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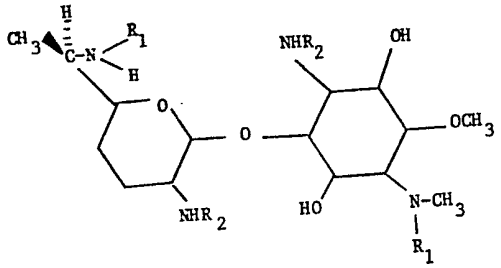
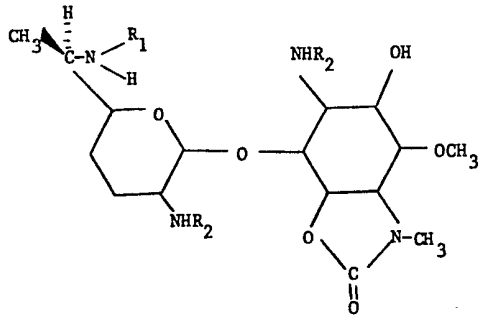
(54) **6'-Modified fortimicin compounds and improved method for preparation**

(57) Described is a method for the preparation of 6'-modified fortimicin compounds including 6'-epi fortimicin by converting 1,2'-di-*N*-protected fortimicin B into 4,6'-di-*N*-substituted-1,2'-di-*N*-protected fortimicin B(I) which is further converted to 1,2'-di-substituted fortimicin B-4,5-carbamate (II), a compound whose substitution pattern is particularly suited to modification at the 6'-amino group. Compounds (I) and (II) have the formula:-



and



respectively, R_1 being hydrogen or a protecting group and R_2 being an optionally substituted alkoxycarbonyl or aryloxycarbonyl group.

GB 2 061 265 A

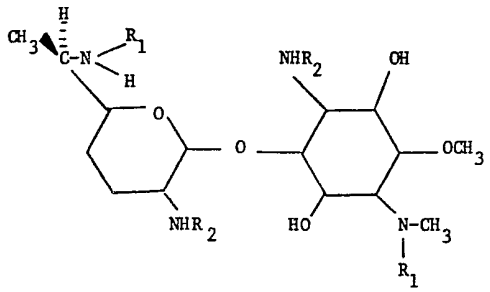
Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

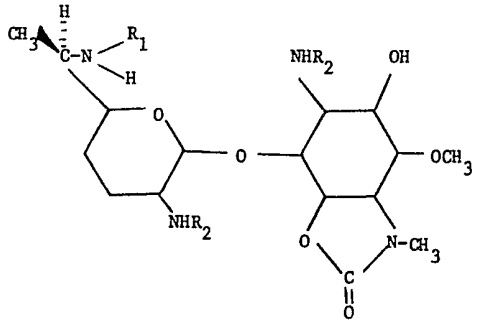
6'-modified fortimicin compounds and improved method for preparation

This invention relates to fortimicin compounds.

6'-modified fortimicin compounds such as 6'-epi fortimicin A and B and derivatives thereof such as described in commonly assigned U.S. patent application, Serial No. 863,004, filed December 21, 1977 are useful as antibiotics, can be incorporated into antibacterial scrub solutions and are further useful as intermediates in preparing other useful fortimicin derivatives of this invention are represented by:



wherein R is an *N*-protecting group and R_2 is a substituted alkoxycarbonyl group, and



wherein R_1 is hydrogen or an *N*-protecting group and R_2 is a substituted alkoxy carbonyl group, and pharmaceutically acceptable acid addition salts thereof.

The term "*N*-protecting group" is well recognized in the art and includes such groups as substituted and unsubstituted acyl and substituted and unsubstituted alkoxycarbonyl and arylalkoxycarbonyl.

The term "pharmaceutically acceptable salts" as used herein refers to the nontoxic acid addition salts which are generally prepared by reacting the compounds of this invention which a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, disulfate, acetate, oxylate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumerate, succinate, tartrate, napsylate and the like.

The compounds are useful as systemic antibiotics when administered parenterally in dosages of from 1-100 mg./kg. daily to mammalian or avian patients with infections caused by susceptible organisms. The compounds can also be administered orally to combat infections.

Briefly, the improved method of this invention for the preparation of 6'-modified fortimicin compounds including 6'-epi fortimicin comprises converting 1,2'-di-*N*-protected fortimicin B into 4,6'-di-*N*-substituted alkoxycarbonyl-1,2'-di-*N*-protected fortimicin B which is further converted to 1,2'-di-*N*-substituted fortimicin B-4,5-carbamate, a compound whose substitution pattern is particularly suited to modification at the 6'-amino group.

1,2'-di-*N*-benzyloxycarbonylfortimicin B (prepared as disclosed in commonly assigned U.S. patent application, Serial No. 863,018, filed December 21, 1977 (5) is converted to the 1,4-di-*N*-(2,2,2-trichloroethoxycarbonyl) derivative (6) with *N*-(2,2,2-trichloroethoxycarbonyloxy)phthalimide (15), prepared as in Example 12. Alternately, (6) may be prepared with 2,2,2-trichloroethoxycarbonyl chloride (Cl_3CH_2O-COCl), in which case it is preferable to carry out the reaction in the presence of sodium bicarbonate.

The product (6), detected by thin layer chromatography, is converted, without isolation, to 6'-*N*-(2,2,2-trichloroethoxycarbonyl)1,2-di-*N*-benzyloxycarbonyl fortimicin B 4,5-carbamate (7). Treatment of the latter with zinc in acetic acid cleaves the trichloroethoxycarbonyl group of (7) to give 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8). The latter (8) is converted to the 6'-*N*-chloro compound (9)

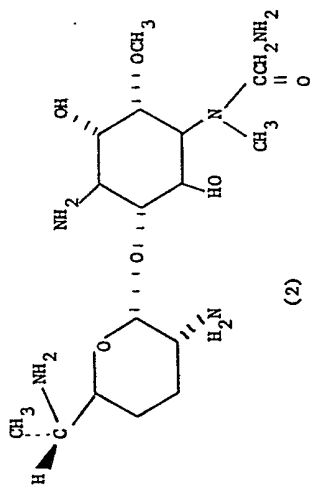
which is dehydrohalogenated with triethylenediamine to give the imine (10). Mild acid-catalyzed hydrolysis of (10) gives the 6'-oxo derivative (11).

Reductive amination of the 6'-oxo derivative (11) with sodium cyanoborohydride ($NaBH_3CN$) and ammonium acetate (NH_4OAc) gives a mixture of 1,2'-di-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B-4,5-carbamate (12) and 1,2-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8) which were readily separated by chromatography to give 18% of (12) and 12% of (8) based on (5).

Alternatively, reduction of the imine (10) with $NaBH_4$ gave 41% of the 6'-*epi* compound (12) and 3% of the 6'-normal derivative (8), isolated by chromatography.

Alkaline hydrolysis of (12) gave 6'-*epi*-fortimicin B (1) which was converted to 1,2',6'-tri-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B 16. The latter was converted to 1,2',6',2''-tetra-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin A (14). Catalytic hydrogenolysis of (14) in the presence of hydrochloric acid gave 6'-*epi*-fortimicin A (2) isolated as the tetrahydrochloride salt (2a). The latter was converted to the disulfate salt (2b).

Although all intermediates, with the exception of (6) and (9) have been purified for analysis, a particular advantage of the process is that 6'-ketone (11) and 6'-imine (10) may be prepared from (5), without purification of satisfactory purity for subsequent steps.



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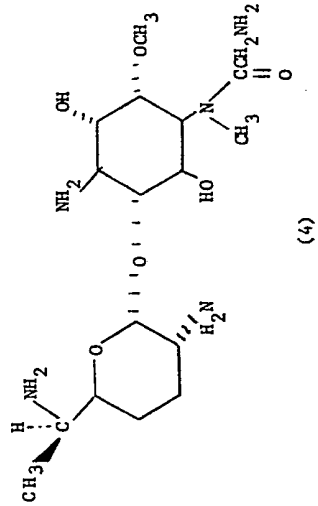

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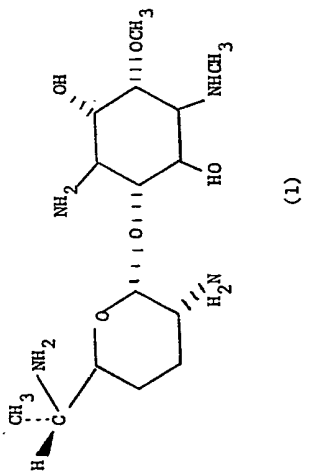

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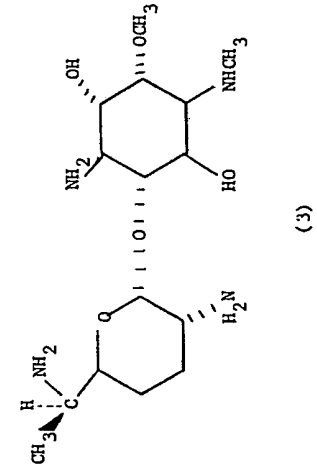

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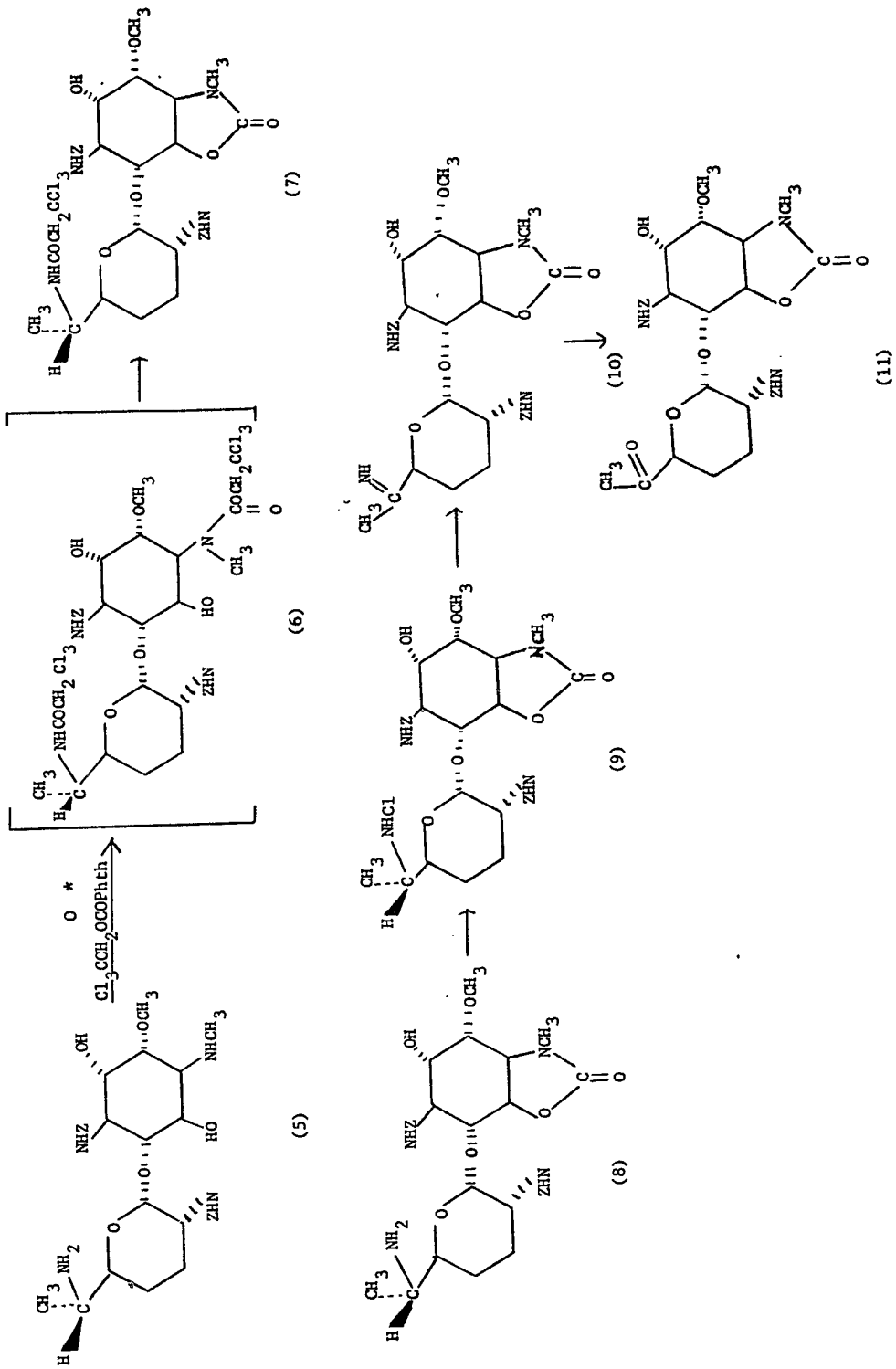
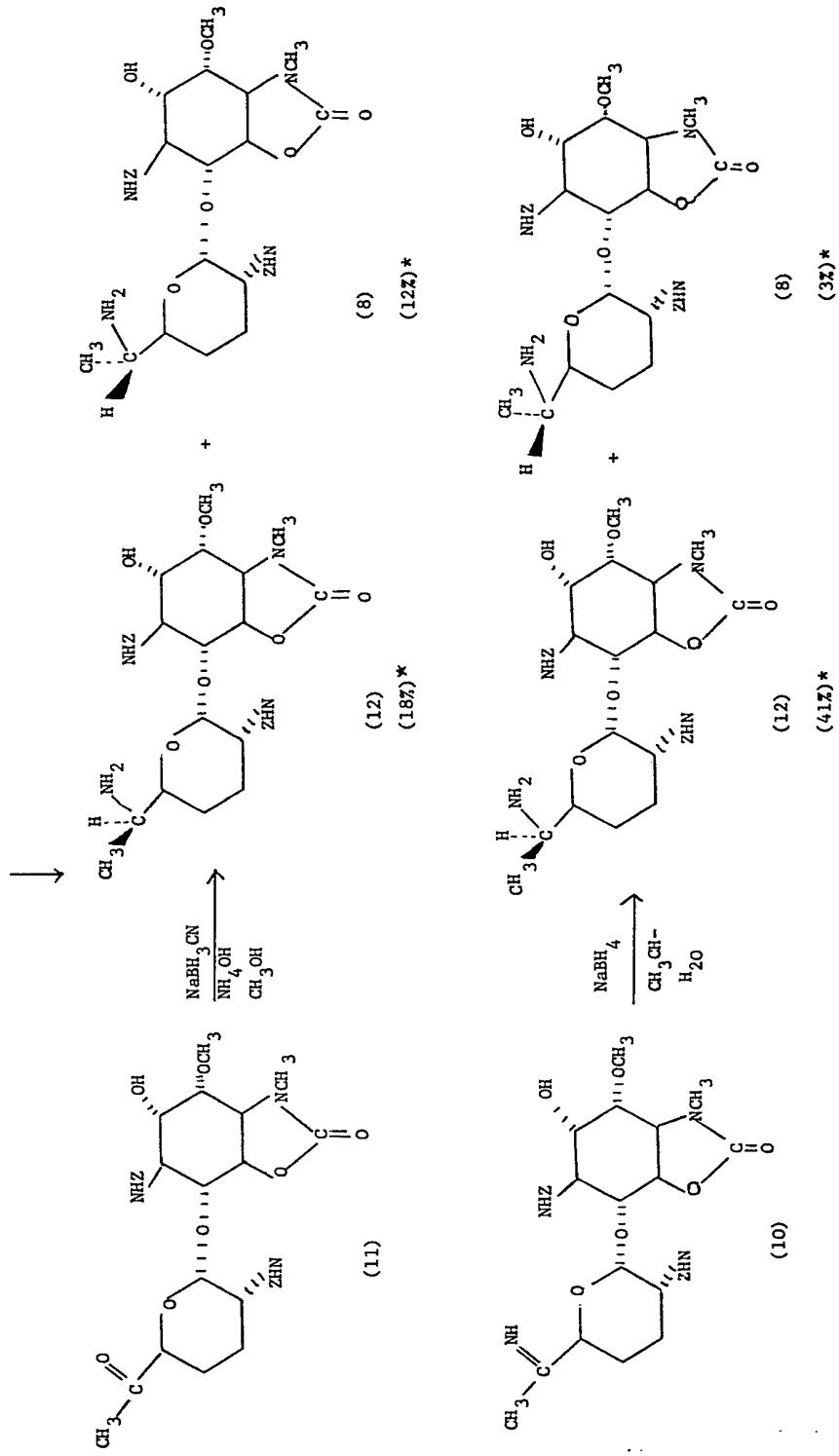
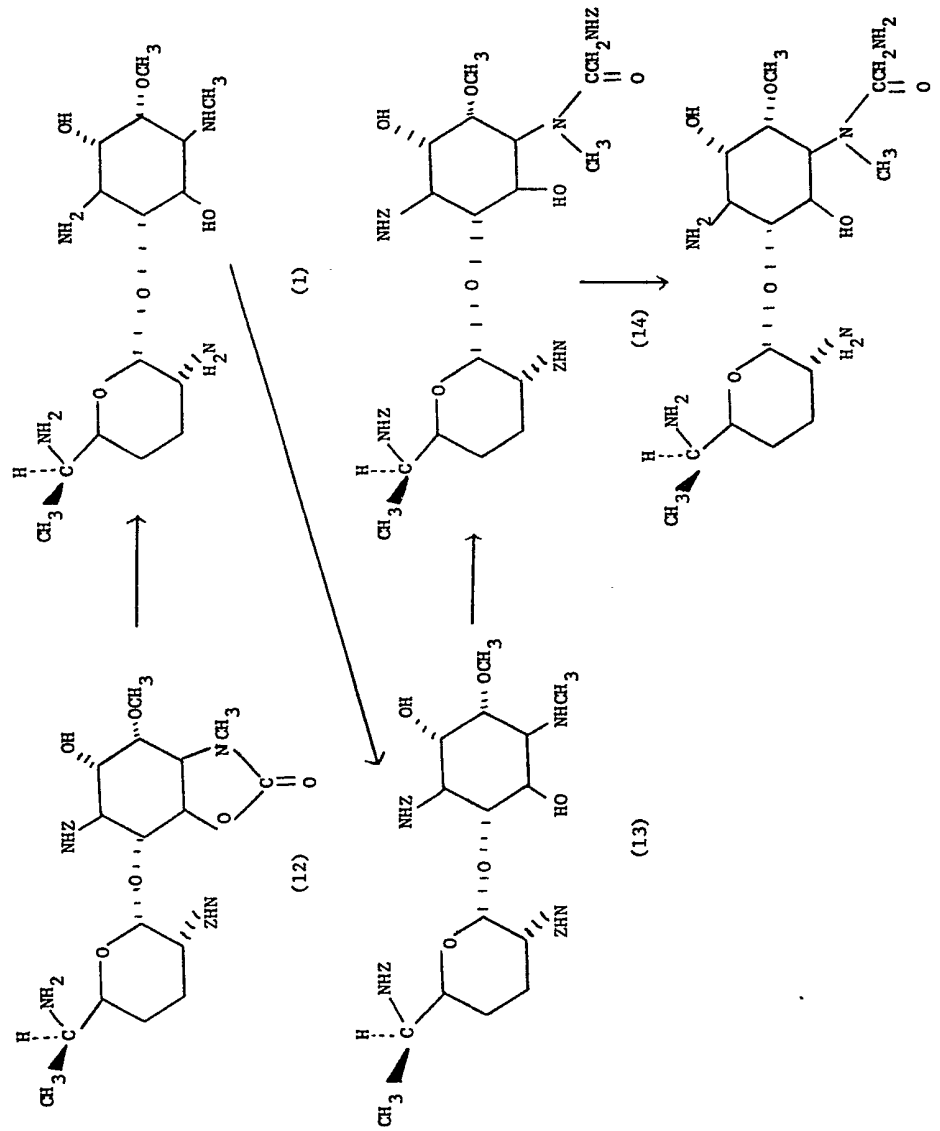
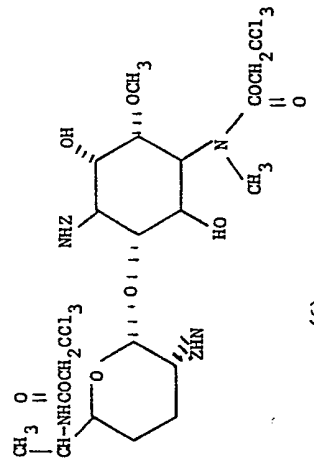




*Yields based on 1,2'di-N-benzyloxycarbonyl fortimicin B (5)



(2a) Tetrahydrochloride Salt (.4HCl)
(2b) Disulfate Salt (.2H_2SO_4)



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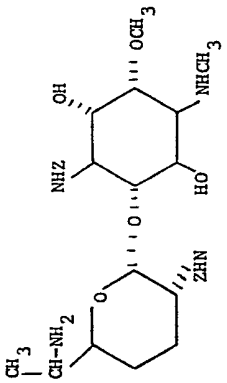

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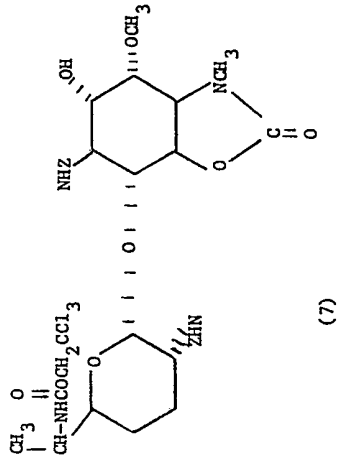


(7)

EXAMPLE 1

1,2'-Di-N-benzyloxycarbonyl-6'-N-(2,2,2-trichloroethoxycarbonyl)fortimicin B-4,5-carbamate (7)

A magnetically stirred solution of 6.2 g. of 1,2-di-*N*-benzyloxycarbonylfortimicin B (5), 10.2 g. of *N*-(2,2,2-trichloroethoxycarbonyloxy)phthalimide and 120 ml. of $CHCl_3$ is kept at ambient temperature overnight. The resulting solution is shaken with a mixture of 500 ml. of 5% aqueous $NaHCO_3$ and 300 ml. of $CHCl_3$. The $CHCl_3$ solution is separated, and the $CHCl_3$ is evaporated leaving 1,2'-di-*N*-benzyloxycarbonyl-4,6-di-*N*-(2,2,2-trichloroethoxy)fortimicin B (6) as a light yellow oil. The latter is heated under reflux for 1.5 hours in a solution prepared from 100 ml. of CH_3CH, 20 ml. of water, and 8.5 g. of $NaHCO_3$. The resulting solution is shaken with a mixture of 600 ml. of 5% aqueous $NaHCO_3$ and 250 ml. of $CHCl_3$. The $CHCl_3$ solution is separated, and the aqueous solution is washed with two 250 ml. portions of $CHCl_3$. The $CHCl_3$ solutions are combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure leaves 10.3 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-*N*-(2,2,2-trichloroethoxycarbonylfortimicin B-4,5-carbamate (7) as a glass.

The crude product (7) (12.0 g.) prepared as described above was chromatographed on a column of 400 g. of silica gel packed and eluted with a solvent system composed of 1,2-dichloroethane/methanol/ammonium hydroxide [17.2:2.8:0.1 (v/v/v)] to yield 8.4 g. of pure (7): $[\alpha]_D^{24}$ + 0.19° (C 1%, CH_3OH); IR ($CDCl_3$): 3457, 3435, 3332, 1760, 1717 cm^{-1}, NMR ($CDCl_3$): δ0.989d (J = 6.6 Hz) ($C_{6'}$-CH_3), 2.84 (NCH_3), 3.46 (OCH_3).

Anal. Calcd. for $C_{35}H_{43}N_4O_{12}Cl_3$:	C, 51.38;	H, 5.30;
	N, 6.85;	Cl, 13.00.
Found:	C, 51.40;	H, 5.49;
	N, 6.82;	Cl, 12.41.

EXAMPLE 2

1,2'-Di-N-benzyloxycarbonylfortimicin B-4,5-carbamate (8)

To a magnetically stirred solution of 10.3 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-(2,2,2-trichloroethoxycarbonyl)fortimicin B-4,5-carbamate (7), prepared from 6.2 g. of pure 1,2'-di-*N*-benzyloxycarbonylfortimicin B (5), in 150 ml. of glacial acetic acid, is added 22 g. of zinc dust. The resulting suspension is stirred overnight at ambient temperature. After removal of the zinc by filtration the filtrate is poured into water and the resulting suspension is extracted with $CHCl_3$. The $CHCl_3$ extract is washed to neutrality with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the $CHCl_3$ leaves 7.20 g. of crude 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8). Chromatography of 12.0 g. of the product, prepared as described above, on a column of 400 g. of silica gel, packed and eluted with a solvent system composed of 1,2-dichloroethane/methanol/concentrated ammonium hydroxide [17.2:2.8:0.1 (v/v/v) gives 8.35 g. of pure (8): $[\alpha]_D^{23}$ + 33.2° (C 1%, CH_3OH), IR ($CDCl_3$): 3440, 1750, 1704 cm^{-1}; NMR ($CDCl_3$): δ0.863 (J = 6.2 Hz) ($C_{6'}$-CH_3), 2.83 (NCH_3), 3.43 (OCH_3);

Anal. Calcd. for $C_{32}H_{42}N_4O_{10}$:	C, 59.80;	H, 6.59;	N, 8.72
Found:	C, 59.41;	H, 6.74;	N, 8.96

EXAMPLE 3

1,2'-Di-N-benzyloxycarbonyl-6'-imino-fortimicin B-4,5-carbamate (10)

A magnetically stirred solution of 2.56 g. of pure 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8), 1.56 g. of *N*-chlorosuccinimide, and 100 ml. of methylene chloride is kept at room temperature for 1 hour. The methylene chloride is evaporated under reduced pressure leaving the crude 1,2'-di-*N*-benzyloxycarbonyl-6'-*N*-chlorofortimicin B-4,5-carbamate (9) as a white glass: NMR ($CDCl_3$): δ1.06d (J = 3.2 Hz) ($C_{6'}$, (CH_3), 2.95 (NCH_3); 3.55 (OCH_3); IR ($CDCl_3$): 3553, 3439, 1754, 1713 cm^{-1}.

The latter (9) is dissolved in 200 ml. of a solution of 1% triethylenediamine in ethanol, dried over 3A molecular sieve, and the resulting solution is kept at ambient temperature for 80 minutes and then shaken with a mixture of 200 ml. of $CHCl_3$ and 500 ml. of 5% aqueous $NaHCO_3$. The $CHCl_3$ solution is separated and washed with 500 ml. of 5% aqueous NaCl solution. The aqueous solutions are washed in series with four 200 ml. portions of $CHCl_3$. The $CHCl_3$ solutions are combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure leaves 3.0 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-iminofortimicin B-4,5-carbamate (10) as a white glass. The product (3.0 g.) in 5 ml. of CH_3OH was applied to a column of 50 ml of AG-2-X8(OH) resin packed and washed with CH_3OH. Elution of the column with CH_3OH gave 2.54 g. of (10), free of *N*-chlorosuccinimide and succinimide. Chromatography of the latter on a column of 250 g. of silica gel packed and eluted with 1,2-dichloroethane/methanol [18.5:1.5 (v/v)] gave 1.2 g. of pure (10): $[\alpha]_D^{23}$ + 14.9° (C 1%, CH_3OH); IR ($CDCl_3$): 3556, 3434, 1758, 1712, 1616 w; NMR ($CDCl_3$): δ2.05 s ($NH=C-CH_3$); 3.86 (NCH_3); 3.44 (OCH_3).

Anal. Calcd. for $C_{32}H_{40}N_4O_{10}.0$: $35CHCl_3$:	C, 56.92;	H, 5.95;	
	N, 8.21;	Cl, 5.45	
Found:	C, 5709;	H, 5.89;	
	N, 8.01;	Cl, 5.54	

EXAMPLE 4

1,2'-Di-N-benzyloxycarbonyl-6'-oxo-fortimicin B-4,5-carbamate (11)

A solution of 0.910 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-imino-fortimicin B-4,5-carbamate (10), prepared from 1,2'-di-*N*-benzyloxycarbonylfortimicin B (5), without purification of any intermediats, 20 ml. of 0.4 *N* hydrochloric acid and 60 ml. of tetrahydrofuran is kept at ambient temperature overnight. The resulting solution is shaken with a mixture of 200 ml. of $CHCl_3$ and 500 ml. of 5% aqueous $NaHCO_3$. The $CHCl_3$ solution is separated and washed with 250 ml. of water. The aqueous solutions are washed in series with 200 ml. of $CHCl_3$. The $CHCl_3$ solutions are combined, and dried ($MgSO_4$). Evaporation of the $CHCl_3$ leaves 0.794 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-oxo-fortimicin B-4,5-carbamate (11). Chromatography of the latter (11) on a column (1.6 x 71 cm) of silica gel, packed and eluted with a solvent system composed of 1,2-dichloroethane/methanol [18.5:1.5 (v/v)], gave 0.396 g. of pure (11): $[\alpha]_D^{23}$ + 8.6° (C 1%, CH_3OH), IR ($CDCl_3$): 3559, 3439, 1760, 1713 cm^{-1}; NMR ($CDCl_3$): δ 2.06 s ($O=C-CH_3$); 2.86(NCH_3); 3.45(OCH_3);

Anal. Calcd. for $C_{32}H_{39}N_3O_{11}$:	C, 59.89;	H, 6.13;	N, 6.55
Found:	C, 59.81;	H, 6.40;	N, 6.62

EXAMPLE 5

1,2'-Di-N-benzyloxycarbonyl-6'-epi-fortimicin B-4,5-carbamate (12)

A solution of 0.6459 g. of 1,2'-di-*N*-benzyloxycarbonyl-6'-oxofortimicin B-4,5-carbamate (11), prepared from 0.939 g. of 1,2'-di-*N*-benzyloxycarbonylfortimicin B (5), without purification of any intermediates, 0.0852 g. of sodium cyanoborohydride, 0.945 g. of ammonium acetate, and 12.5 ml. of CH_3OH is stirred at ambient temperature for 18 hours. The resulting solution is shaken with a mixture of 100 ml. of $CHCl_3$ and 200 ml. of 5% aqueous $NaHCO_3$. The $CHCl_3$ solution is separated and washed with 200 ml. of water. The aqueous solutions are washed in series with three 80 ml. portions of $CHCl_3$. The $CHCl_3$ solutions are combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ leftr 0.5698 g. of white glass. Chromatography of the latter on a column of 40 g. of silica gel packed and eluted with a solvent system composed of methylene chloride/ethanol/methanol/concentrated ammonium hydroxide [18:1:1:0.1 (v/v/v/v)] gives 0.122 g. of 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8) in the early fractions, followed by 0.180 g. of 1,2'-di-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B-4,5-carbamate (12), as a white glass" $[\alpha]_D^{23}$ + 36.7° (C 1%, CH_3OH); IR ($CDCl_3$): 3437, 1750, 1702 cm^{-1}, NMR($CDCl_3$): δ1.02d (J=5.6 Hz) ($C_{6'}$-CH_3), 2.82 (NCH_3); 3.44 (OCH_3).

Anal. Calcd. for $C_{32}H_{42}N_4O_{10}.H_2O$:	C, 58.17;	H, 6.71;
	N, 8.48	
Found:	C, 58.36;	H, 6.68;
	N, 8.55	

EXAMPLE 6

1,2'-Di-N-benzyloxycarbonyl-6'-epi-fortimicin B-4,5-carbamate (12)

To a magnetically stirred solution of 5.41 g. of crude 1,2'-di-*N*-benzyloxycarbonyl-6'-iminofortimicin B-4,5-carbamate (10), prepared from 5.01 g. of pure 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8), 120 ml. of CH_3OH and 24 ml. of water, cooled in an ice bath is added, portionwise, 5.8 g. of $NaBH_4$. After the addition is complete, stirring is continued with cooling for 2 hours. The resulting solution is shaken with a mixture of 400 ml. of 5% aqueous $NaHCO_3$ and 250 ml. of $CHCl_3$. The $CHCl_3$ solution is separated and washed with 400 ml. of saturated aqueous NaCl. The aqueous solutions are washed in series with four 200 ml. portions of $CHCl_3$. The $CHCl_3$ solutions are combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure leaves 4.91 g. of white glass. Chromatography of the latter on a column of 400 g. of silica gel, packed and eluted with a solvent system composed of methylene chloride/ethanol/methanol/concentrated ammonium hydroxide [18:1:1:0.1 (v/v/v/v)], gives 0.276 g. of 1,2'-di-*N*-benzyloxycarbonylfortimicin B-4,5-carbamate (8) in the early fractions, followed by 2.73 g. of 1,2'-di-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B-4,5-carbamate (12) as a white glass identical with that described in Example 5.

EXAMPLE 7

6'-epi Fortimicin B (1)

A magnetically stirred solution of 17.8 g. of pure 1,2'-di-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B-4,5-carbamate (12) in a solution prepared with 125 ml. of 6*N* KOH and 250 ml. of ethanol is purged with nitrogen and heated in an oil bath at 80° overnight under nitrogen. The resulting solution is cooled in an ice bath and brought to pH 7 by addition of 2*N* hydrochloric acid. The solvent is evaporated under reduced pressure, and residual water is removed by co-distillation with ethanol under reduced pressure. The residue was triturated several times with CH_3OH and the CH_3OH supernatant is separated from insoluble salt by filtration. The CH_3OH is evaporated from the filtrate under reduced pressure. The residue (11.9 g.) is chromatographed on a column of 550 g. of silica gel packed and eluted with a solvent system composed of the lower phase of a mixture prepared from methylene chloride/methanol/water/concentrated ammonium hydroxide [2:2:1:1 (v/v/v/v)] to yield 8.10 g. of pure 6'-*epi*-fortimicin B (1): $[\alpha]_D^{23}$ + 28.4° (C 1%, CH_3OH); NMR (D_2O, pH 11.02): δ1.544 d (J=7.5 Hz) ($C_{6'}$-CH_3); 2.86 (NCH_3), 3.94 (OCH_3), 5.55 d (J=3.6 Hz) ($C_{1'}$-H).

EXAMPLE 8

1,2',6'-Tri-N-benzyloxycarbonyl-6'-epi-fortimicin B (13)

To a magnetically stirred solution of 8.88 g. of pure 6'-*epi*-fortimicin B (1), 260 ml. of CH_3OH and 130 ml. of water, cooled in an ice bath, is added 21.0 g. of *N*-[benzyloxycarbonyloxy]succinimide. Stirring is continued with cooling for 3 hours, and then at ambient temperature overnight. The resulting solution is poured into 1 liter of 5% aqueous $NaHCO_3$, and the aqueous suspension extracted three times with 500 ml. portions of $CHCl_3$. The $CHCl_3$ extracts are combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ leaves 20.7 g. of crude 1,2',6'-tri-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B (13). Chromatography of the latter on a column of 750 g. of silica gel packed and eluted with a solvent system composed of 1,2-dichloroethane/ethanol/concentrated ammonium hydroxide [18:2:0.1 (v/v/v)] yields 13.8 g of pure (13): $[\alpha]_D^{23}$ + 24.7° (C 1%, CH_3OH); IR ($CDCl_3$): 3554, 3334, 1708 cm^{-1}. NMR ($CDCl_3$): δ 1.018 d (J=6.4 Hz) ($C_{6'}$-CH_3), 2.34 (NCH_3), 3.42 (OCH_3).

Anal. Calcd. for $C_{39}H_{50}N_4O_{11}$:	C, 62.39;	H, 6.71;	N, 7.46
Found:	C, 62.13;	H, 6.77;	N, 7.37

EXAMPLE 9

1,2',6',2''-Tetra-N-benzyloxycarbonyl-6'-epi-fortimicin A (14)

A magnetically stirred solution of 12.8 g of 1,2',6'-tri-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin B (13), 5.75 g. of *N*-)benzyloxycarbonylglycyloxy)succinimide and 450 g. of tetrahydrofuran is kept at ambient temperature overnight. An additional 0.85 g. of *N*-(benzyloxycarbonylglycyloxy)succinimide is added and stirring is continued for overnight. The solvent is evaporated under reduced pressure. The residue is taken up in 500 ml. of $CHCl_3$ and the $CHCl_3$ solution is washed with two 250 ml. portions of 5% aqueous $NaHCO_3$ and dried ($MgSO_4$). The $CHcl_3$ is evaporated under reduced pressure leaving 17.1 g. of crude 1,2',6',2''-tetra-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin A (14). Chromatography of the latter on a column of 750 g. of silica gel packed and eluted with ethyl acetate yields 11.8 g. of pure (14): $[\alpha]_D^{23}$ + 74.1° (C 1%, CH_3OH); IR ($CDCl_3$): 3552, 3415, 1713, 1637 cm^{-1}. NMR ($CDCl_3$): δ1.78 d (J= 3.9 Hz) ($C_{6'}$-H); 2.82 (major), 2.98 (minor) (NCH_3 rotamers), 3.26 (OCH_3).

Anal. Calcd. for $C_{49}H_{59}N_5O_{14}$:	C, 62.48;	H, 6.31;	N, 7.43
Found:	C, 62.32;	H, 6.30;	N, 7.34

EXAMPLE 10

6'-epi-Fortimicin A tetrahydrochloride (2a)

A solution of 2.83 g. of 1,2',6',2''- tetra-*N*-benzyloxycarbonyl-6'-*epi*-fortimicin A (14) in 240 ml. of 0.2 *N* hydrochloric acid in CH_3OH is hydrogenated under 3 atmospheres of hydrogen for 4 hours in the presence of 2.8 g. of 5% Pd/C. The catalyst is removed by filtration, and solvent is separated under reduced pressure. Residual water is removed by co-distillation with CH_3OH under reduced pressure leaving 1.70 g. of 6'-*epi*-fortimicin A tetrahydrochloride (2a): $[\alpha]_D^{23}$ + 77.7° (C 1%, CH_3OH); IR (KBr): 1646 cm^{-1}, NMR (D_2O, pH 2.39): δ1.78 d (J=7.8 Hz) ($C_{6'}$-CH_3); 3.60 (NCH_3), 3.96 (OCH_3).

M^{+1}: Calcd. for $C_{17}H_{35}N_5O_6$:	405.2587
Meas:	405.2584
Cyclitol: Calcd. for $C_{10}H_{22}N_3O_5$:	264.1559
Meas:	264.1558
Diaminosugar: Calcd. for $C_7H_5N_2O$:	143.1184
Meas:	143.1209

EXAMPLE 11

6'-epi-Fortimicin A Bis-dihydrogen sulfate (2b)

A solution of 6.61 g. of 6'-*epi*-fortimicin A tetrahydrochloride (2a) in 25 ml. of deionized water is applied to a column (2.5 cm x 32 cm) of AG2-X1($SO_4^=$) resin. Elution with deionized water yields 7 g. of 6'-*epi*-fortimicin A bis-dihydrogen sulfate (2b): $[\alpha]_D^{23}$ +72° (C 1%, H_2O); IR (KBr): 1646 cm^{-1}, NMR (D_2O, pH 4.2); δ 1.75 d (J= 6.9 Hz) (C_6-CH_3); 3.58 (NCH_3); 3.94 (OCH_3).

Anal. Calcd. for $C_{17}H_{39}N_5O_{14}S_2$:	C, 33.94;	H, 6.53;	
	N, 11.64		
Found:	C, 31.67;	H, 6.65;	
	N, 11.47		
MS: M^+: Calcd. for $C_{17}H_{35}N_5O_6$:	405.2587		
Meas:	405.2596		
Cyclitol: Calcd. for $C_7H_{15}N_2O$:	143.1184		
Meas:	143.1209		
Diaminosugar: Calcd. for $C_{10}H_{22}N_3O_5$:	264.1559		
Meas:	264.1553		

EXAMPLE 12

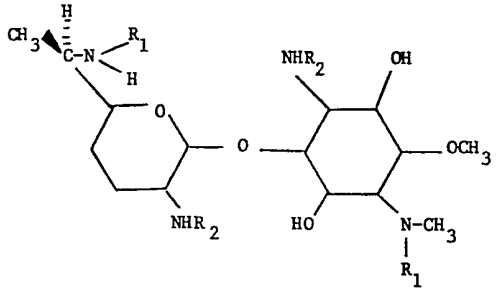
N-(2,2,2-Trichloroethoxycarbonyl)phthalimide (15)

A a magnetically stirred solution of 16.3 g. of *N*-hydroxyphthalimide in 150 ml. of pyridine, cooled in an ice bath, is added slowly, dropwise 15.2 ml. of 2,2,2-trichloroethoxycarbonyl chloride. Stirring is continued with cooling for 0.5 hours, and then at ambient temperature for two days. The resulting solution is poured into 700 ml. of ice water and the crystallized solid which forms is separated by filtration and washed with cold water. The product is dissolved in 500 ml. of $CHCl_3$ and the $CHCl_3$ solution is washed with three 300 ml. portions of 5% aqueous $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure leaves a yellow oil which is crystallized on trituration with hexane. After cooling in a cold room for several hours the product is collected by filtration and washed with hexane and dried at 50° under vacuum overnight to yield 30.7 g. of *N*-(2,2,2-trichloroethoxycarbonyl)phthalimide (15): m.p. 98-100°, IR ($CDCl_3$): δ4.93 s (CH_2), 7.76-7.98 m (aromatic).

Anal. Calcd. for $C_{11}H_6NO_5Cl_3$:	C, 39.02;	H, 1.79;	N, 4.14
Found:	C, 38.92;	H, 1.80;	N, 4.08

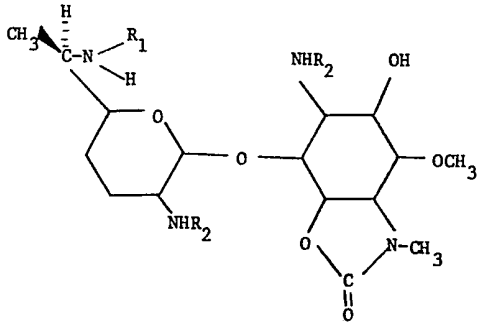
CLAIMS

1. A compound of the formula



wherein R_1 is an *N*-protecting group and R_2 is a substituted or unsubstituted alkoxycarbonyl or aryloxycarbonyl group.

2. The compound of Claim 1 wherein R_2 is benzyloxycarbonyl.
3. The compound of Claim 1 wherein R_1 is 2,2,2-trichloroethoxycarbonyl.
4. The compound 4,6'-di-*N*-(2,2,2-trichloroethocycarbonyl)1,2'-di-*N*-benzyloxycarbonylfortimicin B.
5. A compound of the formula



wherein R_1 is hydrogen or an *N*-protecting group and R_2 is a substituted or unsubstituted alkoxycarbonyl or aryloxycarbonyl group.

6. The compound of Claim 5 wherein R_2 is benzyloxycarbonyl.
7. A compound of Claim 5 in which R_1 is 2,2,2-trichloroethoxycarbonyl.
8. The compound 6'-*N*-(2,2,2-trichloroethoxy-carbonyl)-1,2'-di-*N*-benzyloxycarbonyl fortimicin B-4,5-carbamate.
9. A method of preparing a selected 1,2'-di-*N*-protected fortimicin B-4,5-carbamate which comprises reacting an appropriate 1,2'-di-*N*-protected fortimicin B with an alkoxycarbonyl alkylating agent, converting the resulting 4,6'-di-*N*-alkoxycarbonyl-1,2'-di-*N*-substituted fortimicin B-4,5-carbamate by reacting with a suitable base, and removing the alkoxycarbonyl group to obtain the desired 1,2'-di-*N*-protected fortimicin B-4,5-carbamate.
10. The compound prepared substantially according to any one of Examples 1 to 12 herein.

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