NEW AROMATIC ETHEREAL SALTS FORMED BY THE INTERACTION OF o-SULFOBENZOIC ANHYDRIDE AND PHENOLS IN THE PRESENCE OF WATER AND AN ALKALIN HYDROXIDE.

By Arnold H. C. Heitman.

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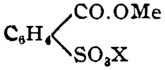
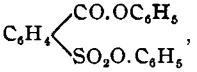
Remsen and Dohme[1] prepared the methyl and ethyl salts with the general formula:



$$C_6H_4\Big\langle\begin{matrix}CO.OMe\\SO_3X\end{matrix}$$

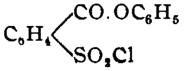
by treating the acid chlorides of *o*-sulfobenzoic acid with the corresponding alcohols, and neutralizing the reaction products with carbonates; also, by passing hydrogen chloride gas through an alcoholic solution of free acid.

Sohon[2] obtained these salts by treating the anhydride with alcohols; Remsen and Saunders[3] obtained the diphenyl ester of *o*-sulfobenzoic acid,



$$C_6H_4\Big\langle\begin{matrix}CO.OC_6H_5\\SO_2O.C_6H_5\end{matrix}$$

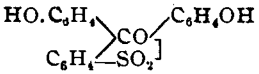
, and a product corresponding to



$$C_6H_4\Big\langle\begin{matrix}CO.OC_6H_5\\SO_2Cl\end{matrix}$$

by treating the acid chlorides with phenol in the presence of water. This work was repeated by Karslake,[4] and List and Stein,[5] and others.

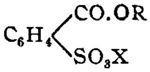
Sohon[6] was first to study the action of *o*-sulfobenzoic anhydride on phenol. He obtained phenolsulfonephthalein:



by heating a mixture of the anhydride and phenol at 130–135°.

The present communication deals with the investigation of the product resulting by the interaction of *o*-sulfobenzoic anhydride and phenolic substances in the presence of water and an alkalin hydroxide.

On account of the strong solubility influence exerted by the sulfonic acid group (SO_3H), this investigation was undertaken mainly with a view to employing the reaction for the production of the hypothetical combinations:



$$C_6H_4\Big\langle\begin{matrix}CO.OR\\SO_3X\end{matrix}$$

(where OR represents a phenolic radicle of remedial value), thereby avoiding direct substitution of the SO_3H group in the molecular structure and subsequent sacrifice of physiological efficiency. It is a well known

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[1] *Am. Chem. J.*, **11**, 340.

[2] *Ibid.*, **20**, 260.

[3] *Ibid.*, **17**, 325.

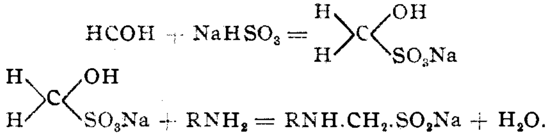
[4] *Ibid.*, **18**, 825.

[5] *Ber.*, **31**, 1659.

[6] *Loc. cit.*

fact that the introduction of the sulfonic acid group into the molecular structure of physiologically active substances materially reduces toxicity and remedial efficiency for the reason that such substituted compounds, when injested into the animal organism, are not again regenerated into their original form. Confirmatory evidence of this fact was even recently given by Ehrlich in the results he obtained with a sulfonated product of *p*-aminophenylarsenic acid.

In this connection, the sulfoxylic acid derivatives described by Bucherer,[1] Knoevenagle,[2] Bucherer and Schwalbe,[3] and others, are worthy of mention, owing to their usefulness in rendering amino compounds neutral and water soluble. These derivatives are obtained by treating primary or secondary amines with formaldehyde and sodium bisulfite. The reaction may be represented:



$$HCOH + NaHSO_3 = {}^{H}_{H}\!>C<^{OH}_{SO_3Na}$$

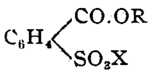
$${}^{H}_{H}\!>C<^{OH}_{SO_3Na} + RNH_2 = RNH.CH_2.SO_2Na + H_2O.$$

Contemplating the use of a sulfonic acidyl derivative, my attention was naturally directed to *o*-sulfobenzoic acid, particularly its anhydride. A supply of the latter, therefore, was necessary, and a convenient method for preparing this was given no little consideration.

o-Sulfobenzoic acid anhydride was prepared by Fahlberg and Barge[4] by the action of acetyl chloride on the free acid in a sealed tube at 170°, also about the same time by Remsen and Dohme,[5] by heating the acid with phosphoric anhydride at 130°; by Sohon,[6] by treating dry potassium acid *o*-sulfobenzoate with phosphorus pentachloride, and later by Cobb,[7] by treating this salt with thionyl chloride.

The difficulties encountered in preparing and handling the anhydride led the author to reject the methods given. It was found, however, that the anhydride could be quickly and conveniently prepared by treating the dry potassium acid salt with phosphorus pentoxide and directly distilling the anhydride at ordinary pressure, or, better still, under reduced pressure. The potassium acid salt used was prepared from commercial saccharin, according to Remsen and Dohme.

The simplest method of preparing the salts:



$$C_6H_4<^{CO.OR}_{SO_2X}$$

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[1] D. R. P., **132**, 621.

[2] *Ber.*, **37**, 4075; **38**, 213.

[3] *Ibid.*, **39**, 2798.

[4] *Ibid.*, **22**, 754.

[5] *Am. Chem. J.*, **11**, 332.

[6] *Loc. cit.*

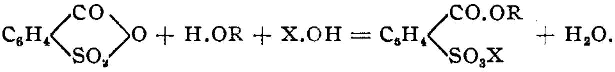
[7] *Am. Chem. J.*, **35**, 486.

would appear to be by direct interaction of the anhydride of *o*-sulfobenzoic acid and phenol. Sohon,[1] however, found it to yield only phenolsulfonephthalein.

Hence, it was necessary to deviate entirely from the original idea of effecting the desired reaction in dry form, and various solvents, including pyridine and water, were employed. After several unsuccessful attempts to bring about a reaction between the anhydride and phenol in the presence of water, the author was led to consider the possibility of a probable retarding influence arising from the strong SO_3H group, so that it was deemed advisable to try the effect of the addition to the water of a molecular quantity (1 mol.) of an alkalin hydroxide, and thereby completely neutralize the acid as it was being formed during the reaction.

This method immediately proved to be successful. The examination of the solution revealed the presence of a new product.

As already suggested, the explanation of this result is possibly to be found in the fact that the hydrolytic influence of the SO_3 Hgroup formed from the anhydride probably was of sufficient power to prevent esterification, while the alkali added neutralized this and permitted the free benzoyl group to esterify. From the results obtained, the mechanism of the reaction may be represented:



$$C_6H_4\left\langle\begin{matrix}CO\\SO_2\end{matrix}\right\rangle O + H.OR + X.OH = C_6H_4\left\langle\begin{matrix}CO.OR\\SO_3X\end{matrix}\right. + H_2O.$$

The following is a satisfactory method, found generally applicable to all phenolic substances: Molecular proportions of phenol, alkali hydroxide, and *o*-sulfobenzoic anhydride are used. The anhydride in fine powder is suspended in about five parts of ice water, and to this is added the alkali and phenol, previously dissolved in an equal portion of ice water. The mixture is thoroughly agitated without further cooling, until solution results. The solution is then filtered and the free phenol extracted with ether, the aqueous solution concentrated to about $^1/_5$ the original volume, preferably under reduced pressure, and allowed to crystallize. If the crystals do not form, the product is evaporated to dryness, the residue dissolved in alcohol, and the insoluble salts filtered from the alcoholic solution, which is again evaporated to dryness.

The lowest homolog, *viz.*, the phenyl ester, is the typical member of this series. It shows the greatest inclination to form crystals, while with rise in molecular weight this property is apparently lost.

These ethereal salts, as a class, are characterized by their solubility in water and alcohol, their stability in air or solution, and the ease with which they hydrolyze in warm, dilute alkalin carbonate solutions. They should particularly lend themselves to practical application in the syn-

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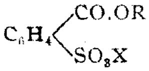
[1] *Loc. cit.*

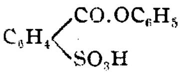
thesis of medicinal substances. It would seem that the condensation of phenolic substances with *o*-sulfobenzoic anhydride, forming neutral soluble compounds,



$$C_6H_4\left\langle\begin{matrix}CO.OR\\SO_3X\end{matrix}\right.$$

which are readily hydrolyzed, should play an important role in the field of chemotherapy.

In connection with this work, the author desired to mention an interesting observation of a case in which the free ester acid,



$$C_6H_4\left\langle\begin{matrix}CO.OC_6H_5\\SO_3H\end{matrix}\right.$$

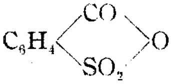
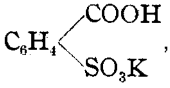
must necessarily have been present.

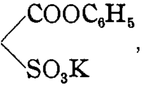
A product, which was obtained by treating the free *o*-sulfobenzoic acid with acetyl chloride under reflux condenser, and distilling the excess of acetyl chloride and acetic acid under reduced pressure at a temperature not exceeding 70°, was suspended in water and treated with an excess of phenol. The mixture was thoroughly agitated until the suspended matter disappeared, the solution filtered, extracted with ether, and carefully neutralized with potassium bicarbonate. The aqueous solution was then concentrated under reduced pressure.

It yielded a considerable quantity of phenyl benzoate-*o*-sulfonate of potassium, which was identical with the product obtained from the anhydride, phenol, and potassium hydroxide.

The presence of chlorides in the solution of the reaction product gave unmistakable evidence that an acid chloride must have been present in the residue obtained by treating *o*-sulfobenzoic acid with acetyl chloride at a low temperature. The residue, thoroughly powdered and dried *in vacuo* over sulfuric acid, did display a characteristic acid chloride odor, and contained chlorine. As soon as opportunity affords, the writer desires to study this new phase of the reaction.

Experimental.

o-Sulfobenzoic Anhydride.  $C_6H_4\left\langle\begin{matrix}CO\\SO_2\end{matrix}\right\rangle O$. was prepared by mixing 50 grams of finely powdered potassium acid sulfobenzoate,  $C_6H_4\left\langle\begin{matrix}COOH\\SO_3K\end{matrix}\right.$, and 40 grams of phosphorus pentoxide in a side-neck flask (which is afterwards sealed off above the side neck), heating the same to about 400° in a bath consisting of an eutectic mixture of nitrates (the nitrate mixture melting approximately at 220°, consists of 27 parts KNO_3 and 23 parts $NaNO_3$. It lends itself well for high temperature work) and directly distilling the anhydride, which solidified upon cooling to a nearly colorless mass. The side neck distilling tube is directly passed into an air-cooled, round bottomed flask, which is sufficient to condense the distilling anhydride. The anhydride obtained by this method is quite pure and suitable for all practical purposes. It is obtained pure by recrystallizing from benzene or carbon tetrachloride.

Phenyl benzoate-o-*sulfonate of potassium*,  $C_6H_4\begin{cases}COOC_6H_5\\SO_3K\end{cases}$, was prepared by suspending 9 grams of *o*-sulfobenzoic anhydride in 200 cc. of ice water containing 6 grams of phenol and 2.8 grams of potassium hydroxide in solution, agitating the mixture until the anhydride in suspension has disappeared. The resulting slightly acid solution is extracted with ether to remove free phenol, the aqueous solution concentrated to a volume of about 50 cc., preferably under reduced pressure, when the potassium salt will crystallize in stout needles. Recrystallizing once from water, the substance is obtained pure. The yield was 12 grams.

It appears in the form of stout needles, permanent in air, and melting colorless at 277–280°. It is very soluble in hot water and glacial acetic acid, in 10 parts of cold water, less in alcohol, and insoluble in all other ordinary organic solvents. The addition of a few drops of ether to the concentrated aqueous solutions will oftentimes hasten crystallization.

It is very stable in neutral solutions, even on boiling, while, by warming with very dilute alkalin carbonate, it is readily decomposed into free phenol and the neutral salt of *o*-sulfobenzoic acid. The substance crystallized from water and dried over sulfuric acid, was used for analysis:

Calculated for $C_{13}H_9O_5SK$: C, 49.35; H, 2.85; S, 10.15; K, 12.34.
Found: C, 49.39; H, 2.98; S, 9.76; K, 12.01.

One-half gram substance was warmed with potassium hydroxide solution, neutralized with phosphoric acid, the phenol distilled with steam, and estimated by Koppeschaar's method:

Calculated for $KSO_3.C_6H_4CO.OC_6H_5$: phenol, 29.76. Found, 29.37.

An aqueous solution of the substance, unless previously hydrolyzed, is not affected by the addition of bromine water. The corresponding sodium salt was not obtained crystallin.

Phenylbenzoate-o-*sulfonate of barium*, $(SO_3C_6H_4CO.OC_6H_5)_2Ba$, was prepared in the usual way, using a molecular quantity of barium hydroxide. The resulting solution was concentrated to 60 cc. and set aside for several days to crystallize. It appeared in clusters of fine, lustrous needles. The moist crystals are very soluble in water, while after drying they dissolve with difficulty. Although the substance is only slightly soluble in alcohol, aqueous solutions of the salt are not precipitated by it.

When heated, it melts with decomposition. The substance recrystallized from water and dried over sulfuric acid was analyzed:

Calculated for $C_{26}H_{18}O_{10}S_2Ba + 3H_2O$: Ba, 18.68. Found, 18.39.

*Ethylsalicylbenzoate-*o*-sulfonate of potassium,* $KSO_3.C_6H_4CO.OC_6H_4$-$COOC_2H_5$, was prepared by suspending 9 grams of *o*-sulfobenzoic anhydride in 200 cc. of ice water containing 3 grams potassium hydroxide and 9 grams of ethyl salicylate in solution and agitating the mixture during two hours. The aqueous solution was extracted with ether, concentrated under reduced pressure to a small volume, and set aside to crystallize. Sometimes seeding or occasional rubbing with a glass rod is necessary to start crystallization.

It is obtained in beautiful, colorless, monoclinic prisms, permanent in air, and melting colorless at 246°. It is very soluble in hot water, glacial acetic acid, less in alcohol, and insoluble in ether, acetone, benzene, chloroform and petroleum ether. Ethyl salicylate is readily split off with warm carbonate solutions.

Recrystallized from water, and dried over sulfuric acid, the substance was pure.

Calculated for $C_{16}H_{13}O_7SK$: C, 49.47; H, 3.35; S, 8.25; K, 10.05.
Found: C, 49.37; H, 3.46; S, 8.25; K, 9.75.

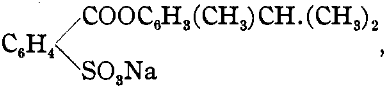
*Guaiacol benzoate-*o*-sulfonate of barium,* $(SO_3C_6H_4CO.OC_6H_4OCH_3)_2.Ba$, was prepared by dissolving 8 grams of barium hydroxide in 200 cc. of ice water and adding 9 grams of guaiacol. To this ice cold solution *o*-sulfobenzoic anhydride was added and kept in suspension by constant agitation, without further cooling. When all anhydride had entered into solution, it was filtered, the free guaiacol extracted with ether, and the aqueous solution evaporated to dryness. The dry residue was dissolved in alcohol and the insoluble salts removed by filtration. The alcoholic solution was again evaporated to dryness and the residue dissolved in about 30 cc. of water and the solution allowed to stand in a covered container for several days to crystallize.

The resulting crystallin mass is collected on a small Büchner filter, washed with a little water, when it is readily recrystallized from water in long slender or clusters of lustrous needles with two molecules of water of crystallization. It is permanent in air and in neutral solution. Heated to a high temperature, it melts with decomposition. It is readily soluble in water and alcohol, slightly soluble in glacial acetic acid and insoluble in ether, acetone, chloroform and petroleum ether. The addition of a small quantity of ether to an alcoholic solution of the substance slowly separates it out in bundles of fine needles. Warmed with alkaline carbonate solution, guaiacol is readily split off. Dried at 100° during 8 hours, it loses the water of crystallization. The substance, crystallized from water, and dried *in vacuo* over sulfuric acid, was used for analysis:

Calculated for $C_{28}H_{22}O_{10}S_2Ba + 2H_2O$: C, 42.75; H, 2.80; Ba, 17.75.
Found: C, 42.35; H, 2.95; Ba, 17.49.

It should be stated that, owing to the fact that the following derivatives could not be obtained in crystallin form, the results are to be regarded as roughly quantitative, the object being to determin the influence and general course of reaction between a larger number of phenols and *o*-sulfobenzoic anhydride.

*Thymylbenzoate-*o*-sulfonate of sodium,*



$$C_6H_4\left\langle\begin{matrix}COOC_6H_3(CH_3)CH.(CH_3)_2\\ \\ SO_3Na\end{matrix}\right.$$

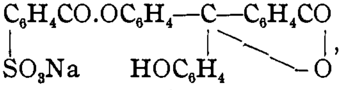
, was obtained in the usual manner, but owing to the fact that crystals did not form, the solution was evaporated to dryness. The residue was dissolved in alcohol, the solution filtered, and the alcohol evaporated.

The substance appears in the form of a colorless amorphous powder, very soluble in water, glacial acetic acid and alcohol. It was found in most respects to be analogous to the other members of the series. It is readily hydrolyzed to free thymol and neutral sulfobenzoate by warm alkalin carbonate solution. Dried at 100° the substance was used for analysis:

Calculated for $C_{17}H_{17}O_5S.Na$: Thymol, 41.86; Na, 6.46.
Found: Thymol, 40.93; Na, 6.58.

The substance was hydrolyzed with potassium hydroxide, acidulated with phosphoric acid, the thymol distilled with steam, and estimated by E. Zderach's[1] modification of Koppeschaar's method.

*Phenolphthaleinbenzoate-*o*-sulfonate of sodium,*



$$\begin{array}{lll}C_6H_4CO.OC_6H_4— & C— & C_6H_4CO\\ | & | \diagdown & \quad | \\ SO_3Na & HOC_6H_4 & \diagdown O\end{array}$$

, was prepared by suspending 16 grams of phenolphthalein and 9 grams of *o*-sulfobenzoic anhydride in 200 cc. of ice water, which is kept in constant agitation while adding a solution containing 3 grams of potassium hydroxide in 50 cc. of water, and being particular to keep the mixture slightly alkalin during the reaction. The solution is filtered, extracted with ether, and subsequently evaporated to dryness. The substance was purified by dissolving in alcohol, filtering the solution and evaporating. It appears as a white amorphous powder which did not form crystals.

Alkalin solutions yield a red color. In other respects, it was found to be analogous to the members already described. Dried at 100° the substance was analyzed for phenolphthalein by hydrolyzing with potassium hydroxide, acidulating with phosphoric acid and extracting with ether.

Required phenolphthalein 60.71, found 60.10.

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[1] *Z. anal. Chem.*, **41**, 227.