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Some Halogenated Sulfonanilides

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An important contribution to the field of chemotherapy of bacterial infections was made by Klarer[2] who noted that *p*-aminomethylbenzenesulfonamide was effective against anaerobic clostridia commonly associated with war-wound infections. The compound was furthermore found to be unaffected by *p*-aminobenzoic acid, an attribute not associated with the common sulfanilamides, *i. e.*, sulfanilamide, sulfapyridine, sulfathiazole, etc.[3] These observations stimulated an interest in the search for other possible sulfanilamides which are effective against anaerobic bacteria and which are likewise unaffected by *p*-aminobenzoic acid. A compound of this type was found when N^1-(3,5-dibromophenyl)-sulfanilamide was investigated.

In an attempt to elucidate the antibacterial activity of N^1-(3,5-dibromophenyl)-sulfanilamide in the presence of *p*-aminobenzoic acid, a series of isomeric benzenesulfonanilides halogenated in the anilido nucleus was prepared and studied. In addition, compounds containing the 3,5-dihaloanilido nucleus with substituents in the *para* position of the benzenesulfonyl group were synthesized and tested.

The results of the bacteriological studies on these compounds will be presented in detail elsewhere by Mr. G. R. Goetchius and Dr. C. A. Lawrence. It suffices to say here that, of the compounds tested, those halogenated in the 2 and /or 6 position demonstrated no significant antibacterial effect *in vitro*; halogenation in the 3 and/or 5 position produced the most active compounds. Of significant interest is the fact that 3′,5′-dibromobenzenesulfonanilide, lacking the *para*-amino group, has antibacterial effects comparable to or greater than the corresponding sulfanilamide analog. In the commonly known sulfanilamides removal of the *para*-amino group reduces or inactivates completely the effects of the compounds against bacteria.

When the anilide was prepared by direct synthesis, the procedure was to reflux one mole of the base dissolved in pyridine with a slight excess (about 1.05 moles) of the sulfonyl chloride dissolved in acetone. The product was isolated by pouring the reaction mixture into ice water and was recrystallized from alcohol.

The N^4-acetyl compounds were deacetylated by hydrolyzing in an alkaline medium (compounds 14, 16, 18, and 21) or in an acid medium (compounds 24 and 26).

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Experimental

Halogenated Anilines.—All the mono-halogenated anilines and the 2,4- and 2,5-dichloroanilines are commercially available. The 3,4-isomer was made from the available 3,4-dichloronitrobenzene The 3,5-isomers were prepared from 2,6-dihalo-4-nitroanilines by removal of the amino group followed by reduction of the nitro group. The 2,6-isomer was made, according to the procedure of Seikel,[4] from sulfanilamide. The 2,3-isomer was prepared from *m*-nitroaniline using the method outlined by Holleman.[5]

2′-Chlorobenzenesulfonanilide (1).—To 11.9 g. of *o*-chloroaniline in 85 cc. of anhydrous pyridine was added 18.7 g. of benzenesulfonyl chloride in 100 cc. of acetone. After refluxing for one hour, the reaction mixture was poured into one liter of ice water with stirring. The solid was filtered off, washed with water, then dissolved in 1 *N* sodium hydroxide solution. The solution was slowly acidified with 10% acetic acid, and the precipitated solid was filtered off, washed with water, and dried; yield 18.7 g. (75%); recrystallized from 95% alcohol; m. p. 129–130°. For analysis of this and all other compounds, see Table I.

Compounds 2 to 11, inclusive, were similarly made from benzenesulfonyl chloride and the appropriate bases.[6]

Compounds 12, 13, 14, 16, 24, and 26 were prepared in like manner from the analogous sulfonyl chlorides and the appropriate bases, with the exception that for compound 13 it was found desirable to substitute benzene for acetone.

N^1-(3,5-Dichlorophenyl)-sulfanilamide (15).—One hundred grams of 3,5-dichloroaniline was condensed as above with *p*-acetaminobenzenesulfonyl chloride (freshly recrystallized from ethylene dichloride). The product obtained upon reprecipitation with 10% acetic acid was filtered off and then refluxed for one hour in one liter of 15% sodium hydroxide solution. The clear, amber-colored solution was charcoaled, filtered hot, and allowed to cool, after which the product was thrown out by acidification, slowly and with rapid stirring, with about 2500 cc. of 10% acetic acid. The product was filtered off, washed with water and dried in the oven at 50 to 60°; yield 180 g. (91.9%). The crude product was recrystallized by dissolving in 150 cc. of hot alcohol, charcoaling and filtering hot, and then adding hot water to incipient turbidity. The compound crystallized out on cooling; it was filtered off, washed with cold aqueous alcohol, and dried; m. p. 152–153°.

Compound 17 was prepared from compound 16 in a similar manner.

N^4-Acetyl-N^1-(3,5-dichlorophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide (18).—Eighteen grams (0.05 mole) of compound 14, 40 cc. of methanol, 5.5 g. (0.1 mole) of potassium hydroxide in 10 cc. of water, and 12.5 g. (0.1 mole) of ethylene bromohydrin were heated in a sealed tube for 1.7 hours at 100°. The reaction mixture was taken up in hot methanol and the potassium bromide filtered off. On cooling the methanol solution and evaporating to small

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(2) Klarer, *Klin. Wochschr.*, **20**, 1250 (1941).

(3) Schreus, *ibid.*, **21**, 671 (1942).

(4) "Organic Syntheses," Vol. 24, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 47.

(5) Holleman, *Rec. trav. chim.*, **35**, 9 (1915).

(6) 4′-Chlorobenzenesulfonanilide came out as an oil. The oil was extracted with ether, and, after removing pyridine by extraction with dilute hydrochloric acid, the product was readily recovered.

TABLE I

No.	Compound	M. p., °C.	Formula	Analyses, % N Calcd.	Found
1	2′-Chlorobenzenesulfonanilide[a]	130–131	$C_{12}H_{10}ClNO_2S$	5.24	5.37
2	3′-Chlorobenzenesulfonanilide[b]	119–120	$C_{12}H_{10}ClNO_2S$	5.24	5.48
3	4′-Chlorobenzenesulfonanilide[c]	121–122	$C_{12}H_{10}ClNO_2S$	5.24	5.54
4	2′,3′-Dichlorobenzenesulfonanilide	111.5–112.5	$C_{12}H_9Cl_2NO_2S$	4.64	4.38
5	2′,4′-Dichlorobenzenesulfonanilide[d]	126–127	$C_{12}H_9Cl_2NO_2S$	4.64	4.74
6	2′,5′-Dichlorobenzenesulfonanilide	130–131	$C_{12}H_9Cl_2NO_2S$	4.64	4.97
7	2′,6′-Dichlorobenzenesulfonanilide	156–157.5	$C_{12}H_9Cl_2NO_2S$	4.64	4.64
8	3′,4′-Dichlorobenzenesulfonanilide	130–130.5	$C_{12}H_9Cl_2NO_2S$	4.64	5.10
9	3′,5′-Dichlorobenzenesulfonanilide	134–135	$C_{12}H_9Cl_2NO_2S$	4.64	4.84
10	3′-Bromobenzenesulfonanilide[e]	117.5–118.5	$C_{12}H_{10}BrNO_2S$	4.49	4.55
11	3′,5′-Dibromobenzenesulfonanilide	130–131	$C_{12}H_9Br_2NO_2S$	3.58	3.59
12	3′,5′-Dichloro-4-methylbenzenesulfonanilide	147–148	$C_{13}H_{11}Cl_2NO_2S$	4.43	4.55
13	3,5-Dibromoethanesulfonanilide	134–135	$C_8H_9Br_2NO_2S$	4.08	4.09
14	N^4-Acetyl-N^1-(3,5-dichlorophenyl)-sulfanilamide[f]	239–240	$C_{14}H_{12}Cl_2N_2O_3S$	7.80	7.96
15	N^1-(3,5-Dichlorophenyl)-sulfanilamide[f]	152–153	$C_{12}H_{10}Cl_2N_2O_2S$	8.83	8.97
16	N^4-Acetyl-N′-(3,5-dibromophenyl)-sulfanilamide[f]	238–239	$C_{14}H_{12}Br_2N_2O_3S$	6.25	6.59
17	N^1-(3,5-Dibromophenyl)-sulfanilamide[f]	154–155	$C_{12}H_{10}Br_2N_2O_2S$	6.90	7.00
18	N^4-Acetyl-N^1-(3,5-dichlorophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide	197–199	$C_{16}H_{16}Cl_2N_2O_4S$	6.94	6.79
19	N^1-(3,5-Dichlorophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide	173–174	$C_{14}H_{14}Cl_2N_2O_3S$	7.75	7.96
20	N^4-Acetyl-N^1-(3,5-dichlorophenyl)-N^1-(2,3-dihydroxypropyl)-sulfanilamide	179–180	$C_{17}H_{18}Cl_2N_2O_5S$	6.46	6.20
21	N^4-Acetyl-N^1-(3,5-dibromophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide	203–204	$C_{16}H_{16}Br_2N_2O_4S$	5.69	5.80
22	N^1-(3,5-Dibromophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide	180–181	$C_{14}H_{14}Br_2N_2O_3S$	6.22	6.21
23	N^1-(3,5-Dibromophenyl)-N^4-(2-hydroxyethyl)-sulfanilamide	168–170	$C_{14}H_{14}Br_2N_2O_3S$	6.22	6.38
24	4-Acetylaminomethyl-3′,5′-dichlorobenzenesulfonanilide	174–175	$C_{15}H_{14}Cl_2N_2O_3S$	7.51	7.18
25	4-Aminomethyl-3′,5′-dichlorobenzenesulfonanilide	198–199	$C_{13}H_{12}Cl_2N_2O_2S$	8.46	8.35
26	4-Acetylaminomethyl-3′,5′-dibromobenzenesulfonanilide	191–193	$C_{15}H_{14}Br_2N_2O_3S$	6.06	6.43
27	4-Aminomethyl-3′,5′-dibromobenzenesulfonanilide	215.5–216.5	$C_{13}H_{12}Br_2N_2O_2S$	6.66	6.70

[a] Raper, Thompson and Cohen, *J. Chem. Soc.*, **85**, 372 (1904), recorded a m. p. of 129–130°. [b] Raper, Thompson and Cohen, *ibid.*, **85**, 374 (1904), gave a m. p. of 121°. [c] Wallach and Huth, *Ber.*, **9**, 426 (1876). [d] Chattaway, *J. Chem. Soc.*, **85**, 1185 (1904), found a m. p. of 128°. [e] Raiford and Hazlett, THIS JOURNAL, **57**, 2173 (1935), gave a m. p. of 117.5–118.5°. [f] U. S. Patent 2,248,911 (1941).

volume, there was obtained 22.9 g. of a solid melting at 197–199°. Recrystallization did not raise the melting point.

N^1-(3,5-Dichlorophenyl)-N^1-(2-hydroxyethyl)-sulfanilamide (19).—The solid from the preceding preparation was refluxed for 1.5 hours with 30 cc. of 35% sodium hydroxide solution and 150 cc. of methanol. The reaction mixture was filtered and slowly cooled, the solid crystallizing out. The yield was 9.8 g. (56%); m. p. 173–174°.

N^4-Acetyl-N^1-(3,5-dichlorophenyl)-N^1-(2,3-dihydroxypropyl)-sulfanilamide (20).—With the substitution of 11.0 g. (0.1 mole) of glycerol-1-monochlorohydrin for ethylene bromohydrin, the procedure was as for compound 18, except that the heating was continued for three hours; yield 5.9 g. (37%); m. p. 179–180°.

Compounds 21 and 22 were made in the same manner as were 18 and 19, starting with compound 16, the dibromo-analog of 14.

N^1-(3,5-Dibromophenyl)-N^4-(2-hydroxyethyl)-sulfanilamide (23).—Eight and two-tenths grams (0.02 mole) of compound 17, 30 cc. of methanol, and 7.0 g. (0.16 mole) of ethylene oxide were heated for three hours at 100° in a sealed tube. The reaction mixture was evaporated to dryness and the residue recrystallized from aqueous ethanol. The yield was 6.5 g. (71.5%); m. p. 168–170°

4-Aminomethyl-3′,5′-dichlorobenzenesulfonanilide (25).—Forty grams of compound 24 was refluxed for six hours in 100 cc. of alcohol and 100 cc. of concentrated hydrochloric acid. The reaction mixture was made alkaline with dilute sodium hydroxide solution and then charcoaled. The product was precipitated with dilute acetic acid and recrystallized from alcohol. A practically quantitative yield resulted; m. p. 198–199°.

The table lists the compounds prepared, together with the analytical data and the melting points (corrected).

Summary

1. A series of sulfonanilides, some of which are sulfanilamides, halogenated in the anilido nucleus has been prepared.

2. Some of these compounds exhibit antibacterial activity in the presence of *p*-aminobenzoic acid.

3. Unlike the commonly known sulfanilamides, the antibacterial activity of these compounds does not depend upon the presence of a *para*-amino group.

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