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COMPLETE SPECIFICATION

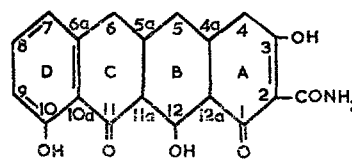
11 α -Halo-Tetracycline-6,12 Hemiketals

We, PFIZER CORPORATION, a corporation of the Republic of Panama of Calle 15½ Avenida Santa Isabel, Colon, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

HALOGEN COMPOUNDS

This invention relates to new tetracycline compounds and processes for the preparation thereof. More particularly, the present invention relates to 11 α -halo-tetracycline-6,12-hemiketals and to processes for the preparation thereof.

The tetracycline antibiotics comprise a group of biologically active perhydronaphthacene derivatives having the following essential structural features. The numbering system indicated is that employed by "Chemical Abstracts".



Among the biologically active members of this group are those containing the following substituent groups:

Substituents
 4-N(CH₃)₂,6-OH,6-CH₃,12a-OH
 4-N(CH₃)₂,5-OH,6-CH₃,12a-OH
 4-N(CH₃)₂,6-OH,6-CH₃,7-Cl,12a-OH
 4-N(CH₃)₂,5-OH,6-CH₃,12a-OH
 4-N(CH₃)₂,6-CH₃,12a-OH
 4-N(CH₃)₂,12a-OH
 4-N(CH₃)₂,6-OH,6-CH₃,7-Br,12a-OH
 4-N(CH₃)₂,6-OH,7-Cl,12a-OH
 4-N(CH₃)₂,6-OH,12a-OH

Common Name
 tetracycline
 5-oxytetracycline
 7-chlorotetracycline
 6-deoxy-5-oxytetracycline
 6-deoxytetracycline
 6-deoxy-6-demethyltetracycline
 7-bromotetracycline
 6-demethyl-7-chlorotetracycline
 6-demethyltetracycline

The new tetracycline compounds of this invention and processes for their preparation are illustrated by the following sequence of reactions and structural formulae, wherein III is a product available from the compounds of the invention, and is the subject matter of our patent application no. 36489/63 (Serial 995,033).

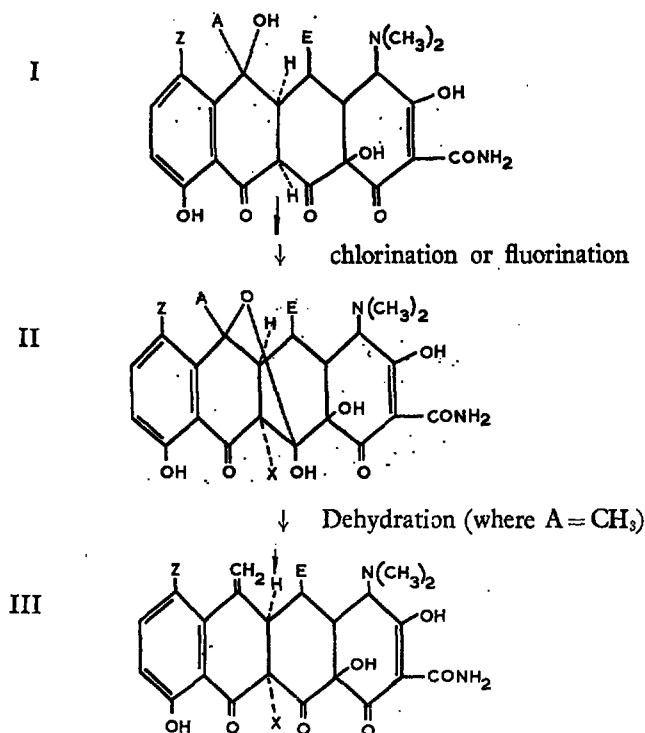
[Price 4s. 6d.]

wherein:

X is CF or F

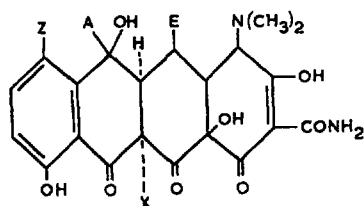
A is CH₃ or H;Z is Cl, Br or H but when X is F and A is CH₃, Z is H;E is H or OH, provided that when E is OH, A is CH₃ and Z is H.

45



11-a-Halogenation

- 5 The new 11a-fluoro or chloro tetracyclines (II) of this invention are prepared by reaction of a suitable tetracycline (I) with an appropriate halogenating agent in a reaction-inert solvent. As is obvious from the structural
- 10 formula, the chlorine or fluorine atom (X) at the 11a-position of the present new compounds exists in both the *cis* and *trans* relationship to the hydrogen at the 5a-position of the tetracycline nucleus. Those compounds in which
- 15 the halogen is *cis* are believed to exist predominately in the structure designated, i.e. the structure containing an oxygen bridge between the 6 and 12 positions of the tetracycline nucleus, resulting from the formation
- 20 of a hemi-ketal between the 12-position carbonyl function and the hydroxy group at the 6-position. In the crystalline state, these compounds appear to be predominately in the form of hemi-ketal structure as is evidenced by
- 25 the lack of carbonyl absorption on infrared analysis (no bands in the 5—6 micron region). Of course, such structures exist in equilibrium with the non-ketalized form:



- 30 particularly in solution and when reference is made herein to the hemi-ketal compounds, it

is fully intended that this designation embraces *cis* 11a-halo non-ketalized compounds as well as the hemi-ketal. The present new epoxy compounds are 11a - halo - 1,4,4a,5,5a,6,11, 11a,12,12a - decahydro - 3,10,12,12a - tetrahydroxy - 1,11 - dioxo - 2 - carboxamido-naphthacene - 6,12 - epoxides. For the sake of simplicity, the present new halo compounds hereinafter will be referred to as tetracycline-6,12-hemi-ketals.

The chlorination is accomplished by reaction of a suitable tetracycline (I) with a chlorinating agent in a reaction-inert solvent. Suitable tetracycline starting compounds include tetracycline, oxytetracycline, chlortetracycline, 6-demethyltetracycline and 6-demethylchlortetracycline. The tetracycline starting compound, of course, should have a 6-hydroxy substituent in order to form the hemi-ketal structure. For the production of the present new 11a-chlorotetracyclines a variety of chlorinating reagents may be employed in a reaction-inert solvent. Suitable chlorinating agents include chlorine; iodochloride; N-chloro, lower alkanolic acid amides wherein lower means having from 1 to 5 carbon atoms e.g. N-chloroacetamide, N-chlorinated hydrocarbon dicarboxylic acid imides, e.g. N-chlorosuccinimide, and phthalimide, and N-chlorinated (as hereinbefore defined) lower-alkanoyl anilides e.g. N-chloroacetanilide and propionanilide; 3-chloro-, and 3,5-dichloro 5,5-dimethylhydantoin; and pyridinium perchloride hydrohalide; and lower as hereinbefore defined alkyl hypochlorites, e.g. tertiary butylhypochlorite. It is obvious that, in general, any chlorinating agent commonly employed in the art is oper-

able, but the above are preferred. In general, it is preferred to use from 1 to 1.2 mols of chlorinating agent per mol of tetracycline starting compound.

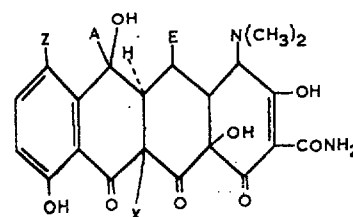
5 By "reaction-inert solvent" as employed herein is meant a solvent which, under the conditions of the reaction, does not react in an undesired manner with either starting compounds or final products. A minimum of
10 laboratory experimentation will permit the selection of suitable solvents for the present process. Exemplary of such solvents are dioxane, tetrahydrofuran, methyl ether of diethylene glycol (diglyme), and the methyl
15 ether of ethylene glycol (monoglyme). Temperature does not appear to be critical in this process, temperatures of from 0° to 50° C. being found suitable. Temperatures above 50°
20 C. should preferably be avoided due to the possible formation of 5a,6-anhydro compounds which reduces the efficiency of the process. The selection of the best reaction conditions, e.g. temperature, solvent and chlorinating agent, is a matter of routine experimentation. It is preferable to choose a solvent system from which
25 the 11a-chloro product crystallizes on formation. It is usually preferable to prepare the chloro hemi-ketal compounds in a water-miscible solvent, such as tetrahydrofuran, dioxane, acetone, di-lower alkyl ethers of ethyleneglycol, wherein lower means having from
30 one to five carbon atom or propyleneglycol. The product is obtained by mere dilution of the reaction mixture with water, which precipitates the 11a-chlorotetracycline-6,12-hemi-ketal.

35 The 11a-chloro compounds are quite stable in aqueous solutions, even at low pH values. For example, 11a-chlorotetracycline-6,12-hemi-ketal hydrochloride on standing in water, at
40 pH of about 1 for 18 hours at room temperature shows no detectable decomposition.

The preparation of 11a-fluorotetracyclines is accomplished by contacting the starting tetracycline compound with perchloryl fluoride in the presence of a strong base, preferably an alkali metal hydroxide or alkoxide. The reaction is usually carried out by dissolving the starting compound in the selected solvent, preferably a alkanol i.e. one containing up to 5
50 carbon atoms, containing at least a molar equivalent of the base and adding perchloryl fluoride, a gas at room temperature. As the reaction proceeds, the pH of the solution drops from alkaline to near neutral values, the product usually commencing to separate at a pH of approximately 8. The crystalline product is collected in the usual fashion and dried.

55 In addition to the 11a-halotetracycline-6, 12-hemi-ketals, the present process also yields 11a-halotetracyclines, i.e., those in which hemi-ketal formation has not occurred, in which it is presumed that the 11a-halo atom is on the reverse side of the 11a-carbon atom from the
60 halogen of the hemi-ketals. It is thought that

the stereochemical relationship of the former prevents formation of the hemi-ketal structure. These compounds are generally obtained by evaporation of the reaction mixture after precipitation of the 6,12-hemi-ketal compounds. The trans 11a-halo compounds are represented by the following formula, wherein Z, A, E and X are as previously defined:



75 The present new 11a-halo compounds of structure II are useful for the preparation of corresponding D-ring substituted tetracyclines by aromatic substitution reactions to give compounds substituted in the 7 and/or 9-positions. Exemplary of such aromatic substitution reactions are halogenation and nitration.

80 This halogenation is brought about by contacting the starting 11a-halo compound with a halogenating (chlorinating, brominating or iodinating) agent in a reaction inert solvent as previously described with respect to synthesis of the 11a-chloro compounds.

85 The halogenated product obtained by this method is determined by the molar ratio of halogenating agent employed. With a substantially equimolar ratio of halogenating agent per mol of 11a-halo compound, monohalogenation occurs. With 2 or more molar equivalents of halogenating agent, dihalogenation occurs.

90 After the halogenation reaction is completed, the products are obtained by the usual methods. Generally, the method employed involves the addition of a non-solvent to the reaction mixture with subsequent collection of the precipitated product.

100 Nitration is accomplished by any of the standard methods used for this purpose. For example, the starting compound is reacted with nitric acid *per se* or formed *in situ*, e.g. potassium nitrate and sulfuric acid. For best results the nitration reaction is carried out in a solvent, such as a lower alkanic acid, wherein lower means having one to five carbon atoms, e.g. acetic acid, although a variety of other solvents may also be used. The preferred
105 solvent is liquid hydrogen fluoride. A minimum of laboratory experimentation will permit the selection of other suitable solvents. While reaction condition may vary appreciably, the use of high temperatures should be avoided.
115 Satisfactory results are obtained over the range of from -25° to 50° C. with room temperature preferred as most convenient. Reaction time is not particularly critical, particularly in view of the stability of the starting compounds to the acid reaction conditions. To in-
120

sure best yields it is preferred to use reaction periods of from as little as 15 minutes to 12 hours.

Further, the present new 11a-halotetracycline 6,12-hemiketals are also useful as starting compounds in coupling reactions with diazonium salts. The coupling reaction with aryldiazonium salts is accomplished according to known methods. For example, the 11a-halotetracycline 6,12-hemiketals is dissolved in water or in a water soluble alcohol or ketone such as acetone to which is added an aqueous solution containing one to three molar equivalents of the selected aryldiazonium salt. The temperature of the mixture is maintained at 0—10° C. The coupling product usually commences to precipitate from the reaction mixture after about 15 minutes, but reaction times of the order of two hours are ordinarily employed to ensure complete reaction. The product usually separates as an amorphous material which is collected, washed and dried. If precipitation does not occur, the product may be obtained by evaporation of the solvent or by extraction of the reaction mixture with such solvents as n-butanol, or methyl isobutyl ketone. The azo products as obtained are generally suited for further chemical transformation or may be further purified by reprecipitation or crystallization from solvents, chromatography, or solvent extraction techniques.

The aryl diazonium salts which provide coupling products of the present type are myriad. The products obtained are 7- and/or 9-arylaazo-11a-halotetracycline - 6,12 - hemiketals. When Z in the starting compound is chloro or bromo, the product is a 9-arylaazo compound; when Z is hydrogen, the product is a mixture of the 7 and 9-isomers.

The aromatic azo coupling products as well as the corresponding nitro compounds produced in accordance with the foregoing description are particularly useful for the production of the corresponding aminotetracyclines. The azo compounds are reduced by electrolytic or chemical methods, but preferably by catalytic hydrogenolysis.

If desired, the 11a-halogen atom of the ring D - substituted - 11a - halotetracycline 6,12-hemiketals obtained from Structure II compounds may be selectively removed by reduction, preferably using chemical means. The 11a-chloro atoms may be readily removed by treatment with sodium hydro-sulfite in aqueous media. This latter reduction, is a particularly facile process and is especially preferred with 11a-chloro compounds containing other reducible groups. Accordingly, 7,11a - dichlorotetracycline - 6,12 - hemi - ketal is reduced to 7 - chlorotetracycline by treatment with sodium hydrosulfite in aqueous dimethylformamide. The 11-a fluoro compounds appear to be more difficult to reduce selectively since they require more vigorous reaction conditions.

For example, the present 11a-fluorotetracycline 6,12 - hemiketals are converted to corresponding 11a - desfluoro compounds by reaction with zinc in mineral acid according to standard practice. The 11a-fluorine may also be removed by hydrogenolysis over noble metal catalysts, preferably at superatmospheric pressures of hydrogen gas, e.g. up to about 1000 atmospheres. The use of temperatures higher than room temperature (20—25° C.) may also be required in some cases to permit substantial yield of the desired product. Under such conditions of hydrogenolysis, other reducible groups, e.g. the 6-hydroxy group and 7 or 9-halogen or 7 or 9 nitro groups, will also be susceptible to reduction. For example, 7-nitro-11a - fluorotetracycline - 6,12 - hemi - ketal on treatment with hydrogen gas over palladium on carbon at a pressure of 1500 psi yields *inter alia*, 7-amino-6-deoxytetracycline as a product.

The present new 11a - halotetracycline 6,12-hemiketals are also useful as intermediates for the synthesis of 6-deoxytetracyclines. On treatment with hydrogen gas in the presence of a mineral acid over a noble metal catalyst, both the 11a-halogen and the 6-hydroxy group are hydrogenolyzed. For this purpose, pressures of hydrogen gas from atmospheric to superatmospheric pressures may be used, although it is usually preferred to employ high pressures, particularly with 11a - fluoro - compounds which are found to be less susceptible to hydrogenolysis and are preferably hydrogenolyzed at elevated temperatures, e.g. up to 100° C. Except in the case of 11a-fluoro compounds, temperatures does not appear to be critical in this reaction, the use of high temperatures (up to 50° C.) mainly serving to shorten reaction time. The new 11a - halotetracycline - 6,12-hemiketals appear to be of only slight biological activity when tested *in vitro* against test organisms such as *klebsiella pneumoniae*.

Employing the procedures hereinbefore described, the present new 11a-halo compounds of structure II may be converted to the following products:

7 - bromo - 11a - chlorotetracycline - 6,12-hemi-ketal

7 and 9 - nitro - 11a - chlorotetracycline-6,12 - hemi - ketal

7 - iodo - 11a - chlorotetracycline - 6,12-hemi-ketal

7 - chloro - 6 - demethyltetracycline

7,11a - dichlorotetracycline - 6,12 - hemi-ketal

7 - fluoro - 6 - demethyltetracycline and corresponding non-ketalized compounds where applicable. The 11a-halogen atoms may be removed by the methods described in parent application 16158/61.

Of particular value are the 11a-halo hemiketals of Structure II in which substituent A is a methyl group and X is chlorine or fluorine. These compounds are converted to substances of a surprisingly high *in vivo* biological

activity against disease causing microorganisms which makes them valuable for use in human therapy as described in parent application 16158/61 (Serial 995,031). These compounds on *in vitro* testing show only moderate albeit significant activity. The conversion is accomplished by treating the starting compound (II) with a strong acid of the dehydrating type. Although a number of such acids may be used for this purpose, it is preferred to use mineral acids, such as concentrated sulfuric acid, phosphoric acid, polyphosphoric acid, perchloric acid, as well as other dehydrating acids, such as glacial acetic acid (containing boron trifluoride), hydrogen fluoride (preferably in liquid form), and trihalo acetic acids, e.g. trifluoroacetic acid.

It is specifically intended to include within the purview of this invention the acid addition salts of the present new amphoteric tetracyclines.

The following examples are given by way of illustration of the preparation of the products of this invention.

EXAMPLE I

11a-Fluorotetracycline-6,12-hemi-ketal

To a suspension of 20 g. of tetracycline base in 800 ml. of water cooled to 0° C. is added 45 ml. (2 equivalents) of 2N Sodium hydroxide solution. The tetracycline dissolves to yield a solution, the pH being approximately 11. Perchloryl fluoride is then bubbled through the stirred solution (maintained under a nitrogen atmosphere) until the pH of the mixture approximates 7. A heavy precipitate starts to form between pH 8 and 8.5. The excess perchloryl fluoride is flushed out with a stream of nitrogen and the nearly white crystalline material is filtered off, washed with water and dried under vacuum at room temperature to obtain 7.9—8.5 g. of product. Ultraviolet absorption shows maxima at 267 and 340 m μ ; infrared shows no carbonyl absorption below 6 microns. Bioassay against *K. pneumoniae* shows an activity of 8 mcg./mg. on the tetracycline scale. Elemental analysis gives the following results:

Calcd. for: $C_{22}H_{23}N_2O_8F \cdot H_2O$: C, 54.95; H, 5.20, N, 5.83
Found: C, 54.97, H, 5.19, N, 5.85.

EXAMPLE II

11a-Fluoro-5-hydroxytetracycline-6,12-hemi-ketal

To a mixture of 6.9 g. of anhydrous oxytetracycline base dissolved in 285 ml. of methanol cooled in an ice bath is added 1 equivalent of 1N sodium methoxide-methanol solution. The yellow sodium salt precipitates. Perchloryl fluoride is bubbled in and the sodium salt redissolves. As the mixture nears neutrality a heavy precipitate starts to form. The excess perchloryl fluoride is swept out

with a stream of nitrogen, the product filtered off, washed with cold methanol and dried under vacuum at room temperature to obtain 5.1 g. of pale yellow crystals. Infrared absorption shows no carbonyl absorption below 6 microns. Bioassay against *K. pneumoniae* shows an activity of 4 mcg./mg. on the tetracycline scale. Ultraviolet absorption shows maxima at 265 and 336 m μ . Elemental analysis gives the following results after recrystallization of the product from water.

Calcd. for: $C_{22}H_{23}O_9N_2F \cdot 2H_2O$: C, 51.4; H, 5.25; N, 5.5
Found: C, 51.2; H, 5.3; N, 5.7.

EXAMPLE III

11a-Chlorotetracycline-6,12-hemi-ketal

To a solution of 2.2 g. of anhydrous tetracycline in 25 ml. of monoglyme (dimethyl ether of ethylene glycol) is added 800 mg. of N-chlorosuccinimide with stirring to dissolve the reagent. The mixture is allowed to stand for seven minutes and then diluted with water (25 ml.). The product, 873 mg., crystallizes as white needles. Bioassay of the product shows a tetracycline activity of about 4 mcg./mg. against *K. pneumoniae*. Infrared analysis shows no carbonyl bands between 5 and 6 microns. Ultraviolet absorption shows maxima at 267 and 340—342 m μ .

On treatment of this product with sodium hydrosulfite in aqueous dimethylformamide at room temperature, tetracycline is regenerated. Bioassay of the reaction mixture shows a tetra-

cycline activity of 520—665 mcg./mg. (*K. pneumoniae*).

The crystalline hydrochloride of this product is obtained by dissolving it in excess aqueous HCl (pH ca. 1) and freeze drying the mixture.

EXAMPLE IV

7,11a - Dichlorotetracycline - 6,12-hemi-ketal

A mixture of 2.4 g. of anhydrous 7-chlorotetracycline, 800 mg. of N-chlorosuccinimide, and 25 ml. of 1,2 - dimethoxyethane is stirred for 2½ minutes, after which 100 ml. of ether is added, followed by 300 ml. of hexane. The precipitate thus formed is collected by filtration, washed with hexane and dried.

In similar fashion, 7-bromo-11a-chlorotetracycline-6,12-hemi-ketal is prepared from 7-bromotetracycline.

EXAMPLE V

11a-Chloro-5-hydroxytetracycline-6,12-hemi-ketal

- Twenty-three grams of anhydrous oxytetracycline is dissolved in 250 ml. of 1,2-dimethoxyethane and 8 g. of N-chlorosuccinimide is next added. The mixture is stirred for two minutes and then poured into 1 liter of stirred water. The product which separates is collected by filtration, water-washed and dried. Infrared analysis of the product (KBr at 1% concentration) shows no carbonyl absorption in the 5—6 micro region but shows the following principal peaks: 6.12, 6.35, 6.66, 6.85, 7.22, 7.55, 7.75, 7.92, 8.14, 8.36, 8.78, 9.18 and 9.43 microns. Bioassay of the product shows a tetracycline activity of 4 mcg./mg.

EXAMPLE VI

Acid salts of 11a-halotetracycline-6,12-hemi-ketals

- The hydrochloride salts of the above-described 11a-halo compounds are prepared by dissolving the free base in water containing an equimolar amount of hydrogen chloride and freeze-drying the resulting solution. In similar fashion, salts are formed with sulfuric, hydrobromic and phosphoric acids.

WHAT WE CLAIM IS:—

1. A compound of structure II as set forth in the specification hereof.
2. 11a - Chlorotetracycline - 6,12-hemiketal.
3. 11a - Chloro - 5 - hydroxytetracycline-6,12-hemiketal.
4. 11a - Fluorotetracycline - 6,12 - hemiketal.
5. 11a - Fluoro - 5 - hydroxytetracycline-6,12 - hemiketal.
6. 7,11a - Dichlorotetracycline - 6,12-hemiketal.
7. Salts of the compounds of any of claims 1—6 with acids.
8. A process for the preparation of an 11a-halo - tetracycline - 6,12 - hemiketal of structure II herein which includes the step of contacting a tetracycline compound of structure I herein with an appropriate halogenating agent in a reaction-inert solvent.
9. A process according to claim 8 wherein the halogenating agent is chlorine; iodochloride; an N-chloro lower alkanolic acid amide, -hydrocarbon dicarboxylic acid imide, or -lower-alkanoyl anilide; 3-chloro- or 3,5-dichloro - 5,5 - dimethyl - hydantoin; a pyridinium perchloride hydrohalide; a lower alkyl hypochlorite; or perchloryl fluoride; the

expression "lower" having the significance hereinbefore defined.

10. A process according to claim 8 or 9, wherein the halogenating agent is employed in an amount of from 1 to 1.2 mols per mol. of the tetracycline compound.

11. A process according to any of claims 8—10, wherein the halogenation is carried out in the presence of a water-miscible solvent.

12. A process according to claim 11, wherein the halogenating agent is perchloryl fluoride and the solvent is a lower alkanol wherein lower means having from one to five carbon atoms.

13. A process according to claim 12 wherein the halogenation is carried out in the presence of a strong base.

14. A process according to claims 8—11, wherein the halogenating agent is N-chlorosuccinimide.

15. A process according to any of claims 8—13 wherein the halogenation is carried out at a temperature of 0° C. to 50° C.

16. A process according to any of claims 8—15 wherein the 11a-halo-tetracycline-6,12-hemiketal is contacted with a halogenating agent in a reaction-inert solvent, to effect halogenation in the D-ring thereof.

17. A process according to claim 16 wherein the preparation of the hemiketal of structure 11 and halogenation in the D-ring thereof are conducted in a single stage by contacting the starting tetracycline compound of formula I herein with an appropriate halogenating agent in an amount of at least 2 mols per mol of the tetracycline compound.

18. A process according to any of the preceding claims 8—17 wherein the starting compound is 5 - oxytetracycline and the product is 11a - fluoro or 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal.

19. A process according to any of claims 8—17 wherein the starting compound is tetracycline and the product is 11a-fluoro or 11a-chlorotetracycline-6,12-hemiketal.

20. A process according to any of claims 8—17, wherein the starting compound is 7-chlorotetracycline and the product is 7,11a-dichlorotetracycline - 6,12 - hemiketal.

21. A compound as claimed in claim 1, substantially as herein described.

22. A process for the preparation of a compound of Structure II, as set forth in the specification hereof, substantially as herein described.

MARKS & CLERK,
Chartered Patent Agents,
Agents for the Applicants.

EXAMPLE V
11a-Chloro-5-hydroxytetracycline-
6,12-hemi-ketal

Twenty-three grams of anhydrous oxytetra-
cycline is dissolved in 250 ml. of 1,2-di-
methoxyethane and 8 g. of N-chlorosuccin-
imide is next added. The mixture is stirred for
two minutes and then poured into 1 liter of
stirred water. The product which separates is
collected by filtration, water-washed and dried.
Infrared analysis of the product (KBr at 1%
concentration) shows no carbonyl absorption in
the 5—6 micro region but shows the follow-
ing principal peaks: 6.12, 6.35, 6.66, 6.85,
7.22, 7.55, 7.75, 7.92, 8.14, 8.36, 8.78, 9.18
and 9.43 microns. Bioassay of the product
shows a tetracycline activity of 4 mcg./mg.

EXAMPLE VI
Acid salts of 11a-halotetracycline-6,12-
hemi-ketals

The hydrochloride salts of the above-
described 11a-halo compounds are prepared by
dissolving the free base in water containing
an equimolar amount of hydrogen chloride and
freeze-drying the resulting solution.

In similar fashion, salts are formed with
sulfuric, hydrobromic and phosphoric acids.

WHAT WE CLAIM IS:—

1. A compound of structure II as set forth
in the specification hereof.
2. 11a - Chlorotetracycline - 6,12-hemi-
ketal.
3. 11a - Chloro - 5 - hydroxytetracycline-
6,12-hemiketal.
4. 11a - Fluorotetracycline - 6,12 - hemi-
ketal.
5. 11a - Fluoro - 5 - hydroxytetracycline-
6,12 - hemiketal.
6. 7,11a - Dichlorotetracycline - 6,12-hemi-
ketal.
7. Salts of the compounds of any of claims
1—6 with acids.
8. A process for the preparation of an 11a-
halo - tetracycline - 6,12 - hemiketal of struc-
ture II herein which includes the step of con-
tacting a tetracycline compound of structure I
herein with an appropriate halogenating agent
in a reaction-inert solvent.
9. A process according to claim 8 wherein
the halogenating agent is chlorine; iodo-
chloride; an N-chloro lower alkanolic acid
amide, -hydrocarbon dicarboxylic acid imide,
or -lower-alkanoyl anilide; 3-chloro- or 3,5-
dichloro - 5,5 - dimethyl - hydantoin; a
pyridinium perchloride hydrohalide; a lower
alkyl hypochlorite; or perchloryl fluoride; the

expression "lower" having the significance
hereinbefore defined.

10. A process according to claim 8 or 9,
wherein the halogenating agent is employed
in an amount of from 1 to 1.2 mols per mol. of
the tetracycline compound.

11. A process according to any of claims
8—10, wherein the halogenation is carried out
in the presence of a water-miscible solvent.

12. A process according to claim 11, where-
in the halogenating agent is perchloryl fluoride
and the solvent is a lower alkanol wherein
lower means having from one to five carbon
atoms.

13. A process according to claim 12 where-
in the halogenation is carried out in the pre-
sence of a strong base.

14. A process according to claims 8—11,
wherein the halogenating agent is N-chloro-
succinimide.

15. A process according to any of claims
8—13 wherein the halogenation is carried out
at a temperature of 0° C. to 50° C.

16. A process according to any of claims
8—15 wherein the 11-a-halo-tetracycline-6,12-
hemiketal is contacted with a halogenating
agent in a reaction-inert solvent, to effect halo-
genation in the D-ring thereof.

17. A process according to claim 16 where-
in the preparation of the hemiketal of structure
11 and halogenation in the D-ring thereof are
conducted in a single stage by contacting the
starting tetracycline compound of formula I
herein with an appropriate halogenating agent
in an amount of at least 2 mols per mol of
the tetracycline compound.

18. A process according to any of the pre-
ceding claims 8—17 wherein the starting com-
pound is 5 - oxytetracycline and the product
is 11a - fluoro or 11a - chloro - 5 - oxytetra-
cycline - 6,12 - hemiketal.

19. A process according to any of claims
8—17 wherein the starting compound is tetra-
cycline and the product is 11a-fluoro or 11a-
chlorotetracycline-6,12-hemiketal.

20. A process according to any of claims
8—17, wherein the starting compound is 7-
chlorotetracycline and the product is 7,11a-
dichlorotetracycline - 6,12 - hemiketal.

21. A compound as claimed in claim 1, sub-
stantially as herein described.

22. A process for the preparation of a
compound of Structure II, as set forth in the
specification hereof, substantially as herein
described.

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