

PATENT SPECIFICATION

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(54) PREPARATION OF α -6-DEOXYTETRACYCLINES

(71) We, PFIZER INC, a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, 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:—

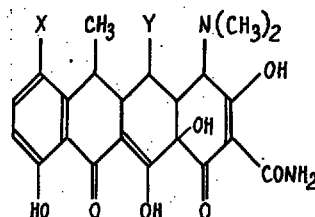
This invention relates to the preparation of α -6-deoxytetracyclines. More particularly, the invention is concerned with a process for the preparation of an α -6-deoxytetracycline which involves hydrogenation of a mixture of a 6-deoxy-6-demethyl-6-methylenetetracycline compound and a catalytic amount of a dicarboxylato(triphenylphosphine)-rhodium(II) or dicarboxylato(substituted triphenylphosphine)rhodium(II) compound, in a reaction-inert solvent. The hydrogenation takes place with a stereo-selectivity which favours the 6α -isomer over the 6β -isomer. The products are known antibacterial agents.

Prior United Kingdom Patent Specification No. 995,032 discloses the production of α -6-deoxytetracycline derivatives by a process which involves hydrogenation of certain 6-deoxy-6-demethyl-6-methylenetetracyclines in the presence of a catalytic amount of a noble metal catalyst such as rhodium or palladium. The process results in the production of β -6-deoxytetracyclines as well as α -6-deoxytetracyclines. The present invention improves upon that process by providing a higher α -isomer to β -isomer ratio.

It has now been found that a higher ratio of α -isomer to β -isomer may be achieved by hydrogenating a mixture of a 6-deoxy-6-demethyl-6-methylenetetracycline compound and a specific, soluble rhodium(II) compound, as herein described, in a reaction-inert solvent.

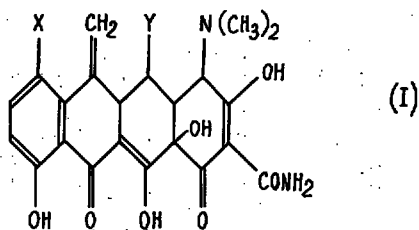
West German Offenlegungsschrift No. 2,308,227 broadly discloses the use of soluble rhodium compounds for the stereoselective reduction of 6-deoxy-6-demethyl-6-methylenetetracyclines. However, the said Offenlegungsschrift exemplifies only the use of rhodium(I) compounds. Hui *et al*, *Inorganic Chemistry*, 12, 757 (1973), and *Journal of the Chemical Society* (London), Part D, 1196 (1970), report that rhodium(II) diacetate is an effective hydrogenation catalyst. However, the use of rhodium(II) diacetate in the hydrogenation of 6-deoxy-6-demethyl-6-methylenetetracyclines does not lead to a favourable α to β ratio, approximately equal amounts of the α - and β -isomers being formed. It has been found, according to the present invention, that the presence of the triphenylphosphine or substituted triphenylphosphine ligand is essential to obtain a stereoselective reduction. Although Legzdins *et al*, *Journal of the Chemical Society* (London), Part D, 825, (1969) have reported the use of rhodium diacetate in the presence of triphenylphosphine as a hydrogenation catalyst, their experiments were run in the presence of a very strong acid. The process of the present invention is carried out under neutral conditions, or on a weakly-acidic tetracycline acid-addition salt.

In accordance with the present invention there is provided a process for the preparation of an α -6-deoxytetracycline of the general formula:

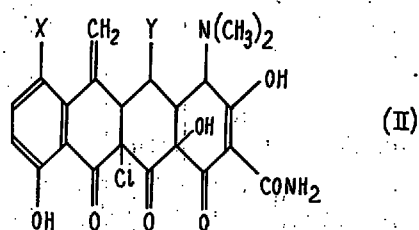


which comprises mixing a catalytic amount of

a compound of the formula $\text{Rh}(\text{OCOR})_2\text{Q}$ with a tetracycline compound of the general formula:—



or



or an acid-addition salt thereof, in a reaction-inert solvent, and maintaining hydrogen in contact with the reaction mixture thus formed, at a temperature of from 20° to 100°C, and at a pressure from 1 to 100 atmospheres until reaction of from 1 to 2 moles of hydrogen per mole of tetracycline compound occurs, the reaction being conducted in the absence of a strong acid, wherein R is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or a chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, chlorophenyl, tolyl or anisyl group, Q is an unsubstituted triphenylphosphine group of the formula $\text{P}(\text{C}_6\text{H}_5)_3$ or a triphenylphosphine group substituted on one or more of the phenyl rings by one or more substituents, each of which is an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a fluorine, chlorine or bromine atom, X is a hydrogen or chlorine atom and Y is a hydrogen atom or a hydroxy group or an alkanoyloxy group having from 2 to 7 carbon atoms.

The process of the present invention results in hydrogenation of the exocyclic methylene group, and proceeds with a stereoselectivity which favours the α -isomers over the β -isomers by a factor of at least 9:1. The specific rhodium compound used in the present invention is a compound of the formula: $\text{Rh}(\text{OCOR})_2\text{Q}$ wherein R and Q are as defined above. However, the preferred catalysts are those wherein the triphenylphosphine group is unsubstituted, i.e., compounds of the formula



Especially preferred catalysts are those wherein

the triphenylphosphine group is unsubstituted and R is an alkyl group, particularly methyl.

The starting materials used in the process of the present invention are tetracycline compounds of the formula (I) and (II) above and the acid addition salts thereof.

The preparation of these starting materials is disclosed in United Kingdom Patent Specification No. 995,032. In general, the preparation involves treatment of an 11a-chloro-6,12-hemiketal derivative of the appropriate tetracycline compound with a strong acid of the dehydrating type such as sulphuric, trifluoroacetic, polyphosphoric or perchloric acid or hydrogen fluoride. Of these, the preferred acid is hydrogen fluoride. Optimum conditions are readily determined by routine experimentation. Generally, the selected 11a-chloroketal is merely added to the selected acid and allowed to react, most appropriately at a temperature within the range of from 0° to 50°C and for a time of up to several hours. After reaction is complete, the product is recovered in an appropriate manner, e.g., in the case of volatile acids by evaporation of the same to obtain the residual product, and in other cases by standard procedures such as stirring with a non-solvent, e.g., diethyl ether, to precipitate the product. These 6-methylene compounds may be converted to acid addition salts or polyvalent metal salt complexes by standard procedures prior to hydrogenation.

Example XXXVII of United Kingdom Patent Specification No. 995,032 illustrates hydrogenation of an 11a-chloro-6-deoxy-6-demethyl-6-methylenetetrahydrochloride to obtain the corresponding 11a-deschloro compound.

When Y of the starting compound for the present invention is an alkanoyloxy group having from 2 to 7 carbon atoms, it is appropriate to use the method disclosed in United Kingdom Patent Specification No. 1,287,493 for the preparation thereof. According to that method, the appropriate 11a-chloro-6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline in the form of the free base or a poly-addition salt is treated with a carboxylic acid having from 2 to 7 carbon atoms in the molecule in the presence of methanesulphonic, ethanesulphonic or hydrofluoric acid, preferably at a temperature of from 20° to 70°C for a period of time generally ranging from 2 to 20 hours. The resulting product may then be reduced to the 11a-deschloro compound by the procedure described above.

The rhodium compounds of the formula $\text{Rh}(\text{OCOR})_2\text{Q}$ are either known in the art, or they are simple analogues or homologues of compounds known in the art, and they may be prepared by methods such as those discussed by Stephenson *et al.*, *Journal of the Chemical Society* (London), 3632 (1965). According to these procedures, rhodium

carboxylates are prepared by refluxing rhodium hydrous oxide in, for example, an excess of formic, acetic or propionic acid and ethanol. The yellow solutions gradually turn
5 amber and then green. The resulting solutions are cooled and the dark green powders which precipitate are filtered off and recrystallized from methanol or water. These products are found to be stable at temperatures up to
10 240°C. The final catalyst complex is prepared by the addition of triphenylphosphine, or the appropriately substituted triphenylphosphine, and diethyl ether to a cold ethanolic solution of the rhodium carboxylate.

15 Appropriate reaction-inert solvents for the process of the present invention include those which serve to substantially dissolve the starting materials or the product. Examples of such solvents include ethers such as diethyl
20 ether, tetrahydrofuran, dioxan, 1,2 - dimethoxyethane; lower aliphatic ketones such as acetone and methyl ethyl ketone; low molecular weight esters such as ethyl acetate and butyl acetate; mono- and polyhydric lower
25 alcohols such as methanol, ethanol, isopropanol, ethylene glycol, propylene glycol and diethylene glycol; lower alkoxy - substituted alkanols such as 2 - methoxyethanol and 2 -
30 (2 - ethoxyethoxy)ethanol; lower alkanolic acids such as acetic acid and propionic acid; tertiary amides such as N,N - dimethylformamide, N,N - dimethylacetamide and N - methyl - 2 - pyrrolidone and mixtures thereof.

35 Introduction of the hydrogen gas into the reaction-inert solvent medium containing the rhodium compound and the tetracycline compound is generally accomplished by carrying out the reaction in a sealed vessel under an
40 atmosphere of hydrogen or of hydrogen mixed with an inert diluent such as nitrogen or argon. The pressure inside the reaction vessel may vary from 1 to 100 atmospheres. The preferred pressure range, when the atmosphere
45 in the reaction vessel is substantially pure hydrogen, is from 10 to 100 psig.

The hydrogenation is conducted at a temperature of from 20° to 100°C, and preferably from 40° to 70°C. Utilizing the preferred
50 temperature and pressure values, hydrogenation generally takes place in a few hours, e.g., from 2 hours to 10 hours.

On hydrogenating a 7 - halo - substituted 6 - methylene - 6 - deoxy - 6 - demethyl
55 tetracycline starting material in the process of this invention, the 7 - halo substituent remains substantially intact. On the other hand, an 11a - chloro substituent is removed.

The expression "catalytic amount" as used
60 herein is well understood by those skilled in the art of known tetracycline hydrogenations. Generally, this amount ranges from 0.1 to 100 mol%, based on the tetracycline compound. The preferred amount is from 1 to
65 10 mol%.

The reaction product of the present invention may be isolated from the reaction medium by standard methods. For example, the product often may be precipitated by the addition
70 of a non-solvent such as hexane or water or by the addition of certain agents which form insoluble salts with the product. Alternatively, the crude product may be isolated by evaporation of the solvent or by dilution
75 of the reaction mixture with a large excess of water, followed by extraction of the product into a water-immiscible organic solvent and subsequent evaporation of the water-immiscible solvent.

The following Examples illustrate the present invention and the manner in which it
80 may be performed.

EXAMPLE 1

Reduction of 6 - Methylene - 6 - demethyl - 6 - deoxy - 5 - hydroxytetracycline using
85 Diacetato(triphenylphosphine)rhodium(II)

A solution of 2.0 g. (4.18 mmol) of 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - hydroxytetracycline hydrochloride and 0.088 g. (4.4 mol-percent) of diacetato(triphenylphosphine)rhodium(II) in 30 ml. of degassed
90 methanol was shaken under an atmosphere of hydrogen, in a sealed vessel, at 60-70°C., for 5.75 hours. The hydrogen pressure in the reaction vessel was 66-71 psig. The vessel was then opened and the reaction solution was filtered. The filtrate was examined by high-
95 pressure liquid chromatography, which indicated that it contained the required α - 6 - deoxy - 5 - hydroxytetracycline, contaminated by 2-3% of its C-6 epimer.

To the filtrate was then added a mixture of 20 ml. of water and 30 ml. of 10% aqueous sulfosalicylic acid, with stirring.
100 Stirring was continued overnight, and then the precipitate was filtered off, giving 2.62 g. (95% yield) of α - 6 - deoxy - 5 - hydroxytetracycline as its sulfosalicylate salt. The product was shown to be 93% pure by ultra-
105 violet spectroscopy.

EXAMPLE 2

The procedure of Example 1 is repeated, except that the 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - hydroxytetracycline used
110 therein is replaced by an equimolar amount of:

- 6 - methylene - 6 - demethyl - 6 - deoxy - tetracycline,
- 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - acetoxytetracycline,
- 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - propionyloxytetracycline,
- 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - butyryloxytetracycline,
- 6 - methylene - 6 - demethyl - 6 - deoxy - 11a - chlorotetracycline,

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- 6 - methylene - 6 - demethyl - 6 - deoxy -
5 - hexanoyloxytetracycline,
6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chlorotetracycline,
5 6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chloro - 5 - hydroxytetracycline,
6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chloro - 5 - acetoxytetracycline,
10 6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chloro - 5 - isobutyryloxytetracycline,
6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chloro - 5 - isovaleryloxytetracycline,
and
15 6 - methylene - 6 - demethyl - 6 - deoxy -
7 - chloro - 5 - heptanoyloxytetracycline,
respectively,

and the diacetato(triphenylphosphine)rhodium-(II) used therein is replaced by an equimolar amount of:

- 20 dipropionato(triphenylphosphine)-
rhodium(II)
dibenzoato(triphenylphosphine)-
rhodium(II)
25 dibutyrate(triphenylphosphine)-
rhodium(II)
di(*p* - chlorobenzoato) (triphenylphosphine)-
rhodium(II),
dibenzoato(triphenylphosphine)-
rhodium(II)
30 diformato(triphenylphosphine)-
rhodium(II)
diacetato(triphenylphosphine)-
rhodium(II)
35 dibenzoato(triphenylphosphine)-
rhodium(II),
di(*m* - toluato) (triphenylphosphine)-
rhodium(II),
dihexanoato(triphenylphosphine)-
rhodium(II),
40 diheptanoato(triphenylphosphine)-
rhodium(II), and
di(*p* - methoxybenzoato) (triphenylphos-
phine)rhodium(II),

respectively.

45 This affords the following compounds, res-
pectively:

- α - 6 - deoxytetracycline,
α - 6 - deoxy - 5 - acetoxytetracycline,
α - 6 - deoxy - 5 - propionyloxytetracycline,
50 α - 6 - deoxy - 5 - butyryloxytetracycline,
α - 6 - deoxytetracycline,
α - 6 - deoxy - 5 - hexanoyloxytetracycline,
α - 6 - deoxy - 7 - chlorotetracycline,
α - 6 - deoxy - 7 - chloro - 5 -
55 hydroxytetracycline,
α - 6 - deoxy - 7 - chloro - 5 -
acetoxytetracycline,
α - 6 - deoxy - 7 - chloro - 5 -
isobutyryloxytetracycline,
60 α - 6 - deoxy - 7 - chloro - 5 -
isovaleryloxytetracycline, and

- α - 6 - deoxy - 7 - chloro - 5 -
heptanoyloxytetracycline.

The following Preparations illustrate the preparation of rhodium compounds used as catalysts in the process of the present invention.

PREPARATION A Rhodium(II) Acetate

A mixture of 1.72 g. of rhodium hydrous oxide (Rh[OH]₃ · H₂O), 6 ml. of glacial acetic acid and 15 ml. of ethanol is heated under reflux for 24 hours. The reaction mixture is cooled, and the volatile components are removed by evaporation *in vacuo* to give the crude product. The crude product is purified by dissolving it in acetone, allowing the solvent to evaporate slowly and then filtering off the solid which precipitates.

PREPARATION B

Reaction of rhodium hydrous oxide with the appropriate carboxylic acid, according to the procedure of Preparation A, produces the following rhodium(II) carboxylates:

- rhodium(II) propionate,
rhodium(II) benzoate,
rhodium(II) butyrate,
rhodium(II) *p* - chlorobenzoate,
rhodium(II) formate,
rhodium(II) *m* - toluate,
90 rhodium(II) hexanoate,
rhodium(II) heptanoate,
rhodium(II) *p* - methoxybenzoate,
rhodium(II) chloroacetate,
rhodium(II) dichloroacetate,
95 rhodium(II) trichloroacetate,
rhodium(II) fluoroacetate,
rhodium(II) difluoroacetate, and
rhodium(II) trifluoroacetate.

PREPARATION C

Diacetato(triphenylphosphine)Rhodium(II)
A mixture of 110 mg. of rhodium(II) acetate and 100 ml. of methanol is cooled to 17°C. and a solution of 131 mg. of triphenylphosphine in 5 ml. of ether is added with stirring. Stirring is continued at ambient temperature for 2 hours and then the precipitate is removed by filtration. This affords 219 mg. of the title compound, m.p. 203°—204°C.

PREPARATION D

The procedure of Preparation C is repeated, except that the rhodium(II) acetate is replaced by the appropriate rhodium(II) carboxylate, to produce the following congeners:

- dipropionato(triphenylphosphine)-
rhodium(II),
dibenzoato(triphenylphosphine)-
rhodium(II),

- dibutyrate(triphenylphosphine)-rhodium(II),
 di(*p* - chlorobenzoato) (triphenylphosphine)-rhodium(II),
 5 diformato(triphenylphosphine)-rhodium(II),
 di(*m* - toluato) (triphenylphosphine)-rhodium(II),
 10 dihexanato(triphenylphosphine)-rhodium(II),
 diheptanato(triphenylphosphine)-rhodium(II),
 di(*p* - methoxybenzoato) (triphenylphosphine)-rhodium(II),
 15 di(chloroacetato) (triphenylphosphine)-rhodium(II),
 di(dichloroacetato) (triphenylphosphine)-rhodium(II),
 di(trichloroacetato) (triphenylphosphine)-rhodium(II),
 20 di(fluoroacetato) (triphenylphosphine)-rhodium(II),
 di(difluoroacetato) (triphenylphosphine)-rhodium(II), and
 25 di(trifluoroacetato) (triphenylphosphine)-rhodium(II).

The following Comparative Example is included to show that the hydrogenation process does not proceed with stereoselectivity if the rhodium compound catalyst does not contain the triphenylphosphine ligand.

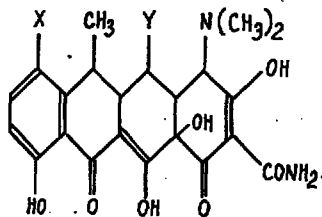
COMPARATIVE EXAMPLE

Reduction of 6 - Deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline using Rhodium(II) Diacetate

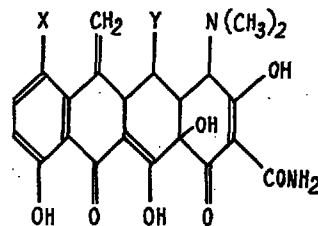
A solution of 2.0 g. (4.18 mmol.) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline hydrochloride and 46 mg. (5 mol-percent) of rhodium(II) diacetate in 30 ml. of de-gassed methanol was shaken under an atmosphere of hydrogen at 65—70°C. for 5.25 hours. The hydrogen pressure in the reaction vessel was 65—70 psig. The cooled reaction vessel was then opened and the contents were filtered. The filtrate was examined by high-pressure liquid chromatography. This indicated that it contained α - 6 - deoxy - 5 - hydroxytetracycline and β - 6 - deoxy - 5 - hydroxytetracycline, in a ratio of about 2:3, together with a small amount of unreduced starting material.

WHAT WE CLAIM IS:—

1. A process for the preparation of an α - 6 - deoxytetracycline of the general formula:

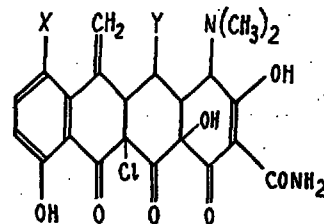


which comprises mixing a catalytic amount of a compound of the formula $\text{Rh}(\text{OCOR})_2\text{Q}$ with a tetracycline compound of the general formula:—



(I) 60

or



(II)

or an acid-addition salt thereof, in a reaction-inert solvent, and maintaining hydrogen in contact with the reaction mixture thus formed, at a temperature of from 20° to 100°C, and at a pressure from 1 to 100 atmospheres until reaction of from 1 to 2 moles of hydrogen per mole of tetracycline compound occurs, the reaction being conducted in the absence of a strong acid, wherein R is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or a chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, chlorophenyl, tolyl or anisyl group, Q is an unsubstituted triphenylphosphine group of the formula $\text{P}(\text{C}_6\text{H}_5)_3$ or a triphenylphosphine group substituted on one or more of the phenyl rings by one or more substituents, each of which is an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a fluorine, chlorine or bromine atom, X is a hydrogen or chlorine atom and Y is a hydrogen atom or a hydroxy group or an alkanoyloxy group having from 2 to 7 carbon atoms.

2. A process according to claim 1, wherein the starting tetracycline compound is 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - hydroxytetracycline or an acid addition salt thereof.

3. A process according to claim 1, wherein the starting tetracycline compound is 6 - methylene - 6 - demethyl - 6 - deoxy - 11a - chlorotetracycline or an addition salt thereof.

4. A process according to any one of claims 1 or 3, wherein the catalyst is a rhodium compound of the formula



wherein R is as defined in claim 1.

100



dibutyrate(triphenylphosphine)-rhodium(II),
 di(*p*-chlorobenzoato)(triphenylphosphine)-rhodium(II),
 diformato(triphenylphosphine)-rhodium(II),
 di(*m*-toluato)(triphenylphosphine)-rhodium(II),
 dihexanato(triphenylphosphine)-rhodium(II),
 diheptanato(triphenylphosphine)-rhodium(II),
 di(*p*-methoxybenzoato)(triphenylphosphine)rhodium(II),
 di(chloroacetato)(triphenylphosphine)-rhodium(II),
 di(dichloroacetato)(triphenylphosphine)-rhodium(II),
 di(trichloroacetato)(triphenylphosphine)-rhodium(II),
 di(fluoroacetato)(triphenylphosphine)-rhodium(II),
 di(difluoroacetato)(triphenylphosphine)-rhodium(II), and
 di(trifluoroacetato)(triphenylphosphine)-rhodium(II).

The following Comparative Example is included to show that the hydrogenation process does not proceed with stereoselectivity if the rhodium compound catalyst does not contain the triphenylphosphine ligand.

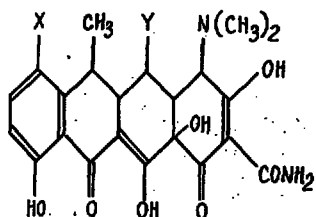
COMPARATIVE EXAMPLE

Reduction of 6 - Deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline using Rhodium(II) Diacetate

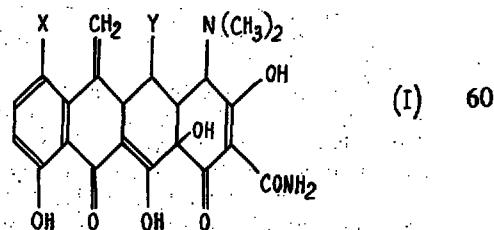
A solution of 2.0 g. (4.18 mmol.) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline hydrochloride and 46 mg. (5 mol-percent) of rhodium(II) diacetate in 30 ml. of de-gassed methanol was shaken under an atmosphere of hydrogen at 65—70°C. for 5.25 hours. The hydrogen pressure in the reaction vessel was 65—70 psig. The cooled reaction vessel was then opened and the contents were filtered. The filtrate was examined by high-pressure liquid chromatography. This indicated that it contained α - 6 - deoxy - 5 - hydroxytetracycline and β - 6 - deoxy - 5 - hydroxytetracycline, in a ratio of about 2:3, together with a small amount of unreduced starting material.

WHAT WE CLAIM IS:—

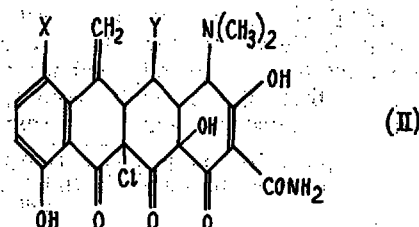
1. A process for the preparation of an α - 6 - deoxytetracycline of the general formula:



which comprises mixing a catalytic amount of a compound of the formula $Rh(OCOR)_2Q$ with a tetracycline compound of the general formula:—



or



or an acid-addition salt thereof, in a reaction-inert solvent, and maintaining hydrogen in contact with the reaction mixture thus formed, at a temperature of from 20°C. to 100°C., and at a pressure from 1 to 100 atmospheres until reaction of from 1 to 2 moles of hydrogen per mole of tetracycline compound occurs, the reaction being conducted in the absence of a strong acid, wherein R is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or a chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, chlorophenyl, tolyl or anisyl group, Q is an unsubstituted triphenylphosphine group of the formula $P(C_6H_5)_3$, or a triphenylphosphine group substituted on one or more of the phenyl rings by one or more substituents, each of which is an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a fluorine, chlorine or bromine atom, X is a hydrogen or chlorine atom and Y is a hydrogen atom or a hydroxy group or an alkanoyloxy group having from 2 to 7 carbon atoms.

2. A process according to claim 1, wherein the starting tetracycline compound is 6 - methylene - 6 - demethyl - 6 - deoxy - 5 - hydroxytetracycline or an acid addition salt thereof.

3. A process according to claim 1, wherein the starting tetracycline compound is 6 - methylene - 6 - demethyl - 6 - deoxy - 11a - chlorotetracycline or an addition salt thereof.

4. A process according to any one of claims 1 or 3, wherein the catalyst is a rhodium compound of the formula



wherein R is as defined in claim 1.

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1,479,123

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5. A process according to claim 4, wherein R is an alkyl group having from 1 to 6 carbon atoms.

5 6. A process according to claim 5, wherein R is methyl.

7. A process according to any one of claims 1 to 6 wherein the temperature employed is from 40° to 70°C.

10 8. A process according to any one of the preceding claims, wherein the catalytic amount of the rhodium compound is 0.1 to 100 mol-percent, based on the tetracycline compound.

15 9. A process according to claim 8, wherein the said catalytic amount is 1 to 10 mol-percent, based on the tetracycline compound.

20 10. A process according to any one of the preceding claims wherein the reaction-inert solvent medium is diethyl ether, tetrahydrofuran, dioxan, 1,2 - dimethoxyethane, acetone, methyl ethyl ketone, ethyl acetate, butyl acetate, methanol, ethanol, isopropanol,

ethylene glycol, propylene glycol, diethylene glycol, 2 - methoxyethanol, 2 - (2 - ethoxyethoxy) - ethanol, acetic acid, propionic acid, N,N - dimethylformamide, N,N - dimethylacetamide, N - methyl - 2 - pyrrolidone or a mixture thereof.

11. A process according to any one of the preceding claims wherein the pressure is 10 to 100 psig.

12. A process for the preparation of an α - 6 - deoxytetracycline according to claim 1 and substantially as hereinbefore described with reference to Examples 1 and 2.

13. An α - 6 - deoxytetracycline whenever prepared by a process according to any one of the preceding claims.

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