PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification** 6 :
C07D 211/72, 211/84, A61K 31/44, 7/06, 31/74, C09K 11/54, 15/32

A1

(11) **International Publication Number:** **WO 95/11233**

(43) **International Publication Date:** 27 April 1995 (27.04.95)

(21) **International Application Number:** PCT/US94/11484

(22) **International Filing Date:** 11 October 1994 (11.10.94)

(30) **Priority Data:**

137,521	18 October 1993 (18.10.93)	US
not furnished	30 September 1994 (30.09.94)	US

(71) **Applicant:** OLIN CORPORATION [US/US]; 350 Knotter Drive, P.O. Box 586, Cheshire, CT 06410-0586 (US).

(72) **Inventors:** HANI, Rahim; 117 Winthrop Drive, Cheshire, CT 06410 (US). BERKOWITZ, Phillip, T.; 21 Barberry Lane, Woodbridge, CT 06525 (US).

(74) **Agents:** CARLSON, Dale, Lynn et al.; Wiggin & Dana, One Century Tower, New Haven, CT 06508-1832 (US).

(81) **Designated States:** AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) **Title:** SUBSTITUTED PYRIDINE-2-ONES AND SUBSTITUTED PYRIDINE-2-THIONES AS BIOCIDES

(57) **Abstract**

The present invention relates to novel 1-hydroxy-6-substituted pyridine-2-one and 1-hydroxy-6-substituted pyridine-2-thione compounds. Also disclosed is a process for producing the compound (s) and an antimicrobial composition comprising the compound (s) and at least one component selected from the group consisting of soaps, adhesives, coatings, elastomers, sealants, shampoos, skin care medicaments, cosmetics, paints and other polymer compositions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

SUBSTITUTED PYRIDINE-2-ONES AND SUBSTITUTED PYRIDINE-2-THIONES AS BIOCIDES

This invention relates to novel 1-hydroxy-6-substituted pyridine-2-ones and 2-thiones, a process for their preparation, and their use as biocides. These compounds exhibit good biocidal activity, particularly antifungal activity.

Compounds exhibiting biocidal activity are well known in the art. For example, pyrithione salts, such as zinc pyrithione, are known to provide excellent biocidal activity, including broad spectrum anti-bacterial and anti-fungal activity. There are many uses for these pyrithiones. By way of illustration, U.S. Patent No. 4,818,436 discloses the use of pyrithiones in metalworking fluids, U.S. Patent No. 4,401,770 discloses urethane shoe inserts having antimicrobial activity; and U.S. Patent No. 4,935,061 discloses their use in paints.

Despite the excellent biocidal (particularly fungicidal) activity attributable to pyrithione salts, these compounds do have drawbacks for certain applications, most notably limited solubility in certain organic solvents and aqueous media. Accordingly, new compounds exhibiting excellent biocidal activity, but also exhibiting good solubility in organic solvents would be useful to the biocides manufacturing community.

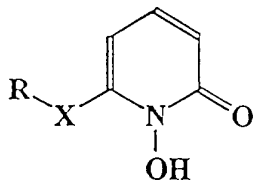
One compound that exhibits good biocidal efficacy and solubility in shampoo formulations is 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone. Unfortunately, this compound is more expensive to manufacture than otherwise might be desired. This compound and related compounds are

disclosed in U.S. Patent 3,883,545; their use in combating dandruff is described in U.S. Patent 4,185,106; and their use in an antidandruff shampoo is described in U.S. Patent 4,711,775. U.S. Patent 4,916,228 discloses the preparation of a broad class of 1-hydroxy-2-pyridones by a process comprising reacting a pyrone having a specified structural formula with a hydroxylammonium salt in the presence of at least one alkali metal carbonate and/or hydrogen carbonate.

A technical journal publication entitled "Quantitative Structure-Activity Analysis in a Series of Antimycotically Active N-Hydroxypyridones", Journal of Medicinal Chemistry, 1974, Vol. 17, No. 7, p. 753, describes a variety of 1-hydroxy-substituted-2-pyridones, including those having para-substitutions of $-SCH_2C_6H_4Cl$ (compound 15 in Table II thereof) and $-OCH_2C_6H_4Cl$ (compound 16 in Table II thereof), as having antimycotic activity. However, the method of preparation of these compounds is not described in this technical publication, and it is believed that these compounds were made from 6-chloro-2-pyrone which is not commercially available.

Other new biocides providing desired solubility characteristics, as well as new processes for their preparation, would be highly desired by the biocides manufacturing community.

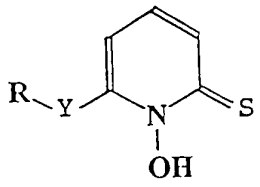
In one aspect, the present invention relates to a compound of the formula:



(I)

wherein X is an oxygen or sulfur moiety and R is a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that R is other than chlorobenzyl.

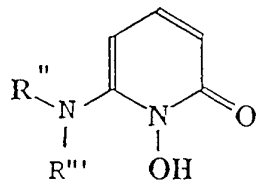
In another aspect, the present invention relates to a compound of the formula:



(II)

wherein Y is an oxygen, sulfur, or NR′ moiety wherein N is nitrogen and R and R′ are independently each a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms.

In yet another aspect, the present invention relates to a compound of the formula:



(III)

wherein R'' and R''' are independently either hydrogen or a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that either R or R' is a hydrocarbon radical.

Preferred hydrocarbon radicals for the R group in the above formulae (I), (II), and (III) are aliphatic hydrocarbons having between 3 and 15 carbons, more preferably a straight chain hydrocarbon having between 5 and 10 carbons. The term "substituted hydrocarbon" is intended to include substituents such as halogen such as chloro, iodo fluoro or bromo, alkoxy such as methoxy, ethoxy, propoxy or butoxy, nitro, thio, amino combinations thereof, and the like. Illustrative hydrocarbon groups include n-octyl, 2,4,4-trimethylpentyl, 3,5,5-trimethylhexyl, combinations thereof, and the like.

In still another aspect, the present invention relates to a process for producing compound of Formulae (I) or (II) wherein X or Y is oxygen which comprises the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a hydroxy compound containing between 1 and 20

carbon atoms (such as an alcohol such as n-octanol or a phenol compound such as 4-methylphenol, preferably selected from the group consisting of alkyl, arylalkyl and aryl compounds containing at least one hydroxyl group, and combinations thereof) and a base (such as sodium hydroxide or potassium hydroxide), optionally in the presence of water or an organic solvent, at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide and

(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a base to produce the corresponding 1-hydroxy-6-substituted-pyridine-2-one.

In yet another aspect, the present invention relates to a process for producing a compound of Formula (II) wherein Y is nitrogen or a compound of Formula (III) which comprises the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a primary or secondary amine containing between 1 and 20 carbon atoms (such as dimethanolamine or triethanolamine) and a base (such as sodium hydroxide or potassium hydroxide), optionally in the presence of water or an organic solvent, at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide and

(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a sulfur-containing base to produce the corresponding 1-hydroxy-6-substituted-pyridine-2-thione.

In still another aspect, this invention relates to a process for producing the compound of Formula (I) or (II), wherein X or Y is sulfur, which comprises the following steps:

(a) reacting a 2,6-dichloro pyridine N-oxide, a thiol compound having between 1 and 20 carbon atoms, (for example alkyl, arylalkyl and aryl thiol compounds, and combinations thereof) and base (such as sodium hydroxide or potassium hydroxide) in an organic solvent at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide and

(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a base to produce the corresponding 1-hydroxy-6-substituted pyridine-2-one (i.e., the compound of formula (I)) or 1-hydroxy-6-substituted pyridine-2-thione (i.e., the compound of formula (II)).

The above processes can be carried out sequentially or simultaneously in a single step. Surfactants and/or phase transfer catalysts are optionally employed to facilitate the step (a) reaction in any of these processes.

In yet another aspect, the present invention relates to an antimicrobial composition comprising a functional component selected from the group consisting of paints, adhesives, coatings, elastomers, sealants, shampoos, skin care medicaments and metalworking fluid plus an antimicrobially effective amount of a compound represented by the above Formula (I) or a salt of the compound of Formula (I). Illustrative salts

include the amine salts, alkali metal and alkaline earth metal salts and the like.

In still another aspect, the invention relates to a method for inhibiting the growth of microorganisms by contacting said microorganisms with a composition containing an antimicrobial effective amount of a one of the above-described 1-hydroxy-6-substituted pyridine-2-ones, 1-hydroxy-6-substituted pyridine-2-thiones, a salt thereof, or a combination thereof, of this invention and at least one component selected from the group consisting of soaps, shampoos, skin care medicaments, cosmetics, and other polymer compounds such as adhesives, coatings, elastomers, sealants and paints.

These and other aspects will become apparent upon reading the following detailed description of the invention.

It has now been surprisingly discovered that a straightforward process can be employed to produce 1-hydroxy-6-substituted-2-pyridones or 1-hydroxy-6-substituted-2-thiones, utilizing readily available starting materials. These compounds provide excellent antimicrobial efficacy and are inexpensive to produce.

The novel 1-hydroxy-6-substituted pyridine-2-one and 1-hydroxy-6-substituted pyridine-2-thione compounds of this invention are shown formulae (I), (II) and (III) given above.

The reactions of the processes of this invention are suitably conducted at atmospheric pressure, although higher or lower pressures may be used if desired. Suitable reaction temperatures for

steps (a) and (b) range between a temperature of about 25°C to about 150°C, preferably employing a reflux temperature of between about 70°C and about 90°C. Total reaction time for the process of this invention can vary over a wide range, but is advantageously between 30 minutes and 5 hours for step (a) and between thirty minutes and 5 hours for step (b).

The reactions of the processes of this invention are suitably carried out in the presence of a base and an organic solvent. Suitable bases include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as calcium or magnesium hydroxide, pyridine, triethylamine and other tertiary amine bases, potassium carbonate, "DABCO" amine catalyst (1,4-diazabicyclo(2.2.2)octane), "DBU" (1,8-diazabicyclo(5.4.0)undec-7-ene), "DBN" (1,5-diazabicyclo(4.3.0)non-5-ene, t-butyltetramethyl-guanidine, combinations thereof, and the like. Preferred bases for step (a) are anhydrous, granular or powdered sodium or potassium hydroxide, and preferred bases for step (b) are concentrated aqueous solutions of sodium or potassium hydroxide having a concentration of base of between about 10% and about 90% by weight based upon the weight of the solution. Preferably, the base is employed in at least an amount equal to the number of moles for each reactant, and a molar excess of base relative to each reactant can be employed as desired.

The reactions of the processes of this invention are suitably carried out in the presence

of a solvent. Suitable organic solvents include, for example, ether, and acetone, methylene chloride, benzene, toluene, pyridine, tetrahydrofuran ("THF"), acetonitrile, dimethylsulfoxide ("DMSO"), dimethylformamide ("DMF"), and combinations thereof. Although the preferred solvent is acetonitrile, it is more preferred to run the reactions neat. As another alternative, a reactive solvent can be employed, if desired, for example by using an organic alcohol, e.g. isopropanol, or n-octanol, in an amount sufficient to provide the desired reactant and solvent characteristics.

The molar ratio of reactants for the processes of this invention can vary over a wide range, but is preferably between 10:1 and 1:10, more preferably between 2:1 and 1:2, most preferably about 1:1.

The antimicrobial compositions of this invention suitably comprise an antimicrobially effective amount of a compound as defined by the structural formulae given herein above, and combinations thereof, and at least one component selected from the group consisting of soaps, shampoos, skin care medicaments, cosmetics and paints. The antimicrobial compound can be employed as is or in the form of a salt, such as an amine salt such as the monoethanolamine ("MEA") salt, and the use of the salt form is preferred. By the term "antimicrobial effective amount" is meant an amount sufficient to impart to the compositions resistance against microbial attack by fungi and/or bacteria. Preferably the antimicrobial compounds are employed in the composition in a total amount of between about .01 and about 10 weight percent, more

preferably between about .01 and about 5 weight percent, based upon the total weight of the composition. A particularly preferred use for the biocidal compounds of the present invention is in personal care products such as in shampoos and other hair care products, as well as in paint, paint bases and polymer compositions such as adhesive coatings, sealants, elastomers, acids and the like.

With respect to paints improved organic solubility and biocidal efficacy associated with the compounds of the present invention are expected to provide advantages when used in a wide variety of paints, including indoor and outdoor household paints, industrial and commercial paints and in particular marine paints for use, for example, or ships hulls.

Typically, a paint composition will contain a resin, a pigment and various optional additives such as thickening agent(s), wetting agents and the like, as is well known in the art. The resin is preferably selected from the group consisting of vinyl, alkyl, epoxy, acrylic, polyurethane and polyester resins, and combinations thereof. The resin is preferably employed in an amount of between about 20% and about 80% based upon the weight of the paint or paint base.

In addition, the paint composition of the present invention contains optional additional additives which have a favorable influence on the viscosity, the wetting power and the dispersibility, as well as on the stability to freezing and electrolytes and on the foaming properties. If a marine paint is being fabricated, the paint

preferably contains a co-biocide such as cuprous oxide or copper thio-cyanate, a swelling agent to cause the paint to gradually "slough off" in its marine environment, thereby causing renewed biocidal efficacy of newly exposed biocide at the surface of the paint in contact with the water medium of the marine environment. Illustrative swelling agents are naturally-occurring or synthetic clays, such as kaolin, montomorillonite (bentonite, clay mica (muscovite), and chlorite (hectonite), and the like. In addition to clays, other swelling agents, including natural or synthetic polymers, such as that commercially available as POLYMERGEL, have been found to be useful in the compositions of the present invention to provide the desired "sloughing off" effect. Swelling agents can be used singly or in combination. The total amount of optional additives is preferably no greater than 20% by weight, more preferably between about 1% and about 5% by weight, based upon the total weight of the paint composition.

Illustrative thickening agents include cellulose derivatives, for example methyl, hydroxyethyl, hydroxypropyl and carboxymethyl cellulose, poly(vinyl alcohol), poly (vinylpyrolidone), poly(ethylene-glycol), salts of poly(acrylic acid) and salts of acrylic acid/acrylamide copolymers.

Suitable wetting and dispersing agents include sodium polyphosphate, salts of low-molecular-weight poly(acrylic acid), salts of poly(ethane-sulfonic acid), salts of poly (vinyl-phosphonic acid), salts of poly(maleic acid) and salts of copolymers of

maleic acid with ethylene, 1-olefins with 3 to 18 carbon atoms and/or styrene.

In order to increase the stability to freezing and electrolytes there may be added to the paint composition various monomer 1,2-diols, for example glycol, propylene-glycol-(1,2), and butylene-glycol-(1,2) or polymers thereof, or ethoxylated compounds, for example reaction products of ethylene oxide with long-chain alkanols, amines, carboxylic acids, carboxylic acid amides, alkyd phenols, poly(propylene-glycol) or poly(butylene-glycol). The minimum temperature of film formation (white point) of the paint composition may be reduced by adding solvents, such as ethylene-glycol, butyl-glycol, ethyl-glycol acetate, ethyl-diglycol acetate, butyl-diglycol acetate, benzene or alkylated aromatic hydrocarbons. As defoaming agents there are suitable for example poly(propylene-glycol) and polysiloxanes.

The compounds of the present invention have many desirable attributes. They possess good antimicrobial activity and are compatible with components of conventional soaps, shampoos, skin-care medicaments, plastics and other polymer compositions and the like. These polymers are also non-volatile, hydrolytically-stable, thermally-stable and may be soluble in water and organic solvents. Furthermore, they form no undesirable colors in typical personal care items. Still further, they are expected to be favorably cost competitive with known antimicrobial additives used in conventional skin care formulations.

The following examples are intended to illustrate, but in no way limit the scope of, the present invention. In the examples, the term "g" denotes grams, "mol" denotes moles, and all percents are given on a weight basis unless otherwise specified.

EXAMPLES

Example 1

Preparation of

1-Hydroxy-6-isopropyloxypyridine-2(1H)-ones

The 0.82 g (0.0050 moles) of 2,6-dichlopyridine N-oxide and 0.78 g (0.013 moles) of isopropanol was reacted with 0.210 g (0.0050 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 80°C overnight to give 2-chloro-6-isopropyloxypyridine N-oxide. The excess of isopropanol was removed in vacuo and 0.800 g (0.020 mole) of ground sodium hydroxide was reacted at 3 hours at 100°C to give 1-hydroxy-6-isopropyloxypyridine-2(1H)-one. After cooling, it was added 74 ml of water and was adjusted with 6N HCl to pH 5. It was extracted with ethyl acetate (3x25 ml). The ethyl acetate extract was washed with water (2x10 ml) and dried over sodium sulfate. The solution was saturated with sodium chloride and was extracted with ethyl acetate (3x25 ml). The ethyl acetate extract was washed with water (2x10 ml) and dried over sodium sulfate. The combined ethyl acetate extracts were filtered and stripped in vacuo to give 0.50 g (59%). It was recrystallized

from 5 ml of ethyl acetate, 5 ml of hexanes, and activated carbon: mp 119-120°C.

Example 2

Preparation of

1-Hydroxy-6-(2,4,4-trimethylpentyloxy)-pyridine-2(1H)-one

The 0.82 g (0.0050 moles) of 2,6-dichloro-pyridine N-oxide and 0.664 g (98%) (0.0050 moles) of 2,4,4-trimethyl-1-pentanol was reacted with 0.211 g (0.0050 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 100°C overnight to give 2-chloro-6-(2,4,4-trimethypentyloxy) pyridine N-oxide. It was reacted with 0.600 g (0.015 moles) of ground sodium hydroxide at 100°C for 4.5 hours to give 1-hydroxy-6-(2,4,4-trimethylpentyloxy)pyridine-2(1H)-one. After cooling, it was added 74 ml of water and was adjusted with 6N HCl to pH 3. It was extracted with ethyl acetate (3x25 ml). The combined ethyl acetate extract was washed with a saturated sodium chloride solution (2x10 ml) and dried over sodium sulfate. The ethyl acetate extract was filtered and stripped in vacuo to give 1.08 g (90%). It was recrystallized from ethyl acetate and hexanes: mp 133.5-134°C.

Example 3

Preparation of

1-Hydroxy-6-(3,5,5-trimethylhexyloxy)-pyridine-2(1H)-one

The 0.82 g (0.0050 moles) of 2,6-dichloro-pyridine N-oxide and 0.80 g (90%) (0.0050 moles) of 3,5,5-trimethyl-1-hexanol was reacted with 0.206 g (0.0050 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 80°C for 8.5 hours to give 2-chloro-6-(3,5,5-trimethylhexyloxy)pyridine N-oxide. It was reacted with 0.600 g (0.015 moles) of ground sodium hydroxide at 80°C for 4 hours to give 1-hydroxy-6-(3,5,5-trimethy-hexyloxy) pyridine-2(1H)-one. After cooling, it was added 74 ml of water and was adjusted with 6N HCL to pH 3. The precipitate was filtered and washed with water to give 0.577 g (45%). It was recrystallized from ethyl acetate and hexanes: mp 130.5-131°C.

Example 4

Preparation of

1-Hydroxy-6-octyloxypyridine-2(1H)-one

The 0.82 g (0.0050 moles) of 2,6-dichloro-pyridine N-oxide and 0.658 g (99%) (0.0050 moles) of 1-octanol was reacted with 0.200 g (0.0050 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 80°C for 4.5 hours to give 2-chloro-6-octyloxypyridine N-oxide. It was reacted with 0.600 g (0.015 moles) of ground sodium hydroxide at 80°C for 2.5 hours to give 1-hydroxy-6-octyoxypyridine-2(1H)-one. After cooling, it was added 74 ml of water and was

adjusted with 6N HCL to pH 3. The precipitate was filtered and washed with water to give 0.577 g (48%). It was recrystallized from ethanol and hexanes: mp 119-120°C.

Example 5
Preparation of
1-Hydroxy-6-octylthiopyridine-2(1H)-one

The 2.01 g (0.0122 moles) of 2,6-dichloro-pyridine N-oxide and 2.10 g (85%) (0.0122 moles) of 1-octylmercaptan was reacted with 0.488 g (0.0122 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 80°C for 6 hours to give 2-chloro-6-octylthio-pyridine N-oxide. It was reacted with 1.47 g (0.0367 moles) of ground sodium hydroxide at 80°C for 3 hours to give 1-hydroxy-6-octylthiopyridine-2 (1H)-one. After cooling, it was added 180 ml of water and was adjusted with 6N HCL to pH 3. The precipitate was filtered, washed with water and washed with 150 ml of petroleum ether to give 1.34 g (43%).

Example 6
Preparation of
1-Hydroxy-6-octylsulfonylpyridine-2(1H)-one

The 0.204 g (0.00080 moles) of 1-hydroxy-6-octylthiopyridine-2(1H)-one was reacted with 0.36 ml (0.0032 moles) of 30% hydrogen peroxide in 2.0 ml of glacial acetic acid for overnight at room temperature to give 1-hydroxy-6-octylsulfonyl

pyridine-2(1H)-one. It was stripped in vacuo and was then dissolved with ethanol and stripped in vacuo three times to give 0.22 g. It was recrystallized from acetone and petroleum ether.

Example 7

Preparation of

1-Hydroxy-6-thiophenylpyridine-2(1H)-one

The 1.64 g (0.010 moles) of 2,6-dichloro-pyridine N-oxide and 1.11 g (99%) (0.010 moles) of thiophenol was reacted with 0.400 g (0.010 moles) of ground sodium hydroxide of 16.4 ml of DMSO at 80°C for 5 hours to give 2-chloro-6-thiophenylpyridine N-oxide. It was reacted with 1.20 g (0.030 moles) of ground sodium hydroxide at 80°C for 2.5 hours to give 1-hydroxy-6-thiophenylpyridine-2(1H)-one. After cooling, it was added 148 ml of water and was adjusted with 6N HCl to pH 3. The precipitate was filtered, washed with water and washed with hexanes to give 1.64 g (75%). It was recrystallized from ethanol: mp 180-181°C.

Example 8

Preparation of

1-Hydroxy-6-thiophenylsulfonypyridine-2(1H)-one

The 1.00 g (0.00456 moles) of 1-hydroxy-6-thiophenylpyridine-2(1H)-one reacted with 1.30 ml (0.0114 moles) of 30% hydrogen peroxide in 5 ml of glacial acetic acid at room temperature overnight. The precipitate was dissolved with more 5 ml of glacial acetic acid and was then added 1.30 ml

(0.0114 moles) of 30% hydrogen peroxide at room temperature over the weekend. The precipitate was filtered and washed with hexanes to give 0.624 g. The acetic acid and the hexanes were stripped in vacuo to give 0.45 g. The combined product gave 1.14 g (93%).

Example 9
Preparation of
1-Hydroxy-6-phenyloxypyridine-2(1H)-one

The 0.82 g (0.0050 moles) of 2,6-dichloro-pyridine N-oxide and 0.47 g (0.0050 moles of phenol was reacted with 0.200 g (0.0050 moles) of ground sodium hydroxide in 8.2 ml of DMSO at 80°C for 6 hours to give 2-chloro-6-phenyloxypyridine N-oxide. It was reacted with 0.600 g (0.015 moles) of ground sodium hydroxide at 80°C for 3.5 hours to give 1-hydroxy-6-phenyoxypyridine-2(1H)-one. After cooling, it was added 74 ml of water and was adjusted with 6N HCl to pH 3. The water solution was extracted with dichloromethane (2x25 ml) and was dried over sodium sulfate. The dichloromethane solution was stripped in vacuo to give 1.29 g which was purified with Flash Chromatography(9:1 ethyl acetate:methanol):0.82 (65%).

Example 10
Preparation of 1-hydroxy-6-octylaminopyridine-2 (1H)-ones

To 1.53 g(.008moles) of 2,6-dichloropyridine in 13.3 ml of toluene was added 1.26 g).0162 moles) 1-

octylamine and refluxed for 3 hours. The reaction content was cooled to room-temperature, washed several times with water to yield 2.02 g of 2-chloro-6-octylaminopyridine-N-oxide as a yellow liquid.

The yellow liquid refluxed with 2.7g of potassium tert-butoxide in tert-butyl alcohol overnight. Water was added to the reaction flask and a precipitate was formed upon adjustment of pH to 3. The precipitate filtered and washed to yield 1.36 g of product.

Example 11
Preparation of 1-hydroxy-6-octyloxpyridine-2(1H)-thiones

2-Chloro-6-octyloxypyridine-N-oxide was prepared according to Example 4 and subsequent reaction with NaSH in acetonitle and extraction with methylene chloride yielded the product as white powder.

Example 12
Preparation of 1-hydroxy-6-octylaminoyridine-2 (1H)-thiones

A reaction mixture of 0.52 g of 2-chloro-6-octylaminopyridine-N-oxide (prepared as described in Example 10), 5 ml DMSO and 0.55 ml of 46% solution of NaSH was heated at 80 degrees for two hours. The reaction was diluted with water, pH was adjusted to three, and the product was extracted with methylene chloride.

Example 13

Proposed example for preparation of 1-hydroxy-6-octylthiopyridine-2 (1H)-thiones

2-Chloro-6-octylthiopyridine-N-oxide is prepared according to the method described in Example 5, and subsequent reaction with aqueous solution of NaSH yields the titled product.

Determination of the Minimum Inhibitory Concentrations (MIC's) for Antimicrobial Compounds of this Invention

Solutions of the experimental compounds in dimethyl sulfoxide were serially diluted in nutrient broth (Tryptic Soy Broth for bacteria and Sabouraud Dextrose Broth for fungi) in microliter plates. Equal volumes of a broth suspension of bacteria (10^6 CFU/ml) or fungi (10^5 cells or spores/ml) were added to each dilution, and the plates were incubated at 37°C (bacteria and yeast) or 28°C (molds). Bacteria, yeast and molds were incubated two, five and seven days respectively before determining the highest inhibitory dilution.

TABLE 1

MIC(ppm)

MIC of the 1-hydroxy-6-substituted-2-pyridones

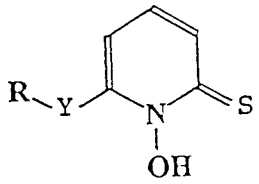
Compound	A	B	C	D	E	F
Example 1	256	≥1024	128	512	512	512
Example 2	64	64	8	32	8	16
Example 3	32	32	2	2	16	2
Example 4	32	16	4	2	32	4
Example 5	256	16	8	32	8	nt
Example 6	512	64	128	256	256	nt
Example 7	64	128	16	64	64	nt
Example 8	256	8	1024	1024	1024	nt
Example 9	256	512	32	256	512	nt
Example 10	32	32	8	16	32	16
Example 11	16	16	4	4	8	16
Example 12	256	64	8	16	64	64
OCTOPIROX® biocide	128	64	2	2	2	16-32

A=Escherichia coli B=Staphylococcus aureus C=Candida albicans D=Fusarium sp. E=Aspergillus niger F=Aureobasidium pullulans "nt" denotes not tested

The results provided in Table 1 show that the compounds of the present invention provide MIC's that are sometimes better than those provided by a commercial biocide, OCTOPIROX® biocide, a product of Hoechst Company. Note that the compounds of Examples 3, 4 and 11 provide particularly excellent MIC results.

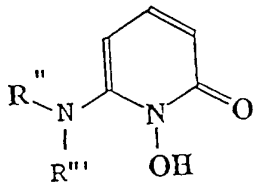
WHAT IS CLAIMED IS:

1. A compound characterized by the formula:



wherein Y is an oxygen, sulfur, or NR′ moiety, wherein N is nitrogen and R and R′ are independently each a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms.

2. A compound characterized by the formula:



wherein R′′ and R′′′ are independently either hydrogen or a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that either R′′ or R′′′ is a hydrocarbon radical.

3. A process for producing the compound of claim 1, wherein Y in the formula of claim 1 is oxygen, which is characterized by the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a hydroxy compound containing between 1 and 20 carbon atoms and a base, optionally in the presence of water or an organic solvent, at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide, and

(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a sulfur-containing base to produce the corresponding 1-hydroxy-6-substituted-pyridine-2-thione.

4. A process for producing a compound of claim 1, wherein Y in the formula of claim 1 is NR' which is characterized by the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a primary or secondary amine containing between 1 and 20 carbon atoms and a base, optionally in the presence of water or an organic solvent, at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide, and

(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a sulfide or hydrosulfide salt to produce the corresponding 1-hydroxy-6-substituted-pyridine-2-thione.

5. A process for producing a compound of claim 1, wherein Y in the formula of claim 1 is sulfur, which is characterized by the steps of:

(a) reacting a 2,6-dichloropyridine N-oxide, a thiol compound having between 1 and 20 carbon atoms, and base in an organic solvent at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide, and

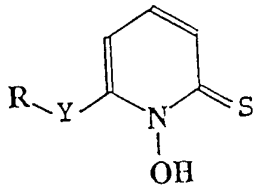
(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a sulfide or hydrosulfide salt to produce the corresponding 1-hydroxy-6-substituted-2-pyridine-2-thione.

6. A process for producing a compound of claim 2 which is characterized by the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a primary or secondary amine containing between 1 and 20 carbon atoms and a base, optionally in the presence of water or an organic solvent, at an elevated temperature to produce a corresponding 2-chloro-6-substituted-pyridine N-oxide, and

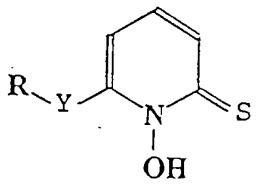
(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a base to produce the corresponding 1-hydroxy-6-substituted-pyridine-2-one.

7. An antimicrobial composition comprising a functional component selected from the group consisting of paints, shampoos, skin care medicaments, metalworking fluids, polymer compositions plus an antimicrobially effective amount of a compound characterized by the formula:



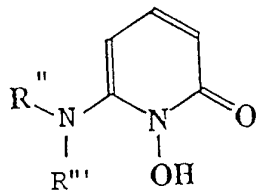
wherein Y is an oxygen, sulfur, or NR′ moiety, wherein N is nitrogen and R and R′ are each a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms.

8. A method for inhibiting the growth of microorganisms by contacting said microorganisms with a composition characterized by containing an antimicrobial effective amount of a compound of the formula:



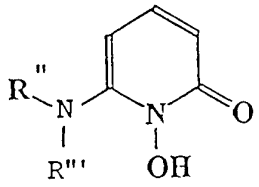
wherein Y is an oxygen, sulfur, or NR′ moiety, wherein N is nitrogen and R and R′ are each a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, and at least one component selected from the group consisting of soaps, adhesives, coatings, elastomers, sealtants, shampoos, skin care medicaments, cosmetics and paints.

9. An antimicrobial composition comprising a functional component selected from the group consisting of paints, shampoos, skin care medicaments, metalworking fluids, polymer compositions plus an antimicrobially effective amount of a compound characterized by the formula:



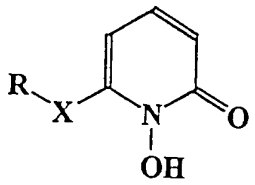
wherein R'' and R''' are independently either hydrogen or a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that either R'' or R''' is a hydrocarbon radical.

10. A method for inhibiting the growth of microorganisms by contacting said microorganisms with a composition characterized by containing an antimicrobial effective amount of a compound of the formula:



wherein R'' and R''' are either hydrogen or a substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, and at least one component selected from the group consisting of soaps, adhesives, coatings, elastomers, sealtants, shampoos, skin care medicaments, cosmetics and paints.

11. A compound characterized by the formula:



wherein X is an oxygen or sulfur moiety and R is substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that R is other than chlorobenzyl.

12. A process for producing the compound of claim 11, wherein X in the formula of claim 11 is oxygen, which is characterized by the steps of:

(a) reacting 2,6-dichloropyridine N-oxide, a hydroxy compound containing between 1 and 20 carbon atoms and a base in an organic solvent at an elevated temperature to produce a corresponding 2-chloro-6-substituted pyridine N-oxide and

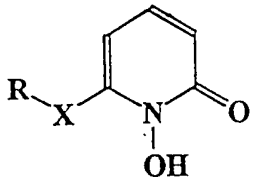
(b) reacting said 2-chloro-6-substituted-pyridine N-oxide with a base to produce a 1-hydroxy-6-substituted 2-pyridone compound.

13. A process for producing the compound of claim 11 wherein X in the formula of claim 11 is sulfur, which is characterized by the steps of:

(a) reacting a 2,6-dichloropyridine N-oxide, a thiol compound having between 1 and 20 carbon atoms and base in an organic solvent at an elevated temperature to produce a corresponding 2-chloro-6-substituted-oxypyridine N-oxide and

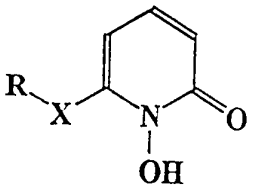
(b) reacting said 2-chloro,6-substituted pyridine N-oxide with additional base to produce the corresponding 1-hydroxy-6-substituted-pyridone.

14. An antimicrobial composition comprising a functional component selected from the group consisting of paints, shampoos, skin care medicaments, metalworking fluids, polymer compositions plus an antimicrobially effective amount of a compound characterized by the formula:



wherein X is an oxygen or sulfur moiety and R is substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that R is other than chlorobenzyl.

15. A method for inhibiting the growth of microorganisms by contacting said microorganisms with a composition characterized by containing an antimicrobial effective amount of a 1-hydroxy-6-substituted-2-pyridone compound of the formula:



wherein X is an oxygen or sulfur moiety and R is substituted or unsubstituted hydrocarbon radical having between 1 and 20 carbon atoms, with the proviso that R is other than chlorobenzyl, and at least one component selected from the group consisting of soaps, adhesives, coatings, elastomers, sealtants, shampoos, skin care medicaments, cosmetics and paints.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11484

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 211/72, 211/84; A61K 31/44, 7/06, 31/74; C09K 11/54, 15/32
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/296,297; 424/67,70,76.1,78.03,78.06,78.07;252/301.16,400.2,400.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN DATABASES: CA,CAS REACT,CAOLD,BEILSTEIN,TOXLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,916,228 (REUSCHLING et al.) 10 APRIL 1990, see entire document.	1,2,3,5,7-9,11-13,14,15
Y	US, A, 4,818,436 (FRENCH et al.) 04 APRIL 1989, see entire document.	1,2,3,5,7-9,11-15
Y	US, A, 4,401,770 (HANCE) 30 AUGUST 1983, see entire document.	1,2,3,5,7-9,11-15
Y	JOURNAL OF MEDICINAL CHEMISTRY, VOL.17, No.7, Issued 1974, DITMAR et al., "QUANTITATIVE STRUCTURE ACTIVITY ANALYSIS IN A SERIES OF ANTIMYCOTICALLY ACTIVE N-HYDROXY PYRIDONES," PAGES 753-756.	1,2,3,5,7-9,11-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 DECEMBER 1994	Date of mailing of the international search report JAN 31 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ALAN L.ROTMAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11484

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

546/296,297; 424/67,70,76.1,78.03,78.06,78.07; 252/301.16,400.2,400.23

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1(in-part),3,5,7-8(in-part),11-13 and 14-15 (in-part) drawn to compounds,namely 1-hydroxy-6-hydrocarbyl-oxy-or thio-pyridine-2-(1H)-2-ones or thiones,methods for their preparation, compositions and method of use containing said compounds as skin care medicaments classified in Class 546; Subclass 296; Class 424; Subclasses 76.1,78.03,78.04,78.06,78.07.

II. Claims 1(in-part),2,9 drawn to 1-hydroxy-6-hydrocarbyl-amino -pyridine-2(1H)-ones,compositions said compounds as skin care medicaments.

III. Claims 8,15 (in-part) involving compounds of inventions I, except the compositions are limited to shampoos and cosmetics. Class 424; Subclass 69 and 70.

IV. Claims 8,15 (in-part) drawn to compounds containing invention I compounds except that said use is restricted to paints, metal working fluids, polymer composition and the like
classified in Class 252; Subclasses 301.16,400.2,400.23.

V. Claims 4, 6 drawn to a method making compound of Group II.

VI. Claim 10 drawn to a method using the compound of Group II as a skin care medicant.

VII. Claims 10 drawn to a method using the compound of Group II as a shampoo/cosmetic.

VIII. Claim 10 drawn to a method using the compound of Group II for paints, metal working fluids, and polymeric compositions.

Lack of unity of invention has beeen found to exist since amino-pyridones are considered independent and distinct from oxy-or thio-pyridones and are separately classified and are not interchangeable isosteres. It is indisputable that skin care medicaments require a different technology than shampoos and the latter two require divese technologies from paints metal working fluids and polymeric compositions. 37 CFR 1.475(d).