Despite the presence of the ammonium salt moiety, which usually decreases stability,[5] **2** seems considerably more stable than the salt 1,4-bis(2-aminoethyldithio)-butane dihydrochloride (19–35%, 3 hr) and indeed seems comparable to the amide of this butane compound (>20%, 72 hr) in being one of the most resistant to disproportionation we have encountered.[5] Similarly, disulfide **3** disproportionated to the extents of 6% in 22 hr and 13% in 72 hr.

Experimental Section[6]

2-Acetamidoethyl 2-(*n*-Decylamino)ethyl Disulfide Hydrochloride (2).—2-(*n*-Decylamino)ethyl 2-(*n*-decylamino)ethanethiolsulfonate dihydrochloride (1, 13.44 g, 25.0 mmoles)[7] was dissolved in a boiling mixture of CH_2Cl_2 and EtOH (500 ml, 1:1), and the solution was cooled to room temperature. 2-Acetamidoethanethiol (2.98 g, 25.0 mmoles)[8] then was added in one portion with stirring. The mixture was stirred for 3 hr more and then was chilled at *ca.* 10° overnight; filtration then removed traces of unreacted thiolsulfonate **1**. Evaporation of solvent below 30° gave solid, which was dissolved in a minimum of $CHCl_3$ (25 ml). The $CHCl_3$ solution was placed on a chromatographic column (24 × 300 mm of Merck acid-washed alumina)[9] and was eluted with $CHCl_3$. Evaporation of the first 500 ml of eluate gave crude **2** (6.51 g). Recrystallization from dioxane gave 5.00 g (54%) of pure **2**, mp 155–156°, unchanged by further recrystallization. The infrared spectrum showed the expected absorptions (cm^{-1}): 3420 (b), 3310 (s), 2440 (m) (characteristic of the *n*-decylamino hydrochloride moiety),[2] 1650 (s) and 1550 (s), in addition to a new absorption band at 1450 (s) not shown by either symmetrical disulfide, and nearly complete absences of 775 (m) and 760 (m) (doublet), which appeared in *n*-decylaminoethyl disulfide dihydrochloride. Similarly prepared material with a somewhat lower melting point (identical infrared spectrum) was analyzed. Thin layer chromatography (95% ethanol on Eastman Chromagram Type K301R; silica gel) showed only a single spot after development by exposure to iodine vapor (R_f 0.52).

Anal. Calcd for $C_{16}H_{35}ClN_2OS_2$: C, 51.79; H, 9.51; N, 7.55; S, 17.28. Found: C, 51.64; H, 9.65; N, 7.36; S, 17.17.

3-Acetamidopropanethiol.—In a modified procedure based on one for 3-amino-1-propanethiol of Turk and co-workers[10] and on an acetylation procedure essentially like one for 2-acetamidoethanethiol,[3] a solution of NaOH (40 g, 1.0 mole) in MeOH (200 ml) was thoroughly saturated with H_2S. A continuous stream of H_2S was maintained throughout the reaction. 3-Chloropropylamine hydrochloride (65 g, 0.50 mole)[11] dissolved in MeOH (70 ml) then was added during 0.5 hr with vigorous stirring at 50–60° (exothermic reaction). Solvent was then removed and $CHCl_3$ (350 ml) added, together with anhydrous $MgSO_4$ (30 g) to remove water. The mixture was heated under reflux for 15 min under N_2 and cooled, and solid then was removed by filtration. Acetyl chloride (25 ml, 0.35 mole) then was added dropwise to the rapidly stirred filtrate over *ca.* 20 min. After having been stirred for 3 hr more, the solution was shaken with saturated Na_2SO_4 solution (20 ml) and the $CHCl_3$ layer was separated and evaporated (760 mm) to 12.0 g (36%) of oil, which on titration with 0.1 *N* I_2–KI indicated 76% purity.

3-Acetamidopropyl 2-(*n*-Decylamino)ethyl Disulfide Hydrochloride (3).—3-Acetamidopropanethiol (5.50 g of 76% thiol, equivalent to 31.4 mmoles of pure thiol) was added to an EtOH–CH_2Cl_2 solution (500 ml, 1:1) of thiolsulfonate **1** (14.00 g, 26.0 mmoles), and the reaction mixture was worked up exactly as described for the 2-acetamidoethyl derivative (**2**). The crude product after being washed with acetone crystallized from EtOH–EtOAc as prisms (6.48 g, 65%), mp 122–123°, unchanged by further crystallization. Similarly prepared **3** (identical infrared spectrum) was analyzed.

Anal. Calcd for $C_{17}H_{37}ClN_2OS_2$: C, 53.02; H, 9.69; N, 7.28; S, 16.65. Found: C, 52.93; H, 9.40; N, 7.41; S, 16.85.

The infrared spectrum showed absorptions as expected and closely resembled the spectrum of **2**.

Disproportionation of 2-Acetamidoethyl and 3-Acetamidopropyl 2-(*n*-Decylamino)ethyl Disulfide Hydrochloride (2 and 3).—The disulfide **2** (about 1 mmole, precisely weighed) in EtOH (10 ml of 95%) was heated at 100° in a sealed vial wrapped with A. foil for either 22 or 72 hr, and the vial then was chilled in ice. Solvent was removed from the contents of the vial, and the residue was rubbed well with purified dioxane (15 ml), in which only acetylcystamine, of components present, is significantly soluble. The resulting slurry was filtered, the residue was washed with a little more dioxane (9 ml), and the filtrate was evaporated. The acetylcystamine left then was dried to constant weight under reduced pressure; its identity and purity were established by its superimposable infrared spectrum. Calculations of the extent of disproportionation were done as usual.[12,13]

The propyl derivative **3** was done in the same way. Identity of the 3-acetamidopropyl disulfide was shown by melting point and mixture melting point and by comparison of the infrared spectrum with that of a sample prepared by reaction of H_2O_2 on 3-acetamidopropanethiol. With both **2** and **3** the reaction mixtures were homogeneous throughout at 100° and a precipitate only appeared on cooling.

(5) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).

(6) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B or Beckman IR10 spectrophotometer with KBr pellets; s, signifies strong; m, medium; w, weak; b, broad. Evaporation of solvents usually was done under reduced pressure using a rotating evaporator.

(7) Kindly provided by Dr. Thomas R. Sweeney of the Walter Reed Army Institute of Research; prepared by the procedure of ref 2.

(8) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

(9) No difficulty was experienced with columns packed with $CHCl_3$. However, with a related series of decylaminoethyl disulfides, we occasionally got very poor separations, which we attribute to too basic an alumina. We got excellent results when such aluminas were stirred 30 sec in $CHCl_3$ saturated with HCl and then were packed in the column using this medium. Should separations with **2** or **3** give difficulty, therefore, this procedure may eliminate the difficulty.

(10) S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **27**, 2846 (1962).

(11) D. S. Tarbell and D. P. Cameron, *J. Am. Chem. Soc.*, **78**, 2731 (1956).

(12) Validity of this means of estimating disproportionation was established by making three sample mixtures of **2**, 2-(*n*-decylamino)ethyl disulfide dihydrochloride, and acetylcystamine, as though disproportionation of **2** had occurred to the extents of 10, 60, and 90%. Calculation of "disproportionation, %" for these mixtures from acetylcystamine, isolated as described, gave reasonable check results of 10, 61, and 85%. We are indebted to Dr. J. D. Buckman for suggesting the use of dioxane after a number of other separations had given poor results.

(13) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

Trifluoromethyl Thiolsulfonates and Their Reactions with Mercaptans and Amines[1]

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Thiolsulfonates of the structure RSO_2S-aryl and RSO_2SCCl_3 (R = alkyl or aryl) have been prepared by the reaction of metal sulfinate and sulfenyl chloride. This paper, following our earlier brief reports, describes the synthesis by a similar procedure of the compounds RSO_2SCF_3 and unique reactions of these compounds with mercaptans and with amines.[2,3]

Trichloromethyl thiolsulfonates have been investi-

(1) This investigation was supported by U. S. Public Health Service Research Grant RH 00429, Division of Radiological Health.

(2) (a) S. S. Block, J. P. Weidner, and A. Walsh, Winter Meeting, American Chemical Society, Phoenix, Ariz., 1966, Abstract A56; (b) S. S. Block and J. P. Weidner, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., 1967, Abstract O 109.

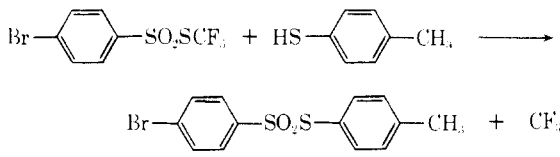
(3) S. S. Block and J. P. Weidner, *Nature*, **214**, 478 (1967).

gated for several years in their roles as pesticides.[4,5] Since the toxicity of the compounds seems to involve the stepwise reaction of the $SCCl_3$ group, it was of interest to prepare the fluorine analogs and to determine their activity against microorganisms. Tests showed that the trifluoromethyl thiolsulfonates were indeed antimicrobial.[3] This finding led us to investigate the nature of the reaction between trifluoromethyl thiolsulfonates and mercaptans, since the SH group in the living cell may be the site of attack as is believed in the case of the $SCCl_3$ group.[6] In the latter case, the sequence of reactions between trichloromethyl 3,4-dichlorobenzenethiolsulfonate and cystine has been postulated to produce a sulfinic acid, cystine, and thiophosgene.[7] We looked for the fluorine analog of thiophosgene in reactions between mercaptans and trifluoromethyl thiolsulfonates but could detect none. Instead, we isolated two solid products: the disulfide of the mercaptan and a thiolsulfonate RSO_2SR', where R came from the trifluoromethyl thiolsulfonate and R′ from the mercaptan.

The general reaction of thiolsulfonates with mercaptans[8] is rapid, and one cannot generally prepare

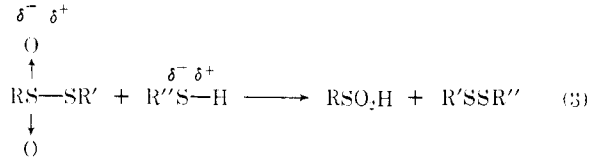
$$RSO_2SR' + R''SH \longrightarrow RSO_2H + R'SSR'' \quad (1)$$

thiolsulfonates from sulfonyl chlorides and mercaptans because reaction 1 follows immediately. When trifluoromethyl thiolsulfonates were treated with mercaptans it was observed that a gas was produced. The reaction was then run in a closed system and the gas was collected and examined by infrared and mass spectroscopy. The mass spectrometric cracking pattern of the sample showed a peak corresponding in molecular weight to SCF_3, suggesting that the gas was CF_3SH and was produced according to eq 2. When

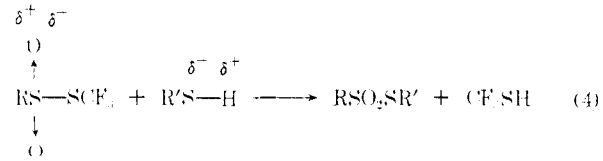


solutions of trifluoromethyl thiolsulfonate and mercaptan were added at once, rather than dropwise, the reaction proceeded nearly mole for mole as in eq 2. In this manner an 80% yield of *p*-tolyl *p*-bromobenzenethiolsulfonate was obtained and no *p*-tolyl disulfide was isolated. In this reaction, which required less than 5 min, the gas was noted effervescing and an offensive odor, attributed to CF_3SH, was immediately apparent.

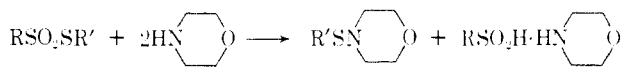
The course of reaction 1 has been explained as being effected by a localization of charges as shown in eq 3.[9]



However, in the case of trifluoromethyl thiolsulfonates, it appears that the three fluorine atoms on the carbon attached to the divalent sulfur are so strongly electronegative that they compete successfully with the oxygen atoms for electrons on the oxidized sulfur. The fluorine atoms essentially reverse the polarity of the molecule making it react like a sulfonyl chloride rather than a thiolsulfonate. Thus, nucleophilic attack by the mercaptide ion occurs on the sulfone sulfur rather than on the divalent sulfur of the thiolsulfonate to produce an exchange of the SR groups of the thiolsulfonate (4).



Evidence that this is a general phenomenon and is not limited to the reactions with mercaptans is found in the behavior of trifluoromethyl thiolsulfonates toward amines. Thiolsulfonates without the trifluoromethyl group react "typically" with amines, *viz.*, to produce a sulfinic acid and a derivative of the divalent sulfur group (5).[10] Our results with RSO_2SCF_3



(5)

compounds (6) and Dunbar's results with trichloromethyl thiolsulfonates[10] and amines further support the concept of reversed polarity.

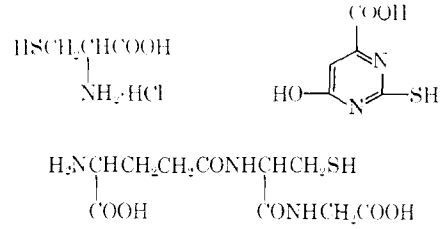
The high yields of thiolsulfonates possible in the reaction with mercaptans suggest it may have value as a synthetic method. The usual methods of preparing mixed thiolsulfonates are eq 7–9.[11] Thus, one

$$RSO_2SNa + R'Br \longrightarrow RSO_2SR' + NaBr \quad (7)$$

$$RSO_2Na + ClSAryl \longrightarrow RSO_2SAryl + NaCl \quad (8)$$

$$RSO_2SR' + R''SO_2Na \longrightarrow R''SO_2SR' + RSO_2Na \quad (9)$$

is limited by the difficulty of preparation of suitable alkyl bromides or sulfenyl chlorides, or in finding a combination of R groups that will exchange as in (9), since not all combinations of R groups exchange.[12] On the other hand, we have found that even polyfunctional mercaptans such as the following react readily with trifluoromethyl thiolsulfonates, and in-



(4) J. H. Uhlenbroek, *Angew. Chem.*, **67**, 764 (1955).
(5) J. H. Uhlenbroek, M. J. Koopmans, and H. O. Huisman, *Rec. Trav. Chim.*, **76**, 129 (1957).
(6) R. J. Lukens and H. O. Sisler, *Phytopathology*, **48**, 235 (1958).
(7) R. J. Lukens, S. Rich, and J. G. Horsfall, *ibid.*, **55**, 658 (1965).
(8) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).
(9) G. Leandri and A. Tundo, *Ann. Chim.* (Rome), **44**, 255 (1954).
(10) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).
(11) R. Conner in "Organic Chemistry, An Advanced Treatise," H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 906.
(12) J. D. Loudon and A. Livingston, *J. Chem. Soc.*, 896 (1935).

TABLE I[a]

TRIFLUOROMETHYL THIOSULFONATES

RSO_2SCF_3

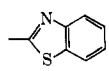
Compd	R	Infrared absorp (SO_2), μ	Carbon, % Caled	Carbon, % Found	Hydrogen, % Caled	Hydrogen, % Found	Fluorine, % Caled	Fluorine, % Found	Sulfur, % Caled	Sulfur, % Found	*In vitro* bactericidal act., MLD[b]
1	CH_3	7.30, 8.50	13.33	13.65	1.66	1.78	31.63	32.24	35.59	36.25	120
2	n-C_4H_9	7.32, 8.55	27.20	27.85	4.08	4.21	25.64	26.03	28.85	28.95	>1000
3	n-C_8H_{17}	7.30, 8.55	38.83	38.88	6.15	6.30	20.47	21.95	23.03	23.20	1000
4	n-$C_{16}H_{33}$	7.38, 8.50, 8.58	52.68	53.43	7.80	8.74	14.70	17.91	16.54	15.39	600
5	C_6H_5	7.30, 8.55	34.71	34.94	2.08	2.04	23.53	24.06	26.47	26.82	120
6	p-$CH_3C_6H_4$	7.32, 8.55	37.49	37.41	2.75	2.67	22.24	23.25	25.02	25.90	120
7	2,5-$(CH_3)_2C_6H_3$	7.37, 8.60	39.99	39.88	3.35	3.37	21.08	22.25	23.72	22.79	120
8	p-ClC_6H_4	7.30, 8.55	30.38	31.46	1.45	1.49	20.31	21.03	23.20	22.76	500
9	p-BrC_6H_4	7.32, 8.57	26.17	26.56	1.22	1.49	17.74	14.24	19.98	20.05	
10	3,5-$(COOH)_2C_6H_3$	7.39, 8.50	32.72	32.88	1.52	1.72	17.25	17.03	19.41		120

[a] Analyses performed by G. Weiler and F. B. Strauss, Oxford, England, and Galbraith Laboratories, Inc., Knoxville, Tenn. [b] Minimum lethal dose in parts per million to *Staphylococcus aureus* (see text).

TABLE II[a]

REACTION BETWEEN TRIFLUOROMETHYL THIOLSULFONATES AND MERCAPTANS

$RSO_2SCF_3 + HSR' \longrightarrow RSO_2SR' + CF_3SH$

			RSO_2SR'											
No.	R	R'	Yield, %	Mp, °C	Lit. mp, °C	Ir (SO_2), μ	C, % Caled	C, % Found	H, % Caled	H, % Found	Br, % Caled	Br, % Found	S, % Caled	S, % Found
1	C_6H_5	$C_6H_4CH_3$-p		50–51	52–54[b]	7.50, 8.70								
2	C_6H_5	$C_6H_4NO_2$-p		104–105	104–105[c]	7.50, 8.72								
3	p-$CH_3C_6H_4$	C_6H_5	43	75–77	77–78[b]	7.52, 8.78								
4	p-$CH_3C_6H_4$	$C_6H_4NO_2$-p	39	130–132	130[c]	7.40, 8.70								
5	p-$CH_3C_6H_4$	$CH_2C_6H_5$		55–56	55[d]	7.50, 8.75								
6	p-$CH_3C_6H_4$	C_6H_4Br-p	67	93.5–94.5	107[e]	7.48, 8.74	45.48	45.50	3.23	3.09	23.28	22.82	18.67	18.35
7	p-BrC_6H_4	$C_6H_4CH_3$-p	80	122–123		7.52, 8.72	45.48	45.50	3.23	3.34	23.28	23.23	18.67	18.75
8	p-$CH_3C_6H_4$		70	138–139	141[f]	7.42, 8.68								
9	3,5-$(COOH)_2C_6H_3$	$C_6H_4CH_3$-m	50	216–217		7.42 7.52, 8.72	51.12	50.95	3.40	3.35			18.19	18.34
10	CH_3	C_6H_4Br-p		117–118		7.55 7.59, 8.77	31.45	32.90	2.64	2.61			24.00	25.62

[a] Melting points are corrected. Analyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Inc., Knoxville, Tenn. [b] Reference 15. [c] G. Kresze and W. Kort, *Chem. Ber.*, **94**, 2624 (1961). [d] E. Fromm and F. Erfurt, *ibid.*, **42**, 3816 (1909). [e] Reference 12. [f] D. Spinelli and A. Salvemini, *Ann. Chim.* (Rome), **51**, 1296 (1961).

frared spectral data indicate the production of their mixed thiolsulfonates.

Like other thiolsulfonates the trifluoromethyl thiolsulfonates possess antibacterial activity. As may be noted in Table I, the aromatic members demonstrated moderately high bactericidal power but, except for the methyl derivative, the aliphatics were low in activity. None of the trifluoromethyl thiolsulfonates exhibited the very high bactericidal potency shown by the trichlorovinyl thiolsulfonates.[13]

Experimental Section

Trifluoromethyl Thiolsulfonates.—Purified zinc p-toluenesulfinate dihydrate (75 g, 0.184 mole), 500 ml of ethyl ether, and 10 drops of dimethylformamide were stirred and 50 g (0.368 mole) of trifluoromethanesulfenyl chloride[14] was slowly introduced over a period of 2.5 hr at a rate which maintained the temperature between 25–31°. Stirring was continued for another 0.5 hr after addition and then the solution was filtered through a sintered-glass funnel. About half of the ether was removed by aspirator and the remaining ether solution was washed well with water. The ether was dried (Na_2SO_4) and then removed (vacuum). The residue of 73 g (78%) of yellowish product had strong infrared absorption at 7.3, 8.5 (typical of SO_2 in trifluoromethyl thiolsulfonates), 9.05, and 9.13 (CF_3) μ. A sample of the compound was purified (tlc). A dilute (*ca.* 5%) ether solution was chromatographed on silica gel GF_{254} (Brinkman) and developed in benzene. Usually one strong band was present on the plate which was easily visible under uv light at about R_f 0.4. This band was extracted with ether, and the ether was removed (vacuum).

Reactions of Trifluoromethyl Thiolsulfonates with Mercaptans and Amines. A. Reactions with Mercaptans (Table II).—Since relatively large amounts were used, the crude RSO_2SCF_3 used after chromatography showed it to contain a minimum of impurities. All mercaptans and disulfides used in the experiments were available commercially from Aldrich Chemical Co. or Eastman Kodak Co.

The general method of preparation of mixed thiolsulfonates can be illustrated by the reaction between trifluoromethyl p-toluenethiolsulfonate and p-bromothiophenol. To a solution of 2.56 g (0.01 mole) of the crude trifluoromethyl p-toluenethiolsulfonate in 10 ml of absolute EtOH was added in one addition 1.89 g (0.01 mole) of p-bromothiophenol (Aldrich, recrystallized twice from absolute EtOH) in 10 ml of absolute EtOH. The solution was swirled and poured into a crystallizing dish and within 5 min small, flat crystals began to precipitate. When precipitation had stopped, the product was removed by filtration, dried, and weighed, giving 1.73 g of material, mp 90°, infrared 7.48 (s) and 8.74 μ (s) (SO_2 in unsubstituted thiolsulfonates). This compound was recrystallized once from EtOH and twice from isopropyl ether and had mp 93.5–94.5°.

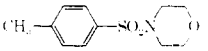
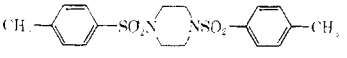
The initial filtrate was chromatographed on silica gel GF_{254} using a solvent system of 30–60° petroleum ether–benzene 1:1 by volume. Under uv light two distinct, nearly equal sized

(13) J. P. Weidner and S. S. Block, *J. Med. Chem.*, **7**, 671 (1964).

(14) Available commercially from Peninsular Chemresearch, Inc., Gainesville, Fla.

TABLE III

REACTION BETWEEN TRIFLUOROMETHYL *p*-TOLUENETHIOLSULFONATE AND SECONDARY AMINES

Amine	*p*-Toluenesulfonamide	Mp, °C	Yield, %
		146.5–148[a]	75
		298–300[b]	85

[a] D. Klamann and H. Bertsch, *Chem. Ber.*, **89**, 2007 (1956), give mp 148°. [b] Lit.[a] mp 296–298°.

bands appeared. Band 1 had R_f *ca.* 0.35, the usual thiolsulfonate position, and band 2 R_f *ca.* 0.8, usually associated with a disulfide. Band 1 was extracted with ether and a crystalline material melting at 90–95° was obtained. Band 2 gave mica-like flakes which melted at 89–90°. Since the two compounds melted so closely and since the previously described compound, *p*-$CH_3C_6H_4SO_2SC_6H_4Br$-*p*, was reported to melt at 107°,[12] it was important to prove that both *p*-bromophenyl *p*-toluenethiolsulfonate and bis(*p*-bromophenyl) disulfide were present. A comparison of the infrared spectrum of the material from band 2 with a spectrum of an authentic sample of bis(*p*-bromophenyl) disulfide, mp 89–91°, showed the two to be identical. The spectrum of the crystals from band 1 was identical with that of the recrystallized compound of mp 93.5–94.5°. With these data and confirmation by the elemental analysis it appears that the compound reported by London[12] may not have been *p*-bromophenyl *p*-toluenethiolsulfonate: total yield of thiolsulfonate (RSO_2SR') from this reaction, 2.3 g (67%).

In order to determine the fate of the SCF_3 group, the reaction between trifluoromethyl *p*-toluenethiolsulfonate and thiophenol was performed in a sealed system containing a gas cell. Trifluoromethyl *p*-toluenethiolsulfonate (2.56 g, 0.01 mole) was dissolved in 10 ml of absolute EtOH in a heavy-wall tube and frozen with liquid N_2. To this was added 1.1 g (0.01 mole) of thiophenol and the system was evacuated. The reaction tube was then allowed to warm to room temperature, the gas cell was removed, and spectra were determined.

The solution from the reaction tube was allowed to stand overnight, and a crystalline product which melted at 75–77° was separated. Chromatography of the remaining solution gave more material melting at 75–77° and another substance melting at 56–58°. The compound, phenyl *p*-toluenethiolsulfonate, has been reported as melting at 76–77°.[13] Commercial phenyl disulfide, mp 59–60°, and the disulfide isolated had identical infrared spectra. Total yield of phenyl *p*-toluenethiolsulfonate was 1.15 g (43%).

B. Reactions with Amines (Table III).—A solution of 0.87 g (0.01 mole) of morpholine in 10 ml of absolute ether was treated with 1.28 g (0.005 mole) of crude trifluoromethyl *p*-toluenethiolsulfonate in 10 ml of absolute ether. (The 100% molar excess of morpholine was not necessary.) The reaction was immediate and exothermic and caused some of the ether to boil away. The remaining ether was removed by moderate heat and the gelatinous mass was taken up in warm 2-propanol, then cooled at 4° for several hours. From the solution 0.9 g (75%) of white crystals were recovered, mp 144°. Two more recrystallations from 2-propanol gave a compound which had strong SO_2 absorption and was identified as *p*-toluenesulfonmorpholide.

A similar experiment using piperazine in absolute EtOH produced a white crystalline material: SO_2 absorption, identified as bis-*p*-toluenesulfonpiperazide.

Antibacterial Testing.—Bactericidal activity as the minimum lethal concentration (MLC) to *Staphylococcus aureus* was determined by the broth dilution method.[16] Trypticase soy broth made up to one-eighth the normal strength was employed to make serial dilutions of the compounds. This lower strength broth still produced heavy growth of the bacteria in 24 hr at 37° but presented less opportunity for undesirable reaction of the ingredients of the medium with the compounds. After 24 hr of incubation, the broth in each dilution tube was streaked onto full-strength trypticase soy agar in Petri plates and incubated for 24 hr to determine the presence or absence of bacterial colonies.

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The Effect of Some Disulfides and Thiols on the Carbohydrate Metabolism of Ehrlich Ascites Tumor[1]

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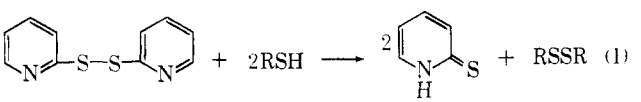
It has recently been found in this laboratory that 2,2′-dithiodipyridine inhibits the respiration and glycolysis of Ehrlich ascites tumor.[2] Further studies[3] have shown that 2,2′-dithiodipyridine and 4,4′-dithiodipyridine react readily and irreversibly with thiols,



as shown in eq 1 and that this reaction, when occurring in metabolically active cells (mouse liver and kidney, Ehrlich ascites tumor), can also cause the enzyme-mediated oxidation of nonsulfhydryl metabolites, such as glucose 6-phosphate.[4,5]

In the present communication we report further studies on the effect of a number of other disulfides, aliphatic and heterocyclic, on the carbohydrate metabolism of Ehrlich ascites tumor. In all cases, the effect of the corresponding thiol has also been studied.

Results and Discussion

Table I reports the results of the manometric experiments. Most of the thiols (or thiones) studied have no significant effect on Ehrlich ascites tumor metabolism; only cysteamine (I) and *N*,*N*′-dimethylcysteamine (II) cause a substantial inhibition of Q_{O_2}. In addition, I stimulates Q_{O_2}(G) and $Q^{O_2}_{CO_2}$ and inhibits $Q^{N_2}_{CO_2}$ if sufficient time is allowed.

Among the disulfides, it is apparent that two types of action can be distinguished: (a) strong inhibition of glycolysis and of respiration by XIII, XIV, XVII, XVIII, XXI, and XXII (the effect of these compounds is similar to that of 2,2′-dithiodipyridine);[2] and (b) moderate or negligible inhibition of anaerobic glycolysis and of respiration, accompanied by apparent stimulation of aerobic glycolysis (accumulation of lactate in the presence of oxygen) by XV, XVI, XIX, and XXIII.

(1) (a) This investigation was supported by Public Health Service Research Grant CA 08538-01, from the National Cancer Institute. (b) Part of the data reported here have been presented at the 3rd International Meeting of Medicinal Chemistry (Chimie Thérapeutique), Paris, France, July 1967.

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