and **6** are the same(5 μg/ml), although the chemical and physical properties of the *n*-butyl, isobutyl, *sec*-butyl, and *t*-butyl compounds vary significantly. Likewise, unsaturation in the alkyl chain does not seem to influence the bacteriostatic activity. The MIC of the 9-*n*-decenyl compound (**14**) is the same as that of the *n*-decyl derivative (**13**). However, slight changes in the anilide portion of the molecule cause considerable variation in activity. For example, 1-(3,4-dichlorophenyl)-3-*n*-octylurea (**10**) inhibited the test organism at 0.2 μg/ml, whereas 1-(4-chlorophenyl)-3-*n*-octylurea (**27**) did not inhibit the organism at 20 μg/ml.

Since the bisureas (**20–26**) were not effective at the highest concentration tested (5 μg/ml), no relationship of chain length to activity can be postulated. It is interesting to note that 3,4-dichloroaniline, an expected hydrolysis product from all these compounds, is not as active under our test conditions as most of the ureas.

These compounds were also tested against *Escherichia coli* ATCC 11229. They were found to be inactive at 50 μg/ml.

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Halonitroanilides and Their Bacteriostatic Activity

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The antibacterial activity of a variety of halo- and nitrosalicylanilides is well documented.[1] Many of these compounds possess good bacteriostatic activity and also are substantive to skin and cloth. We wish to report the preparation and bacteriostatic activity of additional anilides in which the *o*-hydroxyphenyl moiety has been changed to alkyl, haloalkyl, alkenyl, cycloalkyl, benzyl phenethyl, phenoxymethyl, and phenyl groups. The N-aryl portions of the compounds possess both nitro and halo substituents.

The methods of preparation depended upon the anilide or starting materials and were generally modifications of known procedures. For the acid anhydride reactions a trace of sulfuric acid was added to catalyze the condensations with the aniline. When an acid chloride was employed, it was allowed to react in a solvent with the aniline either with or without triethylamine as the hydrogen chloride acceptor. It was necessary to reflux the reaction mixture several hours to remove the HCl when no acceptor was used. The N-methylanilide (**15**) was prepared by the action of dimethyl sulfate on the sodium salt of **14**.

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The infrared spectra of the anilides were examined and characteristic absorptions[2] were observed with the NH stretching band occurring at 3210–3310 cm^{-1} and the amide I and II bands at 1670–1690 and at 1570–1600 cm^{-1}, respectively. The amide II band was obscured somewhat by other absorptions. Amide bands for those derivatives (*e.g.*, **45** and **52**) with *ortho* substituents were shifted to the lower limits of the ranges. The characteristic NH stretching band was absent for **15**, the N-methylanilide.

Bacteriostatic activity of the halonitroanilides against *Staphylococcus aureus* was determined *in vitro*. The scope of activity is limited to those compounds which are substituted in the 3, 4, and 5 positions of the N-phenyl ring with a nitro and one or two halogen groups and in which the acid-derived moiety incorporates alkyl, haloalkyl, alkenyl, or cycloalkyl groups and contains from 5 to 13 carbon atoms. The phenyl, benzyl, phenethyl, and phenoxymethyl derivatives were inactive. Substitution of an alkyl group on the nitrogen forming the N-methylanilide (**15**) destroys the bacteriostatic activity. Those anilides containing a tertiary α-carbon exhibited a lower order of activity.

The requirements for optimum activity attributed to ring substitution parallels, in general, the findings of Beaver, *et al.*,[3] for series of substituted carbanilates and carbanilides in which substitution in the 3 and 4 positions gave maximum activity. Substituents in the *ortho* position reduced drastically or completely suppressed activity. The correlation of activity with the salicylanilides[3,4] is not readily apparent. In the latter case, an *ortho* substituent is allowable for 2',4'-substituted derivatives but not for those containing groups in the 2',5' positions.

Experimental Section

Chemical Procedures.—Most of the acid anhydrides, acid chlorides, and substituted anilines were obtained commercially. 3-Chloro-4-nitroaniline,[5] 3-bromo-4-nitroaniline,[6] 3-chloro-5-nitroaniline,[7] 3,5-dichloro-4-nitroaniline,[8] α-bromononanoyl chloride,[9] 2,4-dichlorophenoxyacetyl chloride,[10] and 2,4,5-trichlorophenoxyacetyl chloride[10] were prepared in a manner similar to those reported in the literature.

α-Chlorononanoyl chloride was prepared from the corresponding acid[11] and $SOCl_2$ by a procedure employed for the preparation of similar acid chlorides;[12] bp 91–95° (2 mm), yield 64%. This intermediate was characterized by conversion to **23**.

Anilides. Method 1.—A mixture of 0.10 mole of required aniline, 15–18 ml of the acid anhydride, and a drop of concentrated H_2SO_4 was heated at reflux for 1–2 hr and poured into cold water. The crude product was collected, washed with water, dried, and recrystallized.

Method 2.—The acid chloride (0.055 mole) was added dropwise to a stirred and refluxed solution of the aniline (0.050 mole) in 150–200 ml of toluene or methylcyclohexane or a mixture of these solvents. The mixture was refluxed until HCl evolution ceased.

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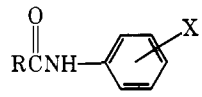
TABLE I

HALONITROANILIDES



Compd[a]	R	X	Prepn method	Recrystn solvent[a]	Yield, %	Mp, °C[b]	Formula	—Halogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found	Concn for inhibition of *S.a.*[c]
1	CH_3	3-Cl-4-NO_2	1	T	98	144–145[d]	$C_8H_7ClN_2O_3$					+
2	CH_3CH_2	3-Cl-4-NO_2	1	T	88	159–160	$C_9H_9ClN_2O_3$	15.5	15.5	12.3	12.2	T
3	$CH_3(CH_2)_2$	3-Cl-4-NO_2	2	M–T	53	83–84	$C_{10}H_{11}ClN_2O_3$	14.6	14.8	11.5	11.4	10T
4	$(CH_3)_2CH$	3-Cl-4-NO_2	2	T	75	145–147	$C_{10}H_{11}ClN_2O_3$	14.6	14.7	11.5	11.6	+
5	$CH_3(CH_2)_3$	3-Cl-4-NO_2	3	H–T	65	64–65	$C_{11}H_{13}ClN_2O_3$	13.8	14.0	10.9	10.9	100T
6	$(CH_3)_2CHCH_2$	3-Cl-4-NO_2	2	T	59	116–118	$C_{11}H_{13}ClN_2O_3$	13.8	14.1	10.9	10.5	10T
7	$CH_3CH_2CH(CH_3)$	3-Cl-4-NO_2	2	T	43	123–125	$C_{11}H_{13}ClN_2O_3$	13.8	14.0	10.9	11.2	10T
8	$(CH_3)_3C$	3-Cl-4-NO_2	2	T	59	133–134	$C_{11}H_{13}ClN_2O_3$	13.8	14.0	10.9	11.2	+
9	$CH_3(CH_2)_4$	3-Cl-4-NO_2	2		37	40–42	$C_{12}H_{15}ClN_2O_3$	13.1	13.2	10.3	10.1	M
10	$(CH_3)_2CH(CH_2)_2$	3-Cl-4-NO_2	2	M–T	62	81–83	$C_{12}H_{15}ClN_2O_3$	13.1	13.0	10.3	10.1	M
11	$CH_3(CH_2)_5$	3-Cl-4-NO_2	2	T	49	55–56	$C_{13}H_{17}ClN_2O_3$	12.5	12.6			M
12	$CH_3(CH_2)_2C(CH_3)_2$	3-Cl-4-NO_2	2	T	64	109–111	$C_{13}H_{17}ClN_2O_3$	12.5	12.7	9.80	10.1	+
13	$CH_3(CH_2)_6$	3-Cl-4-NO_2	2	M–T	21	70–71	$C_{14}H_{19}ClN_2O_3$	11.9	12.2	9.38	9.21	M
14	$CH_3(CH_2)_7$	3-Cl-4-NO_2	3	T	92	79–80	$C_{15}H_{21}ClN_2O_3$	11.3	11.6	8.96	8.79	M
15	$CH_3(CH_2)_7$[e]	3-Cl-4-NO_2	4		58	1.5436[f]	$C_{16}H_{23}ClN_2O_3$[g]	10.8	10.4	8.57	8.46	+
16	$CH_3(CH_2)_8$	3-Cl-4-NO_2	2	H–T	86	65–66	$C_{16}H_{23}ClN_2O_3$	10.8	11.2	8.57	8.23	M
17	$CH_3(CH_2)_5C(CH_3)_2$	3-Cl-4-NO_2	2		64	1.5302[f]	$C_{16}H_{23}ClN_2O_3$			8.57	8.36	T
18	$CH_3(CH_2)_9$	3-Cl-4-NO_2	2	M	77	69–71	$C_{17}H_{25}ClN_2O_3$	10.4	10.5	8.22	8.40	M
19	$CH_3(CH_2)_{10}$	3-Cl-4-NO_2	3	H–T	94	70–71	$C_{18}H_{27}ClN_2O_3$	9.99	10.2	7.89	8.03	M
20	$CH_3(CH_2)_{11}$	3-Cl-4-NO_2	2	T	51	73–75	$C_{19}H_{29}ClN_2O_3$	9.61	9.70	7.59	7.55	100T
21	$CH_3(CH_2)_3C(CH_3)_2$	3-Cl-4-NO_2	3		27	1.5286[f]	$C_{19}H_{29}ClN_2O_3$	9.61	9.92	7.59	7.45	100T
22	$CH_3(CH_2)_{12}$	3-Cl-4-NO_2	2	M–T	63	83–84	$C_{20}H_{21}ClN_2O_3$	9.26	9.40	7.32	7.42	+
23	$CH_3(CH_2)_6CHCl$	3-Cl-4-NO_2	2	M	90	91–92	$C_{15}H_{20}Cl_2N_2O_3$	20.5	20.3	8.08	8.13	M
24	$CH_3(CH_2)_6CHBr$	3-Cl-4-NO_2	2	T	20	139–140	$C_{15}H_{20}BrClN_2O_3$			7.15	7.55	M
25	$CH_2{=}CH(CH_2)_8$	3-Cl-4-NO_2	2		73	36–38	$C_{17}H_{23}ClN_2O_3$	10.5	10.3	8.27	7.91	M
26	Cyclobutyl	3-Cl-4-NO_2	2	T	74	115–116	$C_{11}H_{11}ClN_2O_3$	13.9	14.1	11.0	10.7	100T
27	Cyclopentyl	3-Cl-4-NO_2	2	M–T	60	135–136	$C_{12}H_{13}ClN_2O_3$	13.2	13.4	10.4	10.2	100T
28	Cyclohexyl	3-Cl-4-NO_2	2	T	67	118–119	$C_{13}H_{15}ClN_2O_3$	12.6	12.7	9.98	9.89	100T
29	C_6H_5	3-Cl-4-NO_2	2	T	94	162–164[h]	$C_{13}H_9ClN_2O_3$	12.8	13.1	10.1	9.82	+
30	3,4-$Cl_2C_6H_3$	3-Cl-4-NO_2	2	C	84	227–228	$C_{13}H_7Cl_3N_2O_3$	30.8	30.9	8.11	7.99	+
31	$C_6H_5CH_2$	3-Cl-4-NO_2	2	T	62	112–114	$C_{14}H_{11}ClN_2O_3$	12.2	12.4	9.64	9.98	+
32	$C_6H_5CH_2CH_2$	3-Cl-4-NO_2	2	T	53	111–113	$C_{15}H_{13}ClN_2O_3$	11.6	11.6	9.19	8.89	+
33	2,4-$Cl_2C_6H_3OCH_2$	3-Cl-4-NO_2	2	T	92	223–226	$C_{14}H_9Cl_3N_2O_4$	28.3	28.2	7.46	7.34	+
34	2,4,5-$Cl_3C_6H_2OCH_2$	3-Cl-4-NO_2	2	T	20	224–226	$C_{14}H_8Cl_4N_2O_4$	34.6	34.2	6.83	6.53	+
35	$CH_3(CH_2)_7$	3-Br-4-NO_2	2	M–T	43	82–83	$C_{15}H_{21}BrN_2O_3$	22.4	22.6	7.84	7.66	M
36	CH_3	3-NO_2-4-Cl	1	T	90	155–156[i]	$C_8H_7ClN_2O_3$	44.8[j]	44.9	3.29[k]	3.13	T
37	CH_3CH_2	3-NO_2-4-Cl	1	T	90	100–101	$C_9H_9ClN_2O_3$	15.5	15.5	12.3	12.0	T
38	$CH_3(CH_2)_7$	3-NO_2-4-Cl	3	M–T	99	39–40	$C_{15}H_{21}ClN_2O_3$	11.3	11.0	8.96	9.05	M
39	$CH_3(CH_2)_8$	3-NO_2-4-Cl	2	T	52	60–61	$C_{16}H_{23}ClN_2O_3$	10.9	10.9	8.57	8.29	M
40	$CH_3(CH_2)_9$	3-NO_2-4-Cl	2	M	77	59–60	$C_{17}H_{25}ClN_2O_3$	10.4	10.6	8.22	8.16	M
41	$CH_3(CH_2)_7$	3-Cl-5-NO_2	2	M–H	33	70–71	$C_{15}H_{21}ClN_2O_3$	11.3	11.7	8.96	8.99	M
42	$CH_3(CH_2)_7$	3-I-5-NO_2	2	M	90	89–90	$C_{15}H_{21}IN_2O_3$			6.93	6.91	M
43	$CH_3(CH_2)_7$	2-Cl-4-NO_2	2	M	30	64–65	$C_{15}H_{21}ClN_2O_3$	11.3	11.7	8.96	9.12	+
44	$CH_3(CH_2)_7$	2-Br-4-NO_2	2	T	59	58–60	$C_{15}H_{21}BrN_2O_3$	22.4	22.6	7.84	7.88	+
45	$CH_3(CH_2)_7$	2-NO_2-4-Cl	2	M	61	73–74	$C_{15}H_{21}ClN_2O_3$	11.3	11.3	8.96	9.21	+
46	$CH_3(CH_2)_7$	2-Cl-5-NO_2	2	M	72	104–106	$C_{15}H_{21}ClN_2O_3$	11.3	11.2	8.96	8.78	+
47	CH_3	3,5-Cl_2-4-NO_2		E–W	65	226–228[l]	$C_8H_6Cl_2N_2O_3$					+
48	$CH_3(CH_2)_7$	3,5-Cl_2-4-NO_2	2	HP–T	39	101–102	$C_{15}H_{20}Cl_2N_2O_3$	20.4	20.7	8.07	8.28	M
49	$CH_3(CH_2)_7$	2,5-Cl_2-4-NO_2	2		59	74–75	$C_{15}H_{20}Cl_2N_2O_3$	20.4	20.7	8.07	8.02	+
50	$CH_3(CH_2)_7$	2,6-Cl_2-4-NO_2	2	T	46	126–127	$C_{15}H_{20}Cl_2N_2O_3$	20.4	20.4	8.07	8.10	+
51	$CH_3(CH_2)_7$	2-NO_2-4,5-Cl_2	2	H	88	61–62	$C_{15}H_{20}Cl_2N_2O_3$	20.4	20.8	8.07	8.21	+
52	$CH_3(CH_2)_7$	2-CH_3-4-NO_2-5-Cl	2	M	59	111–112	$C_{16}H_{23}ClN_2O_3$	10.9	11.0	8.57	8.71	+

[a] T = toluene, M = methylcyclohexane, H = hexane, C = chlorobenzene, E = ethanol, W = water, HP = heptane. [b] All melting points, taken on a Fisher-Johns melting point apparatus, are corrected. [c] *S.a.* = *Staphylococcus aureus*; + represents growth at a concentration of 1×10^3; T, 10T, 100T, and M represent no growth at a concentration of 1×10^3, 1×10^4, 1×10^5, and 1×10^6, respectively. [d] F. Beilstein and A. Kurbatow [*Ann.*, **182**, 94 (1876)] give mp 141–142°. [e] Methyl group substituted on N. [f] Refractive index, $n^{25}D$. [g] *Anal.* Calcd: C, 58.8; H, 7.09. Found: C, 58.6; H, 7.28. [h] R. Adams and L. M. Werbel [*J. Org. Chem.*, **22**, 1287 (1957)] give mp 163–164°. [i] F. D. Chattaway, K. J. P. Orton, and R. C. T. Evans [*Ber.*, **33**, 3057 (1900)] give mp 145°. [j] C analysis. [k] H analysis. [l] Lit.[8] mp 222°.

The product was obtained either by cooling the solution to allow precipitation or by removal of the solvent with a rotary evaporator. The solid products were purified by recrystallization after decolorization with activated carbon.

Method 3.—The appropriate acid chloride (0.05 mole) was added dropwise to a stirred solution of the aniline and triethylamine (0.05 mole of each) in 200–300 ml of ethyl ether. The mixture was refluxed for 2–4 hr and cooled, and the insoluble triethylamine hydrochloride was separated by filtration. The solvent was removed with a rotary evaporator and the product was recrystallized, using activated carbon.

Method 4.—An equimolar mixture (0.016 g-atom or mole) of sodium and the anilide in 50 ml of toluene was refluxed for 2 hr. Dimethyl sulfate (0.009 mole) was added and the mixture was refluxed for 2 hr. The mixture was extracted with water, dried, and treated with activated carbon, and the solvent was evaporated to yield the product.

Infrared Spectra.—The infrared spectra of the solid anilides were taken as Nujol mulls using a Beckman IR-5 spectrophotometer. The liquids were examined as thin layers between NaCl plates.

Bacteriostatic Test Procedure.—The standard procedure used in screening the compounds against *Staphylococcus aureus* was as follows. Stock solutions were prepared by dissolving 100 mg of the test compound in 10 ml of acetone, alcohol, or other solvent. The stock solutions were diluted serially by pipetting 2 ml of

the stock solutions into 10 ml of sterile nutrient agar to obtain a 10^3 dilution and continuing in the same manner for dilutions up to 10^6. The agar was poured into Petri dishes, allowed to harden, and spot inoculated with 1 drop of a cell suspension of *S. aureus* which was prepared by suspending the growth from a 24-hr nutrient agar slant culture in 10 ml of distilled water. The plates were incubated at 37° for 48 hr and examined for the presence or absence of growth. The results reported in Table I are the minimum concentration of the test compound which will completely inhibit the growth of the bacteria.

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Derivatives of 5-Carboxymethylthiazolidine-2,4-dione, a New Group of Antiviral Compounds

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Among the many types of organic compounds which have been tested for their antiviral action, thiosemicarbazones of different carbonyl compounds have been found to be active.[1] Most thiosemicarbazones with high activity contain the group $=NNHCSNH_2$ separated by two carbon atoms from a nitrogen or a sulfur atom. We have recently established that the incorporation of the thiosemicarbazone group in a cyclic system also leads to considerable antiviral activity. Thus 3-(4-bromophenyl)-5-carboxymethylthiazolidine-2,4-dione 2-benzylidenehydrazone was found to prevent at 2×10^{-4} *M* the cytopathogenic changes in cell cultures of human embryonic kidneys infected with herpes simplex virus and poliovirus type 1.[2] Now, some new compounds of this type have been prepared in order to examine some structural effects on their activity. The corresponding thiosemicarbazones of some carbonyl compounds were treated with maleic anhydride in benzene or toluene as described before.[3]

Biological Results.—The inhibitory effect of the compounds under investigation on viral growth as well as the prevention of cytopathogenic changes of the infected cells were tested using human embryonic kidney cell monolayers. The cells were infected with tenfold dilutions of the appropriate virus (from 10^{-3} to 10^{-7}). The test compounds were added usually to the culture medium simultaneously. The concentration of the screened compounds in the culture medium was 5×10^{-5} *M*. At the same time the virus was titrated in the culture medium which contained none of the tested compounds.

Thus 3-(4-bromophenyl)-5-carboxymethylthiazolidine-2,4-dione 2-benzylidenehydrazone delayed the cytopathogenic changes produced by herpes simplex virus strain Z and polio virus no. 1 (Brunhilde) when applied to the infected cells by direct contact or even short time intervals (up to 8 hr) after the infection (therapeutic effect). The virus concentration was lowered on the fifth day for 1.3–2.0 log (virus/ml). Similar results were obtained with polio virus type 2 (Saukett) and vaccinia virus. However, it was inactive with measles virus. All other compounds were tested with herpes virus strain Z and found to reduce the virus titer. The most significant effects were presented by the compounds, collected in Table I.

TABLE I

ANTIVIRAL ACTIVITY

Compd	Reduction of virus conen, log (virus/ml)
1	1.5
3	4.1
5	1.1
8	1.1
9	0.8

Experimental Section

Melting points were determined on a Kofler heating microscope. Ultraviolet spectra were measured with a Beckman Model DU spectrophotometer.

Thiosemicarbazones.—The following compounds were prepared as described in the literature: acetophenone thiosemicarbazone,[4] acetophenone 4-*p*-tolylthiosemicarbazone,[5] propiophenone thiosemicarbazone,[4b,d,6] *p*-dimethylaminobenzaldehyde thiosemicarbazone,[4d,7] furfural thiosemicarbazone,[4b,8] and furfural 4-*p*-tolylthiosemicarbazone.[9] The remainder were obtained by refluxing equimolecular amounts of the corresponding thiosemicarbazide and the carbonyl compound (0.01 mole) in an ethanolic solution for 1 hr and evaporating the solvent *in vacuo* to half of its volume. The crystals thus obtained were crystallized from ethanol. New compounds are as follows.

Acetophenone 4-phenylthiosemicarbazone, mp 193–194°, yield 68%.

Anal. Calcd for $C_{15}H_{15}N_3S$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.76; H, 5.52; N, 15.78.

Acetophenone 4-*p*-methoxyphenylthiosemicarbazone, mp 183–184°, yield 71%.

Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.08; H, 5.65; N, 14.22.

Propiophenone 4-*p*-tolylthiosemicarbazone, mp 92–93°, yield 62%. The product separated as an oil but after 2–4 days crystals were formed.

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