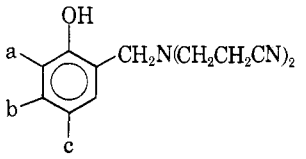
TABLE I

ortho-SUBSTITUTED {[BIS(2-CYANOETHYL)AMINO]METHYL}PHENOLS



	Substituent			M.p., °C.	Yield, %	Molecular formula	Carbon, %		Hydrogen, %		Neut. equiv.	
	a	b	c				Calcd.	Found	Calcd.	Found	Calcd.	Found
I	H	H	Cl	123–124	87[a]	$C_{13}H_{14}ClN_3O$	59.20	58.85	5.35	5.40	263.7	263.0
II	H	H	Br	138–139	50[a]	$C_{13}H_{14}BrN_3O$	50.66	50.86	4.58	4.63	308.2	311.3
III	H	H	CH_3	83–84	34[a]	$C_{14}H_{17}N_3O$	69.11	69.03	7.06	6.96	243.3	246.9
IV	H	H	OC_4H_9	75–76	41[b]	$C_{17}H_{23}N_3O_2$	67.75	67.94	7.69	7.71	301.4	304.3
V	H	CH_3	CH_3	82–83	77[a]	$C_{15}H_{19}N_3O$	70.01	70.00	7.44	7.62	257.3	257.2
VI	Cl	H	$C(CH_3)_3$	105–106	69[a]	$C_{17}H_{22}ClN_3O$	63.84	63.85	6.93	6.75	319.8	321.7
VII	CH_3	H	CH_3	108–109	55[a]	$C_{15}H_{19}N_3O$[c]	70.01	69.84	7.44	7.62	257.3	258.4
VIII	CH_3	H	Cl	115–116	40[e]	$C_{14}H_{16}ClN_3O$	60.53	60.41	5.81	5.73	277.8	281.1
IX	Cl	H	Cl	87–88	87[a]	$C_{13}H_{13}Cl_2N_3O$	52.36	52.27	4.39	4.38	298.2	295.1
X	H	CH_3	OH	116–117	16[d]	$C_{14}H_{17}N_3O_2$	64.84	64.78	6.61	6.67	...	...
XI	H	OH	Cl	146–147	95[a]	$C_{13}H_{14}ClN_3O_2$	55.82	55.99	5.04	5.45	279.7	286.0
XII	H	e	OH	198–199	33[f]	$C_{20}H_{24}N_6O_2$[g]	63.14	62.89	6.36	6.40	...	...
XIII	H	OH	e	171–172	74[f]	$C_{20}H_{24}N_6O_2$[h]	63.14	63.22	6.36	6.70	...	...
XIV	CH_3	OH	e	191–192	83[f]	$C_{21}H_{26}N_6O_2$	63.92	63.95	6.64	6.74	197.2	200.6

[a] Recrystallized from 95% ethanol. [b] Recrystallized from propanol-1. [c] *Anal.* Calcd.: N, 16.33. Found: N, 16.31. [d] Recrystallized from methanol. [e] b or c = $-CH_2N(CH_2CH_2CN)_2$. [f] Recrystallized by dissolving in hot dimethylformamide and then adding methanol. [g] *Anal.* Calcd.: N, 22.09. Found: N, 21.85. [h] *Anal.* Calcd.: N, 22.09. Found: N, 21.86.

Representative examples of N,N-bis(2-cyanoethyl)-aminomethylphenols described in this paper were screened under the direction of the Cancer Chemotherapy National Service Center, for anticancer activity in mice in doses up to 200 mg./kg. and in cell culture tests. All compounds tested were nontoxic at these levels. Against Walker 256, slight activity of the order of 25 to 50% inhibition was shown by compounds II and XIII in Table I. Otherwise no significant inhibition was shown by compounds I–IX, XII, XIII, or XV against Sarcoma 180, Solid Friend Virus Leukemia, Leukemia 1210, Walker 256, or in cell culture tests. Compound XVI showed slight activity against Adenocarcinoma 755, but was inactive against Sarcoma 180 and Leukemia 1210.

Experimental[10]

2,5-Bis{[bis(2-cyanoethyl)amino]methyl}hydroquinone (XII).—Bis(2-cyanoethyl)amine (24.6 g., 0.2 mole) in 50 ml. of methanol was added dropwise to an ice-cooled, stirred solution of 30 ml. of 37% aqueous formaldehyde (0.4 mole) in 30 ml. of methanol. Hydroquinone (11 g., 0.1 mole) was added and the solution stirred for 10 min. on an ice bath. After the solution was refluxed for 4 hr., the solvents were removed by evaporation under the hood. The crude solid was dissolved in 20 ml. of hot dimethylformamide and sufficient methanol was added to the cooled solution to induce crystallization. The product (12.5 g., 33%, m.p. 180–185°) melted at 198–199° after four recrystallizations from dimethylformamide–ethanol.

2,6-Bis{[bis(2-cyanoethyl)amino]methyl}-4-chlorophenol (XV).—To a solution of 2,6-bis(chloromethyl)-4-chlorophenol (22.6 g., 0.10 mole) in 600 ml. of benzene was added 50 ml. of bis(2-cyanoethyl)amine (0.40 mole) with shaking. The solution was warmed at 65° for 15 min. and then cooled. The resulting solid, bis(2-cyanoethyl)amine hydrochloride (32.8 g., m.p. 144–147°), was removed by filtration. Evaporation of benzene from the filtrate gave 25.2 g. (63.2%) of solid; m.p. 123–124° after 5 recrystallizations from 95% ethanol. A 20° depression of melting point was observed for a mixture of this product and the monosubstituted product I, which also melted at 123–124°.

Anal. Calcd. for $C_{20}H_{23}ClN_6O$: C, 60.22; H, 5.81; N, 21.07; neut. equiv., 199.5. Found: C, 60.62; H, 5.65; N, 20.63; neut. equiv., 202.1.

1-{[Bis(2-cyanoethyl)amino]methyl}-2-naphthol (XVI).—This compound was prepared in 74% yield from 2-naphthol by the Mannich reaction; m.p. 101–102° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{17}N_3O$: neut. equiv., 279.3. Found: neut. equiv., 280.6.

Acknowledgment.—We wish to express our appreciation to Mr. George Van Lear for technical assistance.

(10) All melting points are uncorrected. This work was completed before the requirement for melting point corrections went into effect for this journal.

Alkyl and Aryl Thiolsulfonates

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The first thiolsulfonate was reported in 1840 and in 1949 Small, *et al.*, demonstrated antimicrobial activity of thiolsulfonates.[1,2] The structural relationship to allicin (allylthiolsulfinate), the antibiotic found in garlic, stimulated further interest in thiolsulfonates.[3–5] Grishko and Gur'yanova discussed whether the RSO_2- or the RS- is the active moiety, concluding that the former could be substituted without affecting activity while the RS- could not and was responsible for the inhibition towards microorganisms.[6] In order to investi-

(1) C. Lowig and S. Weidmann, *Pogg. Ann.*, **49**, 323 (1840).

(2) L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **71**, 3565 (1949).

(3) C. J. Cavallito, J. S. Buck, and C. M. Suter, *ibid.*, **66**, 1952 (1944).

(4) B. G. Boldyrev, K. A. Gar, and N. V. Evteeva, *Dokl. Akad. Nauk SSSR*, **132**, 346 (1960).

(5) B. G. Boldyrev, L. E. Kolmakova, and T. K. Bilozor, *Zh. Obshch. Khim.*, **33**, 1980 (1963).

(6) N. I. Grishko and E. N. Gur'yanova, *ibid.*, **29**, 878 (1959).

TABLE I[a]

ALKYL AND ARYL THIOLSULFONATES
RSO_2SR'

No.	R	R′	M.p., °C.	Refractive index	Infrared adsorption SO_2 μ		Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Bactericidal activity, MLD[b]
1[c]	CH_3	CH_3		$n^{25}D$ 1.5166	7.62	8.85	19.03	19.00	4.79	4.15	50.81	51.21	1000
2	CH_3	$(ClH)_2CCl_3$	79–80		7.65	8.90	18.65	19.07	2.73	2.86	24.89	24.20	500
3	CH_3	$(ClH_2)_2CN$		$n^{25}D$ 1.5232	7.60	8.82	29.07	29.40	4.27	4.48	38.81	38.20	1000
4	CH_3	$CH_2C{\equiv}ClH$		$n^{25}D$ 1.5405	7.60	8.82	31.98	32.38	4.02	4.13	42.69	42.20	40
5	CH_3	n-C_8H_{17}		$n^{26}D$ 1.4830	7.60	8.84	48.17	48.45	8.98	8.97	28.58	28.48	21
6	CH_3	n-$C_{16}H_{33}$	64–65		7.70	8.90	60.66	60.31	10.78	10.60	19.04	18.45	>1000
7	CH_3	p-$C_6H_4CH_3$		$n^{25}D$ 1.5909	7.52	8.75	47.49	48.12	4.98	4.78	31.70	31.55	1000
8	CH_3	$CH_2C_6H_5$		$n^{25}D$ 1.5850	7.60	8.85	47.49	47.49	4.98	5.17	31.70	31.60	68
9[d]	n-C_4H_9	n-C_4H_9		$n^{25}D$ 1.4877	7.55	8.85	45.67	46.01	8.62	9.19	30.48	30.28	200
10	n-C_8H_{17}	CH_3		$n^{25}D$ 1.4941	7.55	8.55	48.17	48.32	8.98	9.52	28.58	28.61	750
11	n-C_8H_{17}	n-C_8H_{17}		$n^{25}D$ 1.4785	7.60	8.90	59.57	59.76	10.82	10.90	19.88	19.89	200
12	n-C_8H_{17}	n-$C_{16}H_{32}$	45–46		7.65	8.90	66.29	66.49	11.55	11.15	14.76	14.60	>1000
13	n-C_8H_{17}	p-$C_6H_4CH_3$		$n^{26}D$ 1.5478	7.54	8.83	59.95	60.47	8.05	7.50	21.34	21.40	1000
14	n-$C_{16}H_{33}$	CH_3	51–52		7.57	8.85							
					7.75	9.00	60.66	60.01	10.78	10.60	19.04	19.30	1000
15	n-$C_{16}H_{33}$	n-C_8H_{17}	45–46		7.62	8.90	66.29	66.09	11.65	11.59	14.76	15.15	>1000
16[e]	n-$C_{16}H_{33}$	n-$C_{16}H_{33}$	64–65		7.62	8.90	70.26	69.92	12.16	12.28	11.72	11.96	>1000
17	n-C_6H_{35}	p-$C_6H_4CH_3$	57–58		7.62	8.89	66.93	67.23	9.76	9.73	15.54	15.74	>1000
18[f]	p-$CH_3C_6H_4$-	CH_3	57–58		7.50	8.72	47.49	47.22	4.98	5.11	31.70	31.19	317
19[g]	p-$CH_3C_6H_4$-	C_2H_5		$n^{25}D$ 1.5711	7.57	8.76	49.97	50.70	5.59	5.76	29.64	28.82	200
20	p-$CH_3C_6H_4$-	$CH_2C{\equiv}ClH$	45–46		7.62	8.83	53.06	53.06	4.45	4.15	28.33	28.13	40
21	p-$CH_3C_6H_4$-	n-C_4H_9		$n^{26}D$ 1.5510	7.60	8.80	54.05	54.84	6.59	6.78	26.24	25.50	200
22	p-$CH_3C_6H_4$-	n-C_6H_{13}		$n^{26}D$ 1.5402	7.55	8.75	57.31	57.54	7.39	7.51	23.53	23.65	250
23	p-$CH_3C_6H_4$-	n-C_8H_{15}		$n^{26}D$ 1.5311	7.55	8.76	59.95	59.42	8.05	7.93	21.34	20.45	16
24	p-$CH_3C_6H_4$-	n-$C_{10}H_{21}$	30–31		7.55	8.75	62.14	62.10	8.59	8.62	19.52	19.38	250
25	p-$CH_3C_6H_4$-	n-$C_{12}H_{25}$	39–40		7.52	8.75	63.99	63.27	9.01	8.91	17.97	17.35	200
26	p-$CH_3C_6H_4$-	n-$C_{14}H_{29}$	48–49		7.55	8.75	65.54	65.56	9.43	9.52	16.72	16.20	1000
27	p-$CH_3C_6H_4$-	n-$C_{16}H_{33}$	55–56		7.55	8.75	66.93	67.23	9.76	10.77	15.54	15.11	>1000
28[h]	p-$CH_3C_6H_4$-	$C_6H_4CH_3$-p	74–75		7.58	8.80	60.40	60.83	5.06	5.15	23.06	22.90	1000
29[i]	p-$C_2H_5C_6H_4$-	$CH_2C{\equiv}ClH$	30–31		7.60	8.80	54.97	55.20	5.03	4.93	26.68	28.83	125
30	n-$C_8H_{17}SO_2SK$		260 dec.		8.62	9.45	38.67	38.25	6.89	6.94	25.81	26.05	>1000
31	n-$C_{16}H_{33}SO_2SK$		123–126		8.54	9.47	53.28	53.81	9.22	9.44	17.78	15.20	500
32[j]	p-$C_2H_5C_6H_4SO_2SK{\cdot}H_2O$		222–224		8.45	9.50	37.18	37.45	4.29	4.24	21.81	24.63	>1000

[a] Melting points are corrected. Microanalyses and refractive indexes were determined by Weiler and Strauss, Microanalytical Laboratory, Oxford, England. Infrared spectra were run on a Perkin-Elmer Infracord. [b] Minimum lethal dose in parts per million to *Staphylococcus aureus*. [c] W. F. Wolff [U. S. Patent 2,744,937 (1956)] reports $n^{20}D$ 1.5123. [d] G. Leandri and D. Spinelli, *Ann. Chim.* (Rome), **49**, 967 (1960). [e] P. Allen, Jr., and J. W. Brook [*J. Org. Chem.*, **27**, 1020 (1962)] report m.p. 59–60°. [f] D. T. Gibson [*J. Chem. Soc.*, 2637 (1931)] reports m.p. 58°. [g] R. Otto, *Ber.*, **15**, 129 (1882). [h] A. Heidusehka [*J. prakt. Chem.*, [2]**81**, 321 (1910)] reports m.p. 76°. [i] Analyzed by Galbraith Laboratories, Inc., Knoxville, Tenn.

gate this matter further several sets of isomers of RSO_2SR' and $R'SO_2SR$ were prepared, as well as a number of other mixed and symmetrical thiolsulfonates to relate structure with antimicrobial activity.

The unsubstituted S-alkyl members were prepared by alkylation.[7]

$$RSO_2SK + R'Br \longrightarrow RSO_2SR' + KBr$$

The S-tosyl and S-trichlorovinyl esters were prepared by reacting the sulfenyl chloride with the sulfinate[8]

$$RSO_2M + C_7H_7SCl \longrightarrow RSO_2SC_7H_7 + MCl$$

where M is silver or zinc.

The bactericidal activity of these thiolsulfonates is given in Table I. A number of the compounds, namely those of lower molecular weight and the acetylenic derivatives, have high activity. Table II compares the

TABLE II

BACTERIOSTATIC ACTIVITY OF THIOLSULFONATES

RSO_2SR'

R	R'	MID[a]
	Symmetrical	
CH_3	CH_3	12
C_8H_{17}	C_8H_{17}	40
$C_{16}H_{33}$	$C_{16}H_{33}$	200
C_7H_7	C_7H_7	500
	Unsymmetrical	
CH_3	C_8H_{17}	6
C_8H_{17}	CH_3	12
CH_3	$C_{16}H_{33}$	1000
$C_{16}H_{33}$	CH_3	>1000
CH_3	C_7H_7	40
C_7H_7	CH_3	34
C_8H_{17}	$C_{16}H_{33}$	250
$C_{16}H_{33}$	C_8H_{17}	1000
C_8H_{17}	C_7H_7	8
C_7H_7	C_8H_{17}	0.3
$C_{16}H_{33}$	C_7H_7	200
C_7H_7	$C_{16}H_{33}$	200

[a] Minimum inhibitory dose in parts per million to *Staphylococcus aureus*.

bacteriostatic action of a series of symmetrical thiolsulfonates and mixed isomers. It can be concluded from these data that the whole molecule enters into the toxic mechanism and that, although the toxicity toward bacteria of some of the isomers differs, neither the RSO_2- nor the RS- alone can be considered to be the active moiety. Table III presents data on a series of trichlorovinyl thiolsulfonates which were found to have very high bactericidal activity.

TABLE III

BACTERICIDAL ACTIVITY OF TRICHLOROVINYL THIOLSULFONATES

$RSO_2SCCl{=}CCl_2$

R	MLD[a]
CH_3	2
C_2H_5	8
n-C_3H_7	8
n-C_4H_9	8
n-C_8H_{17}	250
C_6H_5	40

[a] Minimum lethal dose in parts per million to *Staphylococcus aureus*.

(7) R. Otto, *Ber.*, **13**, 1282 (1880).

(8) B. G. Boldyrev, *Dokl. Akad. Nauk SSSR*, **131**, 1331 (1960).

Experimental[9]

A.—The preparation of *n*-butyl *p*-toluenethiolsulfonate illustrates the general synthesis of the S-alkyl thiolsulfonates. To a 200-ml. two-necked flask was added a mixture of 12.2 g. (0.05 mole) of recrystallized potassium *p*-toluenethiolsulfonate,[10] 97 ml. of acetone, and 3 ml. of water. The salt was crushed in the solvents to insure small particle size. The flask was fitted with a stirrer, condenser, and heating mantle. To the flask was added at once 6.85 g. of *n*-butyl bromide and the mixture stirred and heated for 20 hr. After completion of the reaction the mixture was diluted with water and transferred to a 300-ml. separatory funnel. The heavy organic layer was removed, diluted with ether, and dried over sodium sulfate. Filtration of the ether solution and evaporation of the ether gave 10.5 g. of crude product. The compound was purified by thin layer chromatography by coating 20-cm. square glass plates to a thickness of 250 μ with silica gel. After activation of the plates by heating for 30 min. at 110°, the crude compound was applied by a small pipet about 2 cm. from the bottom edge, and the plate developed in a solvent mixture of benzene–petroleum ether–chloroform (8:8:1 by volume). After the solvent had risen to the top, the plates were removed, and one was sprayed with 10% sulfuric acid and charred at 110°. The position of the compound on the charred plate indicated where to remove the silica from the other plates. Ether extraction of the silica from 10–20 such plates and evaporation of the ether provided a sufficient amount of compound for analysis and microbiological testing.

B.—The preparation of *p*-tosyl *n*-octanethiolsulfonate illustrates the synthesis of the S-tosyl thiolsulfonates. A 250-ml. erlenmeyer flask containing 50 ml. of absolute ether was set on a magnetic stirrer in the dark and 12.55 g. (0.044 mole, approx. 10% excess) of silver octanesulfinate[11] added. To the stirring suspension 6.85 g. (0.040 mole) of *p*-toluenesulfenyl chloride,[12] dissolved in 45 ml. of absolute ether, was added in small amounts over a period of 2–3 min. During the addition the temperature rose, causing the ether to boil and the orange-red solution of sulfenyl chloride to lose some of its color. After standing 15 min. in the dark the reaction mixture was filtered giving 9.5 g. of yellow solid; the theoretical requirement of silver chloride is 6.87 g. The pale yellow filtrate upon evaporation of the ether gave 8.8 g. of light yellow oil which was purified, as above, by thin layer chromatography.

The S-trichlorovinyl esters were made by reaction of the zinc sulfinate with 1,2,2,2-tetrachloroethanesulfenyl chloride which has been described elsewhere.[13]

Acknowledgment.—This work was supported by the National Institutes of Health under Grant A1-02793.

(9) Microanalyses were performed by G. Weiler and F. B. Strauss, Microanalytical Laboratories, Oxford, England. All melting points are corrected. Infrared spectra were run on a Perkin-Elmer Infracord.

(10) W. Spring, *Ber.*, **7**, 1157 (1874).

(11) T. Zinke, *Ann.*, **412**, 86 (1918).

(12) R. Lecher, with F. Holschneider, K. Köberle, W. Speer, and P. Stöcklin, *Ber.*, **58**, 409 (1925).

(13) S. S. Block and J. P. Weidner, submitted for publication.

Antiviral Compounds. IX. Steroid Derivatives

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In previous articles we had recorded the observation that a combination of a proper functional group with an appropriate radical may lead to compounds which display *in vivo* pharmacodynamic activities.[2]

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(2) G. Cavallini and E. Massarani, *J. Med. Pharm. Chem.*, **1**, 365 (1959).