SOME NEW METHODS FOR PREPARING BUNTE SALTS
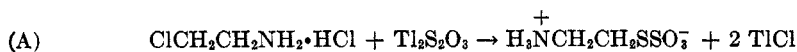
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While considering some industrial uses of S-alkyl and S-aryl thiosulfates, commonly referred to as "Bunte salts," we have investigated some novel methods of preparation which are reported in this paper (I–IV). We discuss the structure and color of aromatic sulfenic acids obtained in the alkaline hydrolysis of the S-aryl thiosulfates (V). There is also described a simple method for the preparation of 3-nitrobenzenethiol (VI).

I. A LABORATORY MODIFICATION OF THE BUNTE REACTION

Bunte (1) prepared sodium S-ethylthiosulfate by heating an aqueous solution of sodium thiosulfate with ethyl bromide, evaporating, and extracting the residue with alcohol. This method has been frequently used for the preparation of salts of S-alkylthiosulfuric acids. It has the disadvantage that both the Bunte salt and the sodium bromide formed in the reaction are soluble in water and are cumbersome to separate.

In attempting to apply the Bunte reaction to the preparation of S-2-amino-ethylthiosulfuric acid (2) from 2-chloroethylamine hydrochloride and sodium thiosulfate, considerable difficulty was encountered in the isolation and the purification of the desired compound. However, when thallous thiosulfate (3) was substituted for sodium thiosulfate, it was quite easy to isolate the compound in pure form.

The reaction proceeds according to the equation:

$$\text{(A)} \qquad \text{ClCH}_2\text{CH}_2\text{NH}_2 \cdot \text{HCl} + \text{Tl}_2\text{S}_2\text{O}_3 \rightarrow \overset{+}{\text{H}}_3\text{NCH}_2\text{CH}_2\text{SSO}_3^- + 2\,\text{TlCl}$$

in aqueous medium. Thallous thiosulfate is easily obtainable from the very soluble thallous formate and sodium thiosulfate. Since thallous chloride is only sparingly soluble in water, it is separated without difficulty from the thiosulfuric acid derivative.

II. PREPARATION OF AROMATIC BUNTE SALTS FROM SULFENYL CHLORIDES AND ALKALI METAL SULFITES

Geigy (4) prepared the sodium salt of S-2-nitro-phenylthiosulfuric acid from 2-nitrobenzenesulfenyl chloride and sodium sulfite in aqueous medium.

(B)
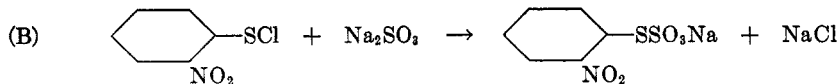
Since Geigy's thesis has not been published, his procedure is reported in the experimental part. We have also prepared the corresponding potassium salt. This method, however, is not generally applicable and works well only with sufficiently stable sulfenyl chlorides.

III. S-ARYL THIOSULFATES FROM AROMATIC SULFENAMIDES AND SULFUROUS ACID

When amides of aromatic sulfenic acids are treated with aqueous sulfurous acid, the following reaction occurs:

$$ArS—NR_2 + H_2SO_3 \rightarrow ArS—SO_3H, HNR_2$$
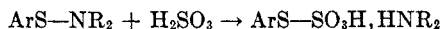
In many cases it is sufficient to slurry the amide in concentrated aqueous sulfurous acid and warm slightly: the amide goes into solution and evaporation gives a very good yield of the ammonium or amine salt of the S-arylthiosulfuric acid. In case the amide is very insoluble in water, it is necessary to work in aqueous alcohol.

By this method the following Bunte salts have been prepared: aniline salt of S-phenylthiosulfuric acid, dimethylamine salt of S-2-nitrophenylthiosulfuric acid, cyclohexylamine and piperidine salts of S-2,4-dinitrophenylthiosulfuric acid, ammonium salt of S-1-anthraquinonylthiosulfuric acid, diethylamine and dicyclohexylamine salts of S-3-nitrophenylthiosulfuric acid. The reaction failed with the morpholide of 2-benzothiazolesulfenic acid which was reduced to 2-mercaptobenzothiazole and morpholine.

We were particularly eager to find a convenient method for the preparation of salts of S-3-nitrophenylthiosulfuric acid because we assumed that they would be efficient preventive and therapeutic drugs against coccidiosis of chickens, an assumption which was later proved to be correct. Bunte salts are hydrolyzed by acids to the corresponding thiol and sulfuric acid and we believed that such a hydrolysis would occur in the stomach. It has been known that 3-nitrobenzene-thiol (5) and the corresponding disulfide are efficient drugs, the latter one being extensively used against coccidiosis. As compared with these compounds, alkali metal salts of S-3-nitrophenylthiosulfuric acid have the advantage of being soluble in water. Therefore, we spent considerable time finding a suitable process for their preparation.

The method dealt with in this chapter proved to be too complicated in this specific instance. The starting material was bis(3-nitrophenyl) disulfide (6). This was chlorinated to the sulfenyl chloride which, however, was a liquid and was not obtained in a pure state. It had been prepared but not isolated before and had been subjected in a crude state to reactions with phenols (7). In order to be sure that the crude chlorination product really contained the desired 3-nitro-benzenesulfenyl chloride, we treated it with N,N-dimethylaniline and obtained a 73.3 % yield of the compound:
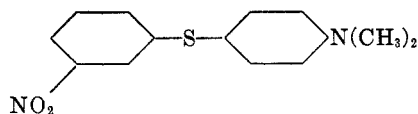
in a reasonably pure state. This method can be recommended for the identification of those sulfenyl chlorides that cannot be isolated in pure form.

The reaction of the crude 3-nitrobenzenesulfenyl chloride with diethylamine and with dicyclohexylamine gave the corresponding sulfenyl amides, which

again were liquid and resisted purification. When they were treated with sulfur dioxide in ethanol containing water, the desired Bunte salts were obtained. Another simpler process is dealt with in the next chapter.

IV. PREPARATION OF AROMATIC BUNTE SALTS FROM DISULFIDES AND ALKALI METAL BISULFITES

In the aliphatic series the reaction of the disulfide cystine with sulfite has been thoroughly investigated, since it plays a part in the colorimetric determination of cystine and cysteine with Folin's "uric acid reagent" (phospho-9-tungstic acid) (8). Cysteine reduces the heteropoly acid to a blue reduction product which is colorimetrically determined; the thiol is oxidized to the disulfide according to the equation:

(C) $2 \, RSH \rightarrow RS\text{—}SR + [2H]$

Cystine *per se* does not reduce Folin's reagent, but does so in the presence of sulfite because of the reversible (9) reaction (10):

(D) $RS\text{—}SR + HSO_3Na \rightleftharpoons RSH + RSSO_3Na$
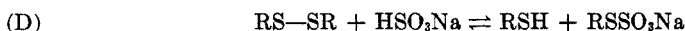
Since the cysteine is reoxidized to cystine by the heteropoly acid, all cystine is eventually converted into the Bunte salt, and when cysteine is treated with the phospho-9-tungstic acid in presence of sulfite, it likewise is converted into the Bunte salt and reduces an amount of the heteropoly acid double that without sulfite (11).

(E) $2 \, RSH + 2 \, HSO_3Na \rightarrow 2 \, RSSO_3Na + [4H]$
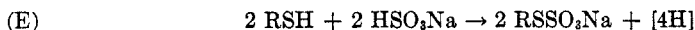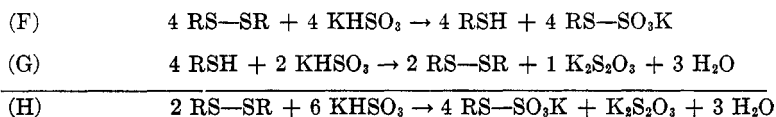
In the aromatic series disulfides substituted by amino groups (and only these) have been converted into Bunte salts by the action of sulfurous acid (12, 13).

We have now thoroughly investigated the reaction of bis(3-nitrophenyl) disulfide with sulfurous acid and sulfites and have found that sodium or potassium bisulfite will convert this disulfide in excellent yield into the corresponding Bunte salt, provided that certain conditions are observed.

According to the equation D, one-half of the disulfide molecule should be recovered as Bunte salt. However, the experiments gave almost theoretical yields for the conversion of both aryl-S groups into the thiosulfate. Thus an oxidation of the thiol must have occurred and we suspected that this oxidation was promoted by air. To our surprise, it was found that the same yield was obtained when the reaction was carried out in an atmosphere of nitrogen thoroughly freed from traces of oxygen. Therefore, it was concluded that it must be the bisulfite that reoxidizes the thiol to the disulfide. Indeed, in a separate experiment it was shown that 3-nitrobenzenethiol is oxidized to the disulfide by the action of bisulfite. What happens to the bisulfite has been determined in another experiment where we treated a large excess of benzenethiol with sodium bisulfite, thus reducing all of the bisulfite to the unknown inorganic reduction product: it was found that the latter is thiosulfate. As a consequence, it can be

said that the conversion of aromatic disulfides into Bunte salts by the action of alkali metal bisulfites involves two independent reactions:

(F)   4 RS—SR + 4 KHSO$_3$ → 4 RSH + 4 RS—SO$_3$K

(G)   4 RSH + 2 KHSO$_3$ → 2 RS—SR + 1 K$_2$S$_2$O$_3$ + 3 H$_2$O

(H)   2 RS—SR + 6 KHSO$_3$ → 4 RS—SO$_3$K + K$_2$S$_2$O$_3$ + 3 H$_2$O

Both reactions must occur if the transformation of the disulfide into the Bunte salt is to be successful. These two reactions are independent of each other. Some thiols are oxidized by bisulfite, but the corresponding disulfide does not react with bisulfite to give the Bunte salt. In other cases the disulfide reacts with bisulfite to give the Bunte salt, but the simultaneously formed thiol is not oxidized back and the yield of the Bunte salt is poor. Reaction G depends obviously upon the oxidation potential of the thiol. According to our limited experience, many aromatic thiols are oxidized by bisulfite while 2,2'-dithiobis-benzothiazole is reduced by it, which finding is in agreement with the scant available information (14) on the corresponding potentials.

The reaction of aromatic disulfides with alkali metal bisulfites must be carried out in a medium which has at least some solvent action on both reactants. Methanol containing a small amount of water is advantageous. It is necessary to use bisulfite. Disodium sulfite or dipotassium sulfite have a harmful effect on account of their alkalinity; they hydrolyze the Bunte salt. Sulfurous acid alone does not work, but it is advantageous to have some sulfur dioxide present in order to avoid the presence of disodium or dipotassium sulfite. The bisulfite may be produced from the hydroxide and sulfur dioxide or from the metabisulfite.

Since the main purpose of our work was to find an inexpensive process for the preparation of S-3-nitrophenyl thiosulfates, the scope of the reactions F, G, and H has been investigated only in a cursory manner. The dehydrogenation of the thiol by bisulfite (reaction G) has been accomplished with benzenethiol, 2-naphthalenethiol, 2-aminobenzenethiol, 2-benzoylaminobenzenethiol, and 3-nitrobenzenethiol; on the other hand, 2,2'-dithiobis-benzothiazole was reduced by sodium bisulfite.

The conversion of the disulfide into the Bunte salt (reaction H) was accomplished in good yield with bis(3-nitrophenyl) disulfide, bis(2-aminophenyl) disulfide, bis(2-benzoylaminophenyl) disulfide, and in poor yield with phenyl disulfide; no Bunte salt was isolated from bis(2-nitrophenyl) disulfide, bis(2-methoxyphenyl) disulfide, and 2,2'-dithiobis-benzothiazole.

With those thiols and disulfides that are substituted by o-amino groups sulfurous acid could be used instead of bisulfite, the reason being that the amino group forms the cation of the bisulfite.

### V. SOME REMARKS ABOUT THE STRUCTURE OF SULFENIC ACIDS

The salts of S-arylthiosulfuric acids described in this paper show the typical behavior of Bunte salts toward hydrolytic agents: acids hydrolyze them to the corresponding thiol plus sulfuric acid, while bases hydrolyze them to sulfite and the corresponding sulfenic acid, which in most cases immediately dispro-

portionates. Gutmann's (15) and Fromm's (16) explanation of the alkaline hydrolysis has been proved by Dornow (17) who isolated the 1-anthraquinone-sulfenic acid formed in the alkaline hydrolysis of the S-1-anthraquinonylthiosul-furic acid.

So far only two sulfenic acids have been isolated in the form of their potassium salts and only one in the form of the free acid (18). They are the just mentioned 1-anthraquinonesulfenic acid and its 4-amino derivative. Their potassium salts show a deep green color while the free acids are red. N. Kharasch (19) considered the possibility that a hydrogen bonding as shown in formula I

I   II   III
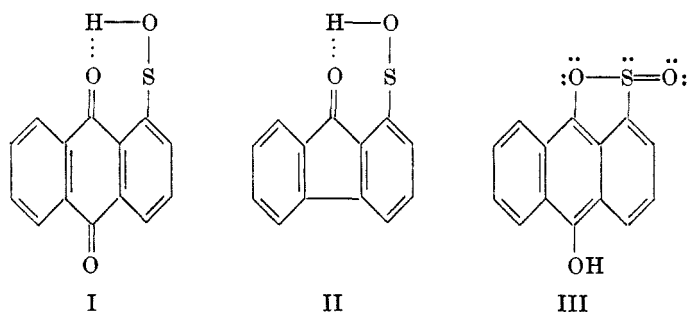
might be responsible for the stability of this sulfenic acid; however, he found later (20, 24) that a corresponding 1-fluorenonesulfenic acid (II) in which a similar hydrogen bonding should be possible was unstable. To us it seems more probable that the strong color as well as the stability of 1-anthraquinonesulfenic acid and its salts is due to the structure III. As far as the salts are concerned, it is probable that their anion is a resonance hybrid between the forms IV, V, VI, VII, and VIII:

IV   V   VI

VII   VIII
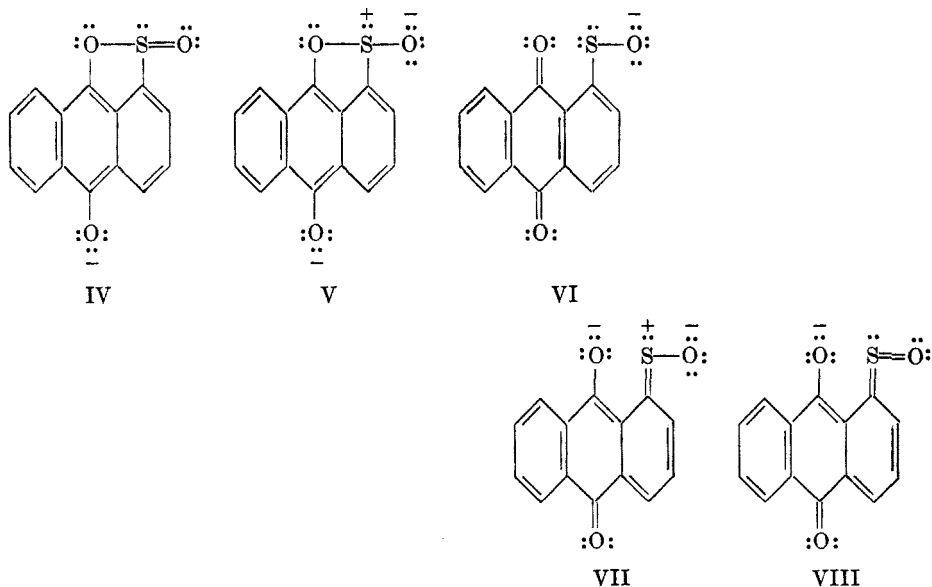
Actually there is no reason why an aromatic sulfenic acid, ArSOH, or its anion should show any conspicuous color. As a matter of fact, such colors have only been observed when the anion of the aromatic sulfenic acid, due to its substitution, is a resonance hybrid. Thus, solutions of the alkali metal salts of benzenesulfenic acid substituted in *ortho* position by a nitro group are blue (21). In this case the resonance hybrids may be formulated as follows:
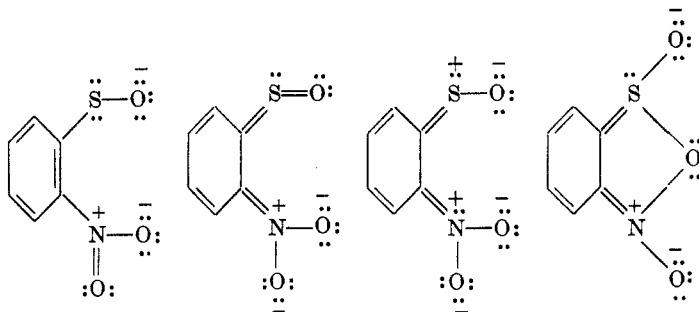
A similar explanation was applied to the formulation of salts of 2-nitrobenzene-selenenic acid (22). Solutions of the alkali metal salts of *p*-nitrobenzenesulfenic acid are cherry red (23). Solutions of the alkali metal salts of 2,4-dinitrobenzene-sulfenic acids are red. Also red are solutions of the alkali metal salts of anthra-quinone-2-sulfenic acid (24). Solutions of the same color are produced by the alkaline hydrolysis of the corresponding S-arylthiosulfuric acids. However, the alkaline hydrolyses of S-phenyl, of S-3-nitrophenyl, and of S-2-aminophenyl-thiosulfuric acids do not give anions of sulfenic acids which are stabilized by resonance or are colored, and these sulfenates decompose (disproportionate) immediately.

VI. PREPARATION OF 3-NITROBENZENETHIOL

The preparation of this simple aromatic thiol has been cumbersome in the past. It has been prepared from *m*-nitroaniline by the diazo xanthate method (25), from bis(3-nitrophenyl) disulfide by reduction with glucose and sodium hydroxide (26), or with sodium sulfide and sodium hydroxide (27). However, the thiol was either not isolated or obtained only in impure form. A very small amount of the pure compound has been obtained recently (28) by distilling the material obtained in the Leuckart reaction in a short-path still under 1 mm. pressure.

When the now easily accessible sodium or potassium salts of S-3-nitrophenyl-thiosulfuric acid are treated with concentrated hydrochloric acid, they are quickly and quantitatively hydrolyzed to sulfuric acid and 3-nitrobenzenethiol which can be extracted by means of an organic solvent. It is easy to prepare any amount of the thiol desired. It is a faintly yellow liquid which solidifies at low temperature. It is easily oxidized to the corresponding disulfide.

EXPERIMENTAL

Thallous thiosulfate. Sodium thiosulfate pentahydrate (24.8 g., 0.1 mole) was dissolved in 50 cc. of water and this solution was added to an agitated solution of 49.8 g. (0.2 mole)

of thallous formate in 60 cc. of water. The thallous thiosulfate—which is sparingly soluble in cold, more in hot water—precipitated as a heavy white solid and was filtered, washed and dried. Yield almost quantitative.

S-2-Aminoethylthiosulfuric acid. 2-Chloroethylamine hydrochloride (2.3 g., 0.02 mole) and 10.4 g. (0.02 mole) of thallous thiosulfate were added to 20 cc. of water and the mixture was agitated on a shaking machine for 20 hours. The thallous chloride formed was filtered and washed with 20 cc. of water; weight 9.4 g. (calc'd 9.6 g.). The aqueous filtrate was evaporated under reduced pressure at approximately 50°. The remaining sirup solidified in the vacuum desiccator; yield of crude product 2.6 g. (calc'd 3.1 g.). A portion (1.6 g.) was dissolved in 50 cc. of boiling methanol. From the clarified and cooled solution ether precipitated the pure S-2-aminoethylthiosulfuric acid, m.p. 195–196° (dec.). It is very soluble in water. Like other S-alkylthiosulfuric acids, it is hydrolyzed by acids and strong bases.

Anal. Calc'd for $C_2H_7NO_3S_2$: C, 15.3; H, 4.48; N, 8.9; S, 40.78.

Found: C, 15.6; H, 4.05; N, 8.84; S, 40.7.

S-2-Nitrophenyl thiosulfates from 2-nitrobenzenesulfenyl chloride. The preparation of the sodium salt has been described by Geigy (4) as follows. Sodium sulfite heptahydrate (25 g., 0.1 mole) and 19 g. (0.1 mole) of 2-nitrobenzenesulfenyl chloride were ground together in a mortar with addition of a little water until a homogeneous, light yellow slurry was formed. Cold water (300 cc.) was added and the solution obtained was clarified and evaporated under reduced pressure, keeping the temperature below 60°. The residue was extracted with 100 cc. of absolute alcohol with slight warming. Ether precipitated from the filtrate the sodium salt of the S-2-nitrophenylthiosulfuric acid in the form of light yellow crystals. Yield 75% of theory.

Anal. Calc'd for $C_6H_4NNaO_5S_2$: N, 5.44; Na, 8.94; S, 24.93.

Found: N, 5.45; Na, 8.76; S, 24.89.

The salt is very soluble in alcohol and water, also soluble in ethyl acetate but insoluble in chloroform and ether.

Acids hydrolyze it to 2-nitrobenzenethiol and sulfuric acid: the salt (1.3 g.) was dissolved in 30 cc. of dilute hydrochloric acid and the solution was evaporated under reduced pressure. From the residue ether extracted 0.6 g. of the thiol, which represents an 80% yield. This method can be used for the preparation of 2-nitrobenzenethiol; in this case, the isolation of the Bunte salt is not necessary and the clarified aqueous solution resulting from the reaction of the sulfenyl chloride with sodium sulfite can be directly treated with hydrochloric acid.

The sodium S-2-nitrophenyl thiosulfate dissolves in aqueous sodium hydroxide with a deep blue color, being hydrolyzed to sulfite and the corresponding sulfenic acid. Ammonia, however, does not convert it into the blue sulfenate.

We prepared in an analogous manner the corresponding potassium salt which is less soluble in water.

Anal. Calc'd for $C_6H_4KNO_5S_2$: C, 26.37; H, 1.47; K, 14.3; N, 5.12; S, 23.4.

Found: C, 26.4; H, 1.45; K, 14.6; N, 5.25; S, 23.2.

Aniline salt of S-phenylthiosulfuric acid. The anilide of benzenesulfenic acid (29) (2.0 g., 0.01 mole) was slurried in 100 cc. of a concentrated solution of sulfur dioxide in water. The slurry was gradually heated to the boil, the solution formed was clarified by filtration, and the filtrate was evaporated under reduced pressure. Crude yield 2.3 g. (calc'd 2.8 g.). The compound was purified by dissolving in alcohol and precipitating with ether; 2.0 g., m.p. 179–181° (dec.). Colorless crystals, soluble in alcohol and water.

Anal. Calc'd for $C_{12}H_{13}NO_3S_2$: C, 50.87; H, 4.62; N, 4.94; S, 22.6.

Found: C, 50.7; H, 4.63; N, 5.42; S, 23.0.

The salt is not very soluble in water but dissolves easily upon addition of sodium hydroxide; however, the solution decomposes very fast. Also a solution of the salt in methanol when treated with potassium hydroxide decomposes quickly.

Other salts of S-phenylthiosulfuric acid have been prepared through a different reaction by Baumgarten (30).

Dimethylamine salt of S-2-nitro-phenylthiosulfuric acid. The dimethylamide of 2-nitro-benzenesulfenic acid (31) (3 g., 0.015 mole) was slurried in 100 cc. of a concentrated aqueous solution of sulfur dioxide. Most of the solid went into solution at room temperature and eventually the reaction was finished at 45–50°. The clarified yellow solution was evaporated under reduced pressure and left behind 3.8 g. (calc'd 4.2 g.) of the yellow crystalline compound. M.p. 105–107°.

Anal. Calc'd for $C_8H_{12}N_2O_5S_2$: C, 34.27; H, 4.31; N, 10.0; S, 22.87.

Found: C, 34.1; H, 4.23; N, 9.85; S, 23.1.

When a solution of potassium hydroxide in methanol is added to a solution of the salt, the yellow potassium salt of S-2-nitrophenylthiosulfuric acid, which is rather insoluble in methanol and in water, precipitates. It is also formed on addition of potassium chloride to an aqueous solution of the dimethylamine salt. The sodium salt is quite soluble. When the aqueous solution is treated with sodium hydroxide, the deep blue color of the sulfenate develops.

Cyclohexylamine salt of S-2,4-dinitro-phenylthiosulfuric acid. The cyclohexylamide of 2,4-dinitro-benzenesulfenic acid (32) (2.0 g.) was dissolved in 50 cc. of alcohol with slight heating. Then 100 cc. of a concentrated aqueous solution of sulfur dioxide was added with agitation. The turbid mixture was heated almost to the boil and then cooled. The yellow crystalline precipitate was filtered and washed with a little water. Yield 1.6 g. The salt decomposes on heating at about 189° and is soluble in water, giving a yellow solution.

Anal. Calc'd for $C_{12}H_{17}N_3O_7S_2$: C, 38.0; H, 4.51; N, 11.07; S, 16.9.

Found: C, 37.9; H, 4.46; N, 10.8; S, 16.6.

When a solution of potassium hydroxide in methanol is added to a solution of the above described salt in methanol, the potassium salt of the thiosulfuric acid precipitates. However, at high concentration hydrolysis takes place and the red sulfenate is formed. The cyclohexylamine salt is not very soluble in water; upon addition of sodium hydroxide a deep red-brown solution of the sulfenate is formed.

Piperidine salt of S-2,4-dinitrophenylthiosulfuric acid. The piperidide of 2,4-dinitro-benzenesulfenic acid was obtained from the sulfenyl chloride and piperidine in ether. M.p. 143–145° after recrystallization from alcohol.

Anal. Calc'd for $C_{11}H_{13}N_3O_4S$: C, 46.6; H, 4.6; N, 14.8; S, 11.0.

Found: C, 46.5; H, 4.24; N, 15.0; S, 11.0.

This piperidide (2.0 g.) was dissolved in 100 cc. of alcohol with heating. Then 50 cc. of a concentrated solution of sulfur dioxide in water was added to the orange solution of the piperidide. The orange color changed immediately to a pale yellow. The solution was heated almost to the boil and then evaporated under reduced pressure. The yellow crystalline residue weighed 2.5 g., representing an almost theoretical yield, and melted at 125–130° (dec.). Easily soluble in water, acetone, alcohol, and chloroform.

Anal. Calc'd for $C_{11}H_{15}N_3O_7S_2$: C, 36.15; H, 4.13; N, 11.5; S, 17.54.

Found: C, 36.4; H, 3.92; N, 11.8; S, 17.1.

Ammonium salt of S-1-anthraquinonylthiosulfuric acid. The amide of 1-anthraquinone-sulfenic acid (24) (1.0 g.) was slurried in a mixture of 100 cc. of alcohol and 10 cc. of water, and sulfur dioxide was passed in. A slightly exothermic reaction took place and the orange solid gradually went into solution. The solution was eventually heated to the boil and clarified. Ether precipitated 1.1 g. of yellow crystals of the desired salt. M.p. above 300°.

Anal. Calc'd for $C_{14}H_{11}NO_5S_2$: C, 49.84; H, 3.29; N, 4.15; S, 19.0.

Found: C, 49.7; H, 3.15; N, 4.18; S, 19.3.

Other salts of S-1-anthraquinonylthiosulfuric acid have been prepared by Dornow (17) through a different reaction.

When a solution of potassium hydroxide in methanol is added to a solution of the above described ammonium salt in methanol, an insoluble and rather stable potassium salt of the S-1-anthraquinonylthiosulfuric acid is precipitated; only on boiling a slow hydrolysis takes place with development of a green coloration. When sodium hydroxide is added to an aqueous solution of the ammonium salt, there is formed immediately a slimy green pre-

cipitate of the sodium salt of the sulfenic acid, which on stirring goes into solution with intense green-blue color.

3-Nitrobenzenesulfenyl chloride. Bis(3-nitrophenyl) disulfide (50 g.) was slurried in 180 cc. of carbon tetrachloride and dry chlorine was bubbled in. The slurry was agitated and protected against the access of humid air. The tan slurry gradually became yellow and within one hour most of the product had gone into solution. Two drops of concentrated sulfuric acid were added as catalyst (33) and the chlorination was continued for half an hour. A small amount of undissolved material was removed by filtration and the resulting amber solution was concentrated under reduced pressure. The residue was a dark oil; all attempts to crystallize it failed. As shown by the next experiment, it was crude 3-nitrobenzenesulfenyl chloride.

Reaction of 3-nitrobenzenesulfenyl chloride with N,N-dimethylaniline. Bis(3-nitrophenyl) disulfide (15.0 g., 0.05 mole) was slurried in 50 cc. of carbon tetrachloride. A solution of 0.052 mole of chlorine was prepared by saturating 15 cc. of carbon tetrachloride with chlorine at 0°. This chlorine solution was added to the slurry of the disulfide. The resulting clear solution was stirred for about an hour and then 25 g. (0.21 mole) of N,N-dimethylaniline dissolved in 25 cc. of carbon tetrachloride was gradually added within 15 minutes. A slightly exothermic reaction took place, but the temperature was kept below 40°. An oily layer separated. The mixture was stirred for a few hours more and then about 100 cc. of 5 N hydrochloric acid was added. The aqueous layer was separated and the carbon tetrachloride layer was extracted with another 20 cc. of 5 N hydrochloric acid. The combined aqueous extracts were neutralized with 5 N sodium hydroxide solution and the excess N,N-dimethylaniline was stripped off with steam. The residual orange slurry was filtered. The crude product weighed 25.2 g. It was treated with 100 cc. of methyl alcohol to leave 20.1 g. of the 3-nitrophenyl-4'-dimethylaminophenyl sulfide; this corresponds to a 73.3% yield of a reasonably pure product. It was finally purified by recrystallization from glacial acetic acid, giving orange crystals. M.p. 115–116°.

Anal. Calc'd for $C_{14}H_{14}N_2O_2S$: C, 61.3; H, 5.14; N, 10.2; S, 11.7.

Found: C, 60.9; H, 4.94; N, 10.3; S, 11.9.

Salts of S-3-nitrophenylthiosulfuric acid. A solution of S-3-nitrobenzenesulfenyl chloride in 50 cc. of carbon tetrachloride was prepared from 25 g. (0.082 mole) of the disulfide as described in the preceding item. This solution was added gradually to a solution of 30 g. (0.4 mole) of diethylamine in 100 cc. of carbon tetrachloride with stirring and cooling. The resulting slurry was filtered to remove the diethylamine hydrochloride formed and then evaporated under reduced pressure, leaving 41 g. of an amber liquid representing the crude diethylamide of the sulfenic acid. Attempts to obtain it in crystalline form were unsuccessful.

Six grams of this crude diethylamide were dissolved in 90 cc. of ethanol and 10 cc. of water and then sulfur dioxide was bubbled into the solution for one hour. There was a slight exothermic reaction and the solution became lighter in color. It was heated to 50–60°, clarified, and allowed to evaporate. The residue was dissolved in alcohol and precipitated by ether; isolated yield 4.3 g.

The diethylamine salt of S-3-nitrophenylthiosulfuric acid melts at 89–90° and is easily soluble in water.

Anal. Calc'd for $C_{10}H_{16}N_2O_5S_2$: C, 38.94; H, 5.23; N, 9.08; S, 20.79.

Found: C, 38.8; H, 4.95; N, 9.15; S, 20.8.

When a solution of potassium hydroxide in methanol is added to a solution of this diethylamine salt in methanol, the potassium salt of S-3-nitrophenylthiosulfuric acid precipitates; m.p. 197–198° (dec.).

Anal. Calc'd for $C_6H_4KNO_5S_2$: C, 26.37; H, 1.47; K, 14.3; N, 5.12; S, 23.4.

Found: C, 26.5, 26.5; H, 1.69, 1.70; K, 14.3; N, 5.26; S, 23.3.

The potassium salt is soluble in water. When an aqueous solution is treated with sodium hydroxide no color develops but the solution gets cloudy immediately and decomposes.

A dicyclohexylamine salt of S-3-nitrophenylthiosulfuric acid was also prepared in the same manner as the diethylamine salt. Yield poor, m.p. 145–147°.

Anal. Calc'd for $C_{18}H_{28}N_2O_5S_2$: C, 51.9; H, 6.77; N, 6.73; S, 15.39.

Found: C, 51.9; H, 6.68; N, 7.04; S, 15.0.

Attempted preparation of 2-benzothiazolylthiosulfuric acid. The morpholide of 2-benzo-thiazolesulfenic acid (5 g.) was slurried in 200 cc. of water and sulfur dioxide was passed into the agitated slurry for three hours. The mixture was filtered hot, leaving behind 2.56 g. undissolved 2-mercaptobenzothiazole which—after recrystallization from benzene—was identified by m.p. and mixture m.p. In an alcoholic medium the reaction proceeded in the same manner.

Reaction of bis(3-nitrophenyl) disulfide with potassium bisulfite. An aliquot of a solution of SO_2 in methanol corresponding to 0.06 mole of SO_2 in 6.3 cc. of methanol was added to a solution of 0.06 mole of KOH in 50 cc. of methanol. The disulfide (4.6 g., 0.015 mole) was rinsed in with 19 cc. of methanol and 5 cc. of water. The mixture was refluxed for $1\frac{1}{2}$ hours. The slurry became yellow and a large portion of the solid went into solution. Potassium hydroxide (0.015 mole) dissolved in methanol was added to convert the excess of bisulfite into sulfite. Then the slurry was filtered hot and the residue was washed with 25 cc. of boiling methanol. The filtrate was eventually cooled to 0°, and the crystalline precipitate was filtered and washed with 25 cc. of cold methanol. A yield of 6.6 g. (80.5% of theory) of potassium S-3-nitrophenyl thiosulfate was obtained. The product was free of sulfite. The mother liquor contained approximately 5% more of the Bunte salt, which was recoverable by evaporation but contaminated with sulfite.

The presence of a small amount of water is necessary to get some $KHSO_3$ into solution. The neutralization of the excess of $KHSO_3$, when the reaction is over, is done in order to produce K_2SO_3, which is less soluble in wet methanol. The preparation of the pure potassium salt of S-3-nitrophenylthiosulfuric acid is simpler than that of the sodium salt because the former is sparingly soluble in the cold reaction medium.

In parallel experiments it was determined that the same yield of potassium salt is obtained regardless of whether the reaction is carried out in a stream of air or nitrogen; with irradiation or in the dark; in absence or presence of hydroquinone. K_2SO_3 does not react with the disulfide in boiling methanol containing a little water; it affects, however, the Bunte salt and therefore its presence during the reaction has a harmful effect. Sulfur dioxide does not react with the disulfide; a little more sulfur dioxide than is needed for the bisulfite formation is advantageous because it eliminates the danger of the presence of K_2SO_3 during the reaction.

Reaction of bis(3-nitrophenyl) disulfide with sodium bisulfite. A mixture of 5.7 g. of sodium metabisulfite (corresponding to 0.06 mole of $NaHSO_3$), 5 cc. of water, 4.6 g. (0.015 mole) of bis(3-nitrophenyl) disulfide, and 75 cc. of methanol was refluxed with stirring for two hours. Then 0.6 g. (0.015 mole) of NaOH was added to convert the excess $NaHSO_3$ to Na_2SO_3. The resulting slurry was filtered at room temperature and the residue was washed with 25 cc. of methanol. The methanol filtrate was evaporated, leaving a crystalline residue of 8.2 g. which contained sulfite. Therefore, the product was treated with 100 cc. of dry methanol, and the solution was clarified to free it from sulfite and again evaporated. Yield of pure sulfite-free sodium S-3-nitrophenyl thiosulfate was 7.4 g. (95% of theory).

Anal. Calc'd for $C_6H_4NNaO_5S_2 + H_2O$: C, 26.18; H, 2.19; N, 5.08; Na, 8.3; S, 23.29.

Found: C, 26.1; H, 1.86; N, 5.03; Na, 8.70; S, 23.2.

Since the sodium salt is much more soluble than the potassium salt, it must be recovered by evaporation and the crude product is contaminated with sulfite which is a little soluble in wet methanol. Therefore, an extraction with dry methanol is necessary.

3-Nitrobenzenethiol. Potassium S-3-nitrophenyl thiosulfate (2.0 g.) and 25 cc. of concentrated hydrochloric acid were charged into a small glass-stoppered bottle. After a few hours' shaking, the salt had disappeared and a yellow oil had separated at the bottom of the solution. The mixture was treated with a little water and benzene. The layers were separated and the organic layer was dried over calcium chloride. The benzene solution left on evaporation pure 3-nitrobenzenethiol. This is a faintly yellow oil which crystallizes only at very low temperature.

When 3-nitrobenzenethiol is treated with sodium metabisulfite in wet methanol, it is converted into the corresponding disulfide.

Reaction of bis(2-benzoylaminophenyl) disulfide with sodium bisulfite. A slurry of 6.8 g. (0.015 mole) of this disulfide and 5.7 g. of sodium metabisulfite (corresponding to 0.06 mole of $NaHSO_3$) in 75 cc. of methanol plus 5 cc. of water was refluxed for half an hour. The slurry turned yellow, then dark brown. It was filtered hot and the inorganic residue was washed with 30 cc. of boiling methanol. Evaporation of the methanol filtrate gave 9.5 g. of a crude Bunte salt contaminated by sulfite. It was extracted with 85 cc. of methanol and on evaporation of the extract there was obtained 8.9 g. (89.5% of theory) of the sodium salt of S-2-benzoylaminophenylthiosulfuric acid. It was free of sulfite, but, as the analysis shows, not quite pure yet.

Anal. Calc'd for $C_{13}H_{10}NNaO_4S_2$: C, 47.12; H, 3.04; N, 4.23; Na, 6.94; S, 19.35.

Found: C, 45.3, 45.4; H, 3.05, 2.83; N, 4.45; Na, 8.04; S, 19.7.

Attempted reaction of bis(2-nitrophenyl) disulfide with sodium bisulfite. When 0.015 mole of this disulfide was refluxed with 0.06 mole of $NaHSO_3$ in 75 cc. of methanol plus 5 cc. of water for four hours, 93.5% of the disulfide was recovered unchanged by slurrying the undissolved portion with water (to remove inorganic salts). The methanol filtrate was evaporated under reduced pressure and left a residue which was largely sodium sulfite. It contained, however, a small amount of the desired Bunte salt, since it gave a deep blue color when treated with 20% NaOH solution.

Attempted reaction of bis(2-methoxyphenyl) disulfide with sodium bisulfite. A slurry of 4.2 g. (0.015 mole) of this disulfide and 5.7 g. of sodium metabisulfite (corresponding to 0.06 mole of $NaHSO_3$) in 75 cc. of methanol plus 5 cc. of water was refluxed for 4 hours. Then 0.6 g. (0.015 mole) of NaOH was added and the slurry was filtered hot and the residue was washed with 30 cc. of boiling methanol. By extraction of the residue with water, 3.18 g. of unchanged starting material was isolated and another 0.35 g. of the disulfide was recovered from the methanol solution, making a total recovery of 84% of unchanged disulfide. No Bunte salt could be isolated.

Reaction of 2,2'-dithiobis-benzothiazole with sodium bisulfite. A slurry of 5.0 g. (0.015 mole) of the disulfide and 5.7 g. of sodium metabisulfite (corresponding to 0.06 mole of $NaHSO_3$) in 75 cc. of methanol plus 5 cc. of water was refluxed for 4 hours. Then 0.6 g. (0.015 mole) of NaOH was added and the slurry was filtered hot and the residue was washed with boiling methanol. The filtrate did not yield any solid on cooling and therefore was diluted with water and chilled; 4.2 g. of 2-mercaptobenzothiazole separated. Its yield amounted to 86% of theory and it was identified by mixture melting point.

Variations of reaction conditions had no effect: the bisulfite always reduced the disulfide to the thiol.

Reaction of bis(2-aminophenyl) disulfide with sulfurous acid in water. The disulfide (40 g.) was stirred with 400 cc. of a freshly prepared saturated solution of sulfur dioxide in water and the slurry was slowly heated to the boil. Most of the solid went into solution which was clarified hot. On cooling, the white crystalline Bunte salt, *i.e.*, the internal salt of S-2-aminophenylthiosulfuric acid separated in a yield of 88.8% of theory; m.p. 189–190° (dec.).

Anal. Calc'd for $C_6H_7NO_3S_2$: C, 35.12; H, 3.44; N, 6.82; S, 31.24.

Found: C, 34.8; H, 3.59; N, 6.75; S, 30.8.

The first phase of this reaction, *i.e.*, the splitting of the S—S bond to give one molecule of thiol and one molecule of Bunte salt, is reversible as shown by the following experiment: 2-Aminobenzenethiol (5.0 g., 0.04 mole) and 8.2 g. (0.04 mole) of S-2-aminophenylthio-sulfuric acid (internal salt) were slurried in 150 cc. of water and heated with stirring to the boil. A tan oil formed which on cooling solidified to a yellow solid. This was 6.6 g. (66% of theory) of crude bis(2-aminophenyl) disulfide.

Reaction of 2-aminobenzenethiol with aqueous sulfurous acid. Sulfur dioxide was passed into 125 cc. of water with stirring and after awhile 10 g. of 2-aminobenzenethiol was added dropwise with stirring within about 1½ hours. The sulfur dioxide stream was continued for another hour and then the mixture was heated to the boil and filtered hot. On cooling there separated 12.2 g. (74.4% of theory) of S-2-aminophenylthiosulfuric acid (internal salt).

Reaction of phenyl disulfide with potassium bisulfite. Air and sulfur dioxide were introduced into a slurry of 6.5 g. (0.03 mole) of phenyl disulfide in a solution of 0.09 mole of KOH in 65 cc. of methanol plus 2 cc. of water. A slightly exothermic reaction took place and the slurry turned a pale yellow. It was refluxed for one hour, cooled to room temperature, and filtered; the methanol filtrate was evaporated and both solid fractions were combined and extracted with ether. The ether extract contained 5.3 g. (81.5%) of the starting material phenyl disulfide. The ether-insoluble portion was extracted with boiling methanol and, on cooling the methanol extract, 1.5 g. (11% of theory) of potassium S-phenyl thiosulfate crystallized out.

Anal. Calc'd for $C_6H_5KO_3S_2$: C, 31.56; H, 2.20; K, 17.12; S, 28.08.

Found: C, 31.7; H, 2.27; K, 17.5; S, 28.2.

Dehydrogenation of benzenethiol by potassium bisulfite. Into a 3-neck flask equipped with stirrer and reflux condenser there were charged 2.0 g. of potassium metabisulfite (corresponding to 0.018 mole $KHSO_3$), 75 cc. of methanol, and 5 cc. of water. The mixture was stirred for 45 minutes while a stream of oxygen-free nitrogen was flowing through the flask to replace the air. Then 10 g. (0.09 mole) of benzenethiol was added and the mixture was refluxed for 5 hours longer with the nitrogen continuing to flow. The slurry was filtered hot into a flask containing mercuric oxide to react with the unchanged benzenethiol. The inorganic filter residue was washed with 37.5 cc. of boiling methanol. After the mercury salt of the benzenethiol was removed, 5.0 g. of phenyl disulfide could be isolated from the methanol solution.

In this experiment there was purposely used an excess of the thiol so that all of the bisulfite would be reduced and its reduction product could be identified. About half of the thiol used or 0.045 mole was oxidized to the disulfide while, according to the equation G, 0.018 mole of bisulfite should have oxidized only 0.036 mole of the thiol; probably some air oxidation occurred during the working up.

The inorganic residue was freed from remaining traces of phenyl disulfide by treatment with ether and then identified as potassium thiosulfate by a number of well-known qualitative reactions (behavior to silver nitrate, acids, ferric chloride, barium chloride, zinc sulfate, cupric sulfate).

A similar experiment was carried out with 0.09 mole of $KHSO_3$ and 0.09 mole of benzenethiol in the presence of 0.8 g. of hydroquinone (nitrogen atmosphere). The residue obtained by evaporating the methanol solution was treated with hexane: 6.4 g. phenyl disulfide (65.2% of theory) went into solution and 1.1 g. (5.4% of theory) of the Bunte salt, potassium S-phenyl thiosulfate, remained undissolved.

Dehydrogenation of 2-naphthalenethiol by sodium bisulfite. A slurry of 4.8 g. (0.03 mole) of the thiol and 5.7 g. of sodium metabisulfite (corresponding to 0.06 mole of $NaHSO_3$) in 75 cc. of methanol and 5 cc. of water was refluxed for 2 hours. Then another 50 cc. of methanol was added and the slurry was filtered hot. The inorganic residue was washed with boiling methanol and then extracted with water, leaving behind 3.5 g. of bis(2-naphthyl) disulfide. Another 0.66 g. of this disulfide was obtained from the methanol solution, *i.e.*, the thiol was dehydrogenated in a yield of 87.5%.

SUMMARY

1. Thallous thiosulfate has been used to advantage instead of sodium thiosulfate in the preparation of S-2-aminoethylthiosulfuric acid.

2. Alkali metal salts of S-2-nitrophenylthiosulfuric acid have been prepared from 2-nitrobenezenesulfenyl chloride and alkali metal sulfite.

3. Ammonium and amine salts of S-arylthiosulfuric acids can be prepared by treating the sulfenamides with sulfurous acid.

4. Alkali metal bisulfites in methanol (containing water) dehydrogenate many aromatic thiols to the disulfides, the bisulfites being reduced to thiosulfates.

5. Alkali metal bisulfites in methanol (containing water) convert some aro-

matic disulfides, among them bis(3-nitrophenyl) disulfide, into the Bunte salts in very good yields. The course of this reaction is discussed.

6. 3-Nitrobenzenethiol is advantageously prepared by acid hydrolysis of the corresponding Bunte salts.

7. The stability and intense color of some aromatic sulfenic acids are probably due to resonance.

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