The Action of Hydrogen Sulfide on Aminoalkanethiosulfuric Acids (Bunte Salts) to Give Di-, Tri-, and Tetrasulfides

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The reaction of hydrogen sulfide with several alkanethiosulfuric acids bearing amino functions has been studied. When primary and secondary aminoalkanethiosulfuric acids were treated with hydrogen sulfide, the product isolated in each case was the bis(aminoalkyl) disulfide thiosulfuric acid salt. 2-Aminoethaneselenosulfuric acid gave the corresponding diselenide XIV. Of the five *tert*-amino compounds treated with hydrogen sulfide, only 2-(dimethylamino)ethanethiosulfuric acid gave the expected disulfide. 2-Morpholinoethanethiosulfuric acid (III) gave the corresponding sulfenyl thiosulfate IV and trisulfide V. The other *tert*-aminoalkanethiosulfuric acids produced tetrasulfides. Of these, di-*n*-heptylaminoethanethiosulfuric acid gave a tetrasulfide which formed an unusually stable complex VII with six molecules of hydrogen sulfide. The synthesis of two unsaturated Bunte salts, 4-amino-2-butene-1-thiosulfuric acid (XVI) and 4-amino-2-butyne-1-thiosulfuric acid (XVII), has been achieved in a novel manner.

The reaction of sulfide ion with organic thiosulfates (Bunte salts) is fascinating in that the type of product obtained varies with the nature of the Bunte salt. For example, Bernthsen[1] and Levkoev, *et al.*,[2] prepared thiophenols from aromatic thiosulfates by treating them with inorganic sulfides. When the reaction was performed with sodium *o*-nitrophenylthiosulfate[3] or aliphatic Bunte salts, such as *N*-cyclohexylcarbamoylmethylthiosulfate,[3] sodium phenoxycarbonylmethylthiosulfate,[3] sodium 2-amino-2-carboxyethylthiosulfate (sodium *S*-sulfocysteine),[3] sodium *S*-2-oxocyclohexylthiosulfate,[4] or potassium 2-ureidoethylthiosulfate,[5] the corresponding disulfides were obtained. However, under essentially identical conditions, sulfide treatment of Bunte salts such as ethyl-,[3,6] allyl-,[3,6] benzyl-,[3] and *p*-tolylthiosulfates[3] gave trisulfides. Disodium trimethylenedithiosulfate[7] and disodium *o*-phenylenedithiosulfate[7] gave cyclic trisulfides, while sodium benzamidoethylthiosulfate[5] gave a mixture of the corresponding di- and trisulfides. By modifying the reaction mixture so that it contained formaldehyde to trap the sulfite formed, the tetrasulfide was obtained in addition to the di- and trisulfides when sodium methylthiosulfate was the starting Bunte salt.[6] Gutmann[8] claimed that the reaction of sodium ethylthiosulfate with potassium sulfide in ethanol gave a yellow solution of ethyl hydrodisulfide. Further information pertaining to this reaction may be found in a recent review.[9]

The apparent lack of predictability of the reaction of sulfide ion with organic thiosulfates has led us to investigate several aspects of it. Since sodium 2-amino-2-carboxyethylthiosulfate was the only amino-Bunte salt studied previously,[3] a number of aminoalkanethiosulfuric acids were treated with hydrogen sulfide to determine what effect, if any, the amino group had on the nature of the final product.

When hydrogen sulfide was bubbled into an essentially neutral aqueous solution of 2-aminoethanethiosulfuric acid (I), a zwitterionic Bunte salt, the precipitation of elemental sulfur occurred within several minutes. Hydrogen sulfide was added until the reaction was complete and after removal of the sulfur from the mixture, bis(2-aminoethyl) disulfide (cystamine) was obtained in good yield as its thiosulfuric acid salt II (eq 1). The latter was identified by elemental analysis

$$\underset{\text{I}}{2H_2NCH_2CH_2SSO_3H} + 3H_2S \longrightarrow \underset{\text{II}}{(H_2NCH_2CH_2S-)_2\cdot H_2S_2O_3} + 3S + 3H_2O \quad (1)$$

and its ir spectrum which showed intense peaks in the region of 9.09, 10.0, and 15.05 μ, typical of a thiosulfuric acid salt.[10] An authentic sample of II was prepared by treating cystamine dihydrochloride with 1 equiv of sodium thiosulfate (eq 2). The stoichiometry

$$(H_2NCH_2CH_2S-)_2\cdot 2HCl + Na_2S_2O_3 \longrightarrow \text{II} + 2NaCl \quad (2)$$

of eq 1 was verified by obtaining >95% of the calculated quantity of sulfur in several runs and was found to apply to reactions of water-soluble Bunte salts bearing primary and secondary amino groups (*cf.* Table I).

The reaction is visualized as taking place by a stepwise mechanism, in which hydrosulfide ion attacks the sulfenyl sulfur atom of I to form the aminoethylhydrodisulfide anion and sulfurous acid (eq 3). The hydrodisulfide anion then reacts with unreacted I to generate cystamine and thiosulfuric acid (eq 4). In a somewhat analogous reaction, Kawamura, *et al.*,[11] proposed that sodium benzylthiosulfate combines with benzylhydrodisulfide to account for the formation of dibenzyl di-

$$\text{I} + HS^- \longrightarrow [H_2NCH_2CH_2SS^-] + H_2SO_3 \quad (3)$$

$$[H_2NCH_2CH_2SS^-] + \text{I} \longrightarrow (H_2NCH_2CH_2S-)_2 + H^+ + S_2O_3^{-2} \quad (4)$$

$$H_2SO_3 + 2H_2S \longrightarrow 3S + 3H_2O \quad (5)$$

(1) A. Bernthsen, *Justus Liebigs Ann. Chem.*, **251**, 1 (1889).
(2) I. I. Levkoev, N. N. Svoshnikov, I. N. Gorbacheva, N. S. Barvyn, and T. V. Krasnova, *Zh. Obshch. Khim.*, **24**, 280 (1954) [English translation: *J. Gen. Chem. USSR*, **24**, 283 (1954)].
(3) B. Milligan, B. Saville, and J. M. Swan, *J. Chem. Soc.*, 4850 (1961).
(4) B. Milligan and J. M. Swan, *ibid.*, 5552 (1961).
(5) K. Schimmelschmidt, H. Hofmann, E. Mundlos, G. Laber, and M. Schorr, *Chem. Ber.*, **96**, 38 (1963).
(6) B. Milligan, B. Saville, and J. M. Swan, *J. Chem. Soc.*, 3608 (1963).
(7) B. Milligan and J. M. Swan, *ibid.*, 2901 (1965).
(8) A. Gutmann, *Ber.*, **48**, 1162 (1915).
(9) D. L. Klayman and R. J. Shine, *Quart. Rep. Sulfur Chem.*, **3** [3], 189 (1968).
(10) F. A. Miller and C. H. Wilkins, *Anal. Chem.*, **24**, 1253 (1952); M. G. Voronkov and A. Ya. Legzdin, *Zh. Org. Khim.*, **3**, 465 (1967).
(11) S. Kawamura, Y. Otsuji, T. Nakabayashi, T. Kitao, and J. Tsurugi, *J. Org. Chem.*, **30**, 2711 (1965).

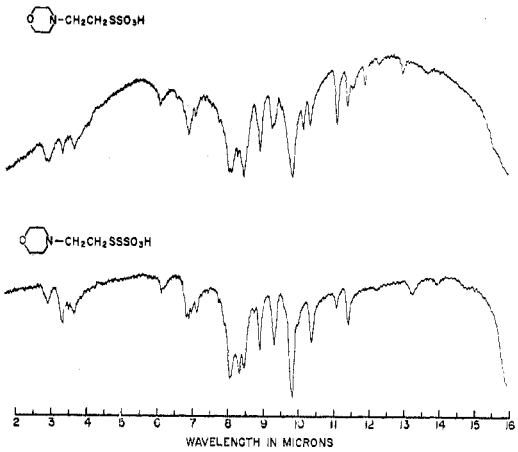


Figure 1.—Ir spectrum of III and IV.

sulfide and thiosulfate ion. In eq 5 the sulfurous acid is reduced by hydrogen sulfide.[12]

No sulfur precipitated when the sodium salt of I reacted with hydrogen sulfide in aqueous solution (eq 6). In addition to II, sodium thiosulfate was isolated

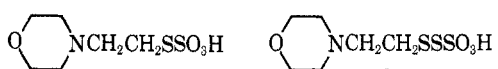
$$2H_2NCH_2CH_2SSO_3Na + H_2S \longrightarrow II + Na_2SO_3 \quad (6)$$

which formed according to eq 7.[13] Those aminoalkane-

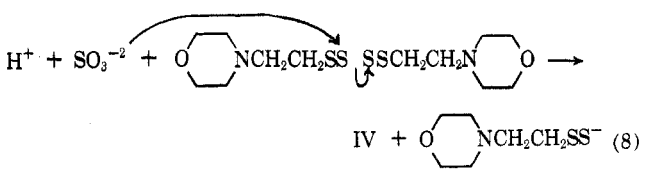
$$4Na_2SO_3 + 2H_2S \longrightarrow 3Na_2S_2O_3 + 2NaOH + H_2O \quad (7)$$

thiosulfuric acids which were water insoluble were solubilized by conversion to their sodium salts in an aqueous–methanolic solution prior to treatment with hydrogen sulfide.

While 2-(dimethylamino)ethanethiosulfuric acid gave the expected product, two anomalous reactions were found to occur with other alkylthiosulfuric acids possessing a tertiary amino group. The most unusual reaction was that of 2-morpholinoethanethiosulfuric acid (III) with hydrogen sulfide which gave a low yield of 2-morpholinoethanesulfenylthiosulfate (IV) and bis(2-



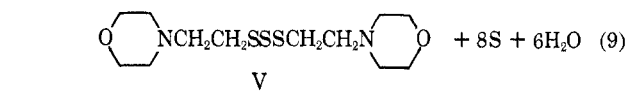
morpholinoethyl) trisulfide (V). The sulfenylthiosulfate IV was identified by elemental analysis and by its ir spectrum (Figure 1), which, while similar to that of III, differs from it in that there is a new peak at 8.30 μ, one missing at 10.10 μ, and an intensified absorption at 10.35 μ. Compound IV is less soluble in water than its parent Bunte salt III and tends to lose sulfur if its aqueous solution is heated excessively. Although the mechanism for its formation is not known with certainty, it is not unlikely that it involves the sulfite cleavage of bis(2-morpholinoethyl) tetrasulfide (eq 8),



(8)

the latter having originated by oxidation of the corresponding hydrodisulfide (*cf.* eq 3). The hydrodisulfide anion, a by-product in eq 8, is probably recycled to the tetrasulfide by a similar oxidative process.

On treating the sulfenylthiosulfate IV in aqueous solution with additional hydrogen sulfide, sulfur and the trisulfide V were isolated in a ratio close to that indicated by eq 9. The trisulfide V is difficult to obtain



in a very pure state due to its tendency to extrude elemental sulfur and leave the disulfide. While the di- and trisulfides have identical ir spectra, their behavior on tlc and their nmr spectra are dissimilar. The yield of the sulfenylthiosulfate could be improved by limiting the quantity of hydrogen sulfide reacting with III. Further investigation would be desirable to ascertain the influence of the morpholino moiety on the course of the above-described reaction.

Only recently has a sulfenylthiosulfate, obtained by a different route, been isolated[14] although another such compound was described earlier as an intermediate.[15]

The reaction of hydrogen sulfide with other Bunte salts bearing a tertiary amino group, *i.e.*, di-*n*-heptyl- and dibenzylaminoethanethiosulfuric acids, was also examined. Both gave difficultly purifiable heavy oils which analyzed as tetrasulfides and whose formation can be rationalized as having occurred through the oxidation of the intermediate hydrodisulfides (Table II).

The initial product obtained from the reaction of di-*n*-heptylaminoethanethiosulfuric acid is a low-melting, bright yellow crystalline solid which is stable at room temperature if kept in a closed container. The compound loses hydrogen sulfide slowly if left open to the atmosphere, at a moderate rate when heated gently *in vacuo*, and very rapidly when dissolved in various solvents, especially chloroform. The resultant chloroform solution, which loses its yellow color as the H_2S is dispelled, on evaporation leaves bis(diheptylaminoethyl) tetrasulfide and, sometimes, elemental sulfur. The yellow complex analyzed for the association of six molecules of hydrogen sulfide with each of the tetrasulfide and could be regenerated from a suspension of the tetrasulfide in methanol by bubbling hydrogen sulfide into it.

Another example of hydrogen sulfide complexation with a tertiary amine was reported by McDaniel and Evans[16] who prepared the hydrosulfide salt of triethylamine in methanol solution at 0°. The hydrosulfide salt reversibly absorbed 2 mol of hydrogen sulfide at −78.5°; however, the complex was not stable at room temperature. Hydrogen bonding of the additional 2 mol of H_2S with the hydrosulfide ion was held responsible for their uptake by the amine salt.

We propose, in our case, that the tetrasulfide which is formed at one of the initial stages of the reaction is converted into its dihydrosulfide salt VI which, in the pres-

(12) R. C. Brasted, "Comprehensive Inorganic Chemistry," Vol. VIII, Van Nostrand, Princeton, N. J., 1961, p 43.

(13) L. C. Schroeter, "Sulfur Dioxide," Pergamon Press, London, 1966, p 92.

(14) S. J. Brois, J. F. Pilot, and H. W. Barnum, *J. Amer. Chem. Soc.*, **92**, 7629 (1970).

(15) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).

(16) D. H. McDaniel and W. G. Evans, *Inorg. Chem.*, **5**, 2180 (1966).

Table I

Bis(aminoalkyl) Disulfide Thiosulfuric Acid Salts, $(RS-)_2 \cdot H_2S_2O_3$

	R	Registry no.	Mp, °C	% yield	Recrystn solvent	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1[a]	$H_2NCH_2CH_2-$		175–182 dec	91	H_2O	$C_4H_{14}N_2O_3S_4$	18.03	5.30	10.51	48.14	18.10	4.97	10.63	47.94
2[b]	$H_2N(CH_2)_6-$	31645-69-9	185–187	90	H_2O	$C_{12}H_{30}N_2O_3S_4$	38.07	7.99	7.40	33.87	38.09	7.96	7.47	33.77
3	$H_2NCH_2CH{=}CHCH_2-$	31645-70-2	143 dec	90	H_2O–EtOH	$C_8H_{18}N_2O_3S_4$	30.16	5.70	8.80	40.27	29.99	5.58	8.69	40.08
4[c]	$H_2NC(=NH)NHCH_2CH_2-$	31645-71-3	190–191 dec	55	H_2O	$C_6H_{18}N_6O_3S_4$	20.56	5.18	23.98	36.59	20.86	5.15	23.99	36.27
5[d]	n-$C_4H_9NHCH_2CH_2-$	31645-72-4	109–112	86	H_2O–EtOH	$C_{12}H_{30}N_2O_3S_4$	38.07	7.99	7.40	33.87	38.14	7.95	7.41	33.82
6[d]	n-$C_{10}H_{21}NHCH_2CH_2-$	31645-73-5	120–122	93[e]	MeOH	$C_{24}H_{54}N_2O_3S_4$	52.70	9.95	5.12	23.45	53.16	10.25	5.09	23.25
7[d]	$C_6H_5(CH_2)_4NHCH_2CH_2-$	31645-74-6	115–120	59[e]	MeOH	$C_{24}H_{38}N_2O_3S_4$	54.30	7.22	5.28	24.16	54.42	7.16	5.19	24.17
8	$(CH_3)_2NCH_2CH_2-$	31645-75-7	103–104	70	H_2O–EtOH	$C_8H_{22}N_2O_3S_4$	29.79	6.88	8.69	39.77	29.62	6.78	8.75	39.55
9[d]	$(CH^3)_3N^+CH_2CH_2-$	31645-76-8	154–154.5	96	H_2O–EtOH	$C_{10}H_{26}N_2O_3S_4$	34.26	7.48	7.99	36.58	34.35	7.95	7.97	36.11
10[d]	$C_6H_5CH_2NHCH_2CH_2-$	31645-77-9	111–113	65	H_2O–EtOH	$C_{18}H_{26}N_2O_3S_4$	48.40	5.87	6.27	28.71	48.32	5.90	6.29	28.44

[a] Bunte salt reported by H. Bretschneider, *Monatsh. Chem.*, **81**, 372 (1950); D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind. (London)*, 1632 (1965). [b] Bunte salt reported in ref 19. [c] Bunte salt reported by A. Kaluszyner, *Bull. Res. Counc. Isr., Sect. A*, **9**, 35 (1960); D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 723 (1969). [d] Bunte salt reported by D. L. Klayman and W. F. Gilmore, *ibid.*, **7**, 823 (1964). [e] Reaction performed on the sodium salt of the aminoalkanethiosulfuric acid.

Table II

Bis(alkylaminoethyl) Tetrasulfides

$$R'{>}NCH_2CH_2SSSSCH_2CH_2N{<}R'$$

R	R′	Registry no.	% yield	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
n-C_7H_{15}	n-C_7H_{15}		39	$C_{32}H_{68}N_2S_4$	63.10	11.25	4.60	21.05	63.03	11.07	4.55	21.40
$C_6H_5CH_2$	$C_6H_5CH_2$	31645-78-0	68	$C_{32}H_{36}N_2S_4$	66.62	6.29	4.86	22.23	66.92	6.17	4.78	22.01
CH_3	$C_6H_5CH_2$	31645-79-1	47	$C_{20}H_{28}N_2S_4$[a]	56.56	6.65	6.60	30.20	55.03	6.60	6.22	32.52

[a] The analytical data suggests the formula, $C_{20}H_{28}N_2S_{4.4}$. If correction is made for $S_{0.4}$, then the analytical data conforms more closely with theory, *i.e.*, C, 56.68; H, 6.79; N, 6.41; S, 31.57.

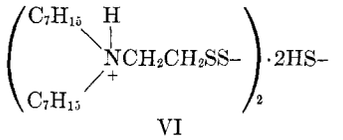
Table III

Aminoethanethiosulfuric Acids

$$RCH_2CH_2X \cdot HX + Na_2S_2O_3 \longrightarrow RCH_2CH_2S_2O_3H$$

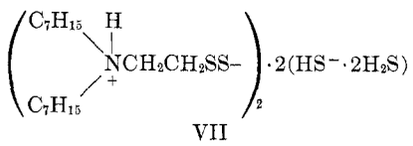
R	Registry no.	Mp, °C	% yield	Recrystn solvent	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
$(CH_3)_2N-$	14013-30-0	187.5	66	MeOH	$C_4H_{11}NO_3S_2$	25.93	5.98	7.56	34.61	25.93	5.97	7.52	34.47
$C_6H_5CH_2(CH_3)N-$	31645-81-5	132–135	68	EtOH	$C_{10}H_{15}NO_3S_2$	45.96	5.78	5.36	24.53	45.79	5.71	5.26	24.80
$(C_6H_5CH_2)_2N-$	31645-82-6	168–169	67	MeCN	$C_{16}H_{19}NO_3S_2$	56.94	5.67	4.15	19.00	57.14	5.89	4.20	19.14
		177.5–179.5	76	H_2O–MeOH	$C_6H_{13}NO_4S_2$	31.70	5.76	6.16	28.21	31.95	6.14	6.03	28.04
$(n\text{-}C_7H_{15})_2N-$	31645-83-7	138.5	52[a]	EtOH	$C_{16}H_{35}NO_3S_2$	54.35	9.98	3.96	18.14	54.05	10.03	3.83	18.07

[a] Prepared by alkylation of 2-aminoethanethanethiosulfuric acid; *cf.* D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).



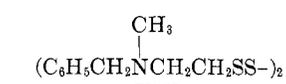
VI

ence of excess hydrogen sulfide, absorbs an additional 2 mol of H_2S per amine moiety present, *i.e.*, 4 mol, to give the observed product VII. An attempt is being made to determine the lattice structure of VII by X-ray crystallography.



VII

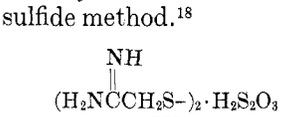
Inasmuch as 2-benzyl- and the water-soluble 2-dimethylaminoethanethiosulfuric acid each give the corresponding disulfides on reaction with hydrogen sulfide, it was of interest to see what would be obtained with *N*-benzyl-*N*-methylaminoethanethiosulfuric acid. In this case, the tetrasulfide VIII was afforded which, like the other tetrasulfides and the trisulfide obtained in this study, was difficult to obtain analytically pure. Reid[17] has reviewed the problems associated with the



VIII

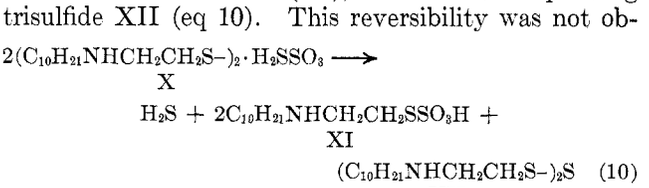
characterization and purification of organic polysulfides.

If one excludes the anomalous results obtained with the morpholino derivative and the water-insoluble *tert*-aminoalkylthiosulfates, the method described here for the conversion of Bunte salts possessing primary and secondary amino groups to disulfides is valuable in that it is very mild and, thus, can be performed in the presence of labile functional groups. It has been reported to us that amidinomethylthiosulfuric acid, for example, was smoothly converted to the disulfide IX by the hydrogen sulfide method.[18]



IX

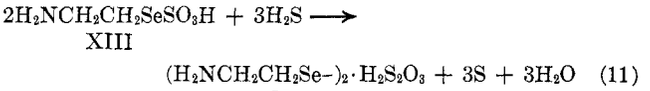
The evolution of hydrogen sulfide was detected in the course of recrystallizing bis(2-decylaminoethyl) disulfide thiosulfuric acid salt (X) from methanol. When a methanol solution of the disulfide was intentionally boiled for 24 hr, the solution rapidly turned yellow and from it was isolated the parent Bunte salt, 2-decylaminoethanethiosulfuric acid (XI), and the corresponding trisulfide XII (eq 10). This reversibility was not observed, however, with II which was recovered essentially unchanged after boiling in methanol for 5 days.



(10)

This is a further example of how N substitution influences, in some way, the reactivity of the sulfur functionality.

The selenium analog of I, 2-aminoethaneselenosulfuric acid (XIII), reacted with hydrogen sulfide in aqueous solution to give, in addition to sulfur, bis(2-aminoethyl) diselenide thiosulfuric acid salt (XIV) (eq 11). 2-Aminoethylphosphorothioate sodium salt (XV) was unaffected by hydrogen sulfide.



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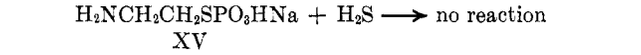
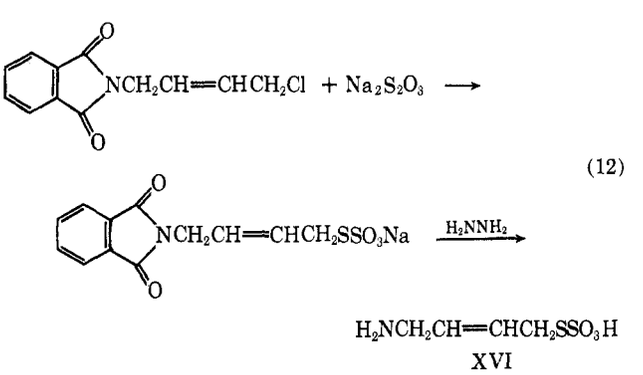


XV

In the course of preparing some new Bunte salts for this study (*cf.* Table III), it was considered desirable to make two unsaturated examples, *i.e.*, 4-amino-2-butene-1-thiosulfuric acid (XVI) and 4-amino-2-butyne-1-thiosulfuric acid (XVII). Attempts to prepare these Bunte salts by the reaction[19] of sodium thiosulfate with the requisite amino halides derived from phthalimidobutenyl- or -butynyl chlorides gave products for which satisfactory microanalytical data could not be obtained. Successful syntheses were achieved, however, by forming the sodium phthalimidothiosulfates from the above-mentioned phthalimidohalides, followed by hydrazinolysis to generate the amine function. This atypical approach of introducing the thiosulfate before the amine moiety into the molecule is illustrated for XVI in scheme (eq 12). This is also the first report of the hydrolysis of a phthalimido group while maintaining the integrity of a thiosulfate moiety, a functional group known for its lability in base. While XVI gave the anticipated disulfide on hydrogen sulfide treatment, XVII gave only polymeric material.



(12)

XVI

Experimental Section[20]

Reaction of H_2S. A. With Water-Soluble Primary and Secondary Aminoalkanethiosulfuric Acids.—Hydrogen sulfide was slowly bubbled for 1–2 hr into an ice-cooled, stirred solution of 0.03 mol of an aminoalkanethiosulfuric acid in 100 ml of H_2O. Elemental sulfur which precipitated in the course of the reaction was removed by filtration, and the filtrate was treated again with H_2S to ensure that the reaction had gone to completion. The

(17) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Rubber Publishing Co., New York, N. Y., 1960, p 387.

(18) R. D. Westland, Parke, Davis and Co., personal communication, 1970.

(19) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 510 (1969).

(20) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, New Hope, Pa. 18938. Infrared spectra were determined as KBr pellets on a Beckman IR-5 spectrophotometer. Nmr spectra were taken on a Varian A-60 using TMS as an internal standard.

solution was evaporated to dryness under reduced pressure and the residual bis(aminoalkyl) disulfide thiosulfuric acid salt was recrystallized from the appropriate solvent.

B. Water-Insoluble Primary and Secondary Aminoalkanethiosulfuric Acids.—In a solution of 0.01 mol of sodium hydroxide in 5 ml of water and 30 ml of methanol was dissolved 0.01 mol of a water-insoluble aminoalkanethiosulfuric acid. An additional 10–20 ml of water was added and hydrogen sulfide was bubbled slowly into the solution for *ca.* 0.5 hr. In contrast to the above procedure, the product, rather than elemental sulfur, precipitated from solution.

C. 2-Aminoethaneselenosulfuric Acid (XIII).—Into a solution of 1.5 g (7.35 mmol) of 2-aminoethaneselenosulfuric acid (XIII)[21] in 15 ml of water was bubbled H_2S for 0.5 hr. The elemental sulfur which formed was filtered off and the filtrate evaporated to dryness under reduced pressure to give 1.22 g (92%) of bis(2-aminoethyl) diselenide thiosulfuric acid salt (XIV). Recrystallization from water gave small white needles, mp 172–175° dec, whose ir spectrum was almost identical with that of II: 9.05 (s), 10.22 (s), 15.05 μ (SSO_3^{-2}).

The sodium salt of XIII, on treatment with H_2S, gave an 87% yield of XIV.

Anal. Calcd for $C_4H_{14}N_2O_3S_2Se_2$: C, 13.38; H, 3.92; N, 7.78; S, 17.80; Se, 43.84. Found: C, 13.11; H, 4.22; N, 7.82; S, 17.74; Se, 43.81.

D. 2-Morpholinoethanethiosulfuric Acid (III).—Into a solution of 4.54 g (0.02 mol) of 2-morpholinoethylthiosulfuric acid in 70 ml of water was bubbled H_2S for 15 min. The S (0.65 g, 0.02 mol) which precipitated in the course of the reaction was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was stirred with several portions of $CHCl_3$ and the solvent removed from the combined extracts leaving bis(2-morpholinoethyl) trisulfide (V) as a pale yellow oil: nmr (CCl_4) δ 3.83–3.58 and 2.60–2.36 (symmetric A_2X_2 triplets centered at 3.70 and 2.48, magnetically nonequivalent morpholino methylene protons, 8 H) and 3.32–2.28 (symmetric A_2X_2 multiplet centered at 2.80, magnetically equivalent ethyl methylene protons, 4 H).

Anal. Calcd for $C_{12}H_{24}N_2O_2S_3$: N, 8.63; S, 29.64. Found: N, 8.21; S, 29.94.

The $CHCl_3$-insoluble material was triturated with methanol to give 1.79 g of 2-morpholinoethylsulfenylthiosulfuric acid (IV) contaminated with a small amount of starting material. Recrystallization of the solid from water gave 1.0 g of IV, mp 184–185° dec; for ir *cf.* Figure 1.

Anal. Calcd for $C_6H_{13}NO_4S_3$: C, 27.78; H, 5.05; N, 5.40; S, 37.09. Found: C, 27.77; H, 4.76; N, 5.45; S, 36.88.

E. 2-Morpholinoethanesulfenylthiosulfuric Acid (IV).—Hydrogen sulfide was bubbled for 15 min into a solution of 100 mg (0.384 mmol) of IV in 10 ml of water. The solvent was removed *in vacuo* and the residue was first extracted with hot hexane to remove the sulfur (20.8 mg, 0.65 mmol) and then with $CHCl_3$. The $CHCl_3$ sol on evaporation gave 24.5 mg (0.076 mmol) of the trisulfide, V, whose nmr spectrum was identical with that described above. Some unreacted IV (46.7 mg, 0.18 mmol) was recovered.

Anal. Calcd for $C_{12}H_{24}N_2O_2S_3$: S, 29.64. Found: S, 29.19.

F. Di-*n*-heptylaminoethanethiosulfuric Acid.—The title compound (1.76 g, 0.005 mol) was dissolved in a solution of 0.2 g (0.005 mol) of sodium hydroxide in 3 ml of water and 25 ml of methanol. Hydrogen sulfide was bubbled into the solution for 0.5 hr which turned orange and from which separated very fine brilliant yellow crystals. After cooling the mixture, the yellow solid was collected (1.0 g) and washed with methanol. H_2S was bubbled into the filtrate which was cooled for *ca.* 16 hr to give an additional 0.3 g of the yellow compound.

The material could not be recrystallized without its losing H_2S. Most of it melted at 65–67° dec while some small particles melted at 111° (sulfur). The solid is remarkably stable in a closed vial but slowly degenerates into an oil (tetrasulfide) after several weeks when exposed to the atmosphere. Upon dissolving the yellow solid in common organic solvents and especially in $CHCl_3$, hydrogen sulfide evolution occurred, a process which could be accelerated by the application of heat. The solvent was evaporated and the oil was separated from any sulfur by extraction with hexane to give the tetrasulfide (*cf.* Table II).

When heated at 50–100° under reduced pressure to constant weight, the yellow complex VII lost 6 equiv of H_2S (25.0% of its weight; theory, 25.1%). The H_2S could also be titrated with I_2 if $CHCl_3$ was added (found 24.6%).

Anal.[22] Calcd for $(C_{32}H_{68}N_2S_4 \cdot 6H_2S)$ $(C_{32}H_{80}N_2S_{10})$: C, 47.23; H, 9.91; N, 3.44; S, 39.41; neut equiv, 407. Found: C, 47.14; H, 9.33; N, 3.38; S, 39.39; neut equiv, 406.

Compound VII could be purified by regeneration from the tetrasulfide by bubbling H_2S into a suspension of the latter in methanol. The oil was solubilized to give a yellow solution and then the yellow solid precipitated from solution.

G. Dibenzylaminoethanethiosulfuric acid was dissolved in a methanol–H_2O solution containing 1 equiv of sodium hydroxide. Hydrogen sulfide was passed into the solution causing the separation of a heavy oil. After the mixture was permitted to stand for several hours, the supernatant liquid was decanted. The residual oil was dissolved in $CHCl_3$, the solution was dried, and the solvent was removed under reduced pressure leaving the bis(dibenzylaminoethyl) tetrasulfide.

H. *N*-Methyl-*N*-benzylaminoethanethiosulfuric acid was treated as above except that 2-days standing was required before the tetrasulfide separated from solution.

Bis(2-aminoethyl) Disulfide Thiosulfuric Acid Salt (II, Alternative Synthesis).—To a soluion of 7.44 g (0.03 mol) of sodium thiosulfate pentahydrate in 50 ml of water was added 6.75 g (0.03 mol) of cystamine dihydrochloride. Complete solution was effected by gentle heating and the product II was collected after cooling and was recrystallized from water (2.84 g, 36%),[23] mp 176–180° dec. Its ir spectrum was identical with that of II prepared by the hydrogen sulfide route.

Anal. Calcd for $C_4H_{14}N_2O_3S_4$: C, 18.03; H, 5.30; N, 10.51; S, 48.14. Found: C, 18.18; H, 5.30; N, 10.48; S, 48.09.

***N*-(4-Chloro-2-butenyl)phthalimide.**—The title compound (mp 104–105°, from 2-propanol) was prepared from 1,4-dichloro-2-butene in 82% yield by the method described earlier.[19]

Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.28; N, 5.94; Cl, 15.05. Found: C, 61.13; H, 4.17; N, 5.95; Cl, 14.91.

***N*-(4-Chloro-2-butynyl)phthalimide.**—This phthalimide was synthesized from 1,4-dichloro-2-butyne as indicated above. The product, mp 120–121° (from MeOH), was obtained in 81% yield.

Anal. Calcd for $C_{12}H_8ClNO_2$: C, 61.68; H, 3.45; N, 6.00; Cl, 15.18. Found: C, 61.98; H, 3.64; N, 6.00; Cl, 15.12.

Sodium 4-Phthalimido-2-butenylthiosulfate.—*N*-(4-Chloro-2-butenyl)phthalimide (4.70 g, 0.02 mol) was added to a solution of 4.96 g (0.02 mol) of $Na_2S_2O_3 \cdot 5H_2O$ in 40 ml of water and 60 ml of methanol. The solution was heated on a steam bath until the test for inorganic thiosulfate was negative. The solution was evaporated to dryness *in vacuo* and the residue was extracted with a large volume of hot EtOH to give the desired product in 82% yield, mp 186–188° dec (from MeOH).

Anal. Calcd for $C_{12}H_{10}NS_2O_5Na \cdot 0.8H_2O$: C, 41.20; H, 3.34; N, 4.01; S, 18.33. Found: C, 41.41; H, 3.24; N, 4.07; S, 18.21.

Sodium 4-Phthalimido-2-butynylthiosulfate.—*N*-(4-Chloro-2-butynyl)phthalimide (11.7 g, 0.05 mol) was added to a solution of 12.4 g (0.05 mol) of $Na_2S_2O_3 \cdot 5H_2O$ in 100 ml of water and 50 ml of MeOH. After heating the solution on a steam bath until the thiosulfate test was negative, it was treated as indicated above. The product, which was obtained in 53% yield, melted at 180–183° dec (from MeOH).

Anal. Calcd for $C_{12}H_8NO_5S_2Na \cdot 3H_2O$: C, 37.21; H, 3.64; N, 3.62; S, 16.56. Found: C, 37.47; H, 3.80; N, 3.66; S, 16.87.

4-Amino-2-butene-1-thiosulfuric Acid (XVI).—To 3.03 g (9 mmol) of sodium 4-phthalimido-2-butenylthiosulfate a solution of 0.5 ml (10 mmol) of 100% hydrazine hydrate (64% hydrazine in water) in 25 ml of EtOH was added. Stirring and heating caused rapid solution of the thiosulfate. After *ca.* 0.5 hr solid material separated from solution and the mixture was heated and stirred for an additional 1–3 hr until no further precipitation occurred. A solution of 5 ml of glacial HOAc in 25 ml of EtOH was then added to the stirred reaction mixture which was refluxed for an additional 10 min. The mixture was evaporated to dryness *in vacuo* and the residue was triturated with *ca.* 25 ml of water. The 1.32 g (90%) of phthalhydrazide, mp 338–343° (lit.

(21) D. L. Klayman, *J. Org. Chem.*, **30**, 2454 (1965); W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, **7**, 229 (1964).

(22) Analysis was performed on a twice regenerated sample which was dried at room temperature for 2 hr *in vacuo*.

(23) No attempt was made to maximize the yield.

mp 341–344°[24]), collected by filtration, was washed again with water. The combined filtrate and washings were decolorized with charcoal, if necessary, and evaporated to dryness *in vacuo*. 4-Amino-2-butene-1-thiosulfuric acid (1.49 g, 90%) was recrystallized from H_2O–EtOH and obtained as shiny white flakes, mp 168–169° dec.

Anal. Calcd for $C_4H_9NO_3S$: C, 26.22; H, 4.95; N, 7.64; S, 34.99. Found: C, 26.32; H, 5.03; N, 7.69; S, 34.78.

4-Amino-2-butyne-1-thiosulfuric Acid (XVII).—To 43.5 g (0.112 mol) of sodium 4-phthalimido-2-butynylthiosulfate was added a solution of 7.19 g (0.144 mol) of 100% hydrazine hydrate (64% hydrazine in water) in 350 ml of MeOH. The yellow solution was stirred and gently refluxed for 1.5 hr. (A solid began to precipitate after *ca.* 15 min of heating.) A solution of 70 ml of glacial HOAc in 350 ml of MeOH was then added to the stirred reaction mixture which was then heated for an additional 20 min. The orange mixture was cooled and filtered. The filtrate was evaporated under reduced pressure at 40°, and the combined solid residues were extracted with three 250-ml portions of water. The insoluble phthalhydrazide (16.8 g, 93%) was collected by filtration and washed with 75 ml of water. The combined filtrate and washings were decolorized with charcoal and evaporated to dryness under reduced pressure at 50°. 4-Amino-2-butyne-1-thiosulfuric acid (11.7 g, 58%), after washing with EtOH, was recrystallized from water, giving the product as shiny off-white flakes, mp >170° dec.

Anal. Calcd for $C_4H_7NO_3S_2$: C, 26.51; H, 3.89; N, 7.73; S, 35.38. Found: C, 26.51; H, 3.94; N, 7.66; S, 35.22.

(24) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

Disproportionation of Bis(decylaminoethyl) Disulfide Thiosulfuric Acid Salt (X).—A solution of 2.73 g (0.005 mol) of X in 80 ml of MeOH was heated under reflux for 24 hr during which time H_2S was evolved. The solution was evaporated to dryness under reduced pressure and the residue was triturated with *ca.* 30 ml of hexane and cooled. The insoluble Bunte salt XI, 1.44 g (96%), was collected by filtration. The hexane filtrate was taken to dryness to give 1.07 g (92%) of the trisulfide XII, a tan-colored oil.

Anal. Calcd for $C_{24}H_{52}N_2S_3$: C, 62.00; H, 11.27; N, 6.03; S, 20.69. Found: C, 61.02; H, 11.09; N, 6.58; S, 21.75.

Registry No.—II, 31645-59-7; III, 31645-60-0; IV, 31645-61-1; V, 31645-62-2; VII, 31645-63-3; XII, 31645-64-4; XIII, 2697-60-1; XIV, 31645-66-6; XVI, 31645-67-7; XVII, 31645-68-8; *N*-(4-chloro-2-butenyl)phthalimide, 31645-84-8; *N*-(4-chloro-2-butynyl)phthalimide, 4819-69-6; sodium 4-phthalimido-2-butenylthiosulfate, 31645-86-0; sodium 4-phthalimido-2-butynylthiosulfate, 31645-87-1; hydrogen sulfide, 7783-06-4.

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Carbodiimide–Sulfoxide Reactions. XII.[1] Reactions of Sulfonamides

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The reactions of aryl- and alkylsulfonamides with DMSO and DCC in the presence of anhydrous orthophosphoric acid has been shown to give *S,S*-dimethyl-*N*-sulfonylsulfilimines in high yields. *N*-Alkylsulfonamides cannot form sulfilimines but rather react slowly with DMSO and DCC to form *N*-alkyl-*N*-(1,3-dicyclohexyl-1-ureidomethyl)sulfonamides. A similar reaction of *N*-benzyl-*p*-toluenesulfonamide with DMSO and phosphorus pentoxide gave *N,N'*-methylenebis(*N*-benzyl-*p*-toluenesulfonamide) as the major product. *N*-Arylsulfonamides such as *p*-toluenesulfonanilide react with DMSO and DCC so as to introduce methylthiomethyl groups in either or both of the unsubstituted ortho positions. Several sulfonanilides containing methyl, nitro, and cyano substituents in the ortho positions of the aniline ring gave products in which methylthiomethyl groups were introduced on nitrogen or at an available ortho position. The very acidic sulfonamide saccharin did not react in a similar way but rather gave a 1:1 adduct with DCC in high yield.

In the preceding paper in this series[1] the previously described mild acid-catalyzed reactions of alcohols,[3] phenols,[4] enols,[5] and oximes[6] with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) were extended to carboxylic acids, hydroxamic acids, and carboxylic acid amides. Simple primary amides of carboxylic acids were found to be readily converted into *N*-acyl-*S,S*-dimethylsulfilimines, while compounds such as benzanilide were completely inert and imides of various sorts reacted slowly to give either *N*-(methylthiomethyl) or *N*-(1,3-dicyclohexyl-1-ureidomethyl) derivatives. In the present paper we extend these studies to the reactions of several types of sulfonamides.

p-Toluenesulfonamide (**1**) reacted quite readily with DMSO and DCC in the presence of 0.5 equiv of anhydrous orthophosphoric acid to form *S,S*-dimethyl-*N*-*p*-toluenesulfonylsulfilimine (**4**), which was isolated in crystalline form in 77% yield without necessity of chromatography. Sulfonylsulfilimines[7] of this type are fairly well-known compounds that have been prepared by the reactions of sulfonylnitrenes[8] with dialkyl sulfides. The nitrenes can be generated *via* either α elimination of chloride ion from salts of *N*-chlorosulfonamides (*e.g.*, chloramine-T)[9] or by photolysis of sulfonylazides.[10] Alternatively, sulfonylsulfilimines have been prepared by the reactions of sulfonamides with DMSO in the presence of either phosphorus pentoxide or acetic anhydride[11] and by the reaction of sulfonyl iso-

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