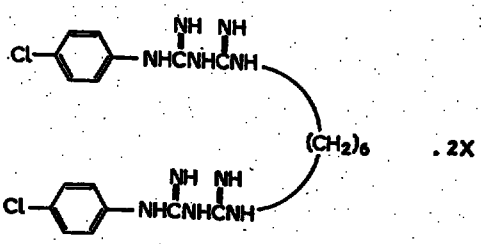
SPECIFICATION

Chlorhexidine salts and compositions of same

I. DESCRIPTION:

Technical field

The present invention relates to antibacterial compounds of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, and compositions containing same. More particularly, the invention relates to these novel chlorhexidine salts and antibacterial dermatological compositions containing these salts, preferably in an amount, calculated on total composition weight, of from about 0.1 to 10% by weight, more preferably 0.25 to 5% by weight, and still more preferably 0.75 to 2.5% by weight.

The novel salts comprise chlorhexidine disorbate, chlorhexidine dinalidixate and chlorhexidine diphosphanilate. Preferably, the chlorhexidine disorbate is employed as the monohydrate while the chlorhexidine diphosphanilate is employed as the dihydrate.

Background art

Chlorhexidine, nalidixic acid, phosphanilic acid and sorbic acid are known in the art. Moreover, as is shown in U.S. Patents 3,960,745, issued June 1, 1976, and 3,855,140, issued December 17, 1974, certain chlorhexidine salts are likewise known. Such salts include the hydrochloride, gluconate, isethionate, formate, acetate, glutamate, succinamate, monodiglycolate, dimethanesulphonate, lactate, di-isobutyrate and the glucoheptonate.

Polyhydroxycarboxylic acid salts of biguanides, such as, for example, chlorhexidine, di-D-gluconate, are disclosed in U.S. Patent 2,990,425, issued June 27, 1961, as being highly soluble in water.

The oral antibacterial use of water soluble salts of chlorhexidine, such as the gluconate, acetate, fluoride, dihydrogenfluoride and the dihydrogen chloride, is disclosed in U.S. Patent 3,976,765, issued August 24, 1976.

An oral antibacterial composition comprising a combination of dodecyl-di-(aminoethyl)glycine and chlorhexidine or its digluconate, diacetate, dichloride or monofluorophosphate salts is disclosed in U.S. Patent 3,932,607, issued January 13, 1976.

Salts of chlorhexidine with certain sequestering amino carboxylic acids are disclosed in U.S. Patent 3,888,947, issued June 10, 1975. Preferred salts include, mono-chlorhexidine nitrilotriacetate, trichlorhexidine di-[diethylene triaminepentaacetate], mono-chlorhexidine-di-[N,N-dihydroxyethylamino-acetate], mono-chlorhexidine N-hydroxyethylenediaminetriacetate and mono-chlorhexidine di-[N-hydroxyethylethylenediaminetriacetate]. Such sequestrates are disclosed to have greater antibacterial activity than the corresponding bisguanido salt (confer column 3, lines 22 through 42 of the patent).

Bis-guanide hydroxyalkane sulphonic acid salts are disclosed in British Patent Specification 815,800. Such salts (including the isethionic acid salt, the 2:3-dihydroxypropane-1-sulphonic acid salt, the 3-chloro-2-hydroxypropane-1-sulphonic acid salt and the 2-hydroxypropane-1-sulphonic acid salt) are asserted to advantageously possess high solubility in water.

U.S. Patent 3,152,181, issued October 6, 1964, discloses monobiguanides having at least one alkoxypropyl group having from about 11 to 19 carbon atoms attached to the N^1 or N^5 terminal nitrogen atoms. Such compounds are said to display exceptional antimicrobial activity and may be employed as the free base or, where water solubility is a factor in their use, as their salts with the inorganic and organic acids (such as mono and polycarboxylic and sulfur-containing mono and poly acids and acidic nitrogen compounds). Exemplary of acid salts are the hydrochloride, hydrobromide, sulfate, phosphate, borate, phosphite, sulfite, sulfonate, nitrite, carbonate, nitrate, acetate, tartrate, propionate, oxalate, maleate, malate, picrate and β-ethoxypropionate salts. Examples of suitable acidic nitrogen compounds are theophylline, substituted theophyllines and similar purines, saccharin, phthalimide, benzoxazine-2, 4-diones, oxazolidine-2,4-dione and substituted oxazolidone-2,4-diones, N-p-methylbenzene sulfonyl-N'-n-butylurea, barbituric acids, mercaptobenzothiazole, 8-chlorotheophylline and succinimide. Patentees teach (at column 11, lines 36 through 70) that their monobiguanides can be employed with other medicaments.

As stated heretofore, nalidixic acid, phosphanilic acid and chlorhexidine are known in the art. The antibacterial agent, nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8 naphthyridine-3-carboxylic acid) is the subject of U.S. Patent 3,590,036, issued June 29, 1971. Nalidixic acid has not to the instant inventors' knowledge been heretofore utilized topically.

Phosphanilic acid (p-$NH_2C_6H_4PO_3H_2$, 4-aminobenzene phosphonic acid) has been synthesized (inter alia Doak et al. JACS 74 (1952)) and found to be active against various organisms (see for example Kuhn et al., Ber. 75,711 (1942); Klotz et al., JACS 69,473 (1947); and Thayer et al., Antibiotics and Chemotherapy, 3,256 (1953)).

U.S. Patent 3,159,537, issued December 1, 1964, teaches that certain phosphonic acid compounds, including phosphanilic acid, increase the oral absorption (viz. increase blood level) of tetracycline antibiotics.

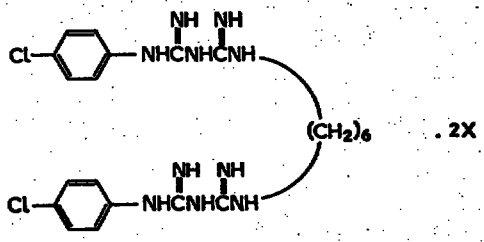
Complexes of phosphanilic acid and an amino-acridine compound (preferably, 9-amino- 3-amino or 6-amino acridine) are disclosed in U.S. Patents 3,694,447, issued September 26, 1972 and 3,794,723, issued February 26, 1974, as having antibacterial and antifungal activity.

Phosphanilic acid has also been reported to show synergistic action with trimethoprim against a variety of bacteria (see U.S. Patent 4,125,610, issued November 14, 1978). It has also been reported to show synergistic action with neomycin and with streptomycin against Enterobacteriaceae (see Ciencia (Mexico) 17, 71-73 (1957)).

Finally, it should be noted that the topical anti-infective, chlorhexidine, (1,6-di(N-p-chlorohenyldianido)hexane) is long known to the prior art having been disclosed in U.S. Patent 2,684,924, issued July 27, 1954.

Detailed description of invention

The novel antibacterial compounds of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, are readily prepared by for example reacting the desired acid, dissolved in suitable solvent therefor (preferably hot ethanol in the case of nalidixic acid and sorbic acid and hot water in the case of phosphanilic acid) with chlorhexidine free base, dissolved in a suitable solvent, preferably hot ethanol or hot methanol.

The resultant precipitate is recovered, washed then recrystallized according to methods known per se whereby the desired novel salt of the present invention is obtained.

The following examples more fully illustrate the method of preparation of the novel salts of the present invention.

Example 1

A solution of 505 mg. (1.0 mmole) of chlorhexidine free base in 50 ml. hot ethanol is cautiously added to a hot solution of 464 mg. (2.0 mmole) of nalidixic acid in 50 ml. hot ethanol. An immediate precipitate results and is filtered off after the mixture has cooled. The recovered precipitate is successively washed with ethanol, chloroform then ether. The washed solid precipitate is then recrystallized from dimethylformamide (DMF) whereby 0.6 g. (representing a yield of 6.19% of theoretical) of off-white solid chlorhexidine dinalidixate having a melting point of 224° to 226°C is obtained. IR (KBr disc): bands at 3330 - 2860 (broad multiplet), 1625, 1492, 1445, 1252, 1132, 1092, 820 and 745 cm^{-1}.

Anal. Calc'd for $C_{46}H_{54}Cl_2N_{14}O_6$ C, 56.96; H, 5.61; N, 20.21; Cl, 7.31; O, 9.90
Found: C, 56.86; H, 5.74; N, 20.21; Cl, 7.25.

Example 2

A warm solution of 505 mg. (1.0 mmole) of chlorhexidine free base in 50 ml. methanol is added to a solution of 346 mg. (1.0 mmole) of phosphanilic acid in 250 ml. of hot water. The resultant solution is then evaporated to approximately 50 ml. and cooled whereby a waxy solid separates. The waxy solid is filtered off, washed with water then recrystallized from water. After drying, 205 mg. of chlorhexidine diphosphanilate dihydrate, having a melting point of 172° - 174°C, are produced. This represents a yield of 23.1% of theoretical.

$\lambda_{max}^{EtOH} = 255$

(Am = 51,600) IR (KBr disc): bands at 3460 to 2930 (broad multiplet), 1650 to 1600 (broad multiplet), 1515, 1490, 1420, 1130 and 828 cm^{-1}.

Anal. Calc'd for $C_{34}H_{50}Cl_2N_{12}O_8P_2$ C, 45.99; H, 5.67; Cl, 7.98; N, 18.93; O, 14.42; P, 6.97.
Found C, 45.94; H, 5.75; Cl, 8.25; N, 19.00; P, 6.85.

Example 3

A hot solution of 224 mg. (2.0 mmole) of sorbic acid in 10 ml. ethanol is added to a hot solution of 505 mg. (1.0 mmole) of chlorhexidine free base in 50 ml. ethanol. The resulting solution is evaporated to a solid. The solid is then crystallized from ethanol/isopropanol (1:1 by volume). The thus crystallized product is dried whereby 527 mg. chlorhexidine disorbate monohydrate are produced. The chlorhexidine disorbate monohydrate is produced as a white powder which shrinks 90° - 100°C and melts at 100° - 104°C. The amount of chlorhexidine disorbate monohydrate recovered represents a yield of 70.5 % of theoretical.

$\lambda_{max}^{EtOH} = 253$

(Am = 79,000) IR (KBr disc): bands at 3460 to 2870 (broad multiplet), 1650 to 1600 (broad multiplet), 1540, 1490, 1390, 1000 and 825 cm^{-1}.

Anal. Calc'd for $C_{34}H_{48}Cl_2N_{10}O_5$ C, 54.61; H, 6.47; Cl, 9.49; N, 18.73; O, 10.70.
Found: C, 54.87; H, 6.65; Cl, 9.68; N, 18.49.

Chlorhexidine dinalidixate and chlorhexidine diphosphanilate produced in Examples 1 and 2, were tested for their activity *in vitro* against 32 strains of *Pseudomonas aeruginosa*, 26 strains of other gram-negative organisms and 18 gram-positive organisms. Minimum inhibitory concentration data for the reference standards, chlorhexidine digluconate, chlorhexidine diacetate, nalidixic acid and phosphanilic acid, were also obtained. Chlorhexidine base could not be employed as a reference as it is unstable. The results of the study are reported in Table I as follows:

TABLE I

Antibacterial activity of chlorhexidine di nalidixate and chlorhexidine di phosphanilate salts

Organism	Gram strain	Number of strains	MIC (μg/ml)[a] Chlorhexidine Nalidixic acid salt	Phosphanilic acid salt	Digluconate[b]	Diacetate[b]	Nalidixic acid	Phosphanilic acid
S. *aureus*	+	6	6.4	4	4	2	44.8	>125
S. *pneumoniae*	+	4	19	16	16	13.5	>125	>125
S. *pyogenes*	+	3	8	5	5	4	>125	>125
S. *Viridans Streptococcus*	+	1	63	32	63	32	125	>125
(β-*hemolytic*)	+	2	11.3	8	5.7	5.7	>125	>125
S. *faecalis*	+	2	16	8	8	5.7	>125	>125
E. *coli*	–	3	8	10	10	5	16	79.4
K. *pneumoniae*	–	2	2.8	88.7	63	32	11.3	32
		1	8	63	32	32	16	>125
E. *cloacae*	–	3	6.4	32	32	16	25.4	>79.4
P. *mirabilis*	–	2	16	22.6	88.7	88.7	11.3	8
		1	16	32	>125	>125	16	125
P. *morganii*	–	2	2.8	22.6	16	5.7	8	44.7
P. *rettgeri*	–	1	1	63	63	32	2	32
		2	11.3	11.3	>125	>125	11.3	1.4
P. *vulgaris*	–	2	2.8	8	>125	>89	4	2.8
		1	16	16	125	125	16	63
S. *marcesceus*	–	3	4	1.3	50.3	>125	6.4	0.5
P. *stuartii*	–	2	11.3	5.7	44.9	32	16	2.8
		1	16	16	125	>125	16	2
P. *aeruginosa*	–	26	48.6	3.2	>125	>125	>125	1.5
		5	42	72.5	>125	~125	>125	36.4
		1	32	63	125	125	>125	>125

[a] Geometric mean MIC values where applicable
[b] In terms of chlorhexidine content

The data of Table I shows that the dinalidixic acid salt of chlorhexidine is more effective than either nalidixic acid or chlorhexidine alone as against many of the strains tested. The data shows chlorhexidine dinalidixate to be particularly active against all strains of *P. aeruginosa* as well as against individual strains of *K. pneumoniae*, *E. cloacae* and *P. morganii* while chlorhexidine diphosphanilate is seen to be effective against 26 out of 32 strains of *P. aeruginosa* and a strain of *P. mirabilis* and *P. vulgaris*.

The results of Table I indicate that the nalidixic acid salt of chlorhexidine is more effective than either of its two components alone.

To more fully investigate the synergistic effect of the novel salts of the present invention, chlorhexidine dinalidixate, chlorhexidine disorbate and chlorhexidine diphosphanilate, as well as nalidixic acid, phosphanilic acid, chlorhexidine diacetate and a 1:1 mixture of chlorhexidine digluconate and nalidixic acid, were tested for activity *in vitro* against 30 strains of *Pseudomonas aeruginosa*, 23 strains of other gram-negative organisms and 15 gram-positive organisms. Minimum inhibitory concentrations of the novel salts of the instant invention as well as the reference standards (viz. chlorhexidine digluconate, chlorhexidine diacetate, chlorhexidine disorbate, nalidixic acid, phosphanilic acid and the 1:1 mixture of chlorhexidine digluconate and nalidixic acid) were obtained. In contrast to the procedure employed in obtaining the results of Table I, all compounds were tested on a straight weight basis and in a medium low in antibiotic antagonists (viz. Mueller-Hinton Broth + 1% Ionagar), thus increasing antibiotic sensitivity.

The results, as reported in Table II which follows, show chlorhexidine dinalidixate to be more effective than either chlorhexidine or nalidixic acid, particularly against strains of *Klebsiella pneumoniae*, and *Enterococcus cloacae* and 28 of 30 strains of *P. aeruginosa*. The phosphanilic acid salt of chlorhexidine shows clear improvement over phosphanilic acid and chlorhexidine alone as against 4 of 30 strains of *P. aeruginosa*. The results aso show chlorhexidine diphosphanilate to be a very effective antipseudomonal. It inhibits 29 of the 30 strains of *P. aeruginosa* at MIC values of 8 µg/ml or less as compared to chlorhexidine digluconate, diacetate and disorbate, which inhibit only 2 strains below 8 µg/ml.

TABLE II

Antibacterial activity of various salts of chlorhexidine in mueller-hinton broth supplemented with 1% ionagar

Organism	Gram stain	Number of stains	M I C (μ g/ml)[a] Chlorhexidine Digluconate + nalidixic acid (1/1)	Nalidixate	Phosphanilate	Digluconate	Diacetate	Disorbate	Nalidixic acid	Phosphanilic acid
S. aureus	+	4	1.2	0.21	0.25	0.25	0.21	0.21	32	>125
S.pneumoniae	+	3	99.5	12.7	10.1	10.1	6.4	12.7	>125	>125
S.pyogenes	+	3	16	4	3.2	3.2	3.2	1.6	>125	>125
S.viridans	+	1	63	16	16	16	8	16	>125	>125
Streptococcus (B- hemolytic	+	2	16	4	4	1.4	1.4	1.4	>125	>125
S. faecalis	+	2	11.3	8	4	2	2	2	>125	>125
E. coli	–	3	1	0.63	0.63	0.63	0.32	0.63	2	32
K. pneumoniae	–	2	1.4	1	2.8	4	2.8	4	2.8	16
		1	2	1	4	4	4	4	4	>125
E. cloacae	–	1	1	1	4	4	1	4	4	16
		2	1.4	1	2.8	2.8	1	2.8	4	>125
P. mirabilis	–	3	6.4	4	4	12.7	8	16	4	3.2
P. rettgeri	–	1	0.5	0.5	1	8	4	4	0.25	1
		3	5	4	6.4	16	8	16	2.5	1.3
P. vulgaris	–	1	4	1	4	2	1	2	0.5	>125
S. marcescens	–	3	2.5	2.5	2	6.4	12.7	6.4	1.3	0.5
P. stuartii	–	2	4	2.8	2	4	2	4	2	2.8
		1	8	4	4	16	16	16	4	4
P. aeruginosa	–	1	8	2	2	4	4	4	63	1
		1	8	4	8	4	4	4	63	63
		1	8	4	16	32	32	32	63	>125
		1	8	4	2	16	16	16	>125	63
		19	8.9	4.5	1.9	19.2	18.5	19.2	65.3	0.77
		5	12.1	8	2.6	18.4	18.4	18.4	>125	1.2
		2	8	8	5.7	16	16	16	63	63

[a] geometric MIC values where applicable.

Inocula: The majority of cultures were diluted 1000-fold; all the streptococci, except S. faecalis were used undiluted.

To more fully amplify the unexpected synergism of the novel salts of the present invention the MIC values, reported in Tables I and II in μg/ml, were converted to MIC values of μ moles/ml using the following molecular formulae and molecular weights:

Chlorhexidine disorbate monohydrate	$C_{34}H_{48}Cl_2N_{10}O_5$ 747.72
Chlorhexidine dinalidixate	$C_{46}H_{54}Cl_2N_{14}O_6$ 969.94
Chlorhexidine diphosphanilate dihydrate	$C_{34}H_{50}Cl_2N_{12}O_8P_2$ 856.72
Chlorhexidine digluconate	$C_{34}H_{54}Cl_2O_{14}N_{10}$ 897.80
Chlorhexidine diacetate	$C_{26}H_{38}Cl_2N_{10}O_4$ 625.56
Nalidixic acid	$C_{12}H_{12}N_2O_3$ 232.23
Phosphanilic acid	$C_6H_8NO_3$ 142.13

Tables III and IV show the results of such conversion and enable a comparison of potencies on a more meaningful molecule to molecule basis rather than gram to gram basis.

TABLE III

Antibacterial activity of chlorhexidine as a nalidixic acid and phosphanilic acid salt

MIC (μmoles/ml × 10^3)

Organism	Gram stain	Number of strains	Chlorhexidine: Nalixidic acid salt	Chlorhexidine: Phosphanilic acid salt	Chlorhexidine: Digluconate	Chlorhexidine: Diacetate	Nalidixic acid	Phosphanilic acid
S. aureus	+	6	6.6	4.6	4.5	3.2	193	>880
S. pneumoniae	+	4	19.6	18.6	17.8	21.5	>539	>880
S. pyogenes	+	3	8.2	5.8	5.6	6.4	>539	>880
S. viridans	+	1	64.9	37.3	70.1	51.1	539	>880
Streptococcus (β-hemolytic)	+	2	11.6	9.3	6.3	9.1	>539	>880
S. faecalis	+	2	16.5	9.3	8.9	9.1	>539	>880
E. coli	−	3	8.2	11.7	11.1	8.0	68.9	559
K. pneumoniae	−	2	2.9	103.5	70.1	51.1	48.7	225
		1	8.2	73.5	35.6	51.1	68.9	>880
E. cloacae	−	3	6.6	37.3	35.6	25.6	109	>559
P. mirabilis	−	2	16.5	26.3	98.8	141.6	48.7	56.3
		1	16.5	37.3	>139	>200	68.9	880
P. morganii	−	2	2.9	26.3	17.8	9.1	34.4	315
P. rettgeri	−	1	1	73.5	70.1	51.1	8.6	225
		2	11.6	13.0	>139	>200	48.7	9.8
P. vulgaris	−	2	2.9	9.3	>139	>142	17.2	19.7
		1	16.5	18.6	139	200	68.9	444
S. marcescens	−	3	4	2	56	>200	27.5	3.5
P. stuartii	−	1	11.6	6.6	50	51.1	68.9	19.7
		2	16.5	18.6	139	>200	68.9	14.1
P. aeruginosa	−	26	50.1	3.6	>139	>200	>539	10.6
		5	43.2	84.3	>139	200	>539	256
		1	32.9	73.5	139	200	>539	>880

TABLE IV

Antibacterial activity of various salts of chlorhexidine in mueller-hinton broth supplemented with 1% ionagar

MIC (µmole/ml × 10^3)

Organism	Gram stain	Number of strains	Chlorhexidine digluconate + nalidixic acid (1:1)	Nalidixate	Chlorhexidine Phosphanilate	Digluconate	Diacetate	Disorbate	Nalidixic acid	Phosphanilic acid
S. aureus	+	4	2.3	0.2	0.3	0.3	0.3	0.2	137	>880
S. pneumoniae	+	3	193	13	11.7	11.2	10.2	17.0	>539	>880
S. pyogenes	+	3	31	4	3.7	3.5	5.1	2.1	>539	>880
S. viridans	+	1	122	1.6	18.6	17.8	12.7	21	>539	>880
Streptococcus (β-hemolytic)	+	2	31	21.9	8.2	4.6	2.2	3.1	>539	>880
S. faecalis	+	2	21.9	8.2	4.6	2.2	3.1	2.6	>539	>880
E. coli	−	3	1.9	0.6	0.7	0.7	0.5	0.8	8.6	225
K. pneumoniae	−	2	2.7	1	3.2	4.4	4.1	5.4	12	112
		1	3.8	1	4.6	4.4	1.5	5.4	17.2	>880
E. colacae	−	1	1.9	1	4.6	4.4	1.5	5.4	17.2	112
		2	2.7	1	3.2	3.1	12.7	3.7	17.2	>880
P. mirabilis	−	3	12.4	4	4.6	14.1	6.4	21	17.2	22.5
P. rettgeri	−	1	0.9	0.5	1	8.9	12.7	5.4	1	7
		3	9.7	4	7.4	17.8	1.5	21	10.7	9
P. vulgaris	−	1	7.7	1	4.6	2.2	20.3	2.6	2.1	>880
S. marcescens	−	3	1.9	2.5	2.3	7.1	3.1	8.6	5.6	3.5
P. stuartii	−	2	7.7	2.8	2.3	4.4	1.6	5.4	8.6	19.7
		1	15.5	4	4.6	17.8	6.4	21	17.2	28
P. aeruginosa	−	1	15.5	2	2.3	4.4	6.4	5.4	271	7
		1	15.5	4	9.3	4.4	51.1	5.4	271	443
		1	15.5	4	18.6	35.6	25.5	4.3	271	>880
		1	15.5	4	2.3	17.8	29.6	2.4	>539	443
		19	17.2	4.5	2.2	21.4	29.4	25	281	5.4
		5	23.4	12.1	2.8	20.5	29.3	24	539	8.4
		2	15.5	8	6.1	17.8	32.4	21	271	443

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The results of Table III clearly indicate that the novel chlorhexidine dinalidixate and diphosphanilic salts of the instant invention are potent and exhibit synergistic effect particularly against *P. aeruginosa* with the nalidixate salt being the most widely synergistic. The novel disorbate salt of the present invention demonstrates clear synergism against several species. The synergistic effect of chlorhexidine dinalidixate is clearly seen by comparison of the results of Table III for *K. pneumonia, E. cloacae, P. mirabilis, P. morganii, P. rettgeri, P. vulgaris, S. marcescens, P. stuartii* and *P. aeruginosa*. For example, chlorhexidine dinalidixate is seen to have an MIC of 2.9 as against two strains of *K. pneumonia* and 8.2 against one strain of this organism. The corresponding values for nalidixic acid are 48.7 and 68.9; while those for chlorhexidine digluconate and chlorhexidine diacetate are respectively 70.1 and 35.6 and 51.1 and 51.1.

The novel chlorhexidine dinalidixate of the present invention is seen to display a most impressive synergistic effect as against *P. aeruginosa*. Against 26 strains of this organism chlorhexidine dinaladixate exhibited an MIC of 50.1; against five strains of such organism, it exhibited an MIC of 43.2; while against one strain of such organism, it exhibited an MIC of 32.9. In contrast thereto, nalidixic acid exhibited against these strains, MIC values, in each case, of more than 539 while chlorhexidine digluconate and chlorhexidine diacetate exhibited, as against the same strains, MIC values of respectively more than 139, more than 139 and 139 and more than 200, 200 and 200.

The synergistic effect of chlorhexidine dinalidixate is also clearly demonstrated from the results of Table IV. Synergisim is seen as against *K. pneumoniae, E. cloacae, P. mirabilis, P. rettgeri, S. marcescens, P. stuartii* and *P. aeruginosa*.

Referring again to Table III, chlorhexidine diphosphanilate of the present invention demonstrates marked synergism against *S. viridans, P. mirabilis, P. vulgaris*, one strain of *P. stuartii* and numerous strains of *P. aeruginosa*.

The results of Table IV demonstrate the asserted synergism of chlorhexidine diphosphanilate as against one strain of *P. rettgeri* and numerous strains of *P. aeruginosa*.

Referring again to Table IV, the synergistic effect of chlorhexidine disorbate is most clearly demonstrated as against *S. pyogenes*, one strain of *P. rettgeri* and numerous strains of *P. aeruginosa*.

The present invention also contemplates dermatological compositions comprising a novel chlorhexidine salt of the instant invention and a dermatologically acceptable carrier therefor.

Suitable compositions include creams, lotions, suspensions, emulsions, ointments and pastes.

Compositions in which a novel chlorhexidine salt of the present invention is produced in such compositions, in situ, are also within the scope of the invention.

The following formulations are offered to illustrate the compositions of the invention. Although a particular formulation utilizes one of the novel compounds of the invention, it should be readily appreciated that any of the novel compounds or, for that matter, a mixture of such compounds, could be employed in lieu thereof.

Formulations 1 through 6, set forth in Table V which follows, are prepared according to the following general procedure.

In a suitably sized premixed container, the Stearyl Alcohol is dissolved in the Petrolatum with the aid of heat and gentle stirring. The temperature is then adjusted to about 62 to 68°C.

The Propylene Glycol and about 99% of the purified water are combined in a suitably sized, preferably jacketed, main mix vessel and stirred until a homogeneous solution is obtained. The resultant solution is heated to 62 to 68°C then subjected to high speed mixing (preferably utilizing a suitable propeller mixture such as the Lightnin model ARL air mixer or similar type apparatus). The Carbomer is then slowly added thereto. High speed mixing is continued until the Carbomer is completely dispersed (approximately one hour). The Sodium Lauryl Sulfate, Sorbic Acid and the Amphoteric-9 are then added, while mixing slowly, and the resultant mixture is mixed slowly until it is homogeneous.

In a suitably sized container, the remainder of the water (about 1%) is heated to about 40 to 45°C then the Dried Sodium Phosphate is added thereto under rapid stirring. The stirring is continued until a clear solution results. The clear Sodium Phosphate solution is then added to the mixture in the main mix vessel while mixing slowly. Mixing is continued until a smooth semi-gel is formed. While mixing slowly, heating is initiated. The temperature is adjusted to about 62 to 68°C.

The Petrolatum and Stearyl Alcohol, constituting the oil phase, are then slowly added to the main mix vessel containing the ingredients constituting the aqueous phase. This addition is made while mixing the aqueous phase at high speed. Mixing is continued for a period of about 5 to 10 minutes then cooling is initiated (preferably by circulation of cold water in the outer jacket of the main mixed vessel). During this cooling operation, the mixture is subjected to slow speed agitation (preferably using a side scraping sweep agitator of the Groen type or the like). The mixture is cooled to a temperature of about 25 to 30°C whereby a finished base is produced.

A small amount of the finished base (an amount sufficient to produce a workable consistency: About 5% in the case of Formulations 1 and 4; about 10% in the case of Formulations 2 and 5 and about 15% in the case of Formulations 3 and 6) is added to a suitably sized container. The novel chlorhexidine salt of the present invention is added thereto and mixed therewith (with the aid of a spatula or suitable mixer) until it is uniformly dispersed in the finished lotion base. The dispersion is passed through a roller mill (preferably of the Asra type or the like) at an appropriate setting to produce a fine non-gritty particle size. This procedure is repeated if necessary whereby a milled concentrate is obtained.

The milled concentrate is then added to the remaining finished base and mixed therewith at slow speed (preferably using a sweep agitator) for one hour or until the uniform dispersion is formed.

TABLE V

Formulation	Percentage (by weight) No. 1	2	3	4	5	6
Chlorhexidine Disorbate	1.00	3.00	5.00	--	--	--
Chlorhexidine Dinalidixate	--	--	--	1.00	3.00	5.00
Chlorhexidine Diphosphanilate	--	--	--	--	--	--
Propylene Glycol, USP	12.00	12.00	12.00	12.00	12.00	12.00
Petrolatum, USP	5.84	5.84	5.84	22.50	22.50	22.50
Stearyl Alcohol, USP	2.00	2.00	2.00	15.00	15.00	15.00
Amphoteric-9	0.66	0.66	0.66	0.66	0.66	0.66
Carbomer-940	0.20	0.20	0.20	0.50	0.50	0.50
Sodium Lauryl Sulfate, USP	0.10	0.10	0.10	0.10	0.10	0.10
Sorbic Acid, NF	0.10	0.10	0.10	0.10	0.10	0.10
Dried Sodium Phosphate	0.10	0.10	0.10	0.25	0.25	0.25
Purified water qs to	100.00	100.00	100.0	100.00	100.00	100.00

Formulations 7, 8 and 9, set forth in Table VI which follows, are prepared according to the following general procedure:

The Peg-8 and the Lactic Acid are added to a, preferably stainless steel, premix container of suitable size and mixed slowly until a homogeneous solution is obtained.

The Petrolatum, Mineral Oil, Lanolin Oil, Cetyl Alcohol, Hydrogenated Polyisobutene, Peg-40 Stearate, Benzyl Alcohol and Sodium Lauryl Sulfate are added to a main mix vessel which is preferably of stainless steel and steam jacketed (e.g. Groen Model TDC/2-20 or the like). The mixture is agitated slowly (preferably using a Lightnin air mixer or a similar type mixture equipped with a propeller type blade) and heated. Mixing and heating is continued until all solids are melted. The temperature is adjusted to about 65 to 70°C. Mixing is continued for about 10 minutes then heating and agitation are discontinued. The mixture is then cooled (preferably by introduction of cold water into the outer jacket) and slow speed mixing is initiated (preferably with a side scraping sweep agitator). The mixture is permitted to cool to about 40 to 45°C during which time continuous mixing is maintained.

The solution of Lactic Acid and Peg-8 is then added to the ingredients contained in the main mix vessel, said ingredients constituting the oil phase. The addition is carried out slowing and with constant mixing. Mixing and cooling are continued until a temperature of about 25 to 30°C is attained whereby a finished base is produced.

A small amount of the finished base (viz. an amount sufficient to produce a workable consistency; approximately 5% in the case of Formulation 7, approximately 10% in the case of Formulation 8 and approximately 15% in the case of Formulation 9) is added to a suitably sized mixing container (for example a Hobart Model A-200D or the like) and the Chlorhexidine Diphosphanilate is added thereto. (The word "Hobart" is a registered Trade Mark). The combination of the Chlorhexidine Diphosphanilate and finished base is mixed slowly until a fairly uniform dispersion of the salt results. The dispersion is passed through a roller mill (preferably of the Asra type or the like) at an appropriate setting to produce a fine non-gritty particle size whereby a milled concentrate is obtained. (The word "Asra" is a registered Trade Mark).

The milled concentrate is added to the finished base and mixed therewith at slow speed (preferably employing a side scraping sweep agitator, for example of the Groen type or the like) for about one hour or until a homogeneous dispersion is obtained.

TABLE VI

Formulation	Percent (by weight) No. 7	8	9
Chlorhexidine Diphosphanilate	1.000	3.000	5.000
Mineral Oil USP	10.000	10.000	10.000
Peg-8	8.000	8.000	8.000
Lanolin Oil	4.000	4.000	4.000
Cetyl Alcohol	3.000	3.000	3.000
Hydrogenated Polyisobutene	3.000	3.000	3.000
Peg-40 Stearate	2.000	2.000	2.000
Benzyl Alcohol	0.500	0.500	0.500
Sodium Lauryl Sulfate USP	0.100	0.100	0.1000
Lactic Acid (88%)	0.002	0.002	0.002
Petrolatum USP qs to	100.000	100.000	100.000

Formulations 10, 11 and 12, set forth in Table VII which follows, are produced according to the following general procedure:

The Glyceryl Oleate/Propylene Glycol, Peg-7-Hydrogenated Castor Oil, Sorbitan Oleate, Oleoyl Hydrogenated Animal Protein, Arlacel 481, Light Mineral Oil, Hydrogenated Polyisobutene, Lanolin Alcohol/Mineral Oil, Caprylic/Capric Triglycerides, Propyl Paraben and Beeswax are added to a, preferably stainless steel and jacketed, premix container of suitable size. The mixture is subjected to heating and slow mixing (preferably with a Lightnin Model ARL air mixer with propeller type agitator or similar apparatus). (The word "Lightnin" is a registered Trade Mark). The temperature is adjusted to about 75 to 85°C whereby an oil phase is produced.

The water, Lactic Acid, Propylene Glycol and Dried Sodium Phosphate are added to a main mixing vessel which is preferably of stainless steel and jacketed (for example the Groen Model TDC/2-20 or similar apparatus). This addition is made while heating and mixing at moderate speed (preferably employing a Lightnin Model ARL air mixer or the like). Mixing is continued until a clear solution is formed, then the Sorbitol, Methyl Paraben and the Titanium Dioxide are added. Mixing and heating are continued until a homogeneous mixture is produced. The temperature is adjusted to about 75 to 85°C whereby a water phase is produced.

When the water phase and the oil phase are at a proper temperature, the oil phase is added slowly to the water phase while mixing constantly at moderate speed (preferably employing a Lightnin Model ARL air mixer or similar apparatus) whereby an emulsion is produced. The Magnesium Stearate is added to the emulsion and mixed therewith for about 20 minutes at a temperature of about 75 to 85°C. The heating is then discontinued (preferably by introduction of cold water into the outer jacket of the main mixing vessel). Slow speed mixing is initiated (preferably using a side scraping sweep agitator (such as the Groen Model TDC/2-20 style agitator or similar apparatus). Mixing and cooling is permitted to continue until the temperature reaches about 25 to 30°C whereby a finished base is produced.

A small amount of the finished base (viz. an amount sufficient to produce a workable consistency; about 5% in the case of Formulation 10, about 10% in the case of Formulation 11 and about 15% in the case of Formulation 12) is added to a suitably sized container. The novel chlorhexidine salt of the present invention is then added thereto and mixed therewith using a spatula or other suitable mixer until a fairly uniformed dispersion of the salt in the ointment base results. This dispersion is passed one or more time through a roller mill of suitable capacity (preferably of the Asra type or the like) at an appropriate mill setting to produce a fine non-gritty particle size whereby a milled concentrate is produced.

The milled concentrate is added to the remaining finished base and mixed therewith (preferably using a Groen sweep agitator or similar equipment) at slow speed for about one hour or until a homogeneous dispersion is formed.

It should be noted that as employed in Formulation 10, Arlacel 481 is a trademark of ICI America Inc. and is a mixture of Sorbitan Oleate, Hydrogenated Castor Oil, Beeswax and Stearic Acid. (The word "Arlacel" is a registered Trade Mark).

TABLE VIII

Formulation	Percent (by weight) No. 10	11	12
Chlorhexidine Disorbate	1.00	--	--
Chlorhexidine Dinalidixate	--	3.00	--
Chlorhexidine Diphosphanilate	--	--	5.00
Propylene Glycol	12.00	12.00	12.00
Light Mineral Oil USP	10.84	10.84	10.84
Hydrogenated Polyisobutene	10.00	10.00	10.00
Caprylic/Capric Triglycerides	10.00	10.00	10.00
Beeswax	10.00	10.00	10.00
Peg-7-Hydrogenated Castor Oil	8.00	8.00	8.00
Lanolin Alcohol/Mineral Oil	6.00	6.00	6.00
Arlacel 481	4.00	4.00	4.00
Sorbitol	3.00	3.00	3.00
Glyceryl Oleate/Propylene Glycol	2.00	2.00	2.00
Sorbitan Oleate	2.00	2.00	2.00
Oleoyl Hydrogenated Animal Protein	2.00	2.00	2.00
Magnesium Stearate	2.00	2.00	2.00
Titanium Dioxide	1.00	1.00	1.00
Methyl Paraben	0.25	0.25	0.25
Propyl Paraben	0.20	0.20	0.20
Dried Sodium Phosphate	0.11	0.11	0.11
Lactic Acid (88%)	0.10	0.10	0.10
Purified water qs to	100.00	100.00	100.00

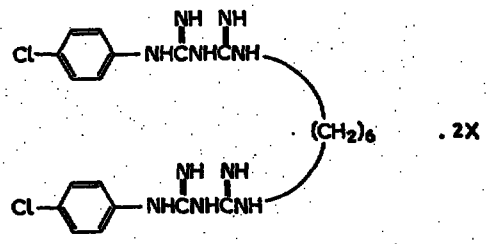
Mixtures of chlorhexidine or pharmaceutically acceptable salts of chlorhexidine (e.g. chlorhexidine digluconate) with nalidixic acid or pharmaceutically acceptable salts of nalidixic acid display synergism when used to prevent growth of microorganisms such as klebsiella pneumoniae, enerobacter cloacae, and pseudomonas aeruginosa. The calculated synergism indices show that said mixtures should contain from 35 to 65 weight percent of chlorhexidine or a pharmaceutically acceptable chlorhexidine salt and from 65 to 35 weight percent of nalidixic acid or a pharmaceutically acceptable salt of nalidixic acid. Preferably said mixtures should contain an approximately equal weight percent of each of the above acceptable compounds selected.

Mixtures of chlorhexidine or pharmaceutically acceptable salts or chlorhexidine (e.g. chlorhexidine digluconate) with phosphanilic acid or pharmaceutically acceptable salts of phosphanilic acid display synergism when used to prevent growth of microorganisms such as staphylococcus aureus, streptococcus pyogenes, streptococcus faecalis, and pseudomonas aeruginosa. Said mixtures should contain from 35 to 65 weight percent of chlorhexidine or a pharmaceutically acceptable chlorhexidine salt and from 65 to 35 weight percent of phosphanilic acid or a pharmaceutically acceptable salt of phosphanilic acid. Preferably

said mixtures should contain an approximately equal weight percent of each of the above acceptable compounds selected. Such compositions are the subject of our application No. 82/29195.

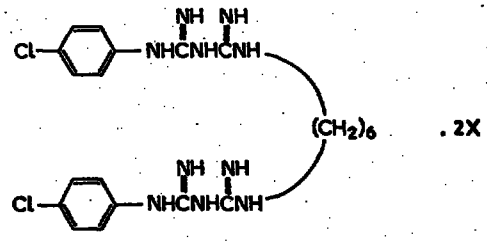
CLAIMS

1. A compound of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid.

2. The compound according to claim 1, wherein X is sorbic acid.
3. The compound according to claim 2, wherein X is the monohydrate of sorbic acid.
4. The compound according to claim 1, wherein X is nalidixic acid.
5. The compound according to claim 1, wherein X is phosphanilic acid.
6. The compound according to claim 5, wherein X is the dihydrate of phosphanilic acid.
7. An antibacterial composition comprising an amount effective to inhibit the growth of a bacterium sensitive thereto of a compound of the formula



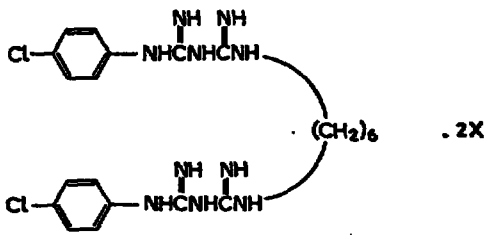
wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, and a dermatologically acceptable carrier therefor.

8. The composition according to claim 7, wherein X is sorbic acid.
9. The composition according to claim 8, wherein X is the monohydrate of sorbic acid.
10. The composition according to claim 7, wherein X is nalidixic acid.
11. The composition according to claim 7, wherein X is phosphanilic acid.
12. The composition according to claim 11, wherein X is the dihydrate of phosphanilic acid.
13. The composition according to claim 7, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
14. The composition according to claim 7, wherein said compound in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
15. The composition according to claim 7, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
16. The composition according to claim 8, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
17. The composition according to claim 8, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
18. The composition according to claim 8, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
19. The composition according to claim 9, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
20. The composition according to claim 9, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
21. The composition according to claim 9, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
22. The composition according to claim 10, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
23. The composition according to claim 10, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.

said mixtures should contain an approximately equal weight percent of each of the above acceptable compounds selected. Such compositions are the subject of our application No. 82/29195.

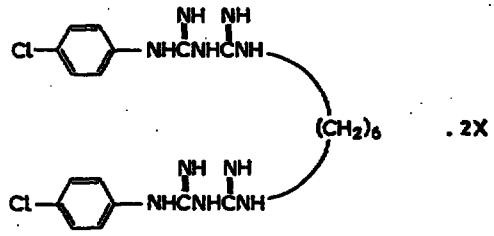
CLAIMS

1. A compound of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid.

2. The compound according to claim 1, wherein X is sorbic acid.
3. The compound according to claim 2, wherein X is the monohydrate of sorbic acid.
4. The compound according to claim 1, wherein X is nalidixic acid.
5. The compound according to claim 1, wherein X is phosphanilic acid.
6. The compound according to claim 5, wherein X is the dihydrate of phosphanilic acid.
7. An antibacterial composition comprising an amount effective to inhibit the growth of a bacterium sensitive thereto of a compound of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, and a dermatologically acceptable carrier therefor.

8. The composition according to claim 7, wherein X is sorbic acid.
9. The composition according to claim 8, wherein X is the monohydrate of sorbic acid.
10. The composition according to claim 7, wherein X is nalidixic acid.
11. The composition according to claim 7, wherein X is phosphanilic acid.
12. The composition according to claim 11, wherein X is the dihydrate of phosphanilic acid.
13. The composition according to claim 7, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
14. The composition according to claim 7, wherein said compound in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
15. The composition according to claim 7, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
16. The composition according to claim 8, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
17. The composition according to claim 8, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
18. The composition according to claim 8, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
19. The composition according to claim 9, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
20. The composition according to claim 9, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.
21. The composition according to claim 9, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.
22. The composition according to claim 10, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.
23. The composition according to claim 10, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.

24. The composition according to claim 10, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.

25. The composition according to claim 11, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.

26. The composition according to claim 11, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.

27. The composition according to claim 11, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.

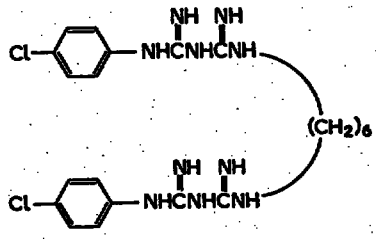
28. The composition according to claim 12, wherein said compound is present in an amount of from about 0.1 to 10% by weight, calculated on total composition weight.

29. The composition according to claim 12, wherein said compound is present in an amount of from about 0.25 to 5% by weight, calculated on total composition weight.

30. The composition according to claim 12, wherein said compound is present in an amount of from about 0.75 to 2.5% by weight, calculated on total composition weight.

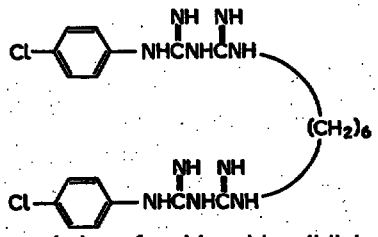
31. The composition as claimed in claim 7, wherein said compound is formed in said composition, in situ, by reaction of chlorhexidine and sorbic acid, when X is sorbic acid; by reaction of chlorhexidine and nalidixic acid, when X is nalidixic acid; or by reaction of chlorhexidine and phosphanilic acid, when X is phosphanilic acid.

32. Process for producing a compound of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, characterized in that the sorbic acid, nalidixic or phosphanilic acid is dissolved in a suitable solvent therefor, preferably hot ethanol in the case of nalidixic acid and sorbic acid and hot water in the case of phosphanilic acid, and reacted therein with chlorhexidine free-base dissolved in a suitable solvent therefor, preferably hot ethanol or hot methanol, then optionally recovering the resultant precipitate and washing, then recrystallizing same.

33. Method for producing an antibacterial composition comprising incorporating an amount effective to inhibit the growth of a bacterium sensitive thereto of a compound of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid in a dermatologically acceptable carrier therefor.

34. A compound in accordance with claim 1 substantially as hereinbefore described in any one of the Examples.

35. An antibacterical composition containing a compound in accordance with claim 1, substantially as hereinbefore described in any one of the Examples.

36. A method of inhibiting the growth of a microorganism on an inanimate surface wherein the microorganism is one sensitive to a compound in accordance with any of claims 1 to 6 or claim 34, or to a composition according to any of claims 7 to 31 and 35, and wherein the microorganism is contacted with an amount of the said compound or composition sufficient to inhibit its growth.

37. A method according to claim 36, wherein the microorganism is *Staphylococcus aureaus, Steptococcus pyogenes, Streptococcus faecalis* or *Pseudomonas aeruginosa*, and wherein the said compound or composition comprises chlorhexidine, or a pharmaceutically acceptable chlorhexidine salt, with phosphanilic acid, or a pharmaceutically acceptable phosphanilic acid salt.

38. A method according to claim 36, wherein the microorganism is *Klebsiella pneumoniae, Enterobacter cloacae* or *Pseudomonas aeruginosa*, and wherein the said compound or composition comprises chlorhexidine, or a pharmaceutically acceptable chlorhexidine salt, with nalidixic acid, or a pharmaceutically acceptable nalidixic acid salt.

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