[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH SECTION, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

N-Heterocyclic Benzenesulfonamides

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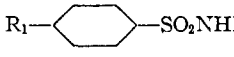
A series of new N-heterocyclic derivatives of 1-phenol-4-sulfonamide and *p*-halogenobenzenesulfonamide have been synthesized for screening as chemotherapeutic agents. In the course of this investigation, variations were made in the heterocyclic radical and the substituents on the heterocycle and on the benzene ring; and certain related types were synthesized, such as N-heterocyclic-*p*-methoxybenzenesulfonamides, N-guanyl-1-phenol-4-sulfonamide and 2-(*p*-hydroxyphenylsulfonyl)-thiazole. The N-heterocyclic-phenolsulfonamides in general were prepared from the corresponding sulfanilamides by diazotization and subsequent decomposition, and from N-heterocyclic-acyloxybenzenesulfonamides by hydrolysis. The acyloxy compounds were prepared from *p*-acyloxybenzenesulfonyl chlorides and aminoheterocycles by reaction in dry pyridine.

Although a great many investigations have been carried out to modify the bactericidal activity and toxicity of phenol, the systematic investigation of phenolsulfonamides as possible chemotherapeutic agents of low toxicity has not been described. Despite the fact that 1-phenol-4-sulfonamide[2] has been reported to have no bacteriostatic activity,[3] it was thought possible that the introduction of heterocyclic substituents on the amide nitrogen might result in new chemotherapeutic agents. The only derivative of this type recorded in the literature is N-(2-pyrimidyl)-1-phenol-4-sulfonamide.[4] It was not characterized fully and its properties other than the anti-malarial screening results are not disclosed. The synthesis of a series of such compounds was undertaken, and the present paper describes their preparation and properties. Variations were made in the heterocyclic radical, and in substituents on the heterocycle and on the benzene ring. Halogen and methoxyl were substituted for the phenolic group in certain cases.

In some instances where the sulfanilamide was available, the phenolsulfonamide was prepared by diazotization and subsequent decomposition of the diazonium salt. Sulfadiazine and sulfathiazole, for example, were diazotized in the usual way in cold dilute sulfuric acid, and the solution of the diazonium salt was then heated to cause decomposition to the phenolsulfonamide. Rapid heating was essential for good results, and even so purification of the product was complicated by the presence of tarry by-products. Therefore, in a method which proved to be very versatile, a *p*-acyloxybenzenesulfonyl chloride was condensed with the appropriate aminoheterocycle in pyridine to give the N-heterocyclic-*p*-acyloxybenzenesulfonamides, and the acyl group was then removed by hydrolysis. The intermediate acyloxy compounds were usually obtained in good yields, and the hydrolysis of the acyl group by alkali or acid proceeded smoothly in most cases. The acyloxybenzenesulfonyl chlorides used were carbethoxy,[5] acetyl,[6] benzoyl[7] and *p*-tosyl. More than one method of synthesis was utilized for some members of the series.

Dr. J. M. A. DeBruyne of this Laboratory has studied the two acid dissociation constants of representative N-(heterocyclic)-1-phenol-4-sulfonamides. From the changes in the ultraviolet absorption curve with changes in *p*H it was determined that pK_1 involved the ionization of the sulfonamide hydrogen. The values for pK_1 varied from 5.37 to 7.29, depending on the N-substituent, while those for pK_2 remained fairly constant at 8.8 to 9.2. Thus it is evident that variations in the N-substituent have very little effect on the ionization of the phenol hydrogen. Furthermore, the values for pK_1 are very nearly the same as the pK_a values for the corresponding sulfanilamides.

TABLE I



		R_1 = OH		R_1 = NH_2
	R_2	pK_1	pK_2	pK_a
IX	2-Pyrimidyl	6.37	9.0	6.48
XI	5-Chloro-2-pyrimidyl	5.59	8.84	
XIII	4,6-Dimethyl-2-pyrimidyl	7.52	9.16	7.37
XXIV	4,6-Dimethoxy-2-pyrimidyl	7.29	9.05	7.12
XXXVIII	5-Methyl-1,3,4-thiadiazol-2-yl	5.37	8.81	5.45

Nine N-heterocyclic-*p*-halogenobenzenesulfonamides have been described by other investigators. These are N-(2-pyridyl)-,[8] N-(2-pyrimidyl)-[9] and N-[6-(γ-diethylaminopropylamino)-pyrimidyl-2]-*p*-chlorobenzenesulfonamide[10]; N-(2-thiazolyl)-,[11] N-(2-pyrimidyl)-[12] and N-(5-chloro-2-pyrimidyl)-*p*-bromobenzenesulfonamide[12]; and N-(2-pyridyl)-, N-(2-thiazolyl)- and N-(2-pyrimidyl)-*p*-fluorobenzenesulfonamide.[13]

The preparation of some of these substances was repeated where the published information

(1) Lederle Laboratories Division, American Cyanamid Company.

(2) W. O. Kermack, W. T. Spragg and W. Tebrich, *J. Chem. Soc.*, 608 (1939).

(3) R. L. Mayer, *Biologie Medicale Supplement*, **27**, 84 (1937).

(4) (a) SN3210; F. Y. Wiselogle, Editor, "The Anti-Malarial Survey," Vol. 2. Ann Arbor, Michigan, 1946, Part 2, p. 1401. (b) Some time after our work was completed K. A. Jensen and S. A. K. Christensen (abstract: *J. Pharm. Pharmacol.*, **1**, 842 (1949)) reported the preparation of the following substances by diazo decomposition from the sulfanilamides: N-(2-thiazolyl)-, m.p. 292°; N-(5-methyl-2-thiazolyl)-, m.p. 231°; and N-(5-methyl-1,3,4-thiadiazol-2-yl)-1-phenol-4-sulfonamide, m.p. 217–218°; also the related N-(guanyl)-1-phenol-4-sulfonamide, m.p. 160–162°, and 2-amino-5-(*p*-hydroxyphenylsulfonyl)-thiazole, m.p. 260°. The synthesis and properties of these compounds are described in the present paper. J. and C. state that their preparations in a concentration of 1 to 5000 had no bacteriostatic action on *D. pneumoniae* (type 1), *E. typhosa*, *S. aureus* and *E. coli*.

(5) T. Zinke and C. Ebel, *Ber.*, **47**, 1103 (1914).

(6) R. Anschütz and Molineus, *Ann.*, **415**, 56 (1918).

(7) F. A. H. Schreinemakers, *Rec. trav. chim.*, **16**, 422 (1897).

(8) T. Curtius and K. Vorbach, *J. prakt. Chem.*, **125**, 353 (1930).

(9) P. S. Winnek and R. O. Roblin, British Patent 555,865, Sept. 10, 1943.

(10) R. G. Shepherd and J. P. English, *J. Org. Chem.*, **12**, 446 (1947).

(11) K. A. Jensen and T. Thorsteinsson, *Dansk. Tids. Farm.*, **15**, 41-77 (1941); *C. A.*, **35**, 5109 (1941).

(12) J. P. English, *et al.*, THIS JOURNAL, **68**, 1039 (1946).

(13) A. Sveinbjornsson and C. A. VanderWerf, Abstracts of the 114th Meeting of the American Chemical Society, St. Louis, Mo., p. 54I. (1948).

appeared incomplete, and several new N-heterocyclic-*p*-halogenobenzenesulfonamides containing fluorine, bromine and chlorine were synthesized from the readily available *p*-halogenobenzenesulfonyl chlorides and aminoheterocycles by reaction in pyridine. The iodo analogs were obtained from the N^1-heterocyclicsulfanilamides, by diazotization and treatment with potassium iodide.

In Table III are listed N-(heterocyclic)-benzenesulfonamides prepared in this investigation. Numbers in column two indicate R_2 in the general formula, and these numbers are keyed to the proper heterocycle radicals in Table II, with suitable references to the aminoheterocycles. The arrangement is according to increasing complexity of the heterocycles. The general methods of preparation of each compound are indicated in the column under "Method," and the general procedure in each case is described in the experimental section, with suitable examples detailed. Substances described in the experimental section are not duplicated in Table III.

TABLE II

N-HETEROCYCLIC RADICALS

No.	R_2 in Tables I and III	Reference to amino heterocycle
I	2-Thienyl	*a*
II	6-Methyl-2-pyridyl	*b*
III	5-Methyl-2-pyridyl	*b*
IV	4-Methyl-2-pyridyl	*b*
V	3-Methyl-2-pyridyl	*b*
VI	5-Chloro-2-pyridyl	*c*
VII	2-Quinolyl	*d*
VIII	2-Benzimidazolyl	*e*
IX	2-Pyrimidyl	*f*
X	4-Methyl-2-pyrimidyl	*f*
XI	5-Chloro-2-pyrimidyl	*g*
XII	4-Methoxy-2-pyrimidyl	*h*
XIII	4,6-Dimethyl-2-pyrimidyl	*f*
XIV	4,6-Dimethoxy-2-pyrimidyl	*i*
XV	2-Pyrazinyl	*j*
XVI	5,6-Dimethyl-2-pyrazinyl	*j*
XVII	2-Quinoxalyl	*k*
XVIII	6-Methyl-3-pyridazinyl	*l*
XIX	1,2,4-Triazol-4-yl	*m*
XX	5-Phenyl-1,2,4-triazol-3-yl	*n*
XXI	4,6-Diamino-2-triazinyl	*l*
XXII	2-Benzoxazolyl	*o*
XXIII	3-Phenyl-5-isoxazolyl	*p*
XXIV	2-Thiazolyl	*f*
XXV	4-Methyl-2-thiazolyl	*q*
XXVI	5-Methyl-2-thiazolyl	*r*
XXVII	5-*n*-Amyl-2-thiazolyl	*s*
XXVIII	4-Phenyl-2-thiazolyl	*q*
XXIX	5-Carboxy-2-thiazolyl	*t*
XXX	4,5-Dimethyl-2-thiazolyl	*u*
XXXI	5-Carbethoxy-2-thiazolyl	*t*
XXXII	2-Benzothiazolyl	*v*
XXXIII	4-Thiazolon-2-yl	*w*
XXXIV	5-Methyl-4-thiazolon-2-yl	*x*
XXXV	5-Ethyl-4-thiazolon-2-yl	*w*
XXXVI	5-Methyl-3-oxadiazolyl	*l*
XXXVII	1,3,4-Thiadiazol-2-yl	*y*
XXXVIII	5-Methyl-1,3,4-thiadiazol-2-yl	*y*
XXXIX	5-*n*-Heptyl-1,3,4-thiadiazol-2-yl	*z*
XL	5-Phenyl-1,3,4-thiadiazol-2-yl	*aa*
XLI	5-Amino-1,3,4-thiadiazol-2-yl	*bb*

[a] R. W. Bost and C. F. Starnes, THIS JOURNAL, 63, 1886 (1941). [b] Reilly Tar and Chemical Corp. [c] A. Tschitschibabin and A. Jegorow, *J. Russ. Phys. Chem. Soc.*, 60, 683 (1928); *Chem. Zentr.*, 99, 1670 (1928). [d] A. E. Tschitschibabin, D. P. Witkowsky and M. I. Lapschin, *Ber.*, 58, 805 (1925). [e] Eastman. [f] Calco Chemical Division, American Cyanamid Company. [g] R. O. Roblin, *et al.*, THIS JOURNAL, 64, 570 (1942). [h] R. R. Adams and F. C. Whitmore, *ibid.*, 67, 735 (1945). [i] F. L. Rose and G. P. Tuey, *J. Chem. Soc.*, 81 (1946). [j] J. Weijlard, M. Tishler and A. E. Erickson, THIS JOURNAL, 67, 804 (1945). [k] Bios Laboratories. [l] G. W. Anderson, *et al.*, THIS JOURNAL, 64, 2902 (1942). [m] S. Ruhemann and R. W. Merriman, *J. Chem. Soc.*, 87, 1772 (1905). [n] D. W. Kaiser, U. S. Patent 2,382,156; August 14, 1945. [o] R. D. Desai, *et al.*, *J. Chem. Soc.*, 1186 (1934); E. Bamberger, *Ber.*, 36, 2051 (1903); S. Skraup, *Ann.*, 419, 68 (1918). [p] P. S. Burns, *J. prakt. Chem.*, 47, 123 (1893). [q] R. M. Dodson and L. C. King, THIS JOURNAL, 67, 2242 (1945). [r] K. Hubacher, *Ann.*, 259, 242 (1890). [s] K. Ganapathi, *et al.*, *Proc. Ind. Acad. Sci.*, 14A, 630 (1941); *C.A.*, 36, 4102 (1942). [t] H. J. Becker and J. deJonge, *Rec. trav. chim.*, 61, 463 (1942); *C. A.*, 38, 2327 (1944). [u] K. A. Jensen and T. Thorsteinsson, *Dansk Tids. Farm.*, 15, 41 (1941); *C.A.* 35, 5109 (1941). [v] A. Hugershoff, *Ber.*, 34, 3134 (1901); *Ibid.*, 36, 3121 (1903). [w] R. Andreasch, *Monatsh.*, 8, 424 (1887); "Beilstein," Vol. 27, p. 234. [z] A. E. Dixon, *J. Chem. Soc.*, 63, 618 (1893). [y] M. Freund and C. Meineke, *Ber.*, 29, 2516 (1896). [z] See Experimental section. [aa] Incorrectly named as 3-phenyl-4-benzoyl-5-thio-1,2,4-triazole by E. Fromm, *Ann.*, 447, 303 (1926). [bb] E. Layer, *ibid.*, 433, 8 (1923).

With the object of obtaining derivatives more water-soluble at neutral *p*H, sulfate esters of certain N-heterocyclic-1-phenol-4-sulfonamides were made by the reaction of the phenolsulfonamide with triethylamine–sulfur trioxide in aqueous sodium carbonate solution. The sulfate esters were usually isolated as the disodium or dipotassium salts.

Since sulfaguanidine is an important sulfanilamide derivative, the phenolsulfonamide and chlorobenzenesulfonamide analogs were prepared also.[4]

Groups introduced on the benzene ring of the phenolsulfonamides included amino, hydroxy, methoxy, methyl and nitro, and these derivatives were usually prepared from the corresponding acyloxybenzenesulfonyl chlorides. However, N-(2-thiazolyl)-2-nitrophenol-4-sulfonamide was obtained by hydrolysis of the 2-chloro compound, and N-(2-thiazolyl)-2-amino-1-phenol-4-sulfonamide resulted from the reduction of the nitrophenol. As an example of the bis-sulfonamides, 4-methyl-1-phenol-2,6-bis-[N-(2-pyridyl)-sulfonamide] was synthesized.

An attempt to prepare N-(2-pyrazinyl)-1-phenol-4-sulfonamide by the reaction of 1-phenol-4-sulfonamide[2] with chloropyrazine gave the oxygen ether, O-(2-pyrazinyl)-1-phenol-4-sulfonamide, rather than the N-substituted derivative. The latter was prepared by other means (Table III).

In connection with this work, to make available some related sulfones, 2-amino-5-(*p*-hydroxyphenylsulfonyl)-thiazole[4b] and 2-(*p*-hydroxyphenylsulfonyl)-thiazole were prepared by the reaction of sodium *p*-tosyloxybenzenesulfinate with 2-amino-5-chlorothiazole and 2-chlorothiazole, respectively.

Various reports have appeared concerning the activity of N-(2-thiazolyl)-1-phenol-4-sulfonamide ("phenosulfazole," "Darvisul") in the treatment

TABLE III

N-HETEROCYCLICBENZENESULFONAMIDES R_1—C$_6$H$_4$—SO_2NHR_2

R_1[a]	R_2 from Table II	Method	Yield, %	Recrystn. solvent	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Cl	I	F	19	Dil. alcohol	116.0-117.0	$C_{10}H_8NO_2S_2Cl$[b]	43.9	43.8	2.94	2.93	5.12	5.24	23.4	23.5
OH	II	E	41	Water[aa]	190.5-192.0	$C_{12}H_{12}N_2O_3S$	54.5	54.5	4.54	4.80	10.6	10.7	12.1	12.3
OH	III	E	54	Alcohol	208.0-210.0	$C_{13}H_{12}N_2O_3S$	54.5	54.4	4.45	4.61	10.6	10.8	12.1	11.9
OH	IV	E	57	Alcohol	254.5-256.0	$C_{12}H_{12}N_2O_3S$	54.5	54.6	4.54	4.62	10.6	10.8	12.1	12.1
OH	V	E	44	Alcohol	216.0-217.0	$C_{12}H_{12}N_2O_3S$	54.5	54.5	4.54	4.74	10.6	10.8	12.1	12.1
Cl	II	F	70	Dil. acet.	101.5-103.0	$C_{12}H_{11}ClN_2O_2S$[c]	51.0	50.9	3.92	4.30	9.91	10.1	12.5	12.8
Cl	III	F	34	Acet. acid	210.5-212.5	$C_{12}H_{11}ClN_2O_2S$[d]	51.0	51.1	3.92	4.17	9.91	10.1	12.5	12.7
Cl	IV	F	53	Acet. acid	242.5-244.5	$C_{12}H_{11}ClN_2O_2S$[e]	51.0	50.7	3.92	4.21	9.91	9.84	12.5	12.8
Cl	V	F	46	Alcohol	142.5-144.5	$C_{12}H_{11}ClN_2O_2S$[f]	51.0	50.9	3.92	3.96	9.91	9.80	12.5	12.8
OH	VI	E	74	Water[aa]	197.5-199.0	$C_{11}H_9ClN_2O_3S$[g]	46.4	46.2	3.19	3.07	9.84	9.88	11.3	11.2
OH	VII	C	37	Methanol	241.0-243.0	$C_{13}H_{12}N_2O_3S$	60.0	59.8	4.03	4.19	9.33	9.31	10.7	10.5
OBz	VII	C	47	Alcohol	181.0-182.0	$C_{22}H_{16}N_2O_4S$								
OH	VIII	E	8	Alcohol	333.0-334.0	$C_{13}H_{11}N_3O_3S$	54.0	54.1	3.83	4.03	14.52	14.8	11.1	10.8
I	IX	A	9	Dil. alcohol	219.0-220.5	$C_9H_8IN_3O_2S$[h]	33.25	33.3	2.23	2.43	11.63	11.6	8.88	9.06
OCb	IX	B	59	Alcohol	190.5-191.7	$C_{13}H_{13}N_3O_5S$	48.35	48.5	4.05	4.23	13.0	12.9	9.90	10.1
OH	X	B, C		Water[bb]	224.0-225.0	$C_{11}H_{11}N_3O_3S$	49.6	46.5	4.62	4.45	14.8	15.0	11.3	11.1
OCb	X	B		Alcohol	190.8-192.9	$C_{14}H_{15}N_3O_5S$	49.8	49.7	4.48	4.71	12.5	12.2	9.50	9.73
OH	XI	A	74	50% Alcohol	240.5-242.0	$C_{30}H_8ClN_3O_3S\cdot H_2O/2$[i]	40.3	40.7	3.08	3.19	14.3	14.2	10.9	11.0
OH	XII	B	6	70% Alcohol	243.9-244.5	$C_{14}H_{11}N_3O_4S$	47.0	46.8	3.94	4.13	14.9	15.1	11.4	11.2
OCH_3	XII	G	46	Water[aa]	198.6-199.2	$C_{14}H_{11}N_3O_3S$	49.8	49.5	4.18	4.42	15.8	16.1	12.1	12.3
OH	XIII	C, E	57	Alcohol	197.5-199.5	$C_{12}H_{13}N_3O_3S$	51.6	51.8	4.69	4.71	15.1	15.2	11.5	11.2
OCH_3	XIII	G	45	Alcohol	165.0-167.0	$C_{12}H_{13}N_3O_3S$	53.2	53.7	5.16	5.23	14.3	14.3	10.8	10.8
OT	XIII	E	74	Alcohol	179.1-180.5	$C_9H_{19}N_3O_5S_2$								
F	XIII	F	25	Dil. alcohol	179.0-180.0	$C_{12}H_{12}FN_3O_2S$	51.2	52.0	4.30	4.8	14.9	15.2	11.4	11.2
Cl	XIII	F	46	Alcohol	181.0-182.5	$C_{12}H_{12}ClN_3O_2S$[j]	48.4	48.6	4.06	3.90	14.1	14.4	10.8	10.7
Br	XIII	F	52	Alcohol	178.0-179.5	$C_{12}H_{12}BrN_3O_2S$[k]	42.1	41.9	3.54	3.36	12.3	12.5	9.39	9.25
OH	XIV	E	20	50% Alcohol	190.1-190.9	$C_{12}H_{13}N_3O_3S$	46.3	46.0	4.21	4.25	13.5	13.3	10.3	10.1
Cl	XIV	F	18	CCl_4	152.6-153.9	$C_{13}H_{12}ClN_3O_3S$[l]	43.7	44.0	3.67	3.73	12.7	12.8	9.72	9.76
OH	XV	B, E	26	Acetic acid	243.0-244.0	$C_{10}H_8N_2O_3S$	47.8	48.0	3.61	3.33	16.7	16.7	12.8	12.6
OH	XVI	E	71	Alcohol	226.7-227.8	$C_{12}H_{13}N_3O_3S$	51.6	51.5	4.69	4.80	15.1	15.1	11.5	11.4
OH	XVII	E	31	Methanol	232.5-234.5	$C_{14}H_{11}N_3O_3S$	56.0	56.0	3.36	3.41	14.0	14.0	10.7	10.7
OT	XVII	E	54	Methanol	178.5-179.5	$C_{21}H_{17}N_3O_5S_2$	55.4	55.4	3.76	4.13	9.24	9.49	14.1	14.2
OH	XVIII	E	82	Water	171.0-172.0	$C_{11}H_{11}O_3N_3S$	49.8	49.6	4.16	4.29	15.9	15.9	12.1	12.9
OT	XVIII	E		Alcohol	188.0-188.5	$C_{18}H_{17}O_5N_3S_2$	51.6	51.8	4.06	3.96	10.1	10.2	15.3	15.5
OH	XIX	C	56	Water[cc]	283.0-284.0	$C_8H_8N_4O_2S$	40.0	39.7	3.36	3.34	23.3	23.2	13.4	13.2
OH	XX	D			149.0-151.0	$C_{14}H_{14}N_4O_5S\cdot H_2O$	50.3	50.2	4.22	4.20	16.7	16.7	9.58	9.48
Cl	XX	D	86	Dil. alcohol	209.0-210.0	$C_{14}H_{11}ClN_4O_2S$[m]	50.2	50.4	3.31	3.46	16.7	16.9	9.58	9.20
OH	XXI	A		Water[dd]	>360	$C_9H_{10}O_3N_6S\cdot 2H_2O$	34.0	33.8	4.44	4.77	26.4	26.2	10.1	11.3
OT	XXII	E	93	Alcohol	215.8-217.1	$C_{20}H_{18}N_2O_7S_2$	51.9	51.9	3.92	3.92	6.06	6.03	13.9	13.7
Cl	XXII	F	52	Dil. alcohol	216.0-217.5	$C_{13}H_9ClN_2O_4S$[n]	50.6	50.8	2.94	3.08	9.08	8.99	10.4	10.5
OH	XXIII	E	15	Dil. alcohol	90.0-91.0	$C_{13}H_{12}N_2O_4S$	54.6	54.7	4.12	4.30	8.50	8.53	9.72	9.70
OT	XXIII	E	19	Alcohol	136.5-138.5	$C_{22}H_{18}N_2O_6S_2$	59.0	58.9	4.21	4.16	7.65	7.77	11.7	11.6
Cl	XXIII	F	24	Alcohol	142.0-144.0	$C_{13}H_{11}ClN_2O_3S$[o]	58.0	58.7	3.90	4.35	10.2	10.1	7.75	7.98
OCH_3	XXIV	G	31	Water[ee]	178.0-178.8	$C_{10}H_{10}N_2O_3S_2$	44.4	44.4	3.73	3.67	10.4	10.5	23.7	23.5
F	XXIV	F	38	Dil. alcohol	174.0-175.0	$C_9H_7FN_2O_2S_2$	41.9	42.1	2.73	2.72	10.9	10.9	24.8	25.0
Cl	XXIV	F	69	Dil. alcohol	203.5-204.0	$C_9H_7ClN_2O_2S_2$[p]	39.4	39.3	2.57	2.33	10.2	10.1	23.3	23.2
OH	XXV	E	57	Water[aa]	209.5-210.5	$C_{10}H_{10}N_2O_3S_2$	44.4	44.5	3.73	3.81	10.4	10.4	23.7	23.8
OH	XXVI	E	46	Acet. acid	233.1-233.6	$C_{10}H_{10}N_2O_3S_2$	44.4	44.4	3.73	3.52	10.4	10.5	23.7	23.6
OH	XXVII	E	40	Alcohol	223.2-224.0	$C_{14}H_{18}N_2O_3S_2$	51.5	51.4	5.56	5.30	8.58	8.67	19.6	19.8
OH	XXVIII	E	84	Water[aa]	251.0-252.0	$C_{14}H_{12}N_2O_3S_2$	54.2	54.1	3.64	3.54	8.43	8.53	19.3	19.4
OH	XXIX	B	6	Water[aa]	212.5-213.9	$C_{10}H_8N_2O_6S_2$	40.0	39.9	2.68	2.82	9.33	9.43	21.3	21.2
OH	XXX	E	74	Water[aa]	243.8-244.6	$C_{11}H_{12}N_2O_3S_2$	46.5	46.4	4.26	4.04	9.85	9.68	22.6	22.7
NHP	XXIV	E	46	Water[aa]	136.0-138.0 (−H_2O)	$C_{18}H_{18}O_6N_2S_2$	41.9	42.1	3.52	3.61	9.78	9.87	22.4	22.2
Cl	XXIX	F	38	Dil. alcohol	238.0-241.0	$C_{10}H_7ClN_2O_4S_2$[q]	37.7	37.4	2.22	2.37	8.79	9.00	20.1	20.0
Cl	XXXI	F	57	Dil. alcohol	204.0-205.0	$C_{12}H_{11}ClN_2O_4S_2$[r]	41.6	40.8	3.20	2.99	8.08	8.45	18.5	19.0
OH	XXXII	E	57	Alcohol	297.0-300.0	$C_{12}H_{16}N_2O_3S_2$	51.0	51.1	3.29	3.20	9.14	9.12	20.9	20.8
OT	XXXII	E	85	Dil. acetone	234.0-235.0	$C_{26}H_{16}N_2O_6S_3$	52.2	52.9	3.50	3.77	6.08	6.22	20.9	20.8
Cl	XXXIII	F	52	Alcohol	244.5-245.5	$C_9H_7ClN_2O_3S_2$[s]	37.2	37.1	2.43	2.53	9.64	9.77	22.0	22.2
OH	XXXIV	D	12	Water	200.0-202.0	$C_{10}H_{10}N_2O_4S_2$	42.0	41.7	3.52	3.57	9.78	10.3	22.4	22.7
OCH_3	XXXIV	D	29	Alcohol	171.0-172.0	$C_{11}H_{12}N_2O_4S_2$	44.0	44.2	4.03	4.18	9.33	9.30	21.4	21.5
Cl	XXXIV	F	20	Alcohol	161.0-162.0	$C_9H_9ClN_2O_3S_2$[t]	39.4	39.4	2.98	3.16	9.19	9.35	21.0	20.8
OH	XXXV	D	13	Water	199.5-200.0	$C_{11}H_{12}N_2O_4S_2$	44.0	43.8	4.03	4.18	9.33	9.30	21.4	21.5
Cl	XXXV	F	38	Dil. alcohol	173.5-174.5	$C_{11}H_{11}ClN_2O_3S_2$[u]	41.5	41.3	3.48	3.42	8.79	8.88	20.1	20.2
OH	XXXVI	A	50	Alcohol	230.0-233.0	$C_9H_9N_3O_4S$	42.4	42.4	3.55	4.40	16.5	16.7	12.6	12.2
OH	XXXVII	A	35	Water	241.5-243.0	$C_8H_7N_3O_3S_2$	37.3	37.5	2.74	2.93	16.3	16.5	24.9	24.9
Cl	XXXVII	F	20	Alcohol	212.0-213.0	$C_8H_6ClN_3O_2S_2$[v]	34.8	34.9	2.20	2.32	15.2	15.1	23.2	23.1
Br	XXXVII	F	17	Alcohol	230.0-231.0	$C_8H_6BrN_3O_2S_2$[w]	30.1	30.1	1.89	1.99	13.1	13.1	20.0	19.7
I	XXXVII	A	8	Dil. alcohol	248.0-249.0	$C_8H_6IN_3O_2S_2$[x]	26.2	26.5	1.65	1.72	11.4	11.5	17.5	17.7
OH	XXXVIII	C	25	Water[aa]	224.5-226.0	$C_9H_9N_3O_3S_2$	39.8	39.6	3.34	3.20	15.5	15.5	23.6	23.5
F	XXXVIII	D	32	Dil. alcohol	177.0-178.0	$C_9H_8FN_3O_3S_2$	39.6	39.6	2.95	3.06	15.4	15.3	23.4	23.6
Cl	XXXVIII	D	39	Alcohol	193.0-194.0	$C_9H_8ClN_3O_3S_2$[y]	37.3	37.4	2.78	2.89	14.5	14.5	22.1	22.1
Br	XXXVIII	D	40	Alcohol	204.0-205.0	$C_9H_8BrN_3O_3S_2$[z]	32.4	32.3	2.41	2.46	12.6	12.7	19.2	19.3
OH	XXXIX	E	24	Dil. ac. acid	130.0-132.0	$C_{18}H_{21}N_3O_3S_2$	50.8	51.1	5.69	6.15	11.8	12.2	18.1	17.5
OH	XL	E	23	Dil. ac. acid	283.0-284.0	$C_{14}H_{11}N_3O_3S_2$	50.5	50.7	3.33	3.46	12.6	12.7	19.2	19.2
OH	XLI	E	28	Dil. ac. acid	262.0-264.0	$C_8H_8N_4O_3S_2\cdot H_2O/2$	34.2	34.0	3.22	3.24	19.9	20.0	22.8	22.6

[a] Ac = CH_3CO-; Bz = C_6H_5CO-; Cb = C_2H_5OOC-; P = *p*-$HOC_6H_5SO_2$-; T = *p*-$CH_3C_6H_4SO_2$-. [b] Chlorine: calcd.,

12.95; found, 13.0. [c] Chlorine: calcd., 11.34; found, 11.4. [d] Chlorine: found, 11.1. [e] Chlorine: found, 11.4. [f] Chlorine: found, 11.6. [g] Chlorine: calcd., 12.45; found, 12.7. [h] Iodine: calcd., 35.14; found, 34.3. [i] Chlorine: calcd., 12.03; found, 12.4. [j] Chlorine: calcd., 11.91; found, 11.9. [k] Bromine: calcd., 23.35; found, 23.3. [l] Chlorine: calcd., 10.75; found, 10.9. [m] Chlorine: calcd., 10.59; found, 10.6. [n] Chlorine: calcd., 11.48; found, 11.3. [o] Chlorine: calcd., 8.57; found, 8.61. [p] Chlorine: calcd., 12.91; found, 13.1. [q] Chlorine: calcd., 11.12; found, 11.3. [r] Chlorine: calcd., 10.22; found, 10.7. [s] Chlorine: calcd., 12.20; found, 12.2. [t] Chlorine: calcd., 11.63; found, 11.8. [u] Chlorine: calcd., 11.12; found, 11.1. [v] Chlorine: calcd., 12.86; found, 12.8. [w] Bromine: calcd., 24.96; found, 24.7. [x] Iodine: calcd., 34.56; found, 34.7. [y] Chlorine: calcd., 12.24; found, 12.5. [z] Bromine: calcd., 23.91; found, 24.1. [aa] Dissolved in water with alkali, clarified with Darco G-60, and precipitated with acid. [bb] A sodium salt was isolated from water, redissolved and precipitated with acid.

of neurotropic virus infections in experimental animals,[14] and poliomyelitis in man.[14f] An extensive screening program on this series of compounds is in progress and the results will be published elsewhere. In preliminary experiments it was found that blood plasma from two dogs treated orally with 400 mg. of phenosulfazole per kg. of body weight contained about 95 mg. per cent. of phenosulfazole, and cerebrospinal fluid from the same dogs contained 2.8 and 6.2 mg. per cent., respectively.[15]

Experimental

Materials.—The aminoheterocycles were commercial products or were prepared by procedures described in the literature (see Table II), with the exception of one thiadiazole.

2-Amino-5-*n*-heptyl-1,3,4-thiadiazole.—Ninety-one grams of thiosemicarbazide in 100 ml. of glacial acetic acid was heated to 100° and 243.9 g. of octanoyl chloride was added at such a rate that the temperature did not go over 110°. After the addition was complete the mixture was heated under reflux for one-half hour, and a complete solution resulted. It was cooled and 400 g. of ice was added; two layers were formed (temp. 30°). After treatment with activated carbon (Darco G-60) and clarification the solution was adjusted to *p*H 8–8.5 with ammonium hydroxide and the solid precipitate was collected on the filter. It was washed with water and dried to give 77.4 g. (38.9%) of crude 2-amino-5-*n*-heptyl-1,3,4-thiadiazole. This was recrystallized from alcohol and then melted at 189.4–190.4°.

Anal. Calcd. for $C_9H_{17}N_3S$: C, 54.24; H, 8.60; N, 21.09; S, 16.09. Found: C, 54.5; H, 8.58; N, 21.1; S, 16.2.

Method A. Diazotization of Sulfanilamides.—The general method consisted of dissolving 0.1 mole of the sulfanilamide derivative in 500 ml. of water with sulfuric acid to give a 10–20% solution. The temperature was lowered to 0–10°, and sodium nitrite (7 g.) in solution was added gradually until a slight excess persisted. After stirring cold for about one hour, the diazonium salt solution was heated rapidly on the steam-bath, with internal steam in addition, to decompose the diazonium salt. After cooling, the phenolsulfonamide was collected and purified by reprecipitation from alkali with acid, by recrystallization of the sodium salt from water, or by recrystallization from a solvent.

The iodobenzenesulfonamide was prepared similarly, except that a concentrated solution of potassium iodide was added after the diazotization, and the decomposition was allowed to proceed slowly at room temperature for one or two days.

Examples of this procedure are detailed below.

N-(2-Thiazolyl)-1-phenol-4-sulfonamide ("Phenosulfazole."[4b,14]—To 127.5 g. (0.5 mole) of sulfathiazole in 2 l. of water was added 100 ml. of concd. sulfuric acid. Some crystallization occurred. One kilogram of ice and then a solution of 35 g. (0.5 mole) of sodium nitrite in 200 ml. of water were added. Some orange crystals of diazonium salt separated.

The solution was heated on a steam-bath, with both external and internal steam, to 90–95°. This temperature was maintained for about one-half hour, during which foaming and some tar-formation took place. The clear, orange solution was decanted while hot from the tar and allowed to stand overnight.

The crystalline product was filtered off and redissolved in 300 ml. water and sodium hydroxide at *p*H 8–9. There were added 90 g. of salt and sodium hydroxide to give *p*H 12 and, after cooling to 5°, the sodium salt was filtered off and washed with saturated sodium chloride solution.

The cake was redissolved in 2 l. of water at 90° and hydrochloric acid to *p*H 7 was added. About 5 g. of Darco G-60 was added, and the solution was clarified. Hydrochloric acid was added to *p*H 3–4 at 90°, 5 g. of Darco G-60 was added, and the solution was clarified again and cooled to 20°. The practically colorless crystals were filtered, washed, and dried to give 32 g. of material melting at 229–230.5°.

Attempted assay by titration with 0.1 *N* sodium hydroxide using phenolphthalein as an indicator did not give a definite end-point.

Anal. Calcd. for $C_9H_8N_2S_2O_3$: C, 42.17; H, 3.14; N, 10.93; S, 25.02. Found: C, 42.1; H, 3.23; N, 11.1; S, 25.4.

N-(2-Pyrimidyl)-1-phenol-4-sulfonamide.[4a]—A solution of 125 g. (0.5 mole) of sulfadiazine in 1 l. of water and 250 ml. of concd. sulfuric acid was cooled to 15°, and a solution of 35 g. of sodium nitrite in 200 ml. of water was added with slight cooling to keep the temperature at 15–20°. There was excess nitrite as shown by a starch–iodide test.

The solution of diazonium salt was added over a period of 15 minutes to a mixture of 1 l. of water and 200 ml. of concd. sulfuric acid maintained at about 90° on the steam-bath. The mixture was held at 90–95° for 30 minutes, and after cooling slightly there was added 50% sodium hydroxide solution to bring the *p*H to about 3–4. After cooling to 20°, the tan crystalline product was filtered and washed with water.

The cake was dissolved in 400 ml. of water and sodium hydroxide was added to give *p*H 9–10, and then 120 g. salt and excess 50% sodium hydroxide solution were added to separate the disodium salt. After cooling to 10°, filtering, and washing with saturated sodium chloride solution, the light orange cake was dissolved in 1.5 l. of water at 80°, hydrochloric acid added to about *p*H 8, 5 g. of Darco G-60 added and the solution clarified at 90–95°. The filtrate was acidified to *p*H 3–4, 5 g. of Darco G-60 added, and it was clarified at 90–95°. On cooling there was obtained, after washing, filtering and drying, 19 g. of practically colorless crystals melting at 230.5–232°.

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.8; H, 3.61; N, 16.72; S, 12.76. Found: C, 47.5; H, 3.74; N, 16.9; S, 12.8.

Di-(N-guanyl-1-phenol-4-sulfonamide) Sulfate.[4b]—To a solution of 106 g. (0.7 mole) of sulfaguanidine in 2800 ml. of water and 140 ml. of concd. sulfuric acid was added ice to bring the temperature to 15°, and a solution of 49 g. (0.7 mole) of sodium nitrite in 175 ml. of water. This mixture was then heated as rapidly as possible with internal steam to 90–95°, and held at this temperature for 15 minutes. On standing overnight to cool, there first separated a light brown oil which crystallized. The product was filtered, and washed. The material was purified by recrystallization twice from 400–500 ml. of water, using about 10-g. portions of Darco G-60. The final purification was done by recrystallization twice from 400-ml. portions of 30% alcohol, using 5-g. portions of Darco G-60. There was obtained 46 g. of colorless, sandy crystals melting at 219.8–220.3°.

Anal. Calcd. for $2(C_7H_9N_3O_3S)\cdot H_2SO_4$: C, 31.81; H, 3.81; N, 15.90; S, 18.20. Found: C, 31.85; H, 3.7; N, 16.1; S, 18.0.

(14) (a) M. Sanders, Y. SubbaRow and R. C. Alexander, *Texas Reports on Biology and Medicine*, **6**, 385 (1948); (b) G. A. Lo Grippo, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **70**, 528 (1949); (c) H. R. Cox, *et al.*, **70**, 530 (1949); (d) M. L. Weil and J. Warren, *ibid.*, **70**, 534 (1949); (e) T. Francis and G. C. Brown, *ibid.*, **70**, 535 (1949); (f) M. Schaeffer and J. A. Toomey, *Am. J. Med.*, **6**, 667 (1949).

(15) R. W. Cunningham, B. K. Harned and J. M. A. deBruyne, unpublished data.

Sulfonyl Chloride Methods (B-G).—One mole of the substituted benzenesulfonyl chloride was added in portions to a mixture of one to two moles of the aminoheterocycle in 500 ml. of dry pyridine. The total reaction time varied from one or two hours at 55–60° (preferred for most reactions) to overnight at room temperature. The reaction mixtures were then worked up by one of several methods, or combinations thereof: (a) poured into cold water, cooled, filtered, and washed; (b) poured into dilute acid to maintain an acid *p*H, cooled, filtered, and washed; (c) poured into alcoholic HCl, etc. The choice depended upon the case of crystallization of the product. The intermediate acyloxy compounds were isolated in some cases; in others it was convenient to hydrolyze directly to the phenolsulfonamide and purify that. Examples of the benzenesulfonyl chloride methods are detailed in Methods B-G.

Method B: N-(2-Thiazolyl)-1-phenol-4-sulfonamide[4b] **from *p*-Carbethoxyoxybenzenesulfonyl Chloride.**—A mixture of 1200 g. of phenol and 800 g. of concd. sulfuric acid was heated 16 hours at 80–90°, and poured into 5 l. of water. Then 2500 g. of salt was added, and the sodium phenol-4-sulfonate[16] which separated was filtered, washed with saturated sodium chloride solution, ice-water and alcohol, and dried at 50°. The yield was 2300 g. of material containing some sodium chloride.

Sodium phenol-4-sulfonate (780 g.) was slurried in 2000 ml. of water and converted to the disodium salt with 50% sodium hydroxide solution. Ethyl chloroformate (427 ml.) was added and the mixture stirred until a precipitate formed. It was then made alkaline to phenolphthalein test paper by the addition of about 200 ml. more of 50% sodium hydroxide solution, cooled to 10–15°, and filtered. The cake was washed with alcohol and acetone, and dried at 100°. The yield was 500 g. (47%).

For the preparation of the acid chloride,[5] 400 g. of sodium *p*-carbethoxyoxybenzenesulfonate from above and 400 g. of phosphorus pentachloride were mixed by adding small portions of each alternately to a flask, and the resulting mixture was stirred for one hour. It was then heated at 80–90° until thickening occurred. The thick slurry was poured into ice and water and stirred one hour, 75 ml. of benzene added, and the precipitate collected on the filter and dried four hours at 40–50°, then in a vacuum desiccator overnight. The yield of *p*-carbethoxyoxybenzenesulfonyl chloride was 330 g., m.p. 69.9–71.0°.

To a mixture of 150 ml. of dry pyridine and 71 g. of 2-aminothiazole was added 150 g. of *p*-carbethoxyoxybenzenesulfonyl chloride. The temperature was maintained at 50–55°. After 15 minutes at 50–55° the mixture was heated at 65–70° for one-half hour. Then 600 ml. of water was added, and sufficient concd. hydrochloric acid to bring the *p*H to about 4. The product was collected on the filter and recrystallized from ethanol to give N-(2-thiazolyl)-*p*-carbethoxyoxybenzenesulfonamide, melting at 155.6–156.5°.

Anal. Calcd. for $C_{12}H_{12}N_2O_5S_2$: C, 43.89; H, 3.68; N, 8.53; S, 19.53. Found: C, 44.0; H, 3.66; N, 8.63; S, 19.4.

The carbethoxyoxy compound was hydrolyzed by heating 12 g. with 52 ml. of water and 12 g. of sodium hydroxide at 85–90° for 30 minutes. The solution was adjusted to *p*H 4 with concd. hydrochloric acid, and the precipitated N-(2-thiazolyl)-1-phenol-4-sulfonamide was filtered and recrystallized from water. It then melted at 229–230.1° and gave no depression in melting point when mixed with a sample prepared by Method A above.

Method C. N-(2-Thiazolyl)-1-phenol-4-sulfonamide[4b] **from *p*-Benzoxybenzenesulfonyl Chloride.**—Ten grams of 2-aminothiazole was mixed with 68 ml. of dry pyridine and 30 g. of *p*-benzoxybenzenesulfonyl chloride.[7] The mixture was heated for 15 minutes at 50–60°, diluted with 200 ml. of water and acidified with hydrochloric acid. A gum was formed which was collected and mixed with 55 ml. of water and 20 ml. of 50% sodium hydroxide solution. After heating 30 minutes at 85–95° a clear solution was obtained. It was treated with activated carbon and filtered, and the filtrate was acidified with hydrochloric acid. The white product obtained on cooling was filtered and extracted with sodium bicarbonate solution to remove benzoic acid. The residue was filtered, washed with sodium bicarbonate solution, then with water. It was recrystallized from ethanol and then melted at 227.5–228.5° and caused no depression in a mixture melting point with N-(2-thiazolyl)-1-phenol-4-sulfonamide prepared by Method A above.

Method D. N-(2-Pyridyl)-1-phenol-4-sulfonamide from *p*-Acetoxybenzenesulfonyl Chloride.—To a mixture of 3.1 g. of 2-aminopyridine and 15 ml. of dry pyridine was added, at 0–5°, 7 g. of *p*-acetoxybenzenesulfonyl chloride.[6] The mixture was allowed to stand overnight at room temperature and then poured into ice-water. The light brown precipitate which separated was filtered, washed and dried to give 7.1 g. of crude product, melting at 180–190°. Recrystallization from ethanol gave N-(2-pyridyl)-*p*-acetoxybenzenesulfonamide as soft white needles melting at 196–197°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.43; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.2; H, 4.24; N, 9.4; S, 10.8.

Five grams of the crude above and 27 g. of 2.5 *N* sodium hydroxide solution were heated at 60° for one hour. The reaction mixture was treated with Darco G-60, clarified, and acidified to *p*H 2.5–3.0, cooled, and filtered. The precipitate was washed with cold water and dried. After recrystallization from alcohol it melted at 224.5–226.5°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.78; H, 4.03; N, 11.19; S, 12.81. Found: C, 52.7; H, 4.02; N, 11.0; S, 12.7.

Method E. N-(2-Pyridyl)-1-phenol-4-sulfonamide from *p*-(*p*-Tosyloxy)-benzenesulfonyl Chloride.—To 92 g. of powdered sodium *p*-(*p*-tosyloxy)-benzenesulfonate dihydrate[17] was added 100 g. of finely divided phosphorus pentachloride in small portions. The first portion reacted at once and the mixture of solids began to liquefy so that stirring was possible during the rest of the reaction. When addition was complete, the resulting thin sirup was heated one hour on the steam-bath. The reaction mixture was then almost clear and colorless. After cooling it was poured onto 500 g. of flake ice and the product separated in white, granular lumps which were broken up, filtered off, washed well with water and dried to constant weight at 40°; yield 73 g. (88%). This crude material had a melting range of 80–82° and was pure enough for condensation with aminoheterocycles. It was quite stable on prolonged storage in a closed container at normal temperatures. This compound is very soluble in benzene, toluene, chloroform, carbon tetrachloride and ether; slightly soluble in petroleum ether. A sample was purified for analysis by recrystallization from a mixture of carbon tetrachloride and petroleum ether using decolorizing carbon (Darco G-60). The pure *p*-(*p*-tosyloxy)-benzenesulfonyl chloride was obtained in the form of white, large granular crystals, m.p. 82.5–83.5°.

Anal. Calcd. for $C_{13}H_{11}O_5S_2Cl$: C, 45.02; H, 3.19; S, 18.49; Cl, 10.22. Found: C, 44.8; H, 3.07; S, 18.4; Cl, 10.3.

Ten grams of 2-aminopyridine was dissolved in 50 ml. of dry pyridine and 35 g. of *p*-(*p*-tosyloxy)-benzenesulfonyl chloride was added in small portions over a period of 10 minutes. The mixture was heated at 50° for 20 minutes, cooled, and poured into 500 ml. of cold water. The yellow product was filtered, washed and dried. It was recrystallized from acetic acid using decolorizing charcoal, and was obtained as minute white plates melting at 202.5–204.5°.

Anal. Calcd. for $C_{18}H_{16}N_2O_5S_2$: C, 53.44; H, 3.99; N, 6.93; S, 15.85. Found: C, 53.5; H, 4.12; N, 6.97; S, 15.6.

The *p*-tosyloxy compound above was hydrolyzed in hot dilute sodium hydroxide solution to give N-(2-pyridyl)-1-phenol-4-sulfonamide, which caused no depression in a mixture melting point with the product obtained from Method D above.

N-Methyl-N-(2-thiazolyl)-1-phenol-4-sulfonamide.—By a procedure similar to that described above, from *p*-(*p*-tosyloxy)-benzenesulfonyl chloride and 2-methylaminothiazole,[18] was prepared the *p*-tosyloxy derivative, m.p. 116–118°.

Anal. Calcd. for $C_{17}H_{16}O_5N_2S_2$: C, 48.2; H, 3.80; N, 6.61; S, 22.65. Found: C, 48.3; H, 3.96; N, 6.40; S, 22.5.

This was hydrolyzed as described above to N-methyl-N-(2-thiazolyl)-1-phenol-4-sulfonamide, m.p. 141–142.5°.

(16) L. Paul, *Z. angew. Chem.*, **9**, 590 (1896).

(17) D. Doherty, W. H. Stein and M. Bergmann, *J. Biol. Chem.*, **135**, 487 (1940).

(18) *Naf. Ann.*, **265**, 112 (1891).

Anal. Calcd. for $C_{10}H_{10}O_3N_2S_2$: C, 44.5; H, 3.74; N, 10.4; S, 23.7. Found: C, 44.8; H, 3.84; N, 10.6; S, 23.3.

Method F. N-Heterocyclic-*p*-halogenobenzenesulfonamides. N-(4,5-Dimethyl-2-thiazolyl)-*p*-chlorobenzenesulfonamide.—2-Amino-4,5-dimethylthiazole (m.p. 80.5–82.5°), 26 g., was dissolved in 200 ml. of dry pyridine and *p*-chlorobenzenesulfonyl chloride,[19] 46 g., was added in small portions while stirring. The mixture was then heated on a steam-bath for 30 minutes and the resulting clear solution poured into 2000 ml. of cold water whereupon the crude material separated in the form of a red gum. The diluted mixture was acidified to a *p*H of about 2 with dilute hydrochloric acid and the gum then crystallized on standing. The solid was filtered, washed well with water, suspended in 500 ml. of fresh water and dissolved by the addition of dilute sodium hydroxide solution. The resulting almost clear solution was treated with 5 g. of decolorizing carbon (Darco G-60), clarified and acidified with dilute hydrochloric acid which caused the product to precipitate as a cream colored gum which quickly hardened. The lumps of solid were ground up, filtered, washed well with water and dried which gave 45 g. (75% yield) of cream colored powder.

The above material was further purified by crystallizing it from 10 times its weight of 80% alcohol using decolorizing carbon. The product recovered from the alcohol crystallization was then recrystallized from 4 times its weight of glacial acetic acid using decolorizing carbon. Pure N-(4,5-dimethyl-2-thiazolyl)-*p*-chlorobenzenesulfonamide was thus obtained in the form of white minute crystals having a melting range of 206.7–207.9°.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2S_2$: C, 43.62; H, 3.66; Cl, 11.71; N, 9.25; S, 21.17. Found: C, 43.8; H, 3.65; Cl, 11.7; N, 9.28; S, 21.3.

p-Bromobenzenesulfonyl chloride[20] and *p*-fluorobenzenesulfonyl chloride[21] were employed in similar fashion, see Table III.

Conversion of N-(2-Thiazolyl)-*p*-bromobenzenesulfonamide to N-(2-Thiazolyl)-1-phenol-4-sulfonamide.—Ten grams of N-(2-thiazolyl)-*p*-bromobenzenesulfonamide, 100 ml. of 5 *N* sodium hydroxide solution, and 0.5 g. of cuprous chloride were placed in a nickel shaker autoclave. The autoclave was purged with nitrogen, closed, and heated for 23 hours at 125°. The liquid was then washed from the autoclave, treated with Darco G-60, clarified, and acidified with 5 *N* hydrochloric acid. The precipitate which formed was filtered and washed with water to give a 52% yield of N-(2-thiazolyl)-1-phenol-4-sulfonamide, which melted at 226–230°. It gave no depression in a mixture melting point with an authentic sample.

Method G. *p*-Methoxybenzenesulfonyl Chloride and N-Heterocyclic-*p*-methoxybenzenesulfonamides.—The preparation of *p*-methoxybenzenesulfonyl chloride[22] from a salt of *p*-methoxybenzenesulfonic acid and phosphorus pentachloride is described. In order to avoid isolation of an intermediate, the following procedure was used:

A mixture of 40 ml. of anisole and 50 ml. of concd. sulfuric acid was heated in a steam-bath for 30 minutes. After cooling to 20°, the reaction mixture was added to 100 ml. chlorosulfonic acid as rapidly as possible, while avoiding foaming over, at 10–15°. After five minutes the mixture was drowned on ice, filtered, washed and dried in a vacuum desiccator. There was obtained 35 g. of crystalline material, having an approximate melting point of 40–45°.

A small sample with ammonia gave *p*-methoxybenzenesulfonamide melting at 112–115°. The literature[23] gives 116°. Direct sulfonation of anisole with chlorosulfonic acid gave at low temperature (20°) a water-soluble product; at higher temperatures (60–80°) apparently a disulfonyl chloride. If the reaction mixture was allowed to stand for about 10 minutes after addition to the chlorosulfonic acid, sulfonation to a soluble product occurred.

N-(5-Methyl-1,3,4-thiadiazol-2-yl)-*p*-methoxybenzenesulfonamide.—To 57.5 g. of 2-amino-5-methylthiadiazole slurried in 200 ml. of dry pyridine was added with stirring, at 20–30°, 103.3 g. of *p*-methoxybenzenesulfonyl chloride. The mixture was stirred and heated at 50° for two hours and then allowed to stand overnight. The mixture was poured into 400 ml. of water and hydrochloric acid was added to *p*H 3. The granular precipitate which resulted was filtered at 10°, washed well with water and dried. The crude product (110.4 g.) was dissolved in the minimum amount of boiling glacial acetic acid, clarified with activated carbon (Darco G-60) and precipitated by gradually adding an equal volume of water. The temperature was lowered to 10° and the crystalline N-(5-methyl-1,3,4-thiadiazol-2-yl)-*p*-methoxybenzenesulfonamide obtained was filtered and washed free of acid. After two more precipitations as above the yield was 86.2 g., m.p. 171–173°.

Anal. Calcd. for $C_{10}H_{11}N_3O_3S_2$: C, 42.07; H, 3.89; N, 14.73; S, 22.47. Found: C, 42.0; H, 3.91; N, 14.7; S, 22.5.

Guanidine Derivatives.—A solution of 13.0 g. (0.1 mole) of 98% guanidine nitrate in 50 ml. of water plus 20 ml. (0.1 mole) of 5 *N* sodium hydroxide was shaken from time to time with a solution of 0.05 mole of the substituted benzenesulfonyl chloride in 50 ml. of benzene. After a few hours the solution formed a stable emulsion which was allowed to stand one to five days at room temperature. The resulting white doughy mass was broken up, filtered, washed well with water and dried to constant weight at 70–75°. The crude product was purified by recrystallization from alcohol or dilute alcohol.

N-Guanyl-1-tosyloxybenzene-4-sulfonamide.—This compound was prepared as indicated above, from 1-tosyloxybenzene-4-sulfonyl chloride and guanidine nitrate. After recrystallization from alcohol it melted at 223.5–224.5°; yield 50%. Attempts to hydrolyze it in alkaline or acid solutions did not give the phenolsulfonamide (see Method A above).

Anal. Calcd. for $C_{14}H_{15}N_3O_5S_2$: C, 45.5; H, 4.09; N, 11.4; S, 17.4. Found: C, 45.2; H, 4.24; N, 11.2; S, 17.3.

N-Guanyl-*p*-chlorobenzenesulfonamide.—From *p*-chlorobenzenesulfonyl chloride and guanidine nitrate this compound was obtained in 25% yield. After recrystallization from dilute alcohol it melted at 198–200°.

Anal. Calcd. for $C_7H_{10}ClN_3O_3S$: C, 33.4; H, 4.01; S, 12.7. Found: C, 33.8; H, 3.91; S, 12.7.

Disodium N-(Heterocyclic)-1-phenol-4-sulfonamide Sulfates. General Procedure.—The N-substituted phenolsulfonamide (0.1 mole) was dissolved (or suspended) in a solution of sodium carbonate (0.3 mole) in 200 ml. of water. Triethylamine–sulfur trioxide (0.2 mole) was then added and the mixture stirred and heated at 45–55° until a clear solution resulted, usually about two hours. The reaction mixture was then made strongly alkaline by the addition of a 50% solution of sodium hydroxide and boiled until substantially all of the triethylamine had been removed. The hot aqueous alkaline solution was then treated with decolorizing carbon, clarified, cooled to 5–10°, seeded with crystals of sodium sulfate decahydrate and put in the icebox overnight. The hydrated sodium sulfate which separated was filtered off, and then the filtrate was saturated with sodium chloride and refrigerated until crystallization of the sodium salt of the sulfuric ester was complete. The crude product, usually in the form of fine needles, was filtered and dried. Purification was effected by recrystallizing the crude from the minimum volume (one to two parts) of boiling water using decolorizing carbon. The crystals obtained in this way were usually hydrated. Samples for analysis were further purified by recrystallization from dilute alcohol, and vacuum dried at 80° over phosphorus pentoxide. The products are listed in Table IV.

3-Nitro-4-chlorobenzenesulfonyl Chloride.—There was heated on a steam-bath for 30 minutes a mixture of 225 g. (0.87 mole) of sodium *o*-nitrochlorobenzenesulfonate and 250 g. of phosphorus pentachloride. This mixture was poured into ice and water, the insoluble matter was washed with water and a little dilute sodium hydroxide solution and filtered to give about 210 g. of wet cake. The cake was dissolved in 75 ml. of hot toluene. There was obtained 40 ml. of water, giving an indicated yield of about 170 g. of acid chloride. The toluene solution was used at once in the next step.

N-(2-Thiazolyl)-3-nitro-4-chlorobenzenesulfonamide.—To a solution of 100 g. (1 mole) of 2-aminothiazole in 300 ml. of dry pyridine was added the solution of 170 g. of 3-

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TABLE IV

N-HETEROCYCLIC-1-PHENOL-4-SULFONAMIDE SULFATE ESTERS $NaOSO_2O-C_6H_3-SO_2N(Na)-R$

R₂ from Table II	Yield, %	Recryst. solvent	M.p., °C.	Empirical formula	Nitrogen, % Calcd.	Found
XXIV	55	W., alc.	275–278 d.	$C_9H_6N_2O_6S_3Na_2$	7.37	7.31
XXIV		90% alc.	$-H_2O$, 125	$C_9H_9N_2O_7S_3Na$[a]	7.45	7.56
XXIV	69	80% alc.	200–250 d.	$C_9H_6N_2O_6S_3K_2$[b]	6.79	7.01
XXX	88	W., 90% alc.	295–300 d.	$C_{11}H_{10}N_2O_6S_3Na_2$	6.86	6.84
IX	50	W., 90% alc.	260–265	$C_{10}H_7N_3O_6S_2Na_2$	11.20	10.9
XI	32	W., 90% alc.	332–335 d.	$C_{10}H_6N_3O_6S_2ClNa_2$[c]	10.26	9.99
XIII	60	W., 90% alc.	315–318 d.	$C_{12}H_{11}N_3O_6S_2Na$	10.42	10.0
XXXVIII	26	W., 90% alc.	280–282 d.	$C_9H_7N_3O_6S_3Na_2$	10.63	10.4

[a] Monosodium salt, by partial neutralization of disodium salt. [b] Dipotassium salt. [c] Chlorine: calcd., 8.67; found 8.21.

nitro-4-chlorobenzenesulfonyl chloride in 75 ml. of toluene at 70–80° with slight cooling. After one hour, the mixture was poured into 1200 ml. of water, and hydrochloric acid was added to *p*H 2.5–3. The granular precipitate, containing some tarry matter, was filtered, washed with alcohol, and dried.

N-(2-Thiazolyl)-2-nitrophenol-4-sulfonamide.—About three-fourths of the N-(2-thiazolyl)-3-nitro-4-chlorobenzenesulfonamide above was dissolved in 300 ml. of water and 60 ml. of 5 *N* sodium hydroxide solution to give about *p*H 8. Another 60 ml. of 5 *N* sodium hydroxide was added, and the solution allowed to stand overnight. Some crystallization had started, so 200 ml. of 50% sodium hydroxide was added, and the mixture was cooled to bring about crystallization. The slurry was filtered, and washed with 5 *N* sodium hydroxide and alcohol. The cake was redissolved in 250 ml. of water at 60°, and the sodium salt was separated as before by addition of 150 ml. of 50% sodium hydroxide and cooling. The filtered and washed cake was redissolved in 500 ml. of water at 80°, hydrochloric acid was added to *p*H 7–8, 5 g. of decolorizing carbon (Darco G-60) was added, the solution was clarified, and the product was precipitated with hydrochloric acid at *p*H 3–4.

The yellow crystalline product after filtering, washing with water and drying weighed 35 g., and melted at 204.1–205.0°.

Anal. Calcd. for $C_9H_7N_3S_2O_5$: C, 35.88; H, 2.34; N, 13.95. Found: C, 35.8; H, 2.34; N, 14.0.

N-(2-Thiazolyl)-2-aminophenol-4-sulfonamide.—By reduction in alcohol solution using a palladium-on-charcoal catalyst and 40 lb./sq. in. pressure of hydrogen at room temperature the nitro compound was reduced to N-(2-thiazolyl)-2-aminophenol-4-sulfonamide, m.p. 230–231°.

Anal. Calcd. for $C_9H_9N_3O_3S_2$: C, 39.84; H, 3.34; N, 15.49; S, 23.63. Found: C, 39.7; H, 3.47; N, 15.5; S, 23.5.

Disodium 2-Methylphenol-4-sulfonate.—A mixture of 225 g. (2.08 moles) of *o*-cresol and 300 g. of concd. sulfuric acid was heated 16 hours on the steam-bath. The solution was added to 1 l. of water and 300 g. of sodium chloride was added. No product separated out on cooling; therefore, 50% sodium hydroxide solution was added until the *p*H was about 12, then 300 g. of additional 50% sodium hydroxide. After cooling to 20°, the slurry was filtered, the cake washed with alcohol and dried to give 275 g. of disodium 2-methylphenol-4-sulfonate.

Sodium 3-Methyl-4-carbethoxyoxybenzenesulfonate.—The disodium salt from above was dissolved in 1 l. of water and 37 g. of 50% sodium hydroxide solution and 162 g. of ethyl chlorocarbonate was added. The mixture was stirred and ice added as necessary to keep the temperature just below 50°. When the ethyl chlorocarbonate had reacted, 100 g. of sodium chloride was added, the solution cooled to 20°, and the crystalline product filtered. After washing with saturated salt solution, a little ice-water, and alcohol, the cake was dried at 90° to give 250 g. of sodium 3-methyl-4-carbethoxyoxybenzenesulfonate.

4-Carbethoxyoxy-3-methylbenzenesulfonyl Chloride.—In alternate small portions, 250 g. of sodium 4-carbethoxyoxy-3-methylbenzenesulfonate and 250 g. of phosphorus pentachloride were mixed and stirred for one hour. The reaction mixture was heated at 80–90° for 30 minutes; it thickened, and was then added slowly to ice and water. An oily layer was formed which on stirring solidified. It was allowed to stand for 16 hours, then filtered. The solid material was dissolved in benzene and the water layer was discarded. The benzene layer was dried over calcium chloride and used in the next experiment.

N-(2-Thiazolyl)-1-carbethoxyoxy-2-methylbenzene-4-sulfonamide.—The benzene solution of 4-carbethoxyoxy-3-methylbenzenesulfonyl chloride from above was added to a mixture of 100 g. of 2-aminothiazole and 250 ml. of dry pyridine. There was some evolution of heat. The mixture was heated one hour at 60–70° and poured into 800 ml. of hot water and heated at 70° for 15 minutes, then cooled and acidified with 200 ml. of concd. hydrochloric acid. A gummy product formed which solidified on standing overnight. It was filtered, washed with water and dried at 50°. The yield was 192.7 g. (60.5%). For analysis a small sample was recrystallized twice from *n*-butanol; it then melted at 125.2–126.8°.

Anal. Calcd. for $C_{13}H_{14}N_2O_5S_2$: C, 45.6; H, 4.12; S, 18.7. Found: C, 45.6; H, 4.32; S, 18.9.

N-(-2-Thiazolyl)-2-methyl-1-phenol-4-sulfonamide.—The carbethoxyoxy compound (191.7 g.) was hydrolyzed by heating in 600 ml. of water and 165 ml. of 50% sodium hydroxide under reflux for one hour. The solution was acidified with 245 ml. of concd. hydrochloric acid, cooled to 10° and the precipitate was collected on the filter. It was dissolved in 400 ml. of water and 50 ml. of 50% sodium hydroxide solution, and the sodium salt was precipitated by the addition of 120 g. of salt and 250 ml. of 50% sodium hydroxide solution. It was filtered, redissolved in dilute alkali, treated with a little sodium hydrosulfite, then with Darco G-60 (decolorizing carbon), and clarified. After a second treatment with sodium hydrosulfite and Darco G-60, the solution was acidified, the product was collected on the filter and washed with water, and then recrystallized from 900 ml. of 50% alcohol. The yield was 39.2 g., m.p. 242.5–243.0°. Recovery from the Darco cake was 21 g., m.p. 243.5–244.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3S_2$: C, 44.43; H, 3.72; N, 10.37; S, 23.72. Found: C, 44.3; H, 3.49; N, 10.5; S, 23.5.

Potassium 2-Methoxy-1-carbethoxyoxybenzene-4-sulfonate and 2-Methoxy-1-phenol-4-sulfonic Acid.—The procedure used was a modification of several in the literature.

A mixture of 500 g. (4 moles) of guaiacol and 400 ml. of concd. sulfuric acid was heated 16 hours on the steam-bath. This was added to 4 l. of water, and about 400 g. of lime was added to *p*H 3–4. The hot slurry was filtered to remove calcium sulfate, 400 g. of calcium chloride was added, and ammonia was added to bring the *p*H to about 8–9. The precipitate was filtered at 20°, washed with water and alcohol, and dried to give 290 g. The 2-methoxy-1-phenol-4-sulfonic acid gives a calcium salt which is much less soluble than that of the isomeric 2-methoxy-1-phenol-5-sulfonic acid. The calcium salt was slurried in portions in 400 ml. of water at 85°, while adding about 150 g. of potassium carbonate. The slurry was filtered hot, and hydrochloric acid was added to bring the *p*H to 3–4. The monopotassium salt of the desired isomer is likewise the least soluble. After cooling to 20°, filtering, washing with a little cold water and alcohol, and drying there was obtained 175 g. of product. The above potassium 2-methoxy-1-phenol-4-sulfonate was dissolved in 500 ml. of water and 42 g. of potassium hydrox-

ide. To this was added 94 g. (0.72 mole plus 20% excess) of ethyl chloroformate, and potassium hydroxide was added as necessary to maintain the *p*H at 8–9. The slurry obtained after standing overnight was cooled to 5°, filtered, washed with a little water and alcohol and dried at 95° to give 167 g. This corresponds to a 74% yield in the last step.

2-Methoxy-1-carbethoxyoxybenzene-4-sulfonyl Chloride and N-(2-Thiazolyl)-2-methoxy-1-phenol-4-sulfonamide.—The 167 g. (0.53 mole) of potassium salt from above was mixed with 150 g. of phosphorus pentachloride, and the mixture was heated to 95–100° for one hour. After cooling, the heavy sirup was drowned on ice, and 100 ml. of benzene was added to dissolve the acid chloride. The benzene layer was washed and dried over calcium chloride. The acid chloride was not isolated, but the benzene solution was used to condense with 2-aminothiazole as described in Method H above. N-(2-thiazolyl)-2-methoxy-1-phenol-4-sulfonamide melted at 131.2–132.5°.

Anal. Calcd. for $C_{10}H_{11}N_2O_4S_2$: C, 41.80; H, 3.86; N, 9.75; S, 22.32. Found: C, 41.9; H, 4.08; N, 9.89; S, 22.2.

N-(2-Thiazolinyl)-1-phenol-4-sulfonamide and 3-(*p*-Hydroxybenzenesulfono)-2-(*p*-hydroxybenzenesulfonimido)-thiazolidine (or 2-[Bis-(*p*-hydroxybenzenesulfonyl)-amino]-thiazoline).—4-Acetoxybenzenesulfonyl chloride (106 g., 0.45 mole) was added over a two-hour period at 0–10° to a mixture of 92 g. (0.9 mole) of 2-aminothiazoline[24] and 225 ml. of dry pyridine. The mixture was stirred at room temperature for four hours longer, cooled to 10° and filtered. The filtrate was poured into 1500 ml. of ice-water and the oil which was obtained was separated and washed with water. The oil was dissolved in 300 ml. of alcohol, 375 ml. of concd. hydrochloric acid was added, and the mixture was left at room temperature overnight. It was then neutralized with 50% sodium hydroxide solution to *p*H 3.0–3.5, and concentrated under reduced pressure on the water-bath to about 300 ml. On cooling, a thick oil and some crystalline material were deposited. The supernatant liquor was decanted and the residue heated with 3500 ml. of water at 85°. This solution was clarified and allowed to cool. The product obtained was separated by repeated fractional precipitations of this sort, into the mono- and bis-compound. The latter was obtained in the greater yield; it is less soluble in water and more soluble in absolute alcohol than the mono-derivative. The formula of the latter is assigned by analogy to the sulfanilamide derivative. The yield of N-(2-thiazolinyl)-1-phenol-4-sulfonamide was 6%, m.p. 203–204° (from alcohol).

Anal. Calcd. for $C_9H_{10}N_2O_3S_2$: C, 41.85; H, 3.90; N, 10.82; S, 24.82. Found: C, 41.9; H, 4.08; N, 11.0; S, 24.6.

No attempt was made to determine which of the two possible structures is correct for the bis-compound. It melted at 214–215°.

Anal. Calcd. for $C_{15}H_{14}O_6N_2S_3$: C, 43.45; H, 3.40; N, 6.76; S, 23.20. Found: C, 43.4; H, 3.57; N, 6.91; S, 23.2.

In an attempt to prepare the analogous N-(2-thiazolinyl)-*p*-chlorobenzenesulfonamide, only the bis-compound was obtained. All attempts to hydrolyze these bis-compounds to a mono-derivative failed.[25]

1,4-Diacetoxybenzene-3-sulfonyl Chloride.—Three hundred grams of ammonium hydroquinone-3-sulfonate,[26] 500 ml. of acetic anhydride and 500 ml. of pyridine were mixed and allowed to stand for three days at room temperature. The mixture was then concentrated under reduced pressure until distillation was essentially over at 70°. Then 500 g. of phosphorus pentachloride was added and the mixture heated for one-half hour at 60°. The solution was poured into 6 l. of water and the precipitate was washed well with water by decantation, and filtered. The precipitate was extracted with 6 l. of hot carbon tetrachloride. The extract was washed once with water, dried briefly over anhydrous sodium sulfate, then concentrated until precipitation began, and cooled overnight. The 1,4-diacetoxybenzene-3-sulfonyl chloride was filtered and dried in a vacuum desiccator. The yield was 318 g. (75%) melting at 103–105°.

Anal. Calcd. for $C_{10}H_9O_6ClS$: C, 41.03; H, 3.10; Cl, 12.11; S, 10.96. Found: C, 41.0; H, 3.30; Cl, 12.3; S, 10.9.

N-(2-Thiazolyl)-1,4-dihydroxybenzene-3-sulfonamide.—A mixture of 176 g. (0.6 mole) of 1,4-diacetoxybenzene-3-sulfonyl chloride, 66 g. (0.66 mole) of 2-aminothiazole and 200 ml. of dry pyridine was allowed to stand for one-half hour at room temperature and then in the ice-box overnight. The yellow mush was poured into 3 l. of water and acidified with dilute hydrochloric acid. Filtration yielded 172 g. of crude N-(2-thiazolyl)-1,4-diacetoxybenzene-3-sulfonamide. A mixture of 143 g. of the above crude and 2000 ml. of 1 *N* sodium hydroxide was stirred at 20–25° for 10 minutes and then filtered. The cake (48 g.) was washed with 200 ml. of water. The alkaline filtrate was heated on the steam-bath for one hour, cooled to 60°, acidified with dilute hydrochloric acid to about *p*H 9, treated with decolorizing carbon (Darco G-60), and the filtrate acidified with dilute hydrochloric acid to *p*H 2–3, and cooled in the ice-box for three days. The light brown precipitate which separated was recrystallized three times from water. The white crystals of N-(2-thiazolyl)-1,4-dihydroxybenzene-3-sulfonamide melted at 222–224°.

Anal. Calcd. for $C_9H_8O_4N_2S_2$: C, 39.69; H, 2.96; N, 10.29; S, 23.55. Found: C, 39.7; H, 2.98; N, 10.3; S, 23.4.

N-(2-Pyridyl)-1,4-diacetoxybenzene-3-sulfonamide.—A mixture of 146 g. of 1,4-diacetoxybenzene-3-sulfonyl chloride, 52 g. of 2-aminopyridine, and 200 ml. of pyridine, after one-half hour at room temperature, was allowed to stand overnight in the ice-box. The yellow mush was poured in 3 l. of water and acidified with dilute hydrochloric acid. The precipitate was filtered, washed with water, and dried. The yield was 139 g. (80%). Pure N-(2-pyridyl)-1,4-diacetoxybenzene-3-sulfonamide melting at 238–239° was obtained from the above by recrystallization from acetone.

Anal. Calcd. for $C_{15}H_{14}O_6N_2S$: C, 51.41; H, 4.02; N, 8.00; S, 9.15. Found: C, 51.4; H, 3.88; N, 7.82; S, 9.02.

N-(2-Pyridyl)-1,4-dihydroxybenzene-3-sulfonamide.—Hydrolysis of the above crude with *N* sodium hydroxide followed by recrystallization from water gave pure N-(2-pyridyl)-1,4-dihydroxybenzene-3-sulfonamide. This decomposed at 203–205°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.62; H, 3.79; N, 10.52; S, 12.04. Found: C, 49.8; H, 3.88; N, 10.27; S, 12.1.

4-Methyl-1-phenol-2,6-bis-[N-(2-pyridyl)-sulfonamide].—4-Methyl-1-phenol-2,6-bis-(sulfonyl chloride)[27] (42.7 g., 0.14 mole) was added over a 15-minute period at 15–20° to 29.1 g. (0.31 mole) of 2-aminopyridine in 120 ml. of dry pyridine. The mixture was allowed to stand at room temperature for one hour and then in the ice-box for 23 hours. It was poured into 800 ml. of water and acidified to a *p*H of 3.5–4.0 with 5 *N* hydrochloric acid. After heating for 15 minutes at 70°, the product was filtered and washed with hot water. It was dissolved in 760 ml. of 0.5 *N* sodium hydroxide, treated with Darco G-60, and filtered. To the filtrate was added 240 ml. of 50% sodium hydroxide. A granular precipitate separated and was filtered at 5°. The precipitate was dissolved in 1500 ml. of water, treated with Darco G-60 twice, and the solution was then acidified with dilute hydrochloric acid. The precipitate was filtered, washed with water and dried. The yield was 47 g. (80%) melting at 235–240°. Recrystallization twice more through the sodium salt gave a product melting at 246–250°.

Anal. Calcd. for $C_{17}H_{16}O_6N_4S_2$: C, 48.55; H, 3.83; N, 13.32; S, 15.26. Found: C, 48.4; H, 3.89; N, 13.3; S, 15.0.

N-(2-Pyridyl)-1,2-diacetoxybenzene-4-sulfonamide.—Fifty-two grams (0.55 mole) of 2-aminopyridine, 146 g. (0.5 mole) of 1,2-diacetoxybenzene-4-sulfonyl chloride[28] and 200 ml. of pyridine were mixed and allowed to stand for one hour at 25–30° and then in the ice-box overnight. The mixture was poured into water and acidified with concd.

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(28) R. T. Williams, *Biochem. J.*, **35**, 1169 (1941).

hydrochloric acid. A heavy gum settled to the bottom and small beads formed above. The beads were separated, washed with water and dried. The yield was 13 g. Recrystallization twice from 2B alcohol yielded white needles melting at 166–167°.

Anal. Calcd. for $C_{15}H_{14}O_6N_2S$: C, 51.41; H, 4.02; N, 8.00; S, 9.15. Found: C, 51.8; H, 4.25; N, 7.84; S, 9.25.

N-(2-Pyridyl)-1,2-dihydroxybenzene-4-sulfonamide.—N-(2-Pyridyl)-1,2-dihydroxybenzene-4-sulfonamide was obtained from the diacetoxy derivative above by hydrolysis overnight at room temperature in 5 *N* sodium hydroxide followed by acidification. After two recrystallizations from water, the N-(2-pyridyl)-1,2-dihydroxybenzene-4-sulfonamide melted at 225–226°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.62; H, 3.79; N, 10.52; S, 12.04. Found: C, 49.8; H, 3.76; N, 10.5; S, 11.9.

O-(2-Pyrazinyl-1-phenol-4-sulfonamide.—Twenty-six grams (0.15 mole) of phenol-4-sulfonamide[2] (m.p. 175–176°), 17.2 g. (0.125 mole) of potassium carbonate and 11.5 g. (0.1 mole) of 2-chloropyrazine (b.p. 152.6–153.6°) were refluxed and stirred for five hours in a 100-ml. flask heated in an oil-bath at 180°. After cooling, the almost solid reaction mixture was dissolved in 200 ml. of water and made strongly alkaline with dilute sodium hydroxide, and steam distilled to remove the unreacted chloropyrazine. The remaining solution was treated with decolorizing carbon, clarified, adjusted to a *p*H of about 10 by the addition of dilute hydrochloric acid and cooled in an ice-bath. The white crystals which separated were filtered off, washed with water and dried at 60°. The yield was 9.0 g. (36%), m.p. 148–150°. A sample was purified for analysis by recrystallizing it twice from alcohol, which gave small white plates melting at 150.6–151.4°.

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.78; H, 3.61; N, 16.72; S, 12.76. Found: C, 47.7; H, 3.75; N, 16.9; S, 12.5.

Sodium *p*-Tosyloxybenzenesulfinate.—This was prepared as described for *p*-acetaminobenzenesulfinic acid,[29] using *p*-tosyloxybenzenesulfonyl chloride as an intermediate. The *p*-tosyloxybenzenesulfinic acid precipitated as a gum, which was washed well with ice-water, suspended in water, and then converted to the sodium salt by the addition of sodium hydroxide to *p*H 8. Sodium chloride was added to the resulting solution to salt out the white product, which was filtered off, washed with saturated sodium chloride solution and dried at 50°. The crude yield was 85%. It was sufficiently pure for use in the experiments below.

2-Amino-5-(*p*-tosyloxyphenylsulfonyl)-thiazole.—To a solution of 159 g. of sodium *p*-tosyloxybenzenesulfinate in 825 ml., of water was added 64 g. (0.475 mole) of freshly purified 2-amino-5-chlorothiazole and 40 g. of sodium bicarbonate. The mixture was heated at 80° for two hours, at the end of which time a solid had precipitated. This was filtered off after cooling. A small sample was removed and recrystallized three times from alcohol with the aid of Darco G-60, yielding a very light yellow product melting at 157.5–158.5°.

Anal. Calcd. for $C_{15}H_{14}N_2O_5S_3$: N, 6.84; S, 23.4. Found: N, 6.74; S, 23.0.

2-Amino-5-(*p*-hydroxyphenylsulfonyl)-thiazole.[4b]—The remainder of the crude product from above was slurried in 800 ml. of 10% sodium hydroxide, heated on the steam-bath 10 minutes, filtered hot, and adjusted to *p*H 6.0–6.5. A brown crystalline precipitate was formed, which after drying weighed 59 g. This represents a 48.5% over-all crude yield. It was extracted into hot alcohol (1500 ml. total) to remove some insoluble impurities, and an equal volume of water was added to the clarified solution. The desired product precipitated. After two recrystallizations from 50% alcohol, shiny white crystals of 2-amino-5-(*p*-hydroxyphenylsulfonyl)-thiazole melting at 275–276° were obtained.

Anal. Calcd. for $C_9H_8N_2O_3S_2$: C, 42.2; H, 3.15; N, 10.95; S, 25.0. Found: C, 42.3; H, 3.23; N, 10.8; S, 25.0.

2-(*p*-Tosyloxyphenylsulfonyl)-thiazole.—Fifty grams of freshly prepared 2-chlorothiazole was mixed with 140 g. of sodium *p*-tosyloxybenzenesulfinate and 250 ml. of diethyl carbitol. The mixture was heated under reflux for four hours, cooled, and poured into 1 l. of water. A white precipitate formed, and after cooling the mixture to 5–10°, the product was collected on the filter, washed with water, and dried. There was obtained 56 g. representing a yield of 36% of 2-(*p*-tosyloxyphenylsulfonyl)-thiazole. After two recrystallizations from alcohol it melted at 146–147°.

Anal. Calcd. for $C_{16}H_{13}N_3O_5S_3$: C, 48.6; H, 3.32; N, 3.55. Found: C, 49.0; H, 3.35; N, 3.43.

2-(*p*-Hydroxyphenylsulfonyl)-thiazole.—The tosyloxy derivative was slurried in 700 ml. of 10% sodium hydroxide plus 150 ml. of alcohol and heated 40 minutes on the steam-bath. The solution was clarified, cooled and neutralized, yielding a precipitate which was filtered off and dried; weight, 23.1 g., representing a 67% yield. After three recrystallizations from 20% alcohol with the aid of Darco G-60, the product melted at 162.5–163.5°.

Anal. Calcd. for $C_9H_7NO_3S_2$: N, 5.81; S, 26.8. Found: N, 5.54; S, 26.4.

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