[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI, AND RESEARCH LABORATORIES OF CHATTEM CHEMICALS]

Synthesis and Antibacterial Activity of Some 4-Substituted Benzenesulfonylhydrazones[1]

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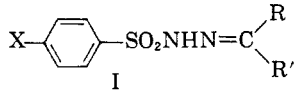
A representative number of 4-amino-, 4-acetamido-, and 4-nitrobenzenesulfonylhydrazones of a great variety of aldehydes and ketones have been prepared. The *in vitro* activity of these compounds against *Streptococcus pyogenes*, *Micrococcus pyogenes*, and *Escherichia coli* is reported.

In view of the physiological activity of many hydrazine derivatives, especially the action of isonicotinic acid hydrazide toward *Mycobacterium tuberculosis*, it was considered of interest to investigate the antibacterial properties of a representative group of hydrazine analogs of the well known sulfa drugs. The compounds prepared for this study are derivatives of 4-acetamido, 4-amino, and 4-nitrobenzenesulfonylhydrazine which may be represented by formula I.

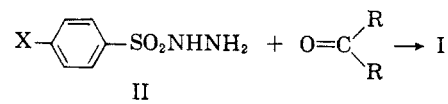


I

where X = CH_3CONH—, O_2N—, or H_2N—
R = H— or alkyl
R′ = alkyl or aryl

A few examples of each series of these compounds have been reported in the literature.[2-8] However, no systematic characterization of the antibacterial properties of compounds of this type has been reported. Lehmann and Grivsky[3] investigated a few 4-aminobenzenesulfonylhydrazones and found them to have some activity against *Pneumococcus* and *Escherichia coli*. However, since this observation was noted after the introduction of the sulfa drugs, the discovery of activity among these hydrazone derivatives was not followed by a more thorough investigation. Offe and Siefken[5] tested five 4-acetamidobenzenesulfonylhydrazones for their activity against *Mycobacterium tuberculosis* and found some *in vitro* inhibition but no *in vivo* activity when tested in mice. An investigation of a representative number of these compounds, therefore, appeared desirable in view of the increasing number of strains of bacteria which are becoming resistant to the sulfa drugs.

The hydrazone derivatives reported in this paper (see tables I, II, and III) were prepared by the chemical interaction of the known hydrazides, 4-acetamido-, 4-nitro, and 4-aminobenzenesulfonylhydrazine (II) with various aldehydes and ketones. These modifications of the parent



II

where X = CH_3CONH—, O_2N—, or H_2N—

molecules were planned with a two-fold purpose in mind. First of all, it was desired to lower the toxicity of the hydrazides toward animals. A concomitant consideration was that the hydrazone formation reaction offered a convenient means of altering the chemical structures so as to uncover a possible relation between structure and activity in these compounds.

The 4-acetamido- and 4-nitrobenzenesulfonylhydrazines were prepared by interaction of the respective acid chlorides with hydrazine under appropriate conditions. The preparation of 4-aminobenzenesulfonylhydrazine was somewhat more difficult due to the instability of the corresponding acid chloride. After investigating several approaches to the preparation of this compound, we found the method of Jensen and Hansen[9] to be useful in our laboratory. This method entails the conversion of 4-acetamidobenzenesulfonyl chloride to the corresponding acid fluoride, hydrolysis of the 4-acetamidobenzenesulfonylfluoride to the rather stable 4-aminobenzenesulfonylfluoride, and subsequent reaction with hydrazine to yield the desired hydrazide.

In most cases the chemical interaction of the hydrazide and the aldehyde or ketone occurred rapidly, leading to the desired hydrazone in good yield. However, some combinations were achieved

(1) This paper was presented before the 134th Meeting of the American Chemical Society, Chicago, September 1958.

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(3) R. Lehmann and E. Grivsky, *Bull. soc. chim. Belges*, **55**, 52-97 (1946).

(4) V. M. Rodionov and A. M. Fedorova, *Izvest. Akad. Nauk. S.S.S.R.*, 1049 (1952).

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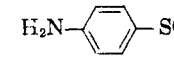
(7) W. Davies, F. R. Storrie, and S. H. Tucker, *J. Chem. Soc.*, 624 (1931).

(8) A. A. M. Witte, *Rec. trav. chim.*, **51**, 299 (1932).

(9) K. A. Jensen and O. R. Hansen, *Acta Chem. Scand.*, **6**, 195 (1952).

TABLE I



AND SOME CARBONYL DERIVATIVES

Carbonyl Compound	Molecular Formula	Calculated			Found			M.P., °C. (dec.)	Lit. Ref.	Biological Assay		
		C	H	N	C	H	N			sp	mp	ec
...	$C_6H_9N_3O_2S$	...	...	...	...	...	...	131–132	[a]	2	4	2
Trifluoroacetone	$C_9H_{10}F_3N_3O_2S$	38.42	3.58	14.94	38.41	3.74	15.12	150–151		4	4	2
Acetone	$C_9H_{13}N_3O_2S$	...	...	...	...	...	...	181–182	[b]	4	4	4
Butanone-2	$C_{10}H_{15}N_3O_2S$	49.77	6.27	17.41	49.73	6.45	17.47	163–164		4	4	4
5-Nitrofurfural	$C_{11}H_{10}N_4O_5S$	42.57	3.25	18.06	43.50	3.20	17.23	160–161		4	3	1
Furfural	$C_{11}H_{11}N_3O_3S$	49.80	4.18	15.84	49.91	4.29	15.82	142–143		4	4	1
Cyclopentanone	$C_{11}H_{15}N_3O_2S$	52.15	5.97	16.59	51.92	6.11	16.41	182–183		4	4	4
Levulinic acid	$C_{11}H_{15}N_3O_4S$	46.31	5.30	14.73	46.25	5.35	14.56	145–146		4	4	4
2-Acetylthiophene	$C_{12}H_{13}N_3O_2S_2$	48.79	4.43	14.22	48.48	4.35	14.02	206–207		4	4	4
Mesityl oxide	$C_{12}H_{17}N_3O_2S$	...	...	...	...	...	...	155–156	[c]	4	4	4
Cyclohexanone	$C_{12}H_{17}N_3O_2S$	...	...	...	...	...	...	170–171	[d]	4	4	4
Ethyl acetoacetate	$C_{12}H_{17}N_3O_4S$	48.15	5.73	14.04	48.33	5.96	13.82	146–147		3	4	4
Pinacolone	$C_{12}H_{19}N_3O_2S$	53.50	7.11	15.60	53.59	7.09	15.65	186–187		4	2	2
3,4-Dichlorobenzaldehyde	$C_{13}H_{11}Cl_2N_3O_2S$	45.36	3.22	12.21	45.21	3.23	12.28	168–169		4	4	4
2-Chlorobenzaldehyde	$C_{13}H_{12}ClN_3O_2S$	50.40	3.90	13.56	50.43	3.81	13.47	149–150		4	2	4
5-Chlorosalicylaldehyde	$C_{13}H_{12}ClN_3O_3S$	47.97	3.71	12.90	47.68	3.91	12.69	193–194		4	2	3
2-Nitrobenzaldehyde	$C_{13}H_{12}N_4O_4S$	48.74	3.78	17.49	48.60	3.78	17.90	168–169		4	4	4
3-Nitrobenzaldehyde	$C_{13}H_{12}N_4O_4S$	48.74	3.77	17.49	48.53	3.88	17.36	163–165		4	4	4
5-Nitrosalicylaldehyde	$C_{13}H_{12}N_4O_5S$	46.43	3.60	16.66	45.86	3.50	16.18	208–209		4	1	4
Benzaldehyde	$C_{13}H_{13}N_3O_2S$	...	...	...	...	...	...	172–173	[e]	1	4	4
Salicylaldehyde	$C_{13}H_{13}N_3O_3S$	53.60	4.50	14.42	53.71	4.60	14.36	176–177		1	4	1
4-Hydroxybenzaldehyde	$C_{13}H_{13}N_3O_3S$	53.59	4.50	14.42	53.45	4.57	14.62	154–155		4	4	4
2-Methylcyclohexanone	$C_{13}H_{19}N_3O_2S$	55.48	6.81	14.93	55.49	6.98	15.07	149–150		4	4	4
4-Methylcyclohexanone	$C_{13}H_{19}N_3O_2S$	55.48	6.81	14.93	55.60	6.90	15.02	172–173		4	4	4
2-Heptanone	$C_{13}H_{21}N_3O_2S$	55.09	7.47	14.83	54.89	7.47	14.72	168–169		4	4	4
3-Heptanone	$C_{13}H_{21}N_3O_2S$	55.09	7.47	14.83	55.05	7.67	14.96	155–156		2	4	4
Acetophenone	$C_{14}H_{15}N_3O_2S$	...	...	...	...	...	...	193–194	[f]	4	4	4
4-Methylbenzaldehyde	$C_{14}H_{15}N_3O_2S$	58.12	5.23	14.52	58.11	5.33	14.62	177–178		4	4	4
Anisaldehyde	$C_{14}H_{15}N_3O_3S$	...	...	...	...	...	...	166	[g]	4	4	4
2-Hydroxyacetophenone	$C_{14}H_{15}N_3O_3S$	55.07	4.95	13.76	54.76	4.94	13.66	184–185		1	4	3
Vanillin	$C_{14}H_{15}N_3O_4S$	52.33	4.71	13.08	52.38	4.79	13.32	174–175		2	4	4
2,4-Dihydroxyacetophenone	$C_{14}H_{15}N_3O_4S$	52.33	4.71	13.08	52.39	4.76	13.00	212–213		4	4	2
4-Aminoacetophenone	$C_{14}H_{16}N_4O_2S$	55.24	5.30	18.41	55.02	5.25	18.21	196–197		4	4	3
2-Methoxybenzaldehyde	$C_{14}H_{15}N_3O_3S$	55.06	4.95	13.76	54.76	5.13	13.51	162–163		4	4	4
2-Nitrocinnamaldehyde	$C_{15}H_{14}N_4O_4S$	52.01	4.07	16.18	52.11	4.10	16.05	161–162		3	4	4
Cinnamaldehyde	$C_{15}H_{15}N_3O_2S$	59.77	5.02	13.94	59.92	5.19	13.70	179–180		4	4	4
Piperonal	$C_{15}H_{15}N_3O_3S$	52.66	4.10	13.16	52.69	4.23	12.96	174–175		3	4	4
2-Hydroxy-3-methyl-5-nitroacetophenone	$C_{15}H_{16}N_4O_5S$	49.44	4.43	15.38	49.62	4.58	15.25	262–263		..	..	..
2-Hydroxy-5-methyl-3-nitroacetophenone	$C_{15}H_{16}N_4O_5S$	49.44	4.43	15.38	49.38	4.53	15.23	224–225		..	..	..
Phenylacetone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.56	5.85	13.88	166–167		4	4	4
Propiophenone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.42	5.71	13.99	166–167		4	4	4
4-Methylacetophenone	$C_{15}H_{17}N_3O_2S$	59.38	5.65	13.85	59.49	5.58	13.68	215–216		..	..	..
2-Hydroxypropiophenone	$C_{15}H_{17}N_3O_3S$	56.41	5.37	...	56.66	5.32	...	208–209		1	3	3
4-Hydroxypropiophenone	$C_{15}H_{17}N_3O_3S$	56.41	5.37	...	56.24	5.46	...	200–201		3	4	3
2-Ethoxybenzaldehyde	$C_{15}H_{17}N_3O_3S$	56.41	5.37	13.16	56.27	5.53	12.90	170–171		2	4	4
4-Dimethylaminobenzaldehyde	$C_{16}H_{18}N_4O_2S$	56.58	5.70	17.60	56.40	5.69	17.64	186–187		4	4	4
Benzalacetone	$C_{16}H_{17}N_3O_2S$	60.93	5.43	13.32	60.92	5.48	12.77	180–181		..	..	..
4-Isopropylbenzaldehyde	$C_{16}H_{19}N_3O_2S$	60.54	6.03	13.24	60.63	6.04	13.24	162–163		4	4	4
2,4-Dimethylacetophenone	$C_{16}H_{19}N_3O_2S$	60.54	6.03	13.24	60.38	6.05	13.01	176–177		4	4	4
2-Hydroxy-*n*-butyrophenone	$C_{16}H_{19}N_3O_3S$	57.64	5.74	...	57.66	5.66	...	215		3	4	4
4-Hydroxy-*n*-butyrophenone	$C_{16}H_{19}N_3O_3S$	57.64	5.74	...	57.50	5.74	...	181–182		4	4	4
3,4,5-Trimethoxybenzaldehyde	$C_{16}H_{19}N_3O_5S$	52.59	5.24	11.50	52.52	5.18	11.26	167–168		4	4	4
1-Naphthaldehyde	$C_{17}H_{15}N_3O_2S$	62.75	4.65	12.91	62.91	4.57	12.89	162–163		3	4	4
2-Hydroxy-1-naphthaldehyde	$C_{17}H_{15}N_3O_3S$	59.81	4.43	12.31	59.95	4.42	12.11	183–184		4	4	4
2-Hydroxy-*n*-valerophenone	$C_{17}H_{21}N_3O_3S$	58.77	6.09	...	58.54	6.07	...	205–206		3	4	4

TABLE I (*Continued*)

Carbonyl Compound	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	Biological Assay mp	Biological Assay ec
4-Hydroxy-*n*-valerophenone	$C_{17}H_{21}N_3O_3S$	58.77	6.09	...	58.96	6.15	...	176–177		3	4	4
4-Diethylaminobenzaldehyde	$C_{17}H_{22}N_4O_2S$	58.94	6.40	16.17	58.76	6.58	16.12	192–193		4	4	4
4-Bromo-1-hydroxy-2-acetonaphthone	$C_{18}H_{16}BrN_3O_3S$	49.77	3.71	...	49.79	3.78	...	244–245		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{18}H_{16}N_4O_5S$	53.99	4.03	13.99	55.10	4.23	12.56	219–221		..	..	..
1-Hydroxy-2-acetonaphthone	$C_{18}H_{17}N_3O_3S$	60.83	4.82	11.82	60.99	4.79	11.68	218–219		4	4	4
1-Hydroxy-4-acetonaphthone	$C_{18}H_{17}N_3O_3S$	60.83	4.82	11.82	60.80	4.80	11.90	217–218		4	3	4

[a] Reported[2] m.p. 131°; [b] reported[2] m.p. 136°; [c] reported[3] m.p. 164–165°; [d] reported[3] m.p. 172°; [e] reported[2] m.p. 172°; [f] reported[3] m.p. 191.5°; [g] reported[3] m.p. 164°.

TABLE II

CH_3CONH–C$_6$H$_4$–SO_2NHNH_2 AND SOME CARBONYL DERIVATIVES

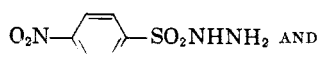
Carbonyl Compound	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	Biological Assay mp	Biological Assay ec
...	$C_9H_{11}N_3O_3S$	...	...	...	...	...	...		[a]	4	4	4
Propionaldehyde	$C_{11}H_{15}N_3O_3S$	49.06	5.61	15.60	49.17	5.66	15.53	128–129		4	4	4
Acetone	$C_{11}H_{15}N_3O_3S$	...	...	...	...	...	...	185–186	[b]	4	3	4
Butyraldehyde	$C_{12}H_{17}N_3O_3S$	50.87	6.05	14.83	50.99	6.18	14.70	122–123		4	4	4
Methyl ethyl ketone	$C_{12}H_{17}N_3O_3S$	50.87	6.05	14.83	50.76	6.14	14.79	160–161		4	4	4
Isovaleraldehyde	$C_{13}H_9N_3O_3S$	52.50	6.44	14.13	52.66	6.57	14.31	132–133		4	4	4
5-Nitrofurfural	$C_{13}H_{12}N_4O_6S$	44.31	3.43	15.90	44.39	3.49	15.71	209–211		4	4	4
2-Furfural	$C_{13}H_{13}N_3O_4S$	50.80	4.26	...	50.95	4.24	...	186–188		4	4	4
Cyclopentanone	$C_{13}H_{17}N_3O_3S$	52.84	5.80	...	52.77	5.91	...	185–186		4	4	4
Levulinic acid	$C_{13}H_{17}N_3O_5S$	47.69	5.23	12.84	47.78	5.25	12.76	174–175		4	4	4
α-Acetylbutyrolactone	$C_{14}H_{17}N_3O_5S$	49.54	5.05	12.38	49.55	5.14	12.14	169–170		4	4	4
Mesityl oxide	$C_{14}H_{19}N_3O_3S$	54.35	6.19	13.58	54.35	6.14	13.65	157–158		4	4	4
Cyclohexanone	$C_{14}H_{19}N_3O_3S$	54.35	6.19	...	54.30	6.37	...	171–172		4	4	4
Ethyl acetoacetate	$C_{14}H_{19}N_3O_5S$	...	...	...	...	...	...	115–117	[c]	4	4	4
n-Hexanal	$C_{14}H_{21}N_3O_3S$	54.00	6.80	13.49	54.22	6.69	13.30	136–137		3	4	4
Pinacolone	$C_{14}H_{21}N_3O_3S$	53.99	6.80	...	54.18	6.93	...	228–229		4	4	4
5-Chlorosalicylaldehyde	$C_{13}H_{13}ClN_3O_4S$	48.98	3.84	11.42	49.13	3.36	11.18	215–216		4	4	4
2,4-Dichlorobenzaldehyde	$C_{15}H_{13}Cl_2N_2O_3S$	46.64	3.39	10.88	46.39	3.46	10.66	216–217		..	..	..
3,4-Dichlorobenzaldehyde	$C_{15}H_{13}Cl_2N_2O_3S$	46.64	3.39	10.88	46.87	3.39	10.49	198–199		2	4	4
2-Chlorobenzaldehyde	$C_{15}H_{14}ClN_3O_3S$	51.21	4.01	...	51.29	4.16	...	209–210		4	4	4
2-Hydroxy-5-nitrobenzaldehyde	$C_{15}H_{14}N_3O_6S$	47.61	3.73	...	48.18	3.81	...	238–239		..	..	..
3-Nitrobenzaldehyde	$C_{15}H_{14}N_4O_5S$	49.71	3.89	15.46	49.70	3.67	14.87	211–212		..	..	..
Benzaldehyde	$C_{15}H_{15}N_3O_3S$	...	...	...	...	...	...	193–194	[d]	4	4	4
Salicylaldehyde	$C_{15}H_{15}N_3O_4S$	54.04	4.54	...	54.34	4.69	...	225–226		4	4	4
4-Hydroxybenzaldehyde	$C_{15}H_{15}N_3O_4S$	54.04	4.54	12.60	53.86	4.63	12.49	178–179		4	4	4
2,4-Dihydroxybenzaldehyde	$C_{15}H_{15}N_3O_5S$	51.57	4.33	...	51.47	4.50	...	196–198		4	4	4
2-Methylcyclohexanone	$C_{15}H_{21}N_3O_3S$	55.71	6.55	12.99	55.63	6.51	12.78	150–151		4	4	4
4-Methylcyclohexanone	$C_{15}H_{21}N_3O_3S$	55.71	6.55	12.99	55.56	6.59	12.74	162–163		4	4	4
n-Heptanal	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	55.66	6.91	12.86	106–107		4	4	4
2-Heptanone	$C_{15}H_{23}N_3O_3S$	55.36	7.12	...	55.07	7.20	...	158–159		4	4	4
3-Heptanone	$C_{15}H_{23}N_3O_3S$	55.36	7.12	12.91	55.59	7.14	12.98	159–160		4	4	4
Piperonal	$C_{16}H_{15}N_3O_5S$	53.17	4.78	11.63	52.94	4.36	11.56	203–204		..	..	..
Acetophenone	$C_{16}H_{17}N_3O_3S$	57.98	5.17	12.68	58.04	5.03	12.51	206–207		..	..	..
4-Methylbenzaldehyde	$C_{16}H_{17}N_3O_3S$	57.98	5.17	12.68	58.11	5.40	12.58	190		4	4	4
2-Methoxybenzaldehyde	$C_{16}H_{17}N_3O_4S$	55.31	4.93	12.10	55.62	5.15	11.97	196–197		4	4	4
Anisaldehyde	$C_{16}H_{17}N_3O_4S$	...	...	...	...	...	...	195	[e]	4	4	4
2-Hydroxyacetophenone	$C_{16}H_{17}N_3O_4S$	55.32	4.93	12.10	55.13	5.09	11.91	227–228		..	..	..
Vanillin	$C_{16}H_{17}N_3O_5S$	52.88	4.72	11.56	53.04	4.84	11.74	186–187		4	2	1
4-Aminoacetophenone	$C_{16}H_{18}N_4O_3S$	55.47	5.24	16.17	55.30	5.47	16.27	206–207		4	4	4
2-Nitrocinnamaldehyde	$C_{17}H_{16}N_4O_5S$	52.55	4.15	...	52.60	4.14	...	200–203		..	..	..
Cinnamaldehyde	$C_{17}H_{17}N_3O_3S$	59.46	4.99	...	59.26	5.17	...	202–203		2	4	4

TABLE II (*Continued*)

Carbonyl Compound	Molecular Formula	Calculated C	H	N	Found C	H	N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	mp	ec
2-Hydroxy-3-nitro-5-methylacetophenone	$C_{17}H_{18}N_4O_6S$	50.24	4.46	...	50.47	4.24	...	241–242		..	..	..
Hydrocinnamaldehyde	$C_{17}H_{19}N_3O_3S$	59.11	5.54	...	59.26	5.67	...	135–136		1	3	4
4-Methylacetophenone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	12.17	59.13	5.77	12.55	199		..	..	..
Phenylacetone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	...	58.46	5.61	...	189–190		4	3	4
Propiophenone	$C_{17}H_{19}N_3O_3S$	59.11	5.54	12.17	59.32	5.47	12.17	178–179		4	4	4
4-Methoxyacetophenone	$C_{17}H_{19}N_3O_4S$	56.49	5.30	11.64	56.52	5.41	11.39	211–212		..	..	..
2-Ethoxybenzaldehyde	$C_{17}H_{19}N_3O_4S$	56.49	5.30	...	56.42	5.48	...	209–210		..	..	..
4-Dimethylaminobenzaldehyde	$C_{17}H_{20}N_4O_3S$	56.65	5.59	...	56.60	5.66	...	219–220		4	4	4
Isophorone	$C_{17}H_{23}N_3O_3S$	58.43	6.63	...	58.28	6.83	...	176–177		4	4	4
3-Acetylthionaphthene	$C_{18}H_{17}N_3O_3S_2$	55.78	4.42	10.84	55.92	4.41	10.60	224–225		..	..	..
Benzalacetone	$C_{18}H_{19}N_3O_3S$	60.48	5.36	...	60.19	5.27	...	186–187		4	4	4
4-Isopropylbenzaldehyde	$C_{18}H_{21}N_3O_3S$	60.14	5.89	...	59.86	5.90	...	195–196		4	4	4
Citral	$C_{18}H_{25}N_3O_3S$	59.48	6.93	...	59.25	7.03	...	138–139		4	4	2
1-Naphthaldehyde	$C_{19}H_{17}N_3O_3S$	62.10	4.66	11.43	61.99	4.53	11.43	201–202		4	4	4
2-Hydroxy-1-naphthaldehyde	$C_{19}H_{17}N_3O_4S$	59.51	4.47	10.96	59.67	4.51	11.09	219–220		4	3	4
4-Diethylaminobenzaldehyde	$C_{19}H_{24}N_4O_3S$	58.74	6.23	14.42	58.79	6.36	14.54	187–188		4	4	4
1-Hydroxy-4-bromo-2-acetonaphthone	$C_{20}H_{18}BrN_3O_4S$	50.43	3.81	8.82	50.40	3.74	8.84	252–253		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{20}H_{18}N_4O_6S$	54.29	4.10	12.66	54.46	4.24	12.64	271–272		..	..	..
1-Hydroxy-2-acetonaphthone	$C_{20}H_{19}N_3O_4S$	60.44	4.82	10.57	60.23	4.88	10.71	271–272		..	..	..
1-Hydroxy-4-acetonaphthone	$C_{20}H_{19}N_3O_4S$	60.44	4.82	10.57	60.48	4.82	10.64	242–243		4	2	4

[a] Reported[2] m.p. 177–178°; [b] reported[4] m.p. 174°; [c] reported[4] m.p. 118–120°; [d] reported[5] m.p. 190–190.5°; [e] reported[5] m.p. 179–180°.

TABLE III



O_2N—C$_6$H$_4$—SO_2NHNH_2 AND SOME CARBONYL DERIVATIVES

Carbonyl Compound	Molecular Formula	Calculated C	H	N	Found C	H	N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	mp	ec
...	$C_6H_7N_3O_4S$	...	...	...	...	...	...	...	[a]	4	4	4
Acetone	$C_9H_{11}N_3O_4S$	...	...	...	...	...	...	176–177	[b–d]	4	4	4
5-Nitrofurfural	$C_{11}H_8N_4O_7S$	38.82	2.37	16.47	38.91	2.35	16.38	182–183		..	..	..
2-Furfural	$C_{11}H_9N_3O_5S$	...	...	...	...	...	...	150–151	[e]	4	4	4
Levulinic acid	$C_{11}H_{13}N_3O_6S$	41.90	4.15	13.33	42.08	4.22	13.55	174–175		4	4	3
Isovaleraldehyde	$C_{11}H_{15}N_3O_4S$	...	...	...	...	...	...	118–119	[f]	4	4	4
2-Acetylthiophene	$C_{12}H_{11}N_3O_4S_2$	44.29	3.41	12.91	44.37	3.19	12.66	167–168		4	4	4
Cyclohexanone	$C_{12}H_{15}N_3O_4S$	...	...	...	...	...	...	157–158	[g]	4	4	4
Pinacolone	$C_{12}H_{17}N_3O_4S$	48.14	5.72	14.04	47.95	5.68	14.20	184–185		2	4	4
Glucose	$C_{12}H_{17}N_3O_9S$	37.99	4.52	11.08	37.95	4.46	10.84	156–157		4	4	4
3,4-Dichlorobenzaldehyde	$C_{13}H_9Cl_2N_3O_4S$	41.72	2.42	11.23	41.30	2.37	11.28	184–185		4	4	4
2-Chlorobenzaldehyde	$C_{13}H_{10}ClN_3O_4S$	45.95	2.97	...	46.55	2.99	...	174–175		4	4	4
5-Chlorosalicylaldehyde	$C_{13}H_{10}ClN_3O_5S$	43.89	2.83	11.81	44.18	2.76	11.54	201–202		3	2	3
2-Nitrobenzaldehyde	$C_{13}H_{10}N_4O_6S$	...	...	...	...	...	...	201–202	[h]	..	..	..
3-Nitrobenzaldehyde	$C_{13}H_{10}N_4O_6S$	...	...	...	...	...	...	204–205	[i]	..	..	..
5-Nitrosalicylaldehyde	$C_{13}H_{10}N_4O_7S$	42.62	2.75	...	42.83	2.60	...	180–185		2	1	4
Benzaldehyde	$C_{13}H_{11}N_3O_4S$	...	...	...	...	...	...	139–141	[j–l]	4	4	4
Salicylaldehyde	$C_{13}H_{11}N_3O_5S$	...	...	...	...	...	...	190–191	[m, n]	2	4	4
2,4-Dihydroxybenzaldehyde	$C_{13}H_{11}N_3O_6S$	46.29	3.29	...	46.21	3.19	...	222–224		4	4	4
2-Methylcyclohexanone	$C_{13}H_{17}N_3O_4S$	50.14	5.50	13.50	50.34	5.44	13.26	124–125		4	4	4
4-Methylcyclohexanone	$C_{13}H_{17}N_3O_4S$	50.14	5.50	13.50	50.14	5.54	13.42	167–168		4	2	2
2-Heptanone	$C_{13}H_{19}N_3O_4S$	49.82	6.11	13.41	49.82	5.99	13.32	144–145		4	4	4
3-Heptanone	$C_{13}H_{19}N_3O_4S$	49.82	6.11	13.41	49.82	6.14	13.55	99–101		4	4	4
Acetophenone	$C_{14}H_{13}N_3O_4S$	52.65	4.10	13.16	52.89	4.13	13.34	188–189		..	..	..
4-Methylbenzaldehyde	$C_{14}H_{13}N_3O_4S$	52.65	4.10	13.16	52.51	3.99	12.69	162–163		4	4	4
2-Methoxybenzaldehyde	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.25	3.73	12.27	159–161		4	4	4

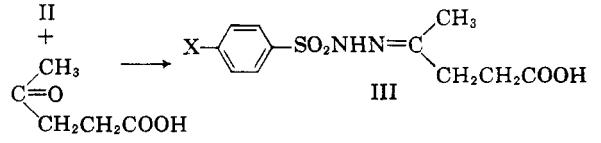
TABLE III (*Continued*)

Carbonyl Compound	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	M.P., °C. (dec.)	Lit. Ref.	Biological Assay sp	Biological Assay mp	Biological Assay ec
Anisaldehyde	$C_{14}H_{13}N_3O_5S$	...	...	...	...	...	...	185–186	[o]	4	4	4
2-Hydroxyacetophenone	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.17	4.07	12.62	165–166		4	4	4
Vanillin	$C_{14}H_{13}N_3O_6S$	...	...	...	...	...	...	167–168	[p]	3	4	4
2,4-Dihydroxyaceto-phenone	$C_{14}H_{13}N_3O_6S$	47.86	3.73	11.96	47.59	3.85	11.72	180–182		4	4	4
4-Aminoacetophenone	$C_{14}H_{14}N_4O_4S$	50.29	4.22	16.76	50.18	4.19	16.58	166–167		4	4	4
2-Nitrocinnamaldehyde	$C_{15}H_{12}N_4O_6S$	47.87	3.21	...	47.98	3.21	...	183–184		..	..	..
Cinnamaldehyde	$C_{15}H_{13}N_3O_4S$	54.37	3.95	12.68	54.27	3.89	12.65	144–145		4	4	4
6-Nitroveratraldehyde	$C_{15}H_{14}N_4O_8S$	43.90	3.44	...	44.13	3.67	...	184–185		..	..	..
Propiophenone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	12.61	54.04	4.35	12.41	160		4	4	4
4-Methylacetophenone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	12.60	54.19	4.55	12.85	191–192		..	..	..
Phenylacetone	$C_{15}H_{15}N_3O_4S$	54.05	4.54	...	54.77	4.63	...	149–151		4	4	4
2-Ethoxybenzaldehyde	$C_{15}H_{15}N_3O_5S$	51.51	4.33	...	51.79	4.36	...	163–165		4	4	4
4-Dimethylaminobenz-aldehyde	$C_{15}H_{16}N_4O_4S$	51.71	4.63	...	52.07	4.70	...	166–167		4	4	4
Isophorone	$C_{15}H_{19}N_3O_4S$	53.40	5.68	...	53.18	5.64	...	149–150		3	4	4
Benzalacetone	$C_{16}H_{15}N_3O_4S$	...	...	...	...	...	...	175–176	[q]	4	4	4
4-Isopropylbenzaldehyde	$C_{16}H_{17}N_3O_4S$	55.32	4.93	...	55.63	4.96	...	142–143		1	3	4
2,4-Dimethylaceto-phenone	$C_{16}H_{17}N_3O_4S$	55.32	4.93	12.09	55.49	5.03	12.01	189–190		4	4	4
Citral	$C_{16}H_{21}N_3O_4S$	54.68	6.02	11.96	54.93	6.10	12.17	116–117		4	4	4
α-Naphthaldehyde	$C_{17}H_{13}N_3O_4S$	57.45	3.69	...	57.50	3.74	...	173–174		3	4	4
2-Hydroxy-1-naphthal-dehyde	$C_{17}H_{13}N_3O_5S$	54.98	3.53	11.31	55.04	3.48	11.44	200–201		4	2	1
Phenyl isobutylketone	$C_{17}H_{19}N_3O_4S$	56.49	5.30	...	56.77	5.24	...	157–158		4	4	4
4-Diethylaminobenzal-dehyde	$C_{17}H_{20}N_4O_4S$	54.24	5.36	...	54.12	5.45	...	165–167		4	4	4
4-Bromo-1-hydroxy-2-acetonaphthone	$C_{18}H_{14}BrN_3O_5S$	46.57	3.04	9.05	46.33	2.95	9.14	223–224		..	..	..
1-Hydroxy-4-nitro-2-acetonaphthone	$C_{18}H_{14}N_4O_7S$	50.23	3.28	13.02	50.33	3.30	12.85	225–226		..	..	..
1-Hydroxy-2-acetonaph-thone	$C_{18}H_{15}N_3O_5S$	...	...	10.90	...	...	10.90	195–196		..	..	..
1-Hydroxy-4-acetonaph-thone	$C_{18}H_{15}N_3O_5S$	...	...	10.90	...	...	10.47	221–222		3	4	3

[a] Reported[7] m.p. 150–152°; [b] reported[6] m.p. 169–171° (from acetone), 183–184° (from methanol); [c] reported[7] m.p. 169–171°; [d] reported[8] m.p. 172°; [e] reported[6] m.p. 152°; [f] reported[6] m.p. 132–133°; [g] reported[6] m.p. 162°; [h] reported[6] m.p. 199–200°; [i] reported[6] m.p. 195–196°; [j] reported[7] m.p. 142–144°; [k] reported[6] m.p. 142–144°; [l] reported[8] m.p. 142°; [m] reported[6] m.p. 192°; [n] reported[5] m.p. 178–179°; [o] reported[8] m.p. 160°; [p] reported[6] m.p. 166–167°; [q] reported[6] m.p. 173–174°.

with great difficulty. In the case of 1-hydroxy-2-acetylnaphthalene, it was found that the usual reaction conditions were inoperable. This difficulty was overcome by a fusion of the reactants in the presence of a catalytic quantity of sulfuric acid. Many structural features were thus included in the products obtained, by the use of a variety of aldehydes and ketones.

For the most part, these hydrazone derivatives are only slightly soluble in aqueous systems. In contrast with the sulfa drugs which usually are soluble in the form of their alkali metal salts, these compounds display no corresponding salt formation. In view of this consideration, certain aldehydes and ketones were selected on the basis of a structural feature which would enhance solubility. For example, the reaction of the hydrazides



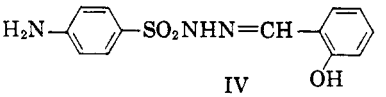
with levulinic acid yielded derivatives (III) soluble in the form of their sodium salts. On the other hand, when aromatic aldehydes and ketones substituted with chloro-, nitro-, and methoxy-groups were used in the hydrazone formation reaction, the products displayed slight solubility, not only in water and alcohols, but also in many common nonpolar solvents.

The products, for the most part, were readily purified by one or two recrystallizations. As is the case with the hydrazides, the hydrazones do not exhibit discrete melting points, but rather are thermally unstable and decompose at elevated temperatures with effervescence. These decompositions are dependent upon the rate of heating and purity of the material. Therefore, in spite of ease of preparation and low solubility of most of the carbonyl derivatives, they are not well suited for the identification of aldehydes and ketones.

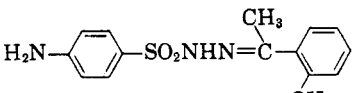
All compounds of sufficient solubility were submitted to a routine screening for *in vitro* activity against *Streptococcus pyogenes*, *Micrococcus*

pyogenes, and *Escherichia coli*. Since these bacteria represent both Gram positive and Gram negative organisms, it was felt that this approach would uncover compounds of potential antibacterial value. The results obtained are qualitative in nature. Test compounds were compared with sulfanilamide and sulfadizine in respect to their ability to produce zones of inhibition of bacterial growth. For the results of these tests see tables I, II, and III. The code used for expressing activity is as follows: sp = *Streptococcus pyogenes*, mp = *Micrococcus pyogenes*, ec = *Escherichia coli*. The numbers 1, 2, 3, and 4 express a comparison with sulfadiazine as the standard: 1, being more active; 2, of equal activity; 3, very low activity; and 4, no apparent activity.

It was found that 4-aminobenzenesulfonylhydrazine, which is structurally related to sulfanilamide, displayed an *in vitro* inhibition to the growth of *Escherichia coli* and *Streptococcus pyogenes* which is comparable to the activity of sulfadiazine. However, as would be expected, this compound proved to be quite toxic in animal studies. Modification of this parent structure by hydrazone formation in some instances yielded derivatives with enhanced antibacterial properties along with a decrease in toxicity. This dual effect was noted also with the other hydrazides. Although this study indicates that a wide variety of structural modifications alter the activity of the parent molecules, a closer inspection of the active structures reveals a re-occurring feature. Two of the compounds which are quite active as agents for the inhibition of *Streptococcus pyogenes* are the 4-aminobenzenesulfonylhydrazones of salicylaldehyde (IV) and 2-hydroxyacetophenone(V). These structures are similar in that they contain aromatic rings substituted in the *ortho* position by a hydroxy group. Derivatives of 5-nitrosalicylaldehyde, 2-hydroxy-1-naphthaldehyde, 2,4-dihydroxyacetophenone, and 2-hydroxypropiophenone, all of which contain a similar structural feature, also display good anti-bacterial properties.

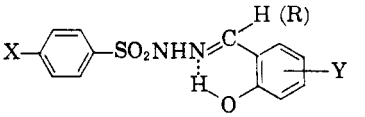


IV



V

At the present, a satisfactory explanation for the activity of these compounds cannot be offered. Experiments indicate that the ability of IV and V to inhibit the *in vitro* growth of *Diplococcus pneumoniae* is not altered by the addition of *p*-aminobenzoic acid to the medium. Since *p*-aminobenzoic acid interferes with the action of the sulfa drugs in the case of this strain of bacteria, it, therefore, is evident that these hydrazones must be acting by some other mechanism. Although the mode of action is unknown, it appears that the chelate ring formed by hydrogen bonding between the hydroxy group and the terminal nitrogen atom of the hydrazone linkage may make a significant contribution to the activity. It is of interest



that H. Erlenmeyer and co-workers[10] found that compounds containing a similar chelate ring are effective against *Mycobacterium tuberculosis* in the form of copper chelates.

At the present, work is in progress to determine if these compounds display *in vivo* antibacterial activity. Results of this investigation will be reported in a subsequent publication.

Because of the similarity in structure to isonicotinic acid hydrazide and derivatives thereof, the following compounds of this series were also tested for activity against *Mycobacterium tuberculosis*, H37Rv, 4-aminobenzenesulfonylhydrazine, 4-nitrobenzenesulfonylhydrazine, 4-acetamidobenzenesulfonylhydrazine, 4-aminobenzenesulfonylhydrazone of salicylaldehyde, 4-aminobenzenesulfonylhydrazone of vanillin, 4-aminobenzenesulfonylhydrazone of 4-dimethylaminobenzaldehyde, 4-aminobenzenesulfonylhydrazone of furfural, 4-aminobenzenesulfonylhydrazone of 3,4,5-trimethoxybenzaldehyde, 4-nitrobenzenesulfonylhydrazone of vanillin. In the experiments conducted no inhibition of the indicated bacteria was noted.

EXPERIMENTAL

Melting points and decomposition points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Muelheim Ruhr, Germany. *Materials:* Generally, Eastman White Label products or comparable grades were employed without further purification.

The following are examples of typical condensations for the three series of compounds.

(1) *4-Acetamidobenzenesulfonylhydrazone of methyl ethyl ketone.* Nine and two-tenths grams (0.040 mole) of 4-acetamidobenzenesulfonylhydrazine were dissolved in 500 ml. of hot water. To the above solution, with vigorous stirring, were added 2.9 g. (0.040 mole) of methyl ethyl ketone. Stirring was continued as the warm solution cooled to room temperature. During this period colorless crystals began to separate from the reaction mixture. After 2 hr., the crystals were collected on a suction filter and dried in a 95° oven. The crude product weighed 7.9 g. (70% yield) and melted with decomposition at 158–161°.

The product was recrystallized from a mixture of three parts methanol and two parts water. The yield was 5.6 g. (50% yield) and the crystals melted with decomposition at 160–161°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83. Found: C, 50.76; H, 6.14; N, 14.79.

(10) E. Sorkin, W. Roth, and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 1736 (1952).

(2) *4-Aminobenzenesulfonylhydrazone of salicylaldehyde.* Seven and five-tenths grams (0.040 mole) of 4-aminobenzenesulfonylhydrazine were dissolved in a hot solution composed of 50 ml. of methanol and 50 ml. of water. To the above solution were added with stirring, 6.1 g. (0.040 mole) of salicylaldehyde. The mixture developed an orange-yellow color and became almost homogeneous. Shortly thereafter yellow-orange crystals began to precipitate from the reaction mixture. The separation of the product was facilitated by the dilution of the reaction mixture with water. The crystals were collected on a suction filter and air dried. The product weighed 11.6 g. (quantitative yield) and melted with decomposition at 167–168°.

The product was recrystallized two times from equal volumes of methanol and water. The yellow crystals weighed 5.6 g. (47% yield) and melted with decomposition at 176.5–177°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.71; H, 4.60; N, 14.36.

(3) *4-Nitrobenzenesulfonylhydrazone of propiophenone.* Seven and four-tenths grams (0.034 mole) of 4-nitrobenzenesulfonylhydrazine were dissolved in 100 ml. of hot methanol containing a little water. Four grams (0.030 mole) of propiophenone were then added dropwise with stirring. Yellow crystals separated from the reaction mixture as it cooled to room temperature. After 2 hr. at room temperature the crystals were collected on a suction filter and dried in a 95° oven. The yellow crystals weighed 9.8 g. (98% yield) and melted with decomposition at 147–150°.

The product was recrystallized from methanol containing a little water. The pale yellow crystals weighed 8.1 g. (81% yield) and melted with decomposition at 150–152°.

Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.04; H, 4.35; N, 12.41.

(4) *4-Acetamidobenzenesulfonylhydrazone of 2-acetyl-1-hydroxynaphthalene.* In a mortar 1.86 g. (0.01 mole) of 2-acetyl-1-hydroxynaphthalene and 2.3 g. (0.01 mole) of 4-acetamidobenzenesulfonylhydrazine were thoroughly mixed. After transferring to a large wide-diameter test tube the contents then were heated to 125° (oil bath). At this temperature the mixture liquefied somewhat and water evaporated; after 15 min., 5 ml. of glacial acetic acid and 2 drops concentrated sulfuric acid together with 15 ml. absolute ethanol were added and the mixture refluxed. After about 1 hr. everything went into solution. Shortly after this a yellow precipitate began to appear, after 1 additional hr. of refluxing, the contents were poured on ice, and washed with alcohol and ether. Yield 2.4 g.

The compound was extremely insoluble in all common solvents. Therefore, the analytical sample was extracted with boiling alcohol.

Anal. Calcd. for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.23; H, 4.88; N, 10.71.

Acknowledgments. A. C. Pronay is indebted to Chattem Chemicals, a Division of the Chattanooga Medicine Company, for financial help. The authors appreciate the stimulating discussions with Drs. I. W. Grote, J. M. Holbert, and J. C. Krantz, Jr. The skillful assistance of Mr. J. E. Giesemann, H. M. Smith, and Mrs. J. Waggoner is appreciated too.

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[CONTRIBUTION FROM THE CITRUS EXPERIMENT STATION OF THE UNIVERSITY OF FLORIDA]

Derivatives of (+)-Limonene. II. 2-Amino-1-*p*-menthanols[1]

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Several new aminoalcohols including 2-amino-1-*p*-menthanol have been synthesized from (+)-limonene. Partial hydrogenation of (+)-limonene followed by oxidation with peracetic acid affords *p*-menthane-1,2-epoxide. The epoxide ring is readily opened by ammonia and amines to give derivatives of 2-amino-1-*p*-menthanol. The direction of ring opening in *p*-menthane-1,2-epoxide and the configurations of the two *trans* isomers of 2-amino-1-*p*-menthanol isolated have been established by an independent synthesis from *trans*-*p*-menthane-1,2-diol of known configuration.

A number of new 2-amino-1-*p*-menthanols have been synthesized from (+)-limonene in connection with a study of limonene derivatives having possible physiological activity.

Hydrogenation of (+)-limonene[2] without solvent, at low pressure, over a 5% platinum on Darco G-60 catalyst proceeds smoothly to afford Δ^1-*p*-menthene (I) in virtually quantitative yield. The details of this hydrogenation have been presented in a previous publication.[3] This ease of partial hydrogenation of (+)-limonene was first described by Vavon[4] and has since been utilized by a number of other authors[5,6] to prepare Δ^1-*p*-menthene (I).

Treatment of (I) with perbenzoic acid in anhydrous chloroform at 10° according to the method of Pigulevskii and Kozhin[6] affords *p*-menthane-1,2 epoxide (II) in 80% yield. Royals[7] has recently reported the preparation of (II) by hydrogenation of (+)-limonene epoxide over Adams' catalyst. Because of the difficulties inherent in the preparation of large quantities of (II) by perbenzoic acid

(1) Florida Agricultural Experiment Stations Journal Series, No. 898.

(2) Samples of citrus D-limonene were supplied by Kuder Citrus Pulp Co., Lake Alfred, Fla.

(3) W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

(4) M. G. Vavon, *Bull. soc. chim. IV*, **15**, 282 (1914).

(5) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **18A**, 455 (1955).

(6) G. V. Pigulevskii and S. A. Kozhin, *Zhur. Obshchei Khim.*, **27**, 803 (1957).

(7) E. Earl Royals, paper no. 92, Southeastern Regional Meeting of American Chemical Society, December 1958.