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Taber et al.

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[54] **N-ACYL-N'-(HALOGENATED ARYL
UREAS AS ANTIBACTERIAL AGENTS)**

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[62] Division of Ser. No. 638,585, May 15, 1967, abandoned.

[52] U.S. Cl.**424/322**, 252/106, 252/107

[51] Int. Cl.**A01n 9/20**

[58] Field of Search.....260/553 G, 552; 424/322;
252/106, 107

[56] **References Cited**

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[57] **ABSTRACT**

The use of N-Acyl-N'-(halogenated aryl) ureas as antibacterial agents and germicidal detergent compositions containing such ureas are disclosed.

2 Claims, No Drawings

N-ACYL-N'-(HALOGENATED ARYL UREAS AS ANTIBACTERIAL AGENTS)

This is a division of application Ser. No. 638,585, filed May 15, 1967, and now abandoned.

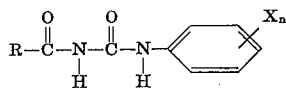
This invention relates to new antibacterial agents and more particularly to new germicidal detergent compositions.

The popularity of detergent compositions, for both laundry and toilet use, containing germicidal agents has increased tremendously over the past few years. It is estimated that more than 20 percent of the toilet bar soap sales are now of products containing a germicidal agent; and this percentage is steadily increasing. Heretofore many compounds have been investigated as possible detergent germicides. While numerous substances indicate a degree of antibacterial activity, few produce the desired results necessary for use as effective detergent germicides. In many cases the germicide is either incompatible with the detergent or else germicidal activity is abated when the germicide is incorporated into the detergent. Further, certain detergent products, such as toilet soap, have the added requirement that the germicide used must not be harmful to the human skin. Thus, it is desirable that a considerable variety of germicides be made available, from which a selection may be made for use in various detergent media.

One aspect of the present invention lies in the discovery that certain acyl ureas have definite antibacterial properties and that these properties are maintained in the presence of an alkaline agent such as soap or other detergent compositions. These compounds are, to the best of our knowledge, not harmful to human skin.

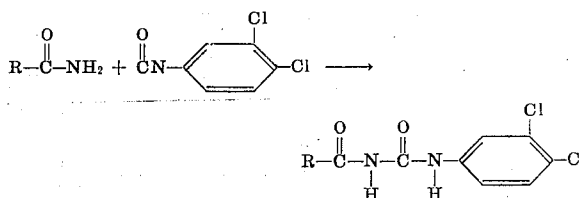
Therefore, it is an object of this invention to provide new antibacterial agents which are compatible with detergent compositions and which maintain this activity even when incorporated into detergent compositions. Other objects and advantages, and a further understanding of this invention, will appear in the ensuing description and examples.

In one specific embodiment, our invention may be exemplified by an antiseptic detergent composition comprising a detergent and a germicidally effective amount of an N-acyl-N'-(halogenated aryl) urea compound of the structure:



wherein R is a radical selected from the group consisting of aliphatic radicals containing from two to 13 carbon atoms and halogenated phenyl radicals, X is halogen such as chlorine, bromine, fluorine, trichloromethyl, trifluoromethyl and the like, and n is an integer from 1 to 5.

N-acyl ureas of the above structure may be prepared generally by reacting either aliphatic amides ($R\text{-CONH}_2$) or halogenated benzamides ($X_n\text{-ArCONH}_2$) with a halogenated aryl isocyanate, such as 3,4-dichlorophenyl isocyanate, in an inert solvent under anhydrous conditions and at reflux temperatures. The above reaction may be illustrated by the following chemical equation using the 3,4-dichlorophenyl isocyanate reactant:



wherein R is as defined hereinabove. The aryl radical of the halogenated aryl isocyanate can contain other substitutions in addition to the halogen, such as nitro and additional phenyl substitutions. Further, the halogen substitutions on our acyl ureas may be varied. Suitable halogenated radicals include chlorobenzyls, bromobenzyls, fluorobenzyls, chloromethylphenyls, dichloromethylphenyls, trichloromethylphenyls, trifluoromethylphenyls, chloronaphthyls, bromonaphthyls, fluoronaphthyls, and the like.

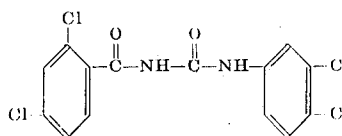
Relatively small amounts of the N-acyl ureas are sufficient to make the detergent composition antiseptic. The amount to be used in particular instance will vary over a wide range depending upon such factors as the degree of effectiveness desired, the particular N-acyl urea employed, and cost. Generally, from 0.2 percent to about 5 percent based on the weight of the detergent will provide desirable antiseptics. It should be understood that lesser or greater amounts are operable but without substantial advantages. A preferred range is an amount in the order of from about 0.5 percent to about 3 percent, based on the final weight of the detergent composition.

In order to more fully describe the nature of the novel compositions of the present invention and the manner in which they may be used, the following illustrative specific examples are provided.

EXAMPLE I

1-(2,4-Dichlorobenzoyl)-3-(3,4-dichlorophenyl) urea

To a 200 ml. round bottom flask fitted with a condenser and a drying tube through a Dean-Stark trap, was added 10.0 grams (0.052 mole) of 2,4-dichlorobenzamide in 50 ml. of benzene. The mixture was heated to reflux and any moisture present was removed by azeotropic distillation with benzene. 3,4-Dichlorophenyl isocyanate (12.0 grams, 0.063 mole) in 70 ml. of o-dichlorobenzene was then added. The temperature was raised sufficiently to cause the solvent to reflux and benzene was drawn off through the Dean-Stark trap. The mixture was then heated under reflux for a total of 12 hours, and gradually cooled to room temperature. A white precipitate was obtained, which was filtered off, air dried and weighed. There was obtained 12 grams (61 percent yield) of 1-(2,4-dichlorobenzoyl)-3-(3,4-dichlorophenyl) urea, (melting point of 222°-225° C.). The reaction product was recrystallized from acetone to give a pure, white crystalline product (melting point of 222° C.) having the formula:

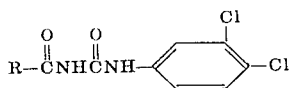


EXAMPLE II

Preparation of N-acyl-N'-(3,4-dichlorophenyl) ureas

In similar procedure as set forth in Example I, other acyl ureas were prepared. Since 3,4-dichlorophenyl isocyanate readily forms 3,3', 4,4'-tetrachlorocarbani-
 lide in the presence of water, it is essential that water be excluded from the reaction. One method to accomplish this is by first heating the amide in benzene and azeotroping any water present. Then, an equimolar amount, plus some excess, of 3,4-dichlorophenyl isocyanate together with o-dichlorobenzene solvent are added and the mixture is heated to a higher temperature, at which the benzene is taken off. The mixture is then reacted for about 10 hours under reflux. At the end of this period most of the solvent is distilled off and the residue is triturated with benzene or another suitable solvent, filtered, and air dried. In most cases, this residue will be found to contain a small amount of 3,3',4,4'-tetrachlorocarbani-
 lide together with the desired acyl urea. By boiling the residue in benzene, filtering while hot, and cooling the filtrate, the N-acyl urea is precipitated. It may then be separated and air dried. The formation of 3,3',4,4'-tetrachlorocarbani-
 lide may also be avoided by carrying out the reaction in dry toluene. By this method, equimolar amounts of 3,4-dichlorophenyl isocyanate and the desired amide reactant may be added to dry toluene and the reaction maintained under reflux. The toluene is then removed, as by distillation, and the residue is either filtered directly or triturated with petroleum ether and then filtered. The reaction product may then be recrystallized from alcohol or other solvents such as benzene.

In order to be sure that the reaction product was free of 3,3',4,4'-tetrachlorocarbani-
 lide when the product was triturated with benzene, the reaction product was boiled in benzene, filtered while hot, and cooled, whereupon the acyl urea precipitated and was separated and air dried. Where the reaction was run in dry toluene, the product was either recrystallized from alcohol or benzene. The acyl ureas obtained are set forth in Table I. In Table I, the compounds are listed by setting forth only the R portion of the general formula



Also, the means by which the removal of 3,3',4,4'-tetrachlorocarbani-
 lide is effected is set forth in the table.

TABLE I

R	melting pt. °C	% yield	% carbon calculated	% carbon found	% Hydrogen calculated	% Hydrogen found	remarks
C ₂ H ₅	173	78	45.9	46.22	3.83	4.05	Recrystallized from alcohol
n-C ₃ H ₇	155-6	38	48.0	47.87	4.35	4.13	Recrystallized from benzene
n-C ₄ H ₉	159	97	50.0	50.21	4.84	4.67	Recrystallized from benzene

n-C ₅ H ₁₁	130-1	86	51.8	51.85	5.28	5.30	Recrystallized from benzene
n-C ₇ H ₁₅	128-9	82	54.2	54.32	6.02	6.38	Recrystallized from alcohol
n-C ₈ H ₁₇	114-5	78	56.4	56.44	6.39	6.04	Recrystallized from alcohol
n-C ₁₁ H ₂₃	105-6	70	59.0	58.87	7.25	7.01	Recrystallized from alcohol
9-n-decenyl	100	69	58.1	57.89	6.45	6.34	Recrystallized from alcohol
n-C ₁₃ H ₂₇	99-100	52	60.8	60.76	7.71	7.63	Recrystallized from alcohol
nicotiny	272-3	94	50.4	50.47	2.90	2.79	Triturate with acetone
o-chlorophenyl	208	70	49.2	49.51	2.63	2.05	Recrystallized from acetone
p-chlorophenyl	273	87	49.2	49.56	2.63	2.90	Triturate with acetone
2,4-dichlorophenyl	222	65	44.5	45.02	2.12	2.32	Recrystallized from acetone
3,4-dichlorophenyl	235-6	96	44.5	44.79	2.12	2.30	Recrystallized from acetone

EXAMPLE III

Germicidal activity of the acyl ureas prepared in the above examples was determined as follows:

The various individual acyl ureas were dissolved in dimethylformamide at a 1.0 percent level. Suspensions in a 10 percent soap solution were then prepared. The "soap" utilized was neutral white toilet soap containing about 20 percent by weight of sodium coco soap and about 80 percent by weight of sodium tallow soap. The concentration of acyl urea in the soap solution was 1,000 ppm, or 0.1 percent. Thereafter, serial dilutions were made containing 100 ppm and 10 ppm respectively of the acyl urea.

Varying amounts of the soap solutions containing the acyl ureas were thoroughly dispersed into measured amounts of sterile liquid nutrient agar so as to obtain concentrations of the acyl urea ranging from 0.05 to 20 ppm. Plates were then poured, allowed to solidify, and streaked with a standard 4 mm. loopful of a 24-hour broth culture of *Staphylococcus aureus* FDA 209. After incubation for 24 hours at 37° C., the bacteriostatic endpoint was determined. The bacteriostatic endpoint, hereinafter called the minimum inhibitory concentration, represents the minimum concentration in ppm of the bacteriostatic agent necessary to completely inhibit all growth of *S. aureus*.

Table II gives the endpoints or the minimum inhibitory concentration of the 10 percent soap solution, without germicide added and with the addition of the

N-acyl-N'-(3,4-dichlorophenyl) ureas prepared in Examples I and II.

TABLE II

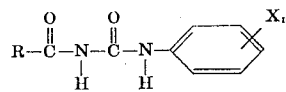
R	Melting Point °C.	Minimum Inhibitory Concentration against <i>S. aureus</i> (ppm)
C ₂ H ₅	173	>20
n-C ₃ H ₇	155-	1-5
n-C ₄ H ₉	159	1-5
n-C ₅ H ₁₁	130-1	>20
n-C ₆ H ₁₃	128-9	>20
n-C ₇ H ₁₅	114-5	>20
n-C ₈ H ₁₇	105-6	>20
n-C ₁₁ H ₂₃	100	5
9-n-decenyl	99-100	>20
n-C ₁₃ H ₂₇	272-3	>20
nicotinyl	208	>20
o-chlorophenyl	208	>20
p-chlorophenyl	273	>20
2,4-dichlorophenyl	222	0.1-0.5
3,4-dichlorophenyl	235-6	1-5
Soap solution alone		3000

The results obtained above with respect to bacteriostatic activity in the specific soap mentioned above (20/80 sodium coco/tallow) are obtained with soaps generally. The activity exhibited by these compounds is independent of the soap vehicle, and other media may be used such as anionic and non-ionic type synthetic detergents. At the same time, soap is a system in which the compounds are highly effective. "Soap" refers to the water-soluble metallic, ammonium, or organic base salts of various fatty acids, such as lard, lauric, oleic, myristic, palmitic, stearic and the like.

While this invention has been described with respect to certain embodiments, it is not so limited; and it is to be understood that variations and modifications thereof, obvious to those skilled in the art, may be made without departing from the spirit of scope of our invention.

What is claimed is:

1. A process for inhibiting the growth of bacteria which comprises contacting said bacteria with a bacteriologically effective amount of an N-acyl-N'-(halogenated aryl) urea of the structure:



wherein R is selected from the group consisting of aliphatic radicals containing from two to 13 carbon atoms



X is selected from the group consisting of chlorine, bromine, fluorine, trichloromethyl, and trifluoromethyl; and n is an integer from 1 to 5.

2. The process of claim 1 in which said urea is 1-(2,4-dichlorobenzoyl)-3-(3,4-dichlorophenyl) urea.

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