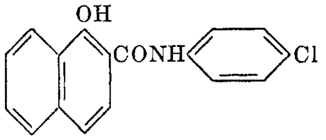

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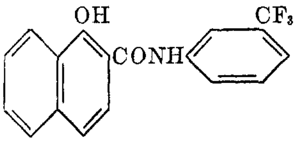

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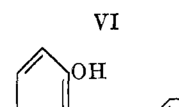

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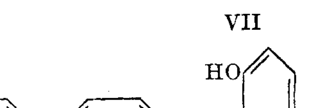
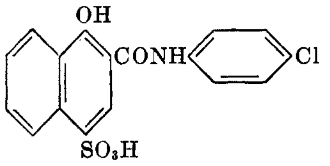
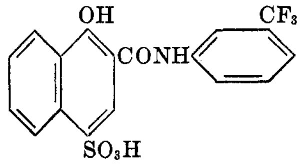


VII

VIII

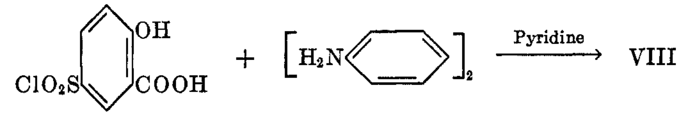


IX



X

The structure of VIII was demonstrated by an independent synthesis, employing Gränacher's (2) method, which consists in treating the sulfonyl chloride (3) of salicylic acid with benzidine in the presence of pyridine. The yield was poor, but the identity of the product with that of the sulfonation procedure was confirmed by the identity of the ultraviolet absorption curves. A sulfonamide (4), isomeric with VIII, was obtained from XI and benzidine in the presence of sodium acetate. Its nonidentity with VIII indicates that a carbamido group is formed in the presence of pyridine. The structure of IX was demonstrated in the same manner, using 4-chlorosulfonyl-1-hydroxy-2-naphthoic acid and 4-chloroaniline. The ultraviolet curves for these compounds, III, IV, VIII, and IX, under both acidic and basic conditions, are shown in Figures 1 and 2. The introduction of a sulfo group has little effect on the spectrum.



XI

A sulfo group in a position *para* to a phenolic group is eliminated by oxidized developer (5). The sulfonated compound, IX, when subjected to the above test, using *p*-aminodimethylaniline as the developer, gave an azomethine dye identical (spectrometrically) with the azomethine dye from IV. This proves that the sulfo group was eliminated and, therefore, that it must have been in a position *para* to the phenolic group. The sulfo groups in the 4′- and 4″-positions of VI and VII, respectively, have been assigned these positions from a consideration of the directive influence of the carbamido group and from the fact that VIII, in which the 4″-position is blocked, gives only a disulfonate.

These substances possess certain unusual properties which are worth mentioning. The sodium sulfonates are sparingly soluble in water. However, if sodium carbonate is added to the neutral suspension of these compounds, the sodium salts of the phenolic groups are formed, and the compounds become soluble. Three distinct salts from VIII, containing two, three, and four atoms of sodium, have been isolated. The disodium salt has been titrated with sodium hydroxide to show the presence of two phenolic groups. Essentially the same results are obtained with sodium carbonate. The tri- and tetra-sodium salts show one and two replaceable sodium atoms, respectively. The sodium on a sulfonic group is not affected by mineral acid. These properties have been utilized in the method of purification.

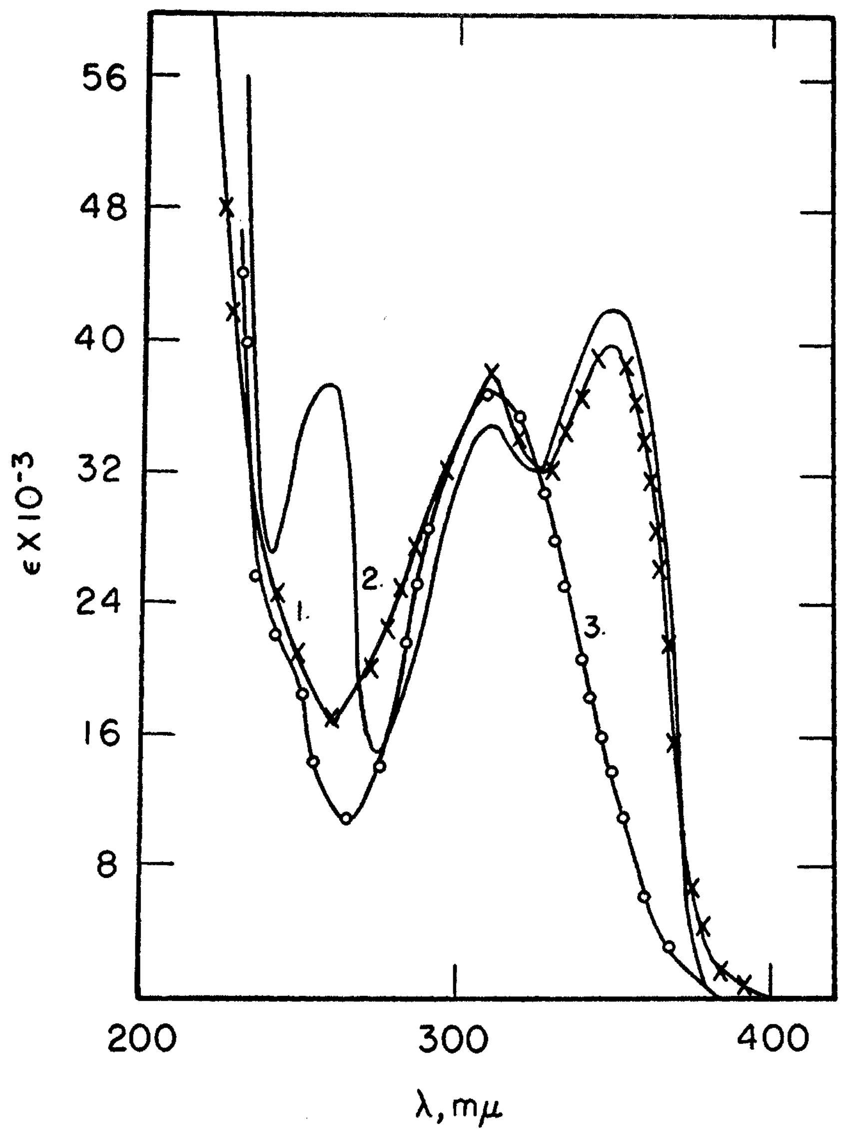


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA OF (1) Disalicylbenzidide (III) in water at *p*H 12; (2) Disodium disalicylbenzididedisulfonate (VIII) in water at *p*H 12; (3) VIII in water at *p*H 7.

## EXPERIMENTAL

The amides I–V were prepared by a known procedure (6, 7). The analytical results and properties are collected in Table I.

*Disodium disalicylbenzididedisulfonate* (VIII). (*A*). *By sulfonation.* Finely pulverized disalicylbenzidide (800 g.) was added to 4.8 l. of concentrated $H_2SO_4$. The reaction mixture was heated on the steam pot for 3½ hours; solution was complete. It was then poured upon 39 kg. of ice and made slightly alkaline with approximately 8.6 l. of 50% NaOH; the heat of neutralization brought the temperature to about 80°. This clear solution was treated with

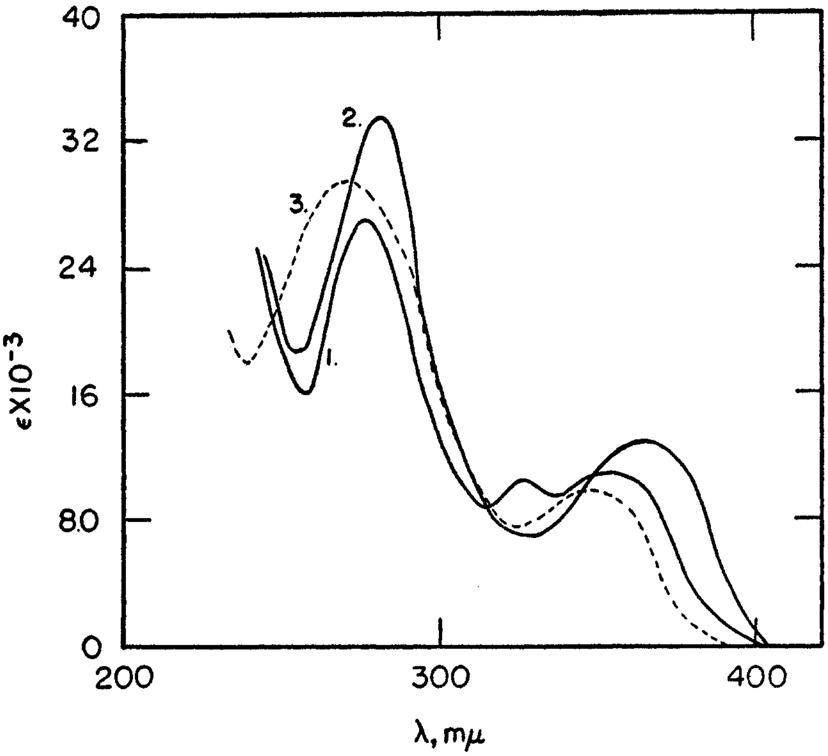


FIGURE 2. ULTRAVIOLET ABSORPTION SPECTRA OF (1) 4′-Chloro-1-hydroxy-4-*sulfo*-2 naphthanilide (IX) in water at *p*H 12; (2) 4′-Chloro-1-hydroxy-2-naphthanilide (IV) in water at *p*H 12; (3) IV in methanol.

TABLE I

*o*-HYDROXYAMIDES

| COMPOUND | M.P., °C. | EMPIRICAL FORMULA | ANALYSIS |  |  |  |
|---|---|---|---|---|---|---|
|  |  |  | Calc'd |  | Found |  |
|  |  |  | C | H | C | H |
| I (7) | 131–132 |  |  |  |  |  |
| II | 183 | $C_{19}H_{16}NO_2$ | 78.5 | 5.5 | 78.6 | 5.4 |
| III | 327–329 | $C_{26}H_{20}N_2O_4$ | 73.5 | 4.7 | 73.3 | 4.3 |
| IV | 179 | $C_{17}H_{12}ClNO_2$ | 68.5 | 4.0 | 68.4 | 3.9 |
| V | 166 | $C_{18}H_{13}F_3NO_2$ | 65.10 | 3.9 | 65.5 | 3.6 |

Nuchar (charcoal) and filtered. The filtrate was diluted to 25 gal. with water, and made acid to Universal Indicator paper with acetic acid. The precipitate was allowed to settle, then was collected, washed with a large amount of water, and dried in a hot oven. The yield was 1,045 g. (102%).

Further purification was effected by dissolving the above sodium salt in dilute sodium carbonate and acidifying with acetic acid. The disodium salt was thus obtained. To obtain the trisodium salt, the solution was adjusted to *p*H 7–7.5, and a saturated salt solution

TABLE II

SULFONATED *o*-HYDROXYAMIDES

| COMPOUND | EMPIRICAL FORMULA | ANALYSIS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Calc'd | | | | | Found | | | | |
| | | C | H | N | S | NA | C | H | N | S | NA |
| VIII a | $C_{26}H_{18}N_2Na_2O_{10}S_2$ | 49.7 | 2.9 | 4.5 | 10.2 | 7.32 | 49.5 | 3.0 | 4.5 | 10.1 | 6.9 |
| b | $C_{26}H_{17}N_2Na_3O_{10}S_2 \cdot 2H_2O$ | 45.5 | 3.0 | 4.1 | 9.4 | 10.0 | 44.7 | 3.0 | 4.0 | 9.4 | 9.6 |
| c | $C_{26}H_{16}N_2Na_4O_{10}S_2 \cdot 2H_2O$ | 44.0 | 2.8 | 4.0 | 9.1 | 13.0 | 44.7 | 3.1 | 4.1 | 9.6 | 12.9 |
| VI | $C_{13}H_9N_2Na_2O_8S_2$ | 35.2 | 2.1 | | 14.8 | 10.7 | 35.3 | 3.2 | | 14.9 | 11.2 |
| VII | $C_{19}H_{13}NNa_2O_8S_2 \cdot 2H_2O$ | 43.2 | 3.2 | | 12.2 | 10.5 | 43.4 | 3.1 | | 13.2 | 8.7 |
| IX | $C_{17}H_{11}ClNNaO_5S \cdot H_2O$ | 49.0 | 2.6 | | 7.7 | | 50.2 | 3.1 | | 7.7 | |
| X | $C_{18}H_{12}F_3NNaO_5S$ | 49.7 | 2.8 | | 7.4 | 13.0 | 49.6 | 2.9 | | 7.4 | |

a = Disodium salt, b = trisodium salt, c = tetrasodium salt.

was added. The tetrasodium salt was obtained in the same manner, but the solution was adjusted to *p*H 9–10. The sulfonation of I, II, IV, and V was effected in essentially the same manner. The analytical results are collected in Table I.

(*B*) *By Gränacher's method.* 5-Chlorosulfonylsalicylic acid (5 g.) was dissolved in dry pyridine (30 ml.); benzidine (1 g.) was added, with stirring, and the light yellow solution was heated to 90° for two hours. The pyridine was removed *in vacuo*, and the residue was dissolved in dilute sodium carbonate solution, treated with 2 g. of Norit (charcoal), filtered, and acidified with acetic acid. The precipitated disodium disalicylbenzidididedisulfonate was collected; yield 2.3 g. Further purification was effected as above.

*4'-Chloro-1-hydroxy-4-sulfo-2-naphthanilide.* 4-Chlorosulfonyl-1-hydroxy-2-naphthoic acid (14 g.) was dissolved, with stirring, in 100 ml. of dry pyridine at 10°. *p*-Chloroaniline (6 g.) was added. A reddish-orange solution formed immediately, the temperature rising to 45°. This solution was heated to 80° for one hour and poured into 1 liter of water. Sodium carbonate was added until the solution was alkaline, and the pyridine was removed with steam. The residual solution was acidified with acetic acid, and the product was collected; the yield was 8 g. It was identical with the product obtained by sulfonation.

*Bis-(4-hydroxy-3-carboxybenzenesulfonyl)benzidide.* 4-Hydroxy-3-carboxybenzenesulfonyl chloride (4.7 g.) was added to 1.8 g. of benzidine in 50 ml. of acetic acid containing 2.3 g. of potassium acetate. After heating for two hours at 95–100°, the product which had separated was collected, washed with water, and recrystallized from alcohol-water. Yield, 5 g., m.p. 295–297°.

*Anal.* Calc'd for $C_{26}H_{20}N_2O_{10}S_2$: C, 53.4; H, 3.4.
Found: C, 53.2; H, 3.8.

*4-(N-4'-Chlorophenylsulfonamido)-1-hydroxy-2-naphthoic acid,* m.p. 238°, was made in a similar manner.

*Anal.* Calc'd for $C_{17}H_{12}ClNO_5S$: C, 54.0; H, 3.2.
Found: C, 54.8; H, 3.3.

## SUMMARY

Several aromatic *ortho* hydroxy carbonamides have been sulfonated with concentrated sulfuric acid at 90–100°. The structures of the sulfonated compounds have been established by independent syntheses. The introduction of a sulfonic acid group has little effect on the ultraviolet absorption spectrum.

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