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Title: NOVEL METHOD OF PRODUCING 7-(SUBSTITUTED)-9-[(SUBSTITUTED GLCYL)-AMIDO]-6-DEMETHYL-6-DEOXYTETRA-
CYCLINES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a novel method for producing [4S-(4alpha,12aalpha)]-4-(dimethylamino)-7-(substituted)-9-[[(substituted amino)substituted]-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, herein after called 7-(substituted)-9-[(substituted glycy]-amido]-6-demethyl-6-deoxytetracyclines, which are useful as antibiotic agents.

The invention also relates to making novel, straight or branched 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline intermediates, which are useful for making the novel compounds of the present invention.

SUMMARY OF THE INVENTION

This invention is concerned with a novel method for producing 7-(substituted)-9-[(substituted glycy]amido]-6-demethyl-6-deoxytetracyclines, represented by formula I:

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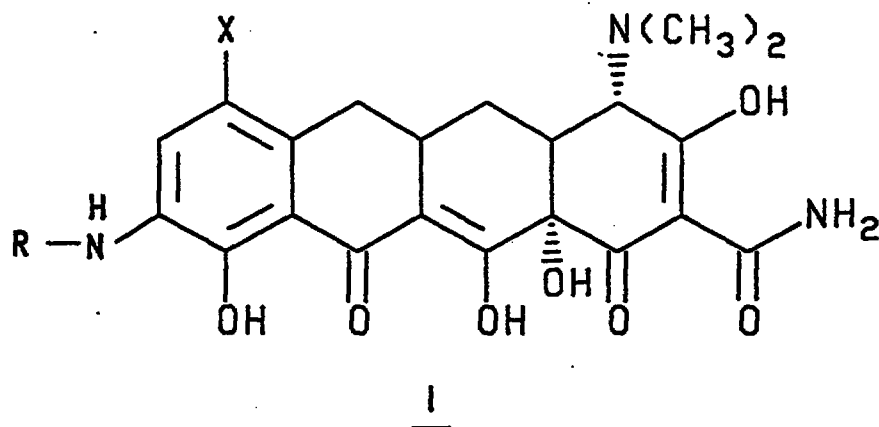


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wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

20
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,

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 $R^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylethyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-butyl}$,

30
 $R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylpropyl}$,

$R^2 = \text{2-methylpropyl}$;

R is selected from $R^4(\text{CH})_n\text{CO-}$, $n = 0-4$,

and when $n = 0$,

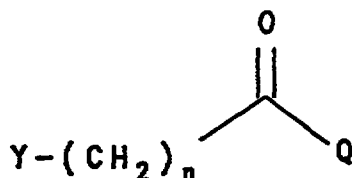
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 R^4 is selected from $\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group [selected from $\alpha\text{-aminomethyl}$, $\alpha\text{-aminoethyl}$, $\alpha\text{-aminopropyl}$, $\alpha\text{-aminobutyl}$ and the enantiomers of said $\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group]; $\alpha\text{-aralkylamino}$ group



[selected from phenylglycyl and the enantiomers of said α -aralkylamino group];

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group [selected from straight or branched (C_1-C_6)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl and 1-methyl-2-ethylpropyl), cyclopropylamino, cyclobutylamino, benzylamino and phenylamino]; disubstituted amino group [selected from dimethylamino, diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)amino, monomethylbenzylamino, aziridinyl, azetidiny, pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl)]; carboxy(C_2-C_4)alkylamino group [selected from aminoacetic acid, α -aminopropionic acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group]; which method comprises reacting a haloacyl halide compound of the formula:



wherein when $n = 0$,

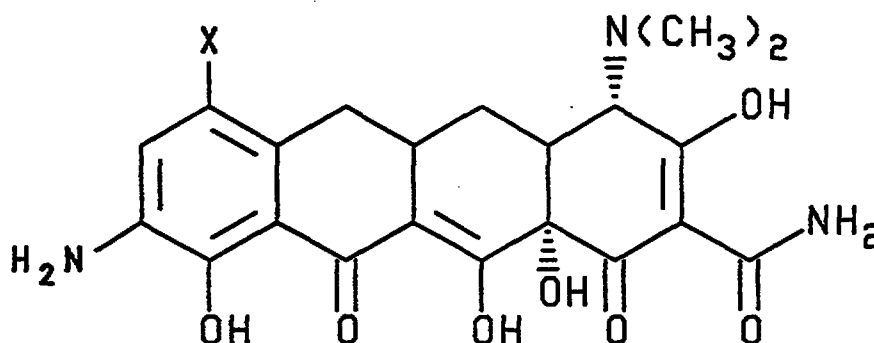
Y is straight or branched α -halo(C_1-C_4)alkyl group [selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl];

and when $n = 1-4$,

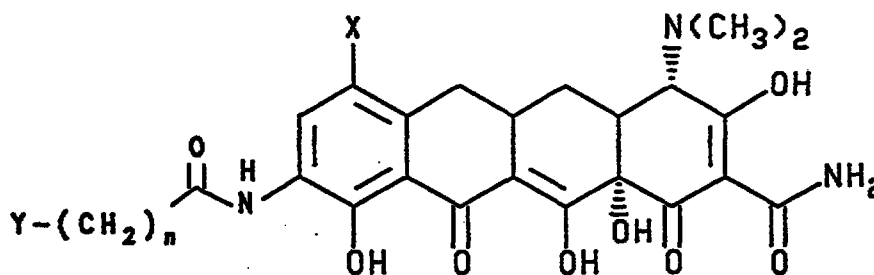


Y is halogen [selected from bromine, chlorine, iodine and fluorine], O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate;

and Q is halogen [selected from bromine, chlorine, fluorine and iodine] with a 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline compound of the formula:



wherein X is as defined hereinabove or the pharmacologically acceptable organic and inorganic salts thereof to obtain a 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline intermediate of the formula:



wherein X, Y and n are as defined hereinabove or the organic or inorganic salts thereof and reacting the intermediate, 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts thereof, with a



nucleophile of the formula R^4H , wherein R^4 is as defined hereinabove, to obtain a 7-(substituted)-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline compound according to formula I or the organic and inorganic salts thereof.

This novel method is an efficient way of preparing the 7-(substituted)-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts. The novel method permits these compounds to be prepared in two reactions. The first reaction results in the formation of a common intermediate, 9-[(haloacyloamido]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts thereof. The second reaction permits the common intermediate to be reacted with a wide variety of amines and results in a wide spectrum of 7-(substituted)-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines or the pharmacologically acceptable organic and inorganic salts thereof. The use of difficult protecting groups is eliminated, thus allowing the final products to be formed in only two reactions.

Preferred is a method for producing compounds according to the above formula I wherein:

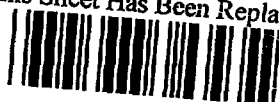
X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;
and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl}$;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,
and when $n = 0$,

R^4 is selected from $\alpha\text{-amino}(C_1-C_4)\text{alkyl group}$
[selected from $\alpha\text{-aminomethyl, } \alpha\text{-aminoethyl}$,



α -aminopropyl, α -aminobutyl and the enantiomers of said α -amino(C_1 - C_4)alkyl group]; α -aralkylamino group [selected from phenylglycyl and the enantiomers of said α -aralkylamino group];

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group [selected from straight or branched (C_1 - C_6)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl and 1-methyl-2-ethylpropyl), cyclopropylamino, cyclobutylamino, benzylamino and phenylamino]; disubstituted amino group [selected from dimethylamino, diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)amino, monomethylbenzylamino, aziridinyl, azetidiny, pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl)]; carboxy(C_2 - C_4)alkylamino group [selected from aminoacetic acid, α -aminopropionic acid and the enantiomers of said carboxy(C_2 - C_4)alkylamino group]; and the pharmacologically acceptable organic and inorganic salts.

Particularly preferred is a method for producing compounds according to formula I wherein: X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;



R is selected from $R^4(CH)_nCO-$, $n = 0-4$,
and when $n = 0$,

5 R^4 is selected from α -amino(C_1-C_4)alkyl group
[selected from α -aminomethyl, α -aminoethyl,
 α -aminopropyl, α -aminobutyl and the enantiomers of said
 α -amino(C_1-C_4)alkyl group]; α -aralkylamino group
[selected from phenylglycyl and the enantiomers of said
 α -aralkylamino group];

10 and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group
[selected from straight or branched (C_1-C_6)alkyl
(substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
15 1,1-dimethylethyl, n-pentyl, 2-methylbutyl,
1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),

20 cyclopropylamino, cyclobutylamino and benzylamino];
disubstituted amino group [selected from dimethylamino,
diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)-
amino, monomethylbenzylamino, aziridinyl, azetidiny,
pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl,
25 morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazo-
lyl) and 4-(1,2,4-triazolyl)]; carboxy(C_2-C_4)alkylamino
group [selected from aminoacetic acid, α -aminopropionic
acid and the enantiomers of said carboxy(C_2-C_4)alkyl-
amino group]; and the pharmacologically acceptable
30 organic and inorganic salts.

Most particularly preferred is a method for
producing compounds according to formula I wherein:
X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
35 and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;



and when R^1 = methyl or ethyl,

R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

5 R is selected from $R^4(CH)_nCO-$, $n = 0-4$,

and when $n = 0$,

R^4 is selected from α -amino(C_1-C_4)alkyl group

[selected from α -aminomethyl, α -aminoethyl,

10 α -aminopropyl, α -aminobutyl and the enantiomers of said α -amino(C_1-C_4)alkyl group];

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group

[selected from straight or branched (C_1-C_6)alkyl

(substitution selected from methyl, ethyl, n-propyl,

15 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,

1,1-dimethylethyl, n-pentyl, 2-methylbutyl,

1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,

n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,

20 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,

1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),

cyclopropylamino, cyclobutylamino and benzylamino];

disubstituted amino group [selected from dimethylamino,

diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)-

amino, monomethylbenzylamino, aziridinyl, azetidyl,

25 pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl,

morpholinyl, imidazolyl and 1-pyrrolyl];

carboxy(C_2-C_4)alkylamino group [selected from

aminoacetic acid]; and the pharmacologically acceptable organic and inorganic salts.

30 Of special interest is a method for producing compounds according to formula I wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the

halogen is selected from bromine, chlorine, fluorine and iodine;

35 and when $X = -NR^1R^2$ and when R^1 = methyl or ethyl,

R^2 = methyl or ethyl;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,

and when $n = 0$,

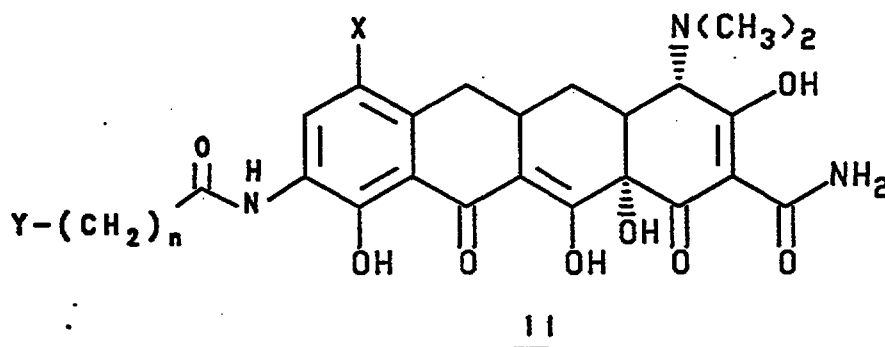


R^4 is selected from α -amino(C_1 - C_4)alkyl group
[selected from α -aminomethyl, α -aminoethyl, and the
enantiomers of said α -amino(C_1 - C_4)alkyl group];

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group
[selected from straight or branched (C_1 - C_6)alkyl
(substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, n-pentyl and n-hexyl),
cyclopropylamino and benzylamino]; disubstituted amino
group [selected from dimethylamino, diethylamino,
methyl(butyl)amino, azetidiny, pyrrolidinyl,
piperidinyl, morpholinyl and 1-imidazolyl];
and the pharmacologically acceptable organic and
inorganic salts.

Also included in the present invention is a
method for making a novel straight or branched
9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxy-
tetracycline intermediate useful for producing the
above compounds of formula I. Such intermediate
includes those having the formula II:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;



and when R^1 = methyl or ethyl,
 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-propyl,
 R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl
 or 2-methylpropyl;

and when R^1 = 1-methylethyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-butyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylpropyl,
 R^2 = 2-methylpropyl;

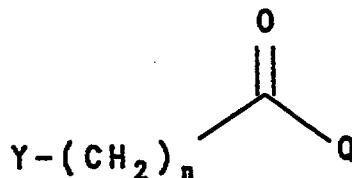
and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group
 [selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine
 and fluorine], O-toluenesulfonate, O-methylsulfonate or
 trifluoromethylsulfonate; and the pharmacologically
 acceptable organic and inorganic salt.

The novel method for producing the
 intermediate compound of formula II comprises reacting
 a 9-amino-7-(substituted)-6-demethyl-6-deoxytetra-
 cycline with a compound of the formula:



wherein Y, n and Q are as defined hereinabove.

Preferred is a method for producing compounds
 according to the above formula II wherein:
 X is selected from amino, $-NR^1R^2$, or halogen; the
 halogen is selected from bromine, chlorine, fluorine
 and iodine;



and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when $R^1 = \text{methyl or ethyl}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl}$;
and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group
[selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine
and fluorine], O-toluenesulfonate, O-methylsulfonate or
trifluoromethylsulfonate; and the pharmacologically
acceptable organic and inorganic salt.

Particularly preferred is a method for
producing compounds according to formula II wherein:
X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when $R^1 = \text{methyl or ethyl}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
1-methylpropyl or 2-methylpropyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group
[selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine
and fluorine], O-toluenesulfonate, O-methylsulfonate or
trifluoromethylsulfonate; and the pharmacologically
acceptable organic and inorganic salt.



Most particularly preferred is a method for producing compounds according to formula II wherein: X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen, $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group [selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine and fluorine], O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

Of special interest is a method for producing compounds according to formula II wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group [selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine and fluorine], O-toluenesulfonate, O-methylsulfonate or



trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 The novel method of the present invention, Scheme III, provides an easier way of preparing 7-(substituted)-9-[(substituted glycyloamido]-6-de-methyl-6-deoxytetracyclines or their pharmacologically acceptable organic and inorganic salts. This novel
10 method provides a way to prepare some of the 7-(substituted)- 9-[(substituted glycyloamido]-6-de-methyl-6-deoxytetracyclines or their pharmacologically acceptable organic and inorganic salts that would be
15 very difficult to prepare using either of the prior art methods shown in Scheme I or II.

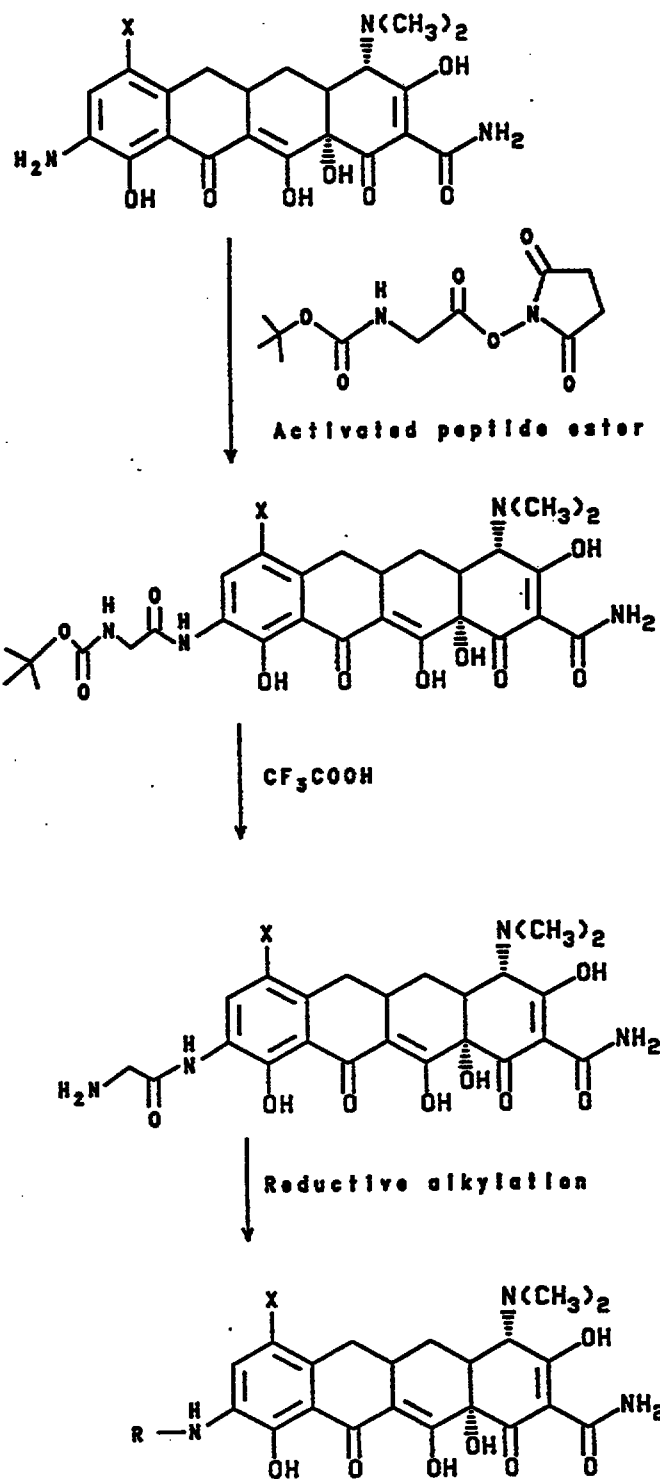
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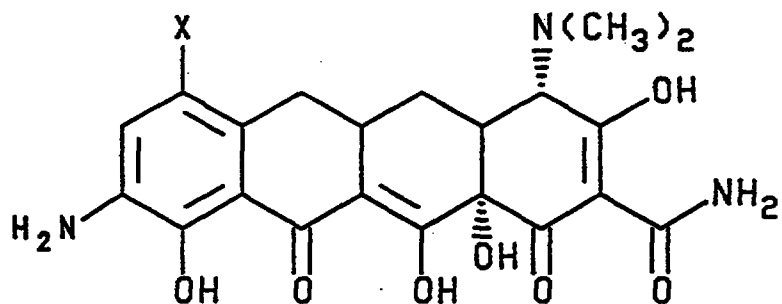
Scheme I



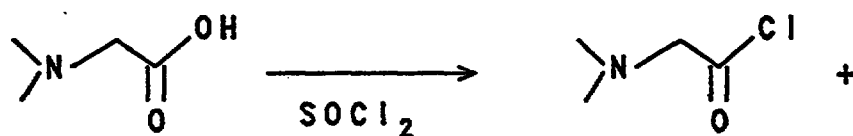
Scheme II

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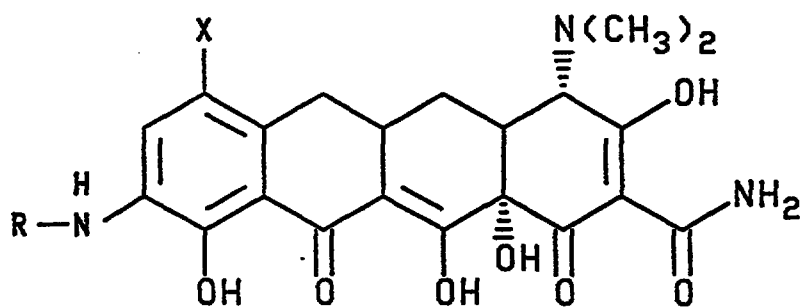
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5 The method shown in Scheme I is premised on a
reductive N-alkylation of the 9-(glycylamido)-7-(sub-
stituted)-6-demethyl-6-deoxytetracycline. It is
possible to use this method only when two identical
substituents are incorporated on the nitrogen. It
would be unworkable to incorporate sequentially two
different substituents on the nitrogen because the
10 reductive alkylation conditions are such that both
hydrogens are substituted at the same time. Thus,
using the method of Scheme I, it would not be possible
to incorporate a single substituent efficiently. In
addition, the initial reaction of the (succinyloxycar-
bonyl)methyl carbamic acid tert-butyl ester with the
15 appropriate 9-amino-7-(substituted)-6-demethyl-6-deoxy-
tetracycline affords only moderate yields.

The method shown in Scheme II is premised on
forming an acid chloride from a mono- or disubstituted
(C₁-C₆)amino substituted acyl acid and reacting the so
20 formed acid chloride with the amine at the 9-position
of the 9-amino-7-(substituted)-6-demethyl-6-deoxytetra-
cycline. Typically, the acid chloride is formed by the
reaction of the appropriate mono- or disubstituted-
(C₁-C₆)amine with either haloacetic acids (or esters)
25 or their synthetic equivalents, e.g., p-toluenesul-
fonyloxyacetic acid or methanesulfonyloxyacetic acid.
In the case of N-(monosubstituted)amino acids, the
method shown in Scheme II may be utilized only via the
use of nitrogen protecting groups. However, the
30 protecting groups must survive the acyl chloride
formation reactions, but also be readily removed from
the final products without detriment to the appended
tetracycline nucleus. The inclusion of protecting
groups in this process incurs additional steps and is
35 operationally complex. By the method shown in Scheme
II, for every new structural entity, e.g. 9-[(substi-
tuted glycyl)amido]-7-(substituted)-6-demethyl-6-deoxy-

tetracycline, a minimum of 4 synthetic steps and as many as 8 synthetic steps would be required.

5 In contrast, the novel method of the present invention allows the formation of the final product in only two synthetic steps. According to the novel method in Scheme III, the incorporation of the monosubstituted(C_1-C_6)amines or disubstituted(C_1-C_6)-amines onto the 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracyclines does not require the use of nitrogen protecting groups. Thus, this process allows use of structurally unique or chemically sensitive amines, e.g. amines which may decompose due to excessive acid. These precious amines could be utilized in the process with operational efficiency. Since many amines are volatile, their removal from the reaction mixture by vacuum distillation will minimize byproducts that can complicate the purification process. By inference, the amines could also be recovered for further use. Most important, a broader diversity of structural entities may be obtained with no more than 2 synthetic steps.

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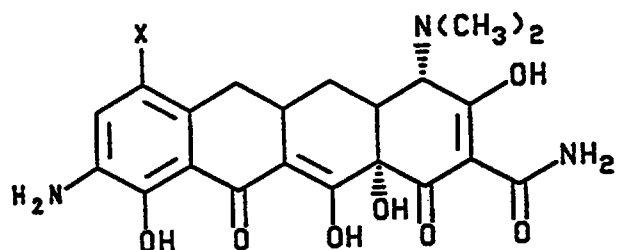
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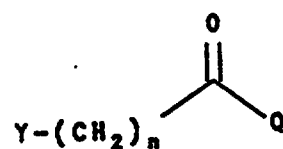
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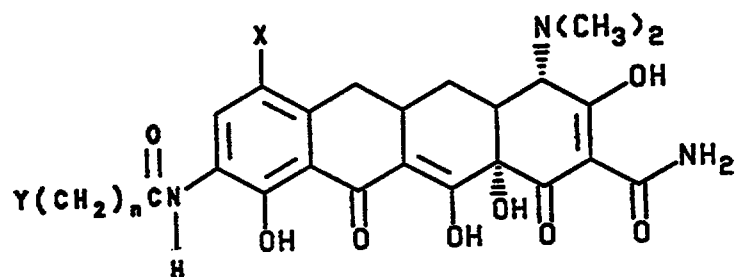
Scheme III



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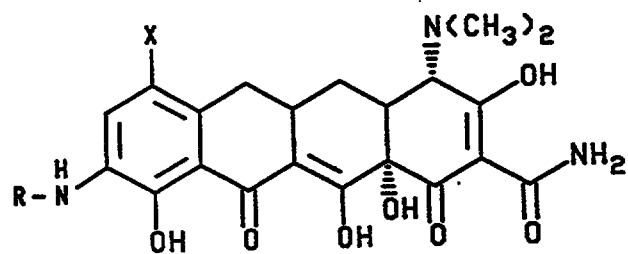


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R^4H



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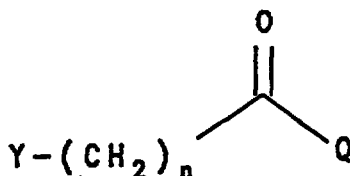
In accordance with the novel method of the present invention, Scheme III, the starting 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt, prepared by the procedure described in U.S. Patent Application, Serial No. 771,576, filed Oct. 4, 1991, is mixed with

a) a polar-aprotic solvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone hereinafter called DMPU, hexamethylphosphoramide hereinafter called HMPA, 1,3-dimethyl-2-imidazolidinone, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane or equivalent thereof;

b) an inert solvent, such as acetonitrile, methylene chloride, tetrahydrofuran, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methyl ether, isopropyl ether or equivalent thereof;

c) a base such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate or bicarbonate equivalents; and

d) a straight or branched haloacyl halide of the formula:



wherein Y, n and Q are as hereinabove defined; such as bromoacetyl bromide, chloroacetyl chloride or 2-bromopropionyl bromide; the halo and halogen in the haloacyl halide can be the same or different and are selected from chlorine, bromine, iodine and fluorine;

e) for 0.5 to 5 hours at from room temperature to the reflux temperature of the reaction;



to form the corresponding 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or their pharmacologically acceptable organic and inorganic salt.

To produce the 7-(substituted)-9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracycline or its pharmacologically acceptable organic and inorganic salts, 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or their pharmacologically acceptable organic and inorganic salts, is treated, under an atmosphere of argon, nitrogen or helium, with

a) a nucleophile R_4H , wherein R_4 is as defined hereinabove, such as an amine or substituted amine for example methylamine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;

b) in a polar-aprotic solvent such as DMPU, HMPA, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane, tetrahydrofuran, or a polar-protic solvent such as water, methanol or equivalents thereof;

c) for from 0.5 - 2 hours at room temperature or under reflux temperature to produce the desired 7-(substituted)-9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracycline, or their pharmacologically acceptable organic and inorganic salts.

In the event that inorganic and organic salt forms are desired, the 7-(substituted)-9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracyclines, may be obtained as inorganic and organic salts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferably, the 7-(substituted)-9-[(substituted glycyloxy)amido]-6-de-

5 methyl-6-deoxytetracyclines are obtained as inorganic
salt such as hydrochloric, hydrobromic, hydroiodic,
phosphoric, nitric or sulfate; or organic salt such as
10 acetate, benzoate, citrate, cysteine or other amino
acids, fumarate, glycolate, maleate, succinate,
tartrate, alkylsulfonate or arylsulfonate. Depending
on the stoichiometry of the acids used, the salt
formation occurs with the C(4)-dimethylamino group (1
15 equivalent of acid) or with both the C(4)-dimethylamino
group and the substituent at the R⁴ group (2 equivalent
of acid). The salts are preferred for oral and
parenteral administration.

15 Some of the compounds of the hereinbefore
described Scheme III have centers of asymmetry at the
carbon bearing the R⁴ substituent. The compounds may,
therefore, exist in at least two (2) stereoisomeric
forms. The present invention encompasses a method of
20 producing the racemic mixture of stereoisomers as well
as all stereoisomers of the compounds whether free from
other stereoisomers or admixed with stereoisomers in
any proportion of enantiomers. The absolute
configuration of any compound may be determined by
conventional X-ray crystallography. The stereochemistry
25 of the centers on the tetracycline unit (i.e. C-4,
C-4a, C-5a and C-12a) remain intact throughout the
reaction sequences.

This invention will be described in greater
detail with the following non limiting examples.

30 Example 1

(Succinyloxycarbonyl)methyl carbamic acid
tert-butyl ester

To a 5° C solution of 8.76 g of N-(tert-
35 butoxycarbonyl)glycine and 5.75 g of N-hydroxy-
succinimide in 100 ml of dioxane and 160 ml of
1,2-dimethoxyethane is added 10.3 g of dicyclohexyl-
carbodiimide. The mixture is kept at 0° C for 24
hours. The reaction mixture is filtered, washed with

dioxane and the filtrate concentrated in vacuo until a solid results. The solid is triturated with diethyl ether, collected and dried to give 12 g of the desired intermediate.

The above experimental is a literature procedure found in JACS, Vol 86, 1839(1939).

Example 2

[7S-(7 α ,10 α)]-2-[[[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester

A mixture of 0.850 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline, 0.680 g sodium acetate in 25 ml of tetrahydrofuran and 5 ml of water is stirred at 25° C for 5 minutes. The solution is treated with 0.359 g of product from Example 1, stirred for 2 hours and extracted with chloroform. The organic layer is concentrated in vacuo to give 0.50 g of the desired product.

MS(FAB): m/z 630 (M+H).

Example 3

[4S-(4 α ,12 α)]-9-[(Aminoacetyl)amino]-4,7-bis-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono(trifluoroacetate)

A solution of 0.030 g of product from Example 2 and 1.0 ml of trifluoroacetic acid is maintained at room temperature for 24 hours followed by concentrating in vacuo. The residue is triturated with methyl alcohol and the solid collected to give 0.024 g of the desired product.

MS(FAB): m/z 530 (M+H).

Example 4

Dimethylaminoacetyl chloride hydrochloride

A mixture of 15 g of N,N-dimethylglycine hydrochloride (pulverized and dried in a vacuum oven at 45-50° C for 24 hours) and 13.85 ml of thionyl chloride

is heated, very slowly, in a sand bath to 78° C and kept at this temperature for 1 1/2 hours. Toluene is added to the mixture and the excess liquid is removed by pipette. This step is repeated several times. The solid is then transferred to a Buchner funnel, washed with methylene chloride and dried under vacuum at 50° C for 24 hours to yield 14.2 g of the desired intermediate.

10

Example 5

[4S-(4 α ,12 α)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

15

To a mixture of 6.68 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate in 120 ml of DMPU and acetonitrile is added 6.57 g of sodium carbonate. The mixture is stirred for 5 minutes, followed by the addition of 2.83 g of product from Example 4. The reaction is stirred for 1 hour, filtered and the filtrate is added slowly to a mixture of methylene chloride/ diethyl ether (1200ml/400ml). The solid is collected, dissolved in 250 ml methyl alcohol and added slowly to 1600 ml of methylene chloride. The precipitate is collected, washed with diethyl ether and dried to give 5.75 g of the desired product.

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MS(FAB): m/z 558 (M+H).

Example 6

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[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

35

To a room temperature solution of 0.334 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 6 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, hereinafter called DMPU, and 2 ml of acetonitrile is added 0.318 g of sodium

carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.068 g of chloroacetyl chloride. The reaction is stirred for 30 minutes, filtered, and the filtrate added dropwise to 100 ml of diethyl ether, containing 1 ml of 1M hydrochloric acid in diethyl ether. The resulting solid is collected and dried to give 0.340 g of the desired intermediate. MS(FAB): m/z 549 (M+H).

Example 6A

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide (free base)

The title compound is prepared by the procedure of Example 6, using 0.51 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride, 50 ml of DMPU, 5 ml of acetonitrile, 0.668 g of sodium carbonate and 0.452 g of chloroacetyl chloride to give 0.52 g of the desired product as the free base.

¹H NMR(DMSO-d₆): δ 9.3(s,1H); 7.9(s,1H); 4.45(s,2H).

Example 7

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide

To a solution of 5.01 g of 9-amino-4,7-bis-(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 100 ml of DMPU and 25 ml of acetonitrile is added 5.0 g of sodium carbonate. The reaction is stirred, under argon, at room temperature for 5 minutes, followed by the addition of 3.03 g of bromoacetyl bromide. The stirring is continued for an additional hour. The solid is collected and the filtrate is added slowly to isopropyl alcohol/diethyl ether (200 ml/750ml). The yellow solid is collected,

washed with isopropanol and diethyl ether to give 5.77 g of the desired intermediate.

MS(FAB): 593 (M+H).

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Example 7A

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide (free base)

10

To 0.20 g of product from Example 7 in 3 ml of 1,3-dimethyl-2-imidazolidinone is added 0.30 g of sodium bicarbonate. The reaction is stirred at room temperature for 15 minutes and filtered. The filtrate is added to 15 ml of diethyl ether and the resulting precipitate is collected to give 0.150 g of the desired intermediate as the free base.

15

MS(FAB): m/z 593 (M+H).

Example 8

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

20

The title compound is prepared by the procedure of Example 6, using 0.668 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 6 ml of DMPU, 2 ml of acetonitrile, 0.636 g of sodium carbonate and 0.215 g of bromoacetyl chloride. Seven tenths of a gram of the desired intermediate is obtained.

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MS(FAB): m/z 593 (M+H).

Example 9

[4S-(4 α ,12 α)]-9-[(2-Bromo-1-oxopropyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide

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The title compound is prepared by the procedure of Example 6, using 1.00 g of 9-amino-4,7-

bis(dimethylamino)-6-demethyl-6-deoxytetracycline
disulfate, 1.0 g of sodium carbonate and 0.648 g of
2-bromopropionyl bromide to give 0.981 g of the desired
intermediate.

MS(FAB): m/z 607 (M+H).

Example 10

[4S-(4 α ,12 α)]-9-[(4-Bromo-1-oxobutyl)amino]-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide dihydrochloride

The title compound is prepared by the
procedure of Example 6, using 1.34 g of 9-amino-4,7-
bis(dimethylamino)-6-demethyl-6-deoxytetracycline
disulfate, 1.3 g of sodium carbonate, 24 ml of DMPU, 8
ml of acetonitrile and 0.389 g of 4-bromobutyryl
chloride to give 1.45 g of the desired product.

Example 11

[4S-(4 α ,12 α)]-4,7-Bis(dimethylamino)-9-[[dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide dihydrochloride

To a solution of 0.15 g of product from
Example 6 in 4 ml of DMPU is added 0.85 g of
dimethylamine (40% in water). The reaction is stirred
for 20 minutes followed by concentration in vacuo to
remove excess dimethylamine. The mixture is filtered
and the filtrate added, dropwise, to 70 ml of isopropyl
alcohol/diethyl ether (1:1). To this solution is added
1 ml of 1M hydrochloric acid/diethyl ether. The
resulting precipitate is collected, washed with
isopropyl alcohol and diethyl ether, and dried to give
0.11 g of the desired product.

MS(FAB): m/z 558 (M+H).

Example 12

[4S-(4 α ,12 α)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
5 [[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacene-
carboxamide dihydrochloride

A mixture of 0.1258 g of product from Example
7, 5 ml of 40% methylamine in water and 5 ml of methyl
alcohol, under Argon, is stirred at room temperature
10 for 30 minutes. The excess methylamine is removed in
vacuo and the residue diluted with a small volume of
methyl alcohol. The diluted reaction solution is added
dropwise to 100 ml of diethyl ether containing 1 ml of
1M hydrochloric acid in diethyl ether and 10 ml of
15 isopropyl alcohol. The resulting solid is collected
and dried to give 0.106 g of the desired product.

MS(FAB): m/z 544 (M+H).

Substantially following the methods described
in detail herein above in Example 12, the compounds of
20 this invention listed below in Examples 13-33 are
prepared.

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Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
13	[7S-(7alpha,10aalpha)]-N-[9-(Amino-carbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-morpholineacetamide dihydrochloride	7	Morpholine	0.5 hr.	600 (M+H)
14	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-9-[[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	Ethylamine (70% in water)	2 hr.	558 (M+H)
15	[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylamino)acetyl]amino]-4,7-bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	Cyclopropyl-amine	2 hr.	570 (M+H)
16	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-9-[[[(butylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	Butylamine	2 hr.	586 (M+H)
17	[4S-(4alpha,12aalpha)]-9-[[[(Diethylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	Diethylamine	2 hr.	586 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
18	[7S-(7alpha,10aalpha)]-N-[9-(Amino-carbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride	7	Pyrrolidine	0.5 hr.	584 (M+H)
19	[7S-(7alpha,10aalpha)]-N-[9-(Amino-carbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride	7	Piperidine	1 hr.	598 (M+H)
20	[7S-(7alpha,10aalpha)]-N-[9-(Amino-carbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-azetidineacetamide	7	Azetidine	0.5 hr.	570 (M+H)
21	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(propylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	7	Propylamine	0.75 hr.	572 (M+H)
22	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-9-[[[(hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	N-Hexylamine	2 hr.	614 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
23	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	9	Dimethylamine (40% in water)	2.5 hr.	572 (M+H)
24	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-(methylamino)-1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	9	Methylamine (40% in water)	2 hr.	558 (M+H)
25	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-alpha-methyl-1-pyrrolidineacetamide dihydrochloride	9	Pyrrolidine	1 hr.	598 (M+H)
26	[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	7	Amylamine	2 hr.	600 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS (FAB): m/z
27	[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	Isobutylamine	2 hr.	586 (M+H)
28	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-imidazole-1-acetamide dihydrochloride	7	Imidazole	1 hr.	581 (M+H)
29	[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-9-[[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate.	7	Dimethylamine	0.5 hr.	558 (M+H)
30	[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-9-[[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide	7	Dimethylamine	0.5 hr.	558 (M+H)

Example #	Name	Starting Material	Reactant	Rx Time	MS(FAB): m/z
		Prod. of Exp.			
31	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[[4-(dimethylamino)-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	10	Dimethylamine (40% in water)	2 hr.	586(M+H)
32	[4S-(4alpha,12aalpha)]-9-[[[Butylmethylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	7	N-Methylbutylamine	2 hr.	600(M+H)
33	[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	7	Benzylamine	1 hr.	620(M+H)

Example 34

[7S-(7 α ,10 α)]-N-[2-[[9-(Aminocarbonyl)-4,7-
bis(dimethylamino)-5,5a,6,7,10a,12-octahydro-1,8,
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyllamino]-
2-oxoethyl]glycine phenylmethyl ester

To 0.30 g of benzylglycine hydrochloride in 3 ml of 1,3-dimethyl-2-imidazolidinone is added 0.60 g of sodium bicarbonate. The mixture is stirred at room temperature for 15 minutes and filtered. To the filtrate is added 0.20 g of product from Example 7A. The reaction mixture is stirred at room temperature for 1 hour and then added to diethyl ether. The resulting solid is collected.

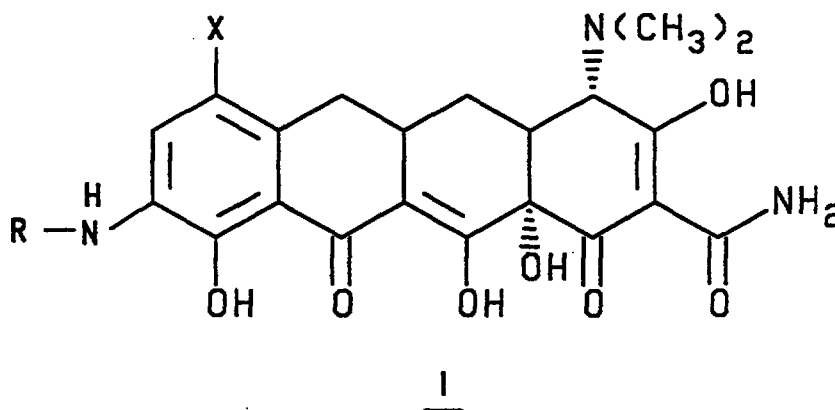
Example 43

[7S-(7 α ,10 α)]-N-[2-[[9-(Aminocarbonyl)-4,7-
bis(dimethylamino)-5,5a,6,7,10a,12-octahydro-1,8,
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyllamino]-
2-oxoethyl]glycine

One-tenth of a gram of product from Example 34 in 10 ml of 2-methoxyethane is reduced catalytically, in a Parr shaker, with 0.10 g of 10% palladium on carbon, at 30 psi of hydrogen, for 2 hours. The reaction mixture is filtered and the filtrate concentrated to give 0.050 g of the desired product. FAB-MS: m/z 588 (M+H).

We Claim:

1. A process for producing 7-(substituted)-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines of the formula:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,

$R^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylethyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-butyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylpropyl}$,

$R^2 = \text{2-methylpropyl}$;

R is selected from $R^4(\text{CH})_n\text{CO-}$, $n = 0-4$,

and when $n = 0$,

R^4 is selected from $\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group [selected from $\alpha\text{-aminomethyl}$, $\alpha\text{-aminoethyl}$, $\alpha\text{-aminopropyl}$,

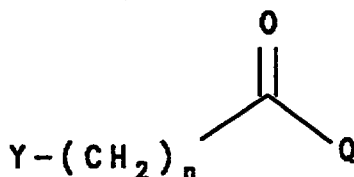


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α -aminobutyl and the enantiomers of said α -amino(C_1 - C_4)alkyl group]; α -aralkylamino group [selected from phenylglycyl and the enantiomers of said α -aralkylamino group];
and when $n = 1-4$,
 R^4 is selected from amino; monosubstituted amino group [selected from straight or branched (C_1 - C_6)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl and 1-methyl-2-ethylpropyl), cyclopropylamino, cyclobutylamino, benzylamino and phenylamino]; disubstituted amino group [selected from dimethylamino, diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)amino, monomethylbenzylamino, aziridinyl, azetidiny, pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl)]; carboxy(C_2 - C_4)alkylamino group [selected from aminoacetic acid, α -aminopropionic acid and the enantiomers of said carboxy(C_2 - C_4)alkylamino group]; which comprises

(a) mixing 9-amino-7-(substituted)-6-de-methyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt thereof with a polar-aprotic solvent, an inert solvent, a base and reacting with a straight or branched haloacyl halide of the formula:



wherein:

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-36-

Q is a halogen [selected from bromine, chlorine, fluorine or iodine];

and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group [selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl];

and when $n = 1-4$,

Y is a halogen [selected from bromine, chlorine, iodine and fluorine], O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate;

for 0.5 to 5 hours at from room temperature to the reflux temperature of the reaction and recovering

9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxy-tetracycline or the pharmacologically acceptable organic and inorganic salt thereof; and

(b) reacting the 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt thereof, in a polar-aprotic solvent, under an inert atmosphere of helium, nitrogen or argon, with a nucleophile having the formula, R^4H , wherein R^4 is hereinabove defined; for from 0.5 to 2 hours at from room temperature to the reflux temperature of the reaction and isolating the compound of formula I or the pharmacologically acceptable organic and inorganic salt thereof.

2. The process of Claim 1 wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,

and when $n = 0$,

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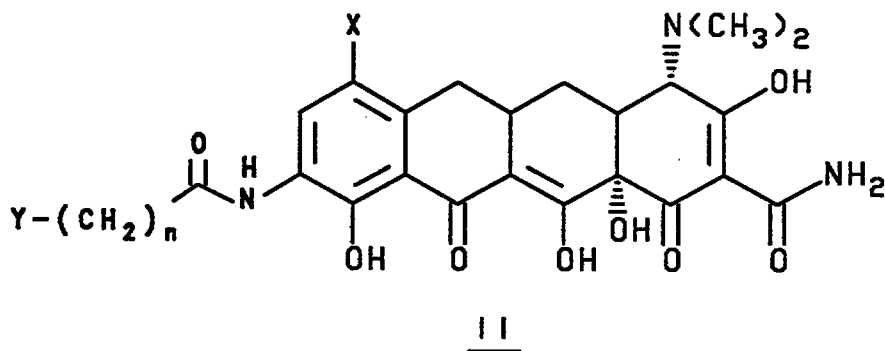


-37-

R^4 is selected from α -amino(C_1 - C_4)alkyl group [selected from α -aminomethyl, α -aminoethyl, and the enantiomers of said α -amino(C_1 - C_4)alkyl group]; and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group [selected from straight or branched (C_1 - C_6)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, n-pentyl and n-hexyl), cyclopropylamino and benzylamino]; disubstituted amino group [selected from dimethylamino, diethylamino, methyl(butyl)amino, azetidiny, pyrrolidinyl, piperidinyl, morpholinyl and 1-imidazolyl]; and the pharmacologically acceptable organic and inorganic salts.

3. The process for producing novel straight or branched 9-[(haloacyl)amido]-7-(substituted)-6-de-methyl-6-deoxytetracyclines of the formula:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

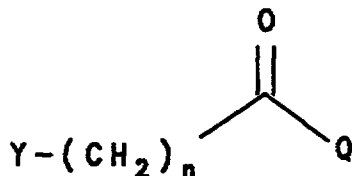


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-38-

and when R^1 = methyl or ethyl,
 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;
and when R^1 = n-propyl,
 R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl
or 2-methylpropyl;
and when R^1 = 1-methylethyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-butyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylpropyl,
 R^2 = 2-methylpropyl;
and when $n = 0$,
Y is straight or branched α -halo(C_1 - C_4)alkyl group [se-
lected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl];
and when $n = 1-4$,
Y is halogen [selected from bromine, chlorine, iodine
and fluorine], O-toluenesulfonate, O-methylsulfonate or
trifluoromethylsulfonate; which comprises

(a) mixing 9-amino-7-(substituted)-6-de-
methyl-6-deoxytetracycline or the pharmacologically
acceptable organic and inorganic salt thereof with a
polar-aprotic solvent, an inert solvent, a base and
reacting with a straight or branched haloacyl halide of
the formula:



wherein Y, n and Q are hereinabove defined;
for 0.5 to 5 hours at from room temperature to the re-
flux temperature of the reaction and isolating the com-
pound of formula II or the pharmacologically acceptable
organic and inorganic salt thereof.

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4. The process of Claim 3 wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group [selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl];

and when $n = 1-4$,

Y is halogen [selected from bromine, chlorine, iodine and fluorine], O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

5. The process of Claims 1 or 3 wherein said polar-aprotic solvent is selected from 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone, 1,3-dimethyl-2-imidazolidinone, hexamethylphosphoramide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane, tetrahydrofuran, water, methanol and equivalent thereof.

6. The process of Claims 1 or 3 wherein said inert solvent is selected from acetonitrile, methylene chloride, tetrahydrofuran, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methyl ether, isopropyl ether and equivalent thereof.

7. The process of Claims 1 or 3 wherein said base is selected from sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate and equivalent thereof.



REPLACEMENT SHEET

30 JUL 1999

-1-

Title: NOVEL METHOD OF PRODUCING 7-(SUBSTITUTED)-9-[(SUBSTITUTED GLYCYL)-AMINO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a novel method for producing [4S-(4alpha,12aalpha)]-4-(dimethylamino)-7-(substituted)-9-[[(substituted amino) substituted]-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, herein after called 7-(substituted)-9-[(substituted glycylo)-amino]-6-demethyl-6-deoxytetracyclines, which are useful as antibiotic agents.

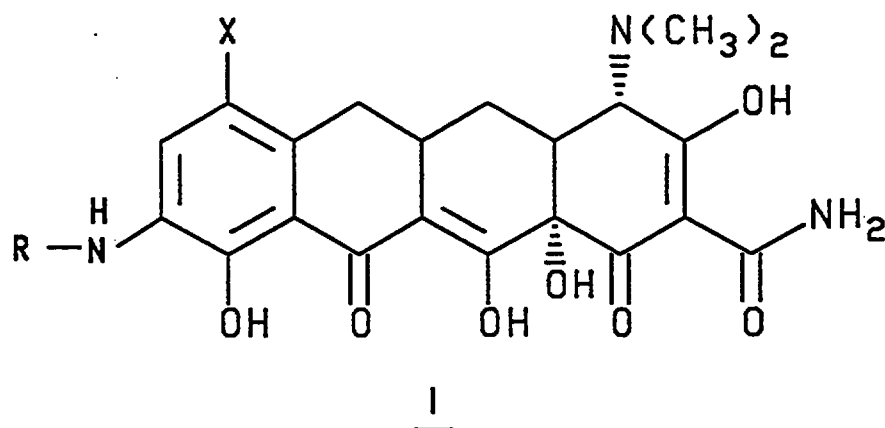
The invention also relates to making novel, straight or branched 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracycline intermediates, which are useful for making the novel compounds of the present invention.

SUMMARY OF THE INVENTION

This invention is concerned with a novel method for producing 7-(substituted)-9-[(substituted glycylo)amino]-6-demethyl-6-deoxytetracyclines, represented by formula I:

30 JUL 1999

-2-



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,

$R^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylethyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-butyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylpropyl}$,

$R^2 = \text{2-methylpropyl}$;

R is selected from $R^4(\text{CH})_n\text{CO-}$, $n = 0-4$,

and when $n = 0$,

R^4 is selected from $\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group selected from $\alpha\text{-aminomethyl}$, $\alpha\text{-aminoethyl}$, $\alpha\text{-aminobutyl}$, $\alpha\text{-amino-isobutyl}$ and the enantiomers of said

$\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group ; $\alpha\text{-aralkylamino}$ group

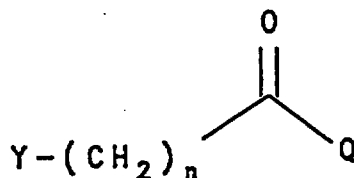
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-3-

selected from alpha-aminobenzyl and the enantiomers of
said α -aralkylamino group;

and when $n = 1-4$,

5 R^4 is selected from amino; monosubstituted amino group
selected from straight or branched (C_1-C_6)alkyl
(substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
1,1-dimethylethyl, n-pentyl, 2-methylbutyl,
10 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),
cyclopropylamino, cyclobutylamino, benzylamino and
15 phenylamino ; disubstituted amino group selected from
dimethylamino, diethylamino, methyl(butyl)amino,
ethyl(1-methylethyl)amino, monomethylbenzylamino,
aziridinyl, azetidiny, pyrrolidinyl,
2-methylpyrrolidinyl, piperidinyl, morpholinyl,
20 imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) and
4-(1,2,4-triazolyl) ; carboxy(C_2-C_4)alkylamino group
selected from aminoacetic acid, α -aminopropionic acid
and the enantiomers of said carboxy(C_2-C_4)alkylamino
group ; which method comprises reacting a haloacyl
25 halide compound of the formula:



wherein when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group
selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
35 α -chloro-isobutyl ;

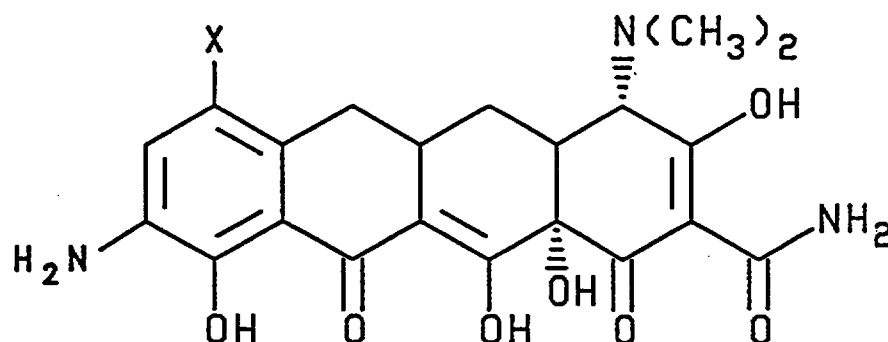
and when $n = 1-4$,

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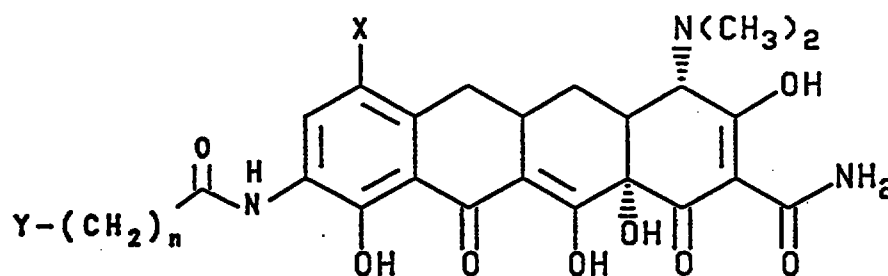
-4-

Y is halogen selected from bromine, chlorine, iodine and fluorine, O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate;

and Q is halogen [selected from bromine, chlorine, fluorine and iodine] with a 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline compound of the formula:



wherein X is as defined hereinabove or the pharmacologically acceptable organic and inorganic salts thereof to obtain a 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracycline intermediate of the formula:



wherein X, Y and n are as defined hereinabove or the organic or inorganic salts thereof and reacting the intermediate, 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts thereof, with a

30 JUL 1999

-5-

nucleophile of the formula R^4H , wherein R^4 is as defined hereinabove, to obtain a 7-(substituted)-9-[(substituted glycyloamino]-6-demethyl-6-deoxytetracycline compound according to formula I or the organic and inorganic salts thereof.

This novel method is an efficient way of preparing the 7-(substituted)-9-[(substituted glycyloamino]-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts. The novel method permits these compounds to be prepared in two reactions. The first reaction results in the formation of a common intermediate, 9-[(haloacyloamino]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salts thereof. The second reaction permits the common intermediate to be reacted with a wide variety of amines and results in a wide spectrum of 7-(substituted)-9-[(substituted glycyloamino]-6-demethyl-6-deoxytetracyclines or the pharmacologically acceptable organic and inorganic salts thereof. The use of difficult protecting groups is eliminated, thus allowing the final products to be formed in only two reactions.

Preferred is a method for producing compounds according to the above formula I wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;
and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl}$;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,

and when $n = 0$,

R^4 is selected from $\alpha\text{-amino}(C_1-C_4)\text{alkyl group}$
selected from $\alpha\text{-aminomethyl, } \alpha\text{-aminoethyl,}$

30 JUL 1999

-6-

α -aminopropyl, α -aminobutyl and the enantiomers of said α -amino(C_1 - C_4)alkyl group ; α -aralkylamino group selected from phenylglycyl and the enantiomers of said α -aralkylamino group ;

5 and when $n = 1-4$,
 R^4 is selected from amino; monosubstituted amino group selected from straight or branched (C_1 - C_6)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 10 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 15 1,3-dimethylbutyl and 1-methyl-2-ethylpropyl), cyclopropylamino, cyclobutylamino, benzylamino and phenylamino ; disubstituted amino group selected from dimethylamino, diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)amino, monomethylbenzylamino, 20 aziridinyl, azetidiny, pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl) ; carboxy(C_2 - C_4)alkylamino group selected from aminoacetic acid, α -aminopropionic acid and the enantiomers of said carboxy(C_2 - C_4)alkylamino group ; and the pharmacologically acceptable organic and inorganic salts.

25

Particularly preferred is a method for producing compounds according to formula I wherein:

30 X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;
and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
35 and when $R^1 =$ methyl or ethyl,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

30 JUL 1999

-7-

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,
and when $n = 0$,

R^4 is selected from α -amino(C_1-C_4)alkyl group

selected from α -aminomethyl, α -aminoethyl,
 α -aminopropyl, α -aminobutyl and the enantiomers of said
 α -amino(C_1-C_4)alkyl group ; α -aralkylamino group
selected from phenylglycyl and the enantiomers of said
 α -aralkylamino group ;

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group
selected from straight or branched (C_1-C_6)alkyl

(substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
1,1-dimethylethyl, n-pentyl, 2-methylbutyl,
1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),

cyclopropylamino, cyclobutylamino and benzylamino ;
disubstituted amino group selected from dimethylamino,
diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)-
amino, monomethylbenzylamino, aziridinyl, azetidiny,
pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl,
morpholinyl, imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazo-
lyl) and 4-(1,2,4-triazolyl) ; carboxy(C_2-C_4)alkylamino
group selected from aminoacetic acid, α -aminopropionic
acid and the enantiomers of said carboxy(C_2-C_4)alkyl-
amino group ; and the pharmacologically acceptable
organic and inorganic salts.

Most particularly preferred is a method for
producing compounds according to formula I wherein:
X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R^1 = methyl or ethyl,
 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;
5 R is selected from $R^4(CH)_nCO-$, $n = 0-4$,
and when $n = 0$,
 R^4 is selected from α -amino(C_1-C_4)alkyl group
selected from α -aminomethyl, α -aminoethyl,
 α -aminopropyl, α -aminobutyl and the enantiomers of said
.0 α -amino(C_1-C_4)alkyl group ;
and when $n = 1-4$,
 R^4 is selected from amino; monosubstituted amino group
selected from straight or branched (C_1-C_6)alkyl
(substitution selected from methyl, ethyl, n-propyl,
.5 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
1,1-dimethylethyl, n-pentyl, 2-methylbutyl,
1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
20 1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),
cyclopropylamino, cyclobutylamino and benzylamino ;
disubstituted amino group selected from dimethylamino,
diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)-
amino, monomethylbenzylamino, aziridinyl, azetidyl,
.25 pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl,
morpholinyl, imidazolyl and 1-pyrrolyl ;
carboxy(C_2-C_4)alkylamino group selected from
aminoacetic acid ; and the pharmacologically acceptable
organic and inorganic salts.

30 Of special interest is a method for producing
compounds according to formula I wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

35 and when $X = -NR^1R^2$ and when R^1 = methyl or ethyl,
 R^2 = methyl or ethyl;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,
and when $n = 0$,

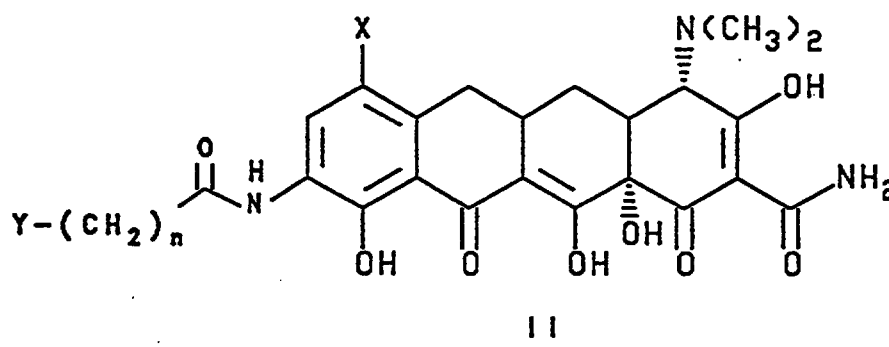
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-9-

R^4 is selected from α -amino(C_1 - C_4)alkyl group
selected from α -aminomethyl, α -aminoethyl, and the
enantiomers of said α -amino(C_1 - C_4)alkyl group ;
and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group
selected from straight or branched (C_1 - C_6)alkyl
(substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, n-pentyl and n-hexyl),
cyclopropylamino and benzylamino ; disubstituted amino
group selected from dimethylamino, diethylamino,
methyl(butyl)amino, azetidiny, pyrrolidinyl,
piperidinyl, morpholinyl and 1-imidazolyl ;
and the pharmacologically acceptable organic and
inorganic salts.

Also included in the present invention is a
method for making a novel straight or branched
9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxy-
tetracycline intermediate useful for producing the
above compounds of formula I. Such intermediate
includes those having the formula II:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

30 JUL 1999

-10-

and when R^1 = methyl or ethyl,
 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-propyl,
 R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl
 or 2-methylpropyl;

and when R^1 = 1-methylethyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-butyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylpropyl,
 R^2 = 2-methylpropyl;

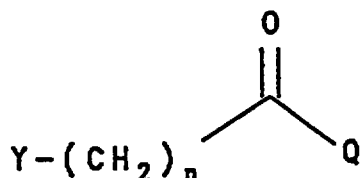
and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group
 selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine
 and fluorine , O-toluenesulfonate, O-methylsulfonate or
 trifluoromethylsulfonate; and the pharmacologically
 acceptable organic and inorganic salt.

The novel method for producing the
 intermediate compound of formula II comprises reacting
 a 9-amino-7-(substituted)-6-demethyl-6-deoxytetra-
 cycline with a compound of the formula:



wherein Y, n and Q are as defined hereinabove.

Preferred is a method for producing compounds
 according to the above formula II wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the
 halogen is selected from bromine, chlorine, fluorine
 and iodine;

30 JUL 1999

-11-

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when $R^1 =$ methyl or ethyl,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl;
and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group
selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine
and fluorine , O-toluenesulfonate, O-methylsulfonate or
trifluoromethylsulfonate; and the pharmacologically
acceptable organic and inorganic salt.

Particularly preferred is a method for
producing compounds according to formula II wherein:
X is selected from amino, $-NR^1R^2$, or halogen; the
halogen is selected from bromine, chlorine, fluorine
and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when $R^1 =$ methyl or ethyl,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group
selected from bromomethyl, chloromethyl, iodomethyl,
 α -bromoethyl, α -chloroethyl, α -bromobutyl and
 α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine
and fluorine , O-toluenesulfonate, O-methylsulfonate or
trifluoromethylsulfonate; and the pharmacologically
acceptable organic and inorganic salt.

30 JUL 1999

-12-

Most particularly preferred is a method for producing compounds according to formula II wherein: X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 =$ hydrogen, $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine and fluorine , O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

Of special interest is a method for producing compounds according to formula II wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine and fluorine , O-toluenesulfonate, O-methylsulfonate or

30 JUL 1999

-13-

trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 The novel method of the present invention, Scheme III, provides an easier way of preparing 7-(substituted)-9-[(substituted glycyloamino]-6-de-methyl-6-deoxytetracyclines or their pharmacologically acceptable organic and inorganic salts. This novel
10 method provides a way to prepare some of the 7-(substituted)- 9-[(substituted glycyloamino]-6-de-methyl-6-deoxytetracyclines or their pharmacologically acceptable organic and inorganic salts that would be
15 very difficult to prepare using either of the prior art methods shown in Scheme I or II.

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30 JUL 1999

-16-

5 The method shown in Scheme I is premised on a reductive N-alkylation of the 9-(glycylamino)-7-(substituted)-6-demethyl-6-deoxytetracycline. It is possible to use this method only when two identical substituents are incorporated on the nitrogen. It would be unworkable to incorporate sequentially two different substituents on the nitrogen because the reductive alkylation conditions are such that both
10 hydrogens are substituted at the same time. Thus, using the method of Scheme I, it would not be possible to incorporate a single substituent efficiently. In addition, the initial reaction of the (succinyloxycarbonyl)methyl carbamic acid tert-butyl ester with the
15 appropriate 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline affords only moderate yields.

The method shown in Scheme II is premised on forming an acid chloride from a mono- or disubstituted (C_1-C_6)amino substituted acyl acid and reacting the so
20 formed acid chloride with the amine at the 9-position of the 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline. Typically, the acid chloride is formed by the reaction of the appropriate mono- or disubstituted- (C_1-C_6)amine with either haloacetic acids (or esters)
25 or their synthetic equivalents, e.g., p-toluenesulfonyloxyacetic acid or methanesulfonyloxyacetic acid. In the case of N-(monosubstituted)amino acids, the method shown in Scheme II may be utilized only via the use of nitrogen protecting groups. However, the
30 protecting groups must survive the acyl chloride formation reactions, but also be readily removed from the final products without detriment to the appended tetracycline nucleus. The inclusion of protecting groups in this process incurs additional steps and is
35 operationally complex. By the method shown in Scheme II, for every new structural entity, e.g. 9-[(substituted glycyl)amino]-7-(substituted)-6-demethyl-6-deoxy-

30 JUL 1999

-20-

to form the corresponding 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracycline or their pharmacologically acceptable organic and inorganic salt.

To produce the 7-(substituted)-9-[(substituted glycylyl)amino]-6-demethyl-6-deoxytetracycline or its pharmacologically acceptable organic and inorganic salts, 9-[(haloacyl)amino]-7-(substituted)-6-demethyl-6-deoxytetracycline or their pharmacologically acceptable organic and inorganic salts, is treated, under an inert atmosphere of argon, nitrogen or helium, with

a) a nucleophile R_4H , wherein R_4 is as defined hereinabove, such as an amine or substituted amine for example methylamine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;

b) in a polar-aprotic solvent such as DMPU, HMPA, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane, tetrahydrofuran, or a polar-protic solvent such as water, methanol or equivalents thereof;

c) for from 0.5 - 2 hours at from room temperature to the reflux temperature of the reaction to produce the desired 7-(substituted)-9-[(substituted glycylyl)amino]-6-demethyl-6-deoxytetracycline, or their pharmacologically acceptable organic and inorganic salts.

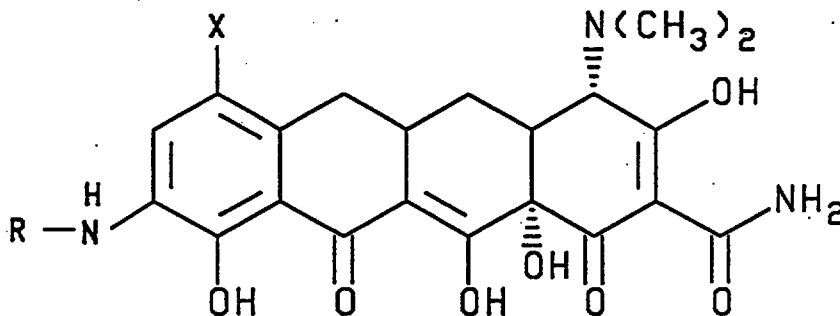
In the event that inorganic and organic salt forms are desired, the 7-(substituted)-9-[(substituted glycylyl)amino]-6-demethyl-6-deoxytetracyclines, may be obtained as inorganic and organic salts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferably, the 7-(substituted)-9-[(substituted glycylyl)amino]-6-de-



30 JUL 1999

We Claim:

1. A process for producing 7-(substituted)-9-[(substituted glycyloamino)]-6-demethyl-6-deoxytetracyclines of the formula:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,

$R^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylethyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-butyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylpropyl}$,

$R^2 = \text{2-methylpropyl}$;

R is selected from $R^4(\text{CH})_n\text{CO-}$, $n = 0-4$,

and when $n = 0$,

R^4 is selected from $\alpha\text{-amino}(\text{C}_1\text{-C}_4)\text{alkyl}$ group selected from $\alpha\text{-aminomethyl, } \alpha\text{-aminoethyl}$,



30 JUL 1999

-35-

α -aminobutyl, α -amino-isobutyl and the enantiomers of said α -amino (C_1 - C_4) alkyl group;

and when $n = 1-4$,

R^4 is selected from amino; monosubstituted amino group

selected from straight or branched (C_1 - C_6)alkyl (substitution selected from methyl, ethyl, n-propyl,

1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,

1,1-dimethylethyl, n-pentyl, 2-methylbutyl,

1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,

n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,

2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,

1,3-dimethylbutyl and 1-methyl-2-ethylpropyl),

cyclopropylamino, cyclobutylamino, benzylamino and

phenylamino ; disubstituted amino group selected from

dimethylamino, diethylamino, methyl(butyl)amino, ethyl(1-methylethyl)amino, monomethylbenzylamino,

aziridinyl, azetidiny, pyrrolidinyl, 2-methylpyrrolidinyl, piperidinyl, morpholinyl, imidazolyl,

1-pyrrolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl) ;

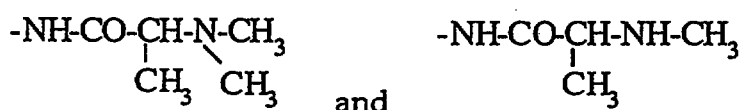
carboxy(C_2 - C_4)alkylamino group selected from

aminoacetic acid, α -aminopropionic acid and the

enantiomers of said carboxy(C_2 - C_4)alkylamino group ;

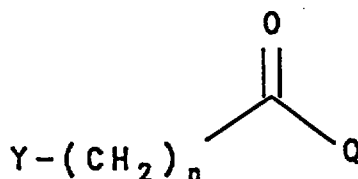
or when X is dimethylamino R is selected from:

or when X is dimethylamino R is selected from:



which comprises

(a) mixing 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt thereof with a polar-aprotic or polar-protic solvent, an inert solvent, a base and reacting with a straight or branched haloacyl halide of the formula:



wherein:



REPLACEMENT SHEET

30 JUL 1999

-36-

Q is a halogen [selected from bromine, chlorine, fluorine or iodine];

and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl ;

and when $n = 1-4$,

Y is a halogen selected from bromine, chlorine, iodine and fluorine , O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate;

for 0.5 to 5 hours at from room temperature to the reflux temperature of the reaction and recovering

9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxy-tetracycline or the pharmacologically acceptable organic and inorganic salt thereof; and

(b) reacting the 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt thereof, in a polar-aprotic solvent, under an inert atmosphere of helium, nitrogen or argon, with a nucleophile having the formula, R^4H , wherein R^4 is hereinabove defined; for from 0.5 to 2 hours at from room temperature to the reflux temperature of the reaction and isolating the compound of formula I or the pharmacologically acceptable organic and inorganic salt thereof.

2. The process of Claim 1 wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

R is selected from $R^4(CH)_nCO-$, $n = 0-4$,

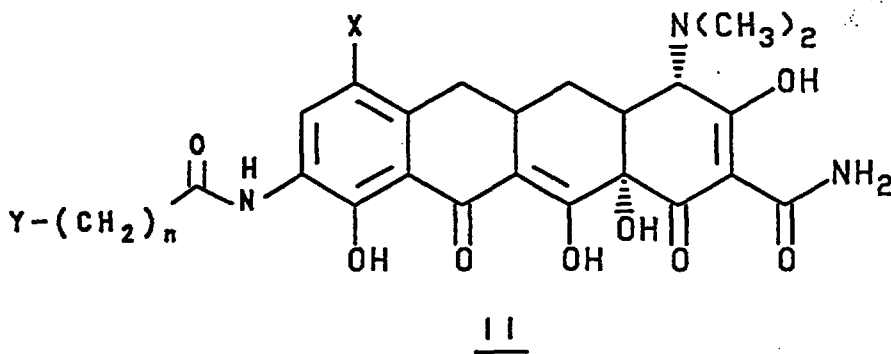
and when $n = 0$,



R^4 is selected from α -amino(C_1 - C_4)alkyl group selected from α -aminomethyl, α -aminoethyl, and the enantiomers of said α -amino(C_1 - C_4)alkyl group ; and when $n = 1-4$,

R⁴ is selected from amino; monosubstituted amino group selected from straight or branched (C₁-C₆)alkyl (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, n-pentyl and n-hexyl), cyclopropylamino and benzylamino ; disubstituted amino group selected from dimethylamino, diethylamino, methyl(butyl)amino, azetidiny, pyrrolidinyl, piperidinyl, morpholinyl and 1-imidazolyl ; and the pharmacologically acceptable organic and inorganic salts.

3. The process for producing novel straight or branched 9-[(haloacyl)amino]-7-(substituted)-6-de-methyl-6-deoxytetracyclines of the formula:



wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;



30 JUL 1999

-38-

and when R^1 = methyl or ethyl,
 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

and when R^1 = n-propyl,
 R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl
or 2-methylpropyl;

and when R^1 = 1-methylethyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-butyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylpropyl,
 R^2 = 2-methylpropyl;

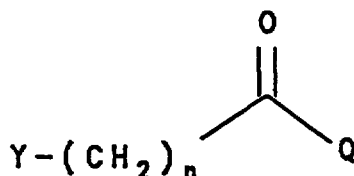
and when $n = 0$,

Y is straight or branched α -halo(C_1 - C_4)alkyl group selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl ;

and when $n = 1-4$,

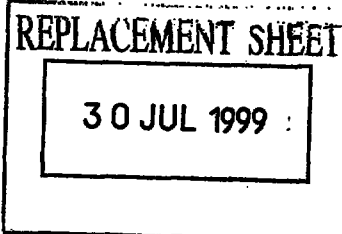
Y is halogen selected from bromine, chlorine, iodine and fluorine , O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate; which comprises

(a) mixing 9-amino-7-(substituted)-6-de-methyl-6-deoxytetracycline or the pharmacologically acceptable organic and inorganic salt thereof with a polar-aprotic or polar-protic solvent, an inert solvent, a base and reacting with a straight or branched haloacyl halide of the formula:



wherein Y, n and Q are hereinabove defined;

for 0.5 to 5 hours at from room temperature to the reflux temperature of the reaction and isolating the compound of formula II or the pharmacologically acceptable organic and inorganic salt thereof.



4. The process of Claim 3 wherein:

X is selected from amino, $-NR^1R^2$, or halogen; the halogen is selected from bromine, chlorine, fluorine and iodine;

and when $X = -NR^1R^2$ and when $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl;

and when $n = 0$,

Y is straight or branched α -halo(C_1-C_4)alkyl group selected from bromomethyl, chloromethyl, iodomethyl, α -bromoethyl, α -chloroethyl, α -bromobutyl and α -chloro-isobutyl ;

and when $n = 1-4$,

Y is halogen selected from bromine, chlorine, iodine and fluorine , O-toluenesulfonate, O-methylsulfonate or trifluoromethylsulfonate; and the pharmacologically acceptable organic and inorganic salt.

5. The process of Claims 1 or 3 wherein said solvent is selected from 1,3-dimethyl-

3,4,5,6-tetrahydro-2(1H)-pyrimidone, 1,3-dimethyl-2-imidazolidinone, hexamethylphosphoramide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane, tetrahydrofuran, water and methanol.

6. The process of Claims 1 or 3 wherein said

inert solvent is selected from acetonitrile, methylene chloride, tetrahydrofuran, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methyl ether and isopropyl ether.

7. The process of Claims 1 or 3 wherein said

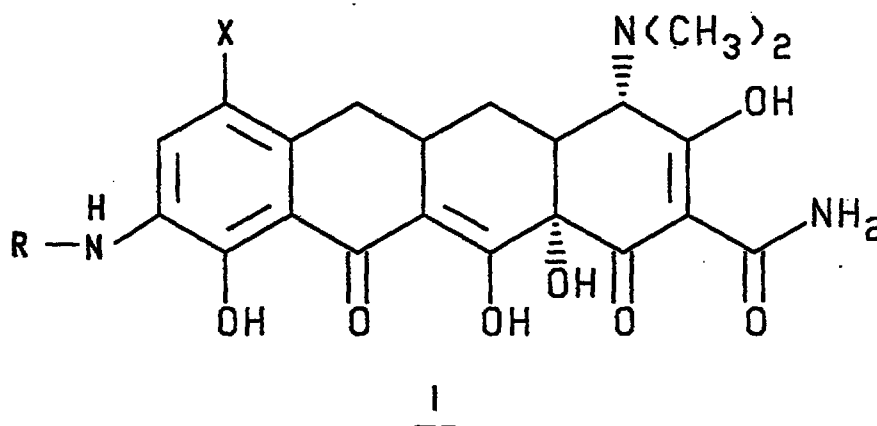
base is selected from sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate and lithium carbonate.

31,928

NOVEL METHOD OF PRODUCING 7-(SUB-
STITUTED)-9-[(SUBSTITUTED GLYCYL)-
AMIDO]-6-DEMETHYL-6-DEOXYTETRA-
CYCLINES

ABSTRACT OF THE INVENTION

The invention provides a novel method for producing compounds of the formula I:



wherein X and R are defined in the specifications. The invention also provides a method for making intermediates useful to produce the compounds of formula I. Utilizing a common intermediate, the novel method efficiently produces compounds of the formula I.