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Synthesis and Bacteriostatic Properties of Acylarylureas and Alkylarylureas

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ABSTRACT

Fatty substituted ureas (RNHCONHR') were prepared where R is an aliphatic acyl or alkyl group and R' is a substituted phenyl group or a thiazole group. The benzene ring was generally substituted with chlorine, nitro, hydroxy, or a combination of these groups. The compounds were ineffective against gram-negative microorganisms but a number of samples inhibited the growth of *Staphylococcus aureus* at 1 ppm. Bacteriostatic activity was generally observed where the acyl or alkyl group contained 6-10 carbon atoms and where R' is 4-nitrophenyl, 4-chloro-3-nitrophenyl or a thiazole group derived from 2-amino-5-nitrothiazole. Scattered activity at 1 ppm was observed where R' is 3-nitrophenyl, 2,4- and 3,5-dichlorophenyl, 2-hydroxy-5-chlorophenyl, 2-hydroxy-5-nitrophenyl, 3-nitro-4-hydroxyphenyl, 3,5-dinitrophenyl and 2-nitro-4-chlorophenyl. The alkylureas appear to be more active than the acylureas.

INTRODUCTION

Three basic types of sanitizing agents have been used in the food processing industry and various health institutions for the last several decades. These include the halogens or hypohalite solutions, halogenated aromatic compounds and quaternary ammonium salts. The halogens usually used as hypohalite solutions are exceptional broad spectrum germicidal agents by virtue of their high chemical reactivity. This characteristic is disadvantageous, for the halogens will react with organic substrates, thereby readily losing their activity. The low stability and high chemical reactivity of halogen-derived agents is associated with destructive oxidative reactions of organic substrates. Halogenated benzene derivatives such as hexachlorophene and trichlorocarbanilide are compatible with anionic and nonionic surfactants and have been used in cleaning formulations, surgical scrub soaps and soap bars. These totally aromatic bactericides possess the disadvantages of high toxicity, allergic sensitization and possible structural instability. Quaternary ammonium compounds are excellent broad spectrum germicides which are deactivated by soap, organic matter and polyvalent cations.

Beaver and coworkers studied substituted urea derivatives to relate structure with bacteriostatic properties (1). They concluded that very small changes in chemical structure lead to profound changes in antimicrobial activity. Of the 10 bridging functions examined, the urea bridging group conferred the highest bacteriostatic activity. The most active compounds were 3,4,3'-, and 3,4,4'-trichlorocarbanilides. Further studies of nitrodiarylureas indicated that meta nitro-substituted derivatives showed very high activity against *Staphylococcus aureus* (2). The rather conspicuous activity of the 3,4-dichloroaniline derivatives stimulated specific studies of this function, resulting in the publication of two patents (3,4). Schenach et al. (5) synthesized a series of N-alkyl-N'-3,4-dichlorophenyl ureas and found that compounds of alkyl groups containing 5-10 carbon atoms were most active with minimal inhibitatory concentrations (MIC) against *S. aureus* of < 1 ppm. This activity is comparable to that of the trichlorocarbanilides. Included in this study were alkylene α,ω-bis (3,4-dichlorophenylureas) with methylene bridges containing 0-8 carbon atoms that had MIC values greater than 5 ppm. A similar study of N-acyl-N'-3,4-dichlorophenyl ureas by Zakaria and Taber (6) indicated that MIC for these compounds in soap were 20 ppm with no sharp deviations in activity for acyl groups containing 2-13 carbon atoms. Work by Baker et al. (7) and a patent (8) obtained by Jerchel showed that aliphatic amides derived from 2-hydroxy 5 chloraniline and various halonitroanilines are active bacteriostats against *S. aureus*. A recent study of fat-based N-aryl-substituted amides (9) at this laboratory confirmed these results and indicated that high activity against *S. aureus* was conferred by a variety of substituted phenyl derivatives. These results and the absence of a general study of acylarylureas, prompted the present program to prepare bacteriostats that are useful with surfactants and effective against gram-negative and gram-

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positive microorganisms. The compounds in this study were effective only against *S. aureus*.

EXPERIMENTAL

Materials

Aliphatic amides were prepared by a standard method (10) or purchased from Aldrich Chemical Co., Milwaukee, WI, as were all the substituted anilines, aliphatic amines and 2-amino-5-nitrothiazole. The 3- and 4-nitrophenyl isocyanate and 3-nitro-4-chlorophenyl isocyanate were purchased from Pfaltz and Bauer Inc., Stamford, CT. All solvents were reagent grade from J.T. Baker Chemical Co., Phillipsburg, NJ. All commercial reagents were used as received without further purification. Florisil was obtained from Floridin Co., Berkley Springs, WV.

Syntheses

The composition of all urea compounds was established by elemental analyses which agreed to within ±0.3% with theory. All melting points are uncorrected. The Perkin-Elmer 257 grating infrared spectrophotometer was used in this study. For reaction mixtures which were highly discolored, the crude products were dissolved in chloroform and treated with carbon black and/or passed through a ½ × 6 in. column of Florisil.

Typical Alkylarylurea Synthesis

To a nitrogen-flushed, 100-mL R.B. flask was added 2 g (.01 M) 4-chloro3-nitrophenyl isocyanate and 60 mL of anhydrous benzene. The mixture was warmed to dissolve the isocyanate. To this solution was added, by drops, 1.4 g (.01 M) nonylamine over a 30-min period. The mixture was refluxed 2 hr and filtered. Benzene was evaporated at reduced pressure to yield 3.0 g of crude product. Repeated crystallization from ether hexane to a constant melting point (mp) gave 2.0 g (63% yield) of N-nonyl-N'-4-chloro-3-nitrophenylurea, mp 66-7 C, carbonyl band 1640 cm^{-1}.

Typical Acylarylurea Synthesis

This is a modification and adaptation of a method developed by Speziale et al. (11) for the synthesis of acyl isocyanates. To a 100-mL R.B. flask was added 2.6 g (.015 M) decanamide and 50 mL of toluene. The system was dried azeotropically by collecting water in a Dean-Stark tube. The Dean-Stark tube was removed and 10 mL of solvent was collected in a flame-dried flask. The amide solution was cooled to room temperature and 1.9 g (.015 M) oxalyl chloride in 10 mL of anhydrous solvent was added. The flask was equipped with a reflux condenser and a Nujol bubbler. The mixture was heated to reflux for 1.5 hr during which time gas evolution continued for about 20-30 min. The clear pale yellow solution of decanoyl isocyanate was cooled to room temperature and 2-hydroxy-5-chloroaniline was added. The reaction mixture was refluxed 2 hr and then filtered to yield 3.9 g of crude product. Crystallization from absolute ethanol to a constant mp gave 3.0 g (60% yield) of N-decanoyl-N'-2-hydroxy-5-chlorophenyl urea, mp 227-8 C, carbonyl band doublet 1680 and 1705 cm^{-1}.

Bacteriostatic Test Method (9)

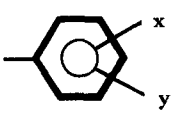
One percent stock solutions were prepared by dissolving 100 mg of test compound in 10 mL 95% ethanol or water. The stock solutions were serially diluted by successively pipetting 2 mL of solution into 18 mL of sterile nutrient agar to obtain 10^3, 10^2, 10^1 and 10^0 ppm concentrations of compound. The agar was poured into sterile Petri dishes, allowed to harden, dried at 37 C for ½ hr with covers off, then inoculated with one drop of a 24-hr culture of test microorganism in nutrient broth. The inoculated dishes were incubated 48 hr at 37 C and examined for the presence or absence of growth. The test compounds were evaluated at essentially neutral pH. Hexachlorophene was used as the control germicidal standard. All tests were run in duplicate.

The following microorganisms were used: *Escherichia coli* ATCC no. 11229, *Staphylococcus aureus* ATCC no. 6538, *Pseudomonas aeruginosa* ATCC no. 8709, *Salmonella typhimurium* (U.S. HEW, CDC) and *S. enteritidis* (U.S. HEW, CDC).

RESULTS AND DISCUSSION

All the urea compounds in this study are white- to canary

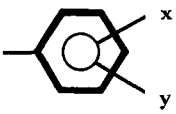
TABLE I

RNHCONH 

Nitro and chloronitroalkylarylureas

Compound	R	x	y	mp (C)	% Yield	Cryst. solvent	*S. aureus* (MIC ppm)
1	$C_{12}H_{25}$	$3NO_2$	H	118-119	68	Ethanol	1000
2	$C_{11}H_{23}$	$3NO_2$	H	113	92	Methanol	1000
3	$C_{10}H_{23}$	$3NO_2$	H	117	85	Methanol	1000
4	C_9H_{19}	$3NO_2$	H	111-112	85	Methanol	1000
5	C_8H_{17}	$3NO_2$	H	115-116	80	Methanol	1000
6	C_7H_{15}	$3NO_2$	H	116-117	74	Methanol	1000
7	C_6H_{13}	$3NO_2$	H	121-122	72	Methanol	1
8	$C_{14}H_{29}$	$3NO_2$	H	121	85	Ethanol	> 1000
9	C_4H_9	$3NO_2$	H	125-126	68	Methanol	> 1000
10	$C_{10}H_{21}$	$4NO_2$	H	116-117	70	Benzene	> 1000
11	C_9H_{19}	$4NO_2$	H	114-115	60	Benzene	1
12	C_8H_{17}	$4NO_2$	H	113-114	62	Ethanol	1
13	C_7H_{15}	$4NO_2$	H	112-113	52	Methanol	1
14	C_6H_{13}	$4NO_2$	H	111-112	60	Benzene	10
15	$C_{10}H_{21}$	$3NO_2$	4Cl	78-79	50	Ether	1
16	C_9H_{19}	$3NO_2$	4Cl	66-67	63	Ether hexane	1
17	C_8H_{17}	$3NO_2$	4Cl	76-77	79	Ether hexane	1
18	C_7H_{15}	$3NO_2$	4Cl	82-83	67	Ether hexane	1
19	C_6H_{13}	$3NO_2$	4Cl	72-73	80	Ether hexane	1
20	C_5H_{11}	$3NO_2$	4Cl	78-79	66	Ether	10

TABLE II

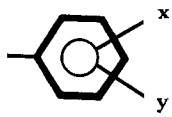
RCONHCONH 

Dichloroacylarylureas

Compound	R	x	y	mp (C)	% Yield	Cryst. solvent	*S. aureus* (MIC ppm)
21[a]	$C_{13}H_{27}$	3Cl	4Cl	100	70	Hexane	1000
22[a]	$C_{11}H_{23}$	3Cl	4Cl	104-105	70	Methanol	> 1000
23	C_9H_{19}	3Cl	4Cl	109-110	70	Methanol	1000
24[a]	C_8H_{17}	3Cl	4Cl	115-116	64	Ethanol	1000
25[a]	C_7H_{15}	3Cl	4Cl	126	60	Ethanol	> 1000
26	C_6H_{13}	3Cl	4Cl	128-129	65	Ethanol	1000
27	C_8H_{17}	2Cl	4Cl	127-128	65	Ethanol	> 1000
28	C_7H_{15}	2Cl	4Cl	130-131	45	Methanol	1
29	C_6H_{13}	2Cl	4Cl	140-141	52	Methanol	> 1000
30	C_4H_9	2Cl	4Cl	148-149	60	Methanol	> 1000
31	C_9H_{19}	3Cl	5Cl	123	65	Ethanol	1
32	C_8H_{17}	3Cl	5Cl	130	65	Ethanol	1000
33	C_7H_{15}	3Cl	5Cl	136-137	82	Ethanol	1000
34	C_6H_{13}	3Cl	5Cl	140-141	73	Methanol	1000
35	C_5H_{11}	3Cl	5Cl	146	86	Methanol	> 1000

[a]Literature melting points for compounds 21, 22, 24 and 25 are 99-100, 104-105, 114-115 and 128-129, respectively.

TABLE III

RCONHCONH 

Chloronitroacylarylureas

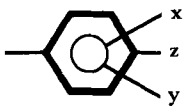
Compound	R	x	y	mp (C)	% Yield	Cryst. solvent	*S. aureus* (MIC ppm)
36	$C_{13}H_{27}$	$3NO_2$	4Cl	95-96	53	Ether	> 1000
37	$C_{11}H_{23}$	$3NO_2$	4Cl	105-106	82	Methanol	> 1000
38	C_9H_{19}	$3NO_2$	4Cl	103-104	65	Methanol	> 1000
39	C_8H_{17}	$3NO_2$	4Cl	105-106	70	Methanol	> 1000
40	C_7H_{15}	$3NO_2$	4Cl	101-102	80	Ethanol	1000
41	C_9H_{19}	$2NO_2$	4Cl	130-131	68	Hexane	> 1000
42	C_8H_{17}	$2NO_2$	4Cl	144	72	Toluene	1
43	C_7H_{15}	$2NO_2$	4Cl	153	65	Toluene	> 1000
44	C_6H_{13}	$2NO_2$	4Cl	161-162	81	Toluene	1000
45	C_5H_{11}	$2NO_2$	4Cl	137-138	60	Toluene	1000
46	C_9H_{19}	$5NO_2$	2Cl	149-150	70	Ethanol	> 1000
47	C_8H_{17}	$5NO_2$	2Cl	152	71	Ethanol	> 1000
48	C_7H_{15}	$5NO_2$	2Cl	162-163	70	Ethanol	> 1000
49	C_6H_{13}	$5NO_2$	2Cl	170-171	61	Methanol	> 1000
50	C_5H_{11}	$5NO_2$	2Cl	173-174	77	Methanol	> 1000
51	C_9H_{19}	$4NO_2$	H	106-107	62	Methanol	1000
52	C_8H_{17}	$4NO_2$	H	102	63	Methanol	> 1000
53	C_7H_{15}	$4NO_2$	H	113-114	72	Ethanol	1000
54	C_6H_{13}	$4NO_2$	H	116-117	62	Methanol	> 1000
55	C_5H_{11}	$4NO_2$	H	134	49	Ethanol	> 1000
56	C_9H_{19}	$3NO_2$	$5NO_2$	168-169	69	Ethanol	> 1000
57	C_8H_{17}	$3NO_2$	$5NO_2$	168	70	Ethanol	1
58	C_7H_{15}	$3NO_2$	$5NO_2$	176	80	Ethanol	> 1000
59	C_6H_{13}	$3NO_2$	$5NO_2$	177-178	82	Ethanol	1
60	C_5H_{11}	$3NO_2$	$5NO_2$	173-174	83	Toluene	1000

yellow, crystalline solids. The alkylarylureas (Table I) were prepared by reacting an aromatic isocyanate with an aliphatic amine in anhydrous benzene. These derivatives are moderate melting solids 65-125 C, generally obtained in 50-85% yields with carbonyl absorptions observed from 1630-1655 cm^{-1}. The acylarylureas (Tables II-V) were prepared by reacting fatty amides with oxalyl chloride in toluene to form the acyl isocyanate (9,10). Treatment of the acyl isocyanate (without isolation or purification) with a substituted aniline or 2-amino-nitrothiazole gave the desired acylarylurea. Both steps in this synthesis occur within 1 hr; however, to insure complete reaction for the various products, longer reaction times were stated in the experimental section. Percentage yields for the acylarylureas are generally better than 50%, indicating that the yields of intermediate aliphatic acyl isocyanate were quite good (12). A study of the acyl isocyanate synthesis indicated that excess oxalyl chloride was not required for complete conversion of the amide. The formation of acyl isocyanate with toluene (bp 110 C) solvent was complete within ½ hr at reflux. Acylarylureas are crystalline solids generally melting above 100 C, with carbonyl absorptions at 1680-1720 cm^{-1}.

The derivations listed in Tables I-V were ineffective

TABLE IV

RCONHCONH

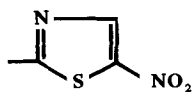


Hydroxychloronitroacylarylureas

Compound	R	x	y	z	mp (C)	% Yield	Cryst. solvent	*S. aureus* (MIC ppm)
61	$CH_2=CHC_8H_{16}$	2OH	5Cl	H	217-218	55	Ethanol	> 1000
62	C_9H_{19}	2OH	5Cl	H	227-228	60	Ethanol	1
63	C_8H_{17}	2OH	5Cl	H	226-227	53	Ethanol	1
64	C_7H_{15}	2OH	5Cl	H	233-234	53	Ethanol	> 1000
65	C_6H_{13}	2OH	5Cl	H	227-228	65	Ethanol	> 1000
66	C_3H_7	2OH	5Cl	H	234	43	Ethanol	1000
67	$CH_2=CHC_8H_{16}$	2OH	$5NO_2$	H	195-196	50	Methanol	> 1000
68	C_9H_{19}	2OH	$5NO_2$	H	206-207	53	Methanol	> 1000
69	C_8H_{17}	2OH	$5NO_2$	H	207-208	54	Methanol	1
70	C_7H_{15}	2OH	$5NO_2$	H	213-214	56	Methanol	> 1000
71	C_6H_{13}	2OH	$5NO_2$	H	213	61	Water methanol	> 1000
72	C_5H_{11}	2OH	$5NO_2$	H	221-222	78	Water methanol	> 1000
73	C_3H_7	2OH	$5NO_2$	H	235-236	40	Ethanol	> 1000
74	$CH_2=CHC_8H_{16}$	H	$3NO_2$	OH	135-136	72	Ethanol	> 1000
75	C_8H_{17}	H	$3NO_2$	OH	133-134	71	Ethanol	1
76	C_7H_{15}	H	$3NO_2$	OH	140-141	69	Ethanol	> 1000
77	C_6H_{13}	H	$3NO_2$	OH	165-166	58	Methanol	1000
78	C_5H_{11}	H	5Cl	OH	181-182	45	Methanol	> 1000
79	C_9H_{19}	3Cl	5Cl	OH	132	45	Benzene	> 1000
80	C_8H_{17}	3Cl	5Cl	OH	141-142	42	Benzene	> 1000
81	C_7H_{15}	3Cl	5Cl	OH	168	43	Benzene	> 1000
82	C_6H_{13}	3Cl	5Cl	OH	197-198	53	Methanol	1
83	C_5H_{11}	3Cl	5Cl	OH	209	25	Methanol	> 1000

TABLE V

RCONHCOHN



Acylureas from 2-amino 5-nitrothiazole

Compound	R	mp (C)	% Yield	Cryst. solvent	*S. aureus* (MIC ppm)
84	$C_{11}H_{23}$	130-131	78	Methanol	> 1000
85	$CH_2=CHC_8H_{16}$	128-129	56	Methanol	1
86	C_9H_{19}	134-135	59	Methanol	1
87	C_8H_{17}	134	43	Ethanol	1
88	C_7H_{15}	146	35	Methanol	1
89	C_6H_{15}	148-149	51	Methanol	10
90	C_5H_{11}	162	42	Methanol	10
91	C_2H_5	198-200	40	Methanol	100
92[a]	$3,4Cl_2C_6H_4$	252	47	Butanol	10
93[a]	$4Cl3NO_2C_6H_4$	240	58	Ethanol	> 1000

[a]Compounds 92 and 93 are diarylureas where the R group as shown is directly attached to the nitrogen atom.

agents for inhibiting the growth of gram-negative microorganisms. However, a number of compounds was found active against *S. aureus* with MIC of 1 ppm. Table I shows the bacteriostatic activity of alkylarylureas wherein the aromatic ring is substituted with 3-nitro, 4-nitro, or 3-nitro-4-chloro groups. Among the compounds derived from 3-nitroaniline, only the N-hexyl-N'-3-nitrophenylurea (no. 7) is active with an MIC of 1 ppm, whereas compounds derived from 4-nitroaniline show a broader range of activity at the same level (nos. 11-14). The studies of Baker et al. (7) and Bistline et al. (9) were confirmed with the high activity found for alkylarylureas derived from 3-nitro-4-chloroaniline with R groups containing 5-10 carbon atoms (nos. 15-20).

Table II summarizes the results obtained with acylarylureas in which the phenyl group is substituted with 3,4-dichloro, 2,4-dichloro and 3,5-dichloro groups. Zakaria and Taber (6) prepared a series of aliphatic-based N-acyl-N'-3,4-dichlorophenylureas, all of which showed MIC = 1-20 ppm with ATCC 6538 *S. aureus* using the agar streak dilution techniques in the presence of soap. Comparable derivatives prepared in this study (nos. 21-26) show no activity below 10^3 ppm. Past work from this laboratory (9) showed that a number of fatty anilides derived from 3,4-dichloroaniline had MIC = 0.1 ppm against *S. aureus*. Acylarylureas derived from 2,4-dichloroaniline were inactive even at 10^3 ppm except the octanoyl derivative (no. 28) which had an MIC = 1 ppm. Similar results were found with the homologous series from 3,5-dichloroaniline with all samples below decanoyl (no. 31) being inactive. The effectiveness of a single sample is surprising because recent studies here (unpublished work) have shown that amides of the type RCONHAr, where R is a fatty acid or α-methylene fatty acid and Ar is a 3,5-dichlorophenyl, actively inhibit growth of *S. aureus* for a broad range of compounds.

Acylarylureas prepared from 3-nitro-4-chloro, 2-nitro-4-

chloro, 5-nitro-2-chloro, 4-nitro and 3,5-dinitroaniline are listed in Table III. Ureas derived from 3-nitro-4-chloroaniline (nos. 36–40) are inactive in stark contrast to the alkylarylureas in Table I (nos. 15–20). The inclusion of a carbonyl function appears to be associated with the inactivity. Similarly, samples (nos. 52–54) are inactive and differ from the corresponding alkyl derivatives Table I (nos. 11–13) by substituting a carbonyl for a methylene group. N-3,5-dinitrophenyl anilides from octanamide and nonanamide (9) were very active (MIC = 0.1 ppm) against *S. aureus* whereas the acylureas (nos 56–60) exhibited lower activity with a skipping pattern. Reevaluation of samples (nos. 57–59) gave no change in the pattern of activity. Beaver et al. (1) concluded that the urea bridging group is considerably more effective than the simple amido function.

In view of the high activity found in fatty acid anilides containing a hydroxy group (9), acylarylureas with a phenolic aryl function were studied (Table IV). Here again, scattered activity is observed in the various homologous series. Compounds derived from 2-hydroxy-5-chloro, 2-hydroxy-5-nitro, 4-hydroxy-3-nitro and 4-hydroxy-3,5-dichloroaniline are highly active growth inhibitors; however, a simple increase or decrease in one methylene group leads to complete inactivity against *S. aureus*.

Acylureas derived from 2-amino-5-nitrothiazole (Table V) show the entire spectrum of activity. Acyl compounds in which R contains 11 carbon atoms or is a 3-nitro-4-chlorophenyl moiety have MIC = $>$1,000 ppm (nos. 84, 93). Compounds in which R contains 7–10 carbon atoms have MIC = 1 ppm (nos 85–88) whereas lower activity is noted for R containing less than 7 carbon atoms or is a 3,4-dichlorophenyl moiety (nos. 89, 92). To establish the activity of urea compounds in the presence of soap, alkylureas (nos. 15–19, Table I) and acylureas (nos. 85–89, Table V) were tested for their activity against *S. aureus* in the presence of 1,000 ppm soap (sodium tallowate). All 10 samples retained their activity in the presence of soap at the levels shown in the respective tables.

These data show that small changes in structure lead to enormous changes in activity. Several highly active single compounds in various homologous series are completely inactivated by adding or subtracting one methylene group. The alkylarylureas appear to be considerably more active than the acylarylureas. The 2-amino-5-nitrothiazole derived compounds are an exception to this rule. Those compounds whose alkyl or acyl groups contain five to ten carbon atoms exhibit the highest activity.

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