

PATENT SPECIFICATION

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(54) IMPROVED PROCESS FOR PRODUCING A -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:—

The present process relates to a new and improved process for producing 6-deoxytetracyclines. More particularly, it comprises an improvement in the process of introducing hydrogen into a reaction-inert solvent medium containing a catalytic amount of rhodium metal and a 6-demethyl-6-deoxy-6-methylenetetra-cycline, the improvement comprising the addition of a phosphine and a promoter to the medium. The process achieves greater conversion of the 6-demethyl-6-deoxy-6-methylenetetra-cyclines to 6-deoxytetracyclines, enhanced ratios of α -6-deoxytetracyclines to β -6-deoxytetracyclines, and minimized formation of degradation products.

United States Patent 3,200,149 discloses and claims, *inter alia*, a novel group of tetracycline compounds which are generally designated as α -6-deoxytetracyclines. The process of United States Patent 3,200,149 for producing α -6-deoxytetracyclines involves noble-metal (including rhodium) hydrogenation of a 6-methyl-6-deoxy-6-methylenetetra-cycline to produce a mixture containing the corresponding α -6-deoxytetracycline and the corresponding β -6-deoxytetracycline. This reaction mixture is then separated to obtain the desired α -isomer. Under preferred operating conditions, the process is generally capable of producing up to about 1:1 mixture of α - to β -isomer. In view of the fact that the α -isomers, particularly α -6-deoxy-5-oxy-tetracycline, are of a higher order of activity than the corresponding β -isomers a significant

improvement in the ratio of α - to β -isomer produced without substantial reduction in the yield of the mixture of isomers is of substantial importance.

An improved process for noble metal catalytic hydrogenation of 6-demethyl-6-deoxy-6-methylenetetra-cyclines which brings about an improvement in the α - to β -isomer ratio and enhanced yield of the mixture of isomers is described in United States Patent No. 3,444,198. The process comprises conducting the reaction in the presence of a noble metal catalyst poisoned with carbon monoxide, quinoline-sulfur or any one of a variety of thiourea derivatives. The susceptibility of metal catalysts to poisons is pointed out by Maxted (Advan. Catalysis 3, 129, 1951). A variety of compounds of elements of Groups V—A and VI—A of the Periodic Classification of the Elements, including nitrogen, phosphorous, oxygen and sulfur compounds, are discussed as poisons.

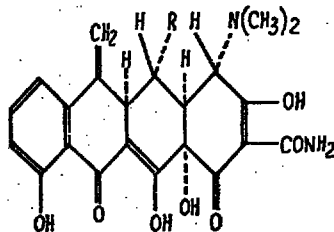
The hydrogenation of unsaturated hydrocarbons (acetylenes and olefins) in inert homogeneous liquid media by contacting the unsaturated hydrocarbon with hydrogen in the presence of a zerovalent compound of palladium or platinum which contains one or more tertiary phosphine ligands dissolved in the liquid media is described in United States Patent 3,463,830. The zerovalent palladium or platinum compounds are prepared by reduction of divalent palladium or platinum compounds with hydrazine, usually in the presence of an excess of the tertiary phosphine.

German Application OS 2,308,227 describes the preparation of α -6-deoxytetracyclines by homogeneous catalytic hydrogenation using tris-(triphenylphosphine)chlororhodium as catalyst. The catalyst can be performed or formed in the reaction mixture (*in situ*) by dissolving rhodium chloride and triphenylphosphine or other ligand in a suitable solvent together with the appropriate

- 6 - demethyl - 6 - deoxy - 6 - methylenetetra-
cyclyne substrate prior to introduction of hydro-
gen. In the case of *in situ* preparation of
5 catalyst, molar proportions of triphenylphos-
phine, or other ligand, to rhodium (present
initially as rhodium chloride) of less than
1:1 are reported to lead to formation of de-
posits of metal in powdered form which act
10 as a heterogeneous catalyst with predominant
formation of β -epimers rather than of the
desired α -epimers. Molar ratios of triphenyl-
phosphine, or other ligand, to metal of greater
than 3:1 are reported to lead to homogeneous
15 catalysts with incomplete conversion of sub-
strate and, of course, reduced yields of the
desired product.

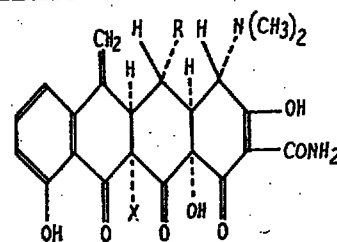
- Homogeneous catalytic hydrogenation of
exocyclic methylene groups using tris(tri-
phenylphosphine)chlororhodium as catalyst in
20 methylenecyclohexanes (Augustine *et al.*,
Ann. N.Y. Acad. Sci. 158, 482-91, 1969);
coronopilin (Ruesch *et al.*, Tetrahedron 25,
807-11, 1969); and in an intermediate in the
stereoselective total synthesis of seychelene
25 (Piers *et al.* Chem. Commun. 1069-70,
1969) is reported.

- It has now been found that the process
which comprises introducing hydrogen into a
reaction-inert solvent medium containing a
30 catalytic amount of rhodium metal and a 6-
demethyl - 6 - deoxy - 6 - methylenetetra-
cyclyne selected from



- or an acid addition salt thereof and/or poly-
35 valent metal salt thereof wherein R is hydro-
gen or hydroxy at an appropriate temperature
and pressure until reduction of the 6-methylene
group occurs; is markedly improved by in-
cluding a phosphine and a promoter in the
40 reaction-inert solvent medium containing the
catalyst and 6-methylenetetra-cyclyne reactant.
Also this process can be used for dehalogena-
tion of 11a-halo compounds with hydrogena-
tion of the 6-methylene group in such com-
45 pounds.

- According to the invention there is pro-
vided a process for the production of 6-methyl-
6-deoxy-tetracyclines wherein hydrogen is
50 introduced into a reaction-inert solvent
medium containing a catalytic amount of
rhodium metal and a tetracycline compound
which is a tetracycline base of the Formula:



or an acid addition salt thereof wherein:

R is hydrogen or hydroxyl; and X is hydro-
55 gen, chloro, or fluoro and the hydrogen is
maintained in contact with the said reaction
mixture at a temperature of from 0° to 100° C.
and at a pressure of from atmospheric to
2000 p.s.i., to hydrogenate the 6-methylene
60 group and dehalogenate the 11a-halo group
if present the reaction being conducted in
the presence of (a) from 2 to 10 moles, per
mole of rhodium metal, of a compound of
the Formula: $R_1R_2R_3P$

wherein each of R_1 and R_2 is the same or
different and is phenyl or substituted phenyl
wherein the substituent is halo, lower alkoxy,
dimethylamino or lower alkyl; and

R_3 is R_1 , hydrogen or lower alkyl; and (b)
70 at least 1 mole of acid per mole of tetracycline
base, or from 0.1 to 1.0 mole of stannous
chloride per mole of tetracycline acid addition
salt.

In a specific embodiment wherein X is
75 fluoro or chloro, the reaction is carried out
until reaction of two moles of hydrogen per
mole of said tetracycline compound occurs.

In one aspect of this embodiment hydrogen
is introduced into said reaction-inert solvent
80 medium containing a catalytic amount of
rhodium metal and a tetracycline compound
of Formula I, wherein X is fluoro or chloro
and hydrogen is maintained in contact with
the reaction mixture at a temperature of from
0° C. to 60° C. until replacement of X group
is substantially complete;

a further catalytic amount of a rhodium
metal is added to the reaction mixture and
90 from 2 to 10 moles per mole of total rhodium
metal present of the compound of the Formula
 $R_1R_2R_3P$ hydrogen is contacted with the re-
action mixture at a temperature of from 70° C.
to 95° C., until reduction of the 6-methylene
95 group is substantially complete.

Thus hydrogen can be introduced into a
reaction-inert solvent medium containing a
compound of Formula I, or a salt thereof,
a catalytic amount of rhodium metal, a pro-
100 moter and a phosphine.

Thereafter, the α - to β -mixture produced is
recovered by conventional procedures involv-
ing catalyst removal and recovery of the
mixture from the solvent medium. This
105 mixture is then subjected to chromatographic
or other known procedures; e.g., addition of
sulfosalicylic acid to precipitate primarily the

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α -isomer as is described in J. Am. Chem. Soc. 84, 2643-51 (1963). A typical method of separation is included in the examples hereinafter.

5 The expression "reaction-inert solvent medium" refers to a medium which is a solvent or suitable suspending agent for the 6-methylene tetracycline reactant, is stable under the hydrogenation conditions, and does not interfere with the effectiveness of the catalyst or interact with the antibiotic. Polar organic solvents are generally suitable and include those enumerated in United States Patents Nos. 3,200,149 and 3,444,198. As is the case in the process of those patents, basic media are undesirable since they tend to promote decomposition, reducing the yield of the desired product.

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15 Excellent results are achieved in a wide range of reaction media including methanol, ethanol, acetone, methyl ethyl ketone, dioxane, formamide, monoalkyl- and dialkylformamides of one to four carbon atoms in each alkyl group (such as N-methylacetamide; N,N-dimethylacetamide; N-methyl, N-acetylformamide; N,N-diethylacetoacetamide), pyrrolidone, N-methyl-2-pyrrolidone, methyl 1-methyl-2-pyrrolidone-4-carboxylate, ethylene glycol, propylene glycol, 2-methoxyethanol, 2-ethoxyethanol, acetonitrile, acetic acid, tetramethylurea, tetrahydrofuran and gamma butyrolactone.

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25 Mixtures of these solvents may also be employed. Preferred solvents for the reaction include methylformamide, N-methylacetamide, methyl 1-methyl-2-pyrrolidone-4-carboxylate and tetramethyl urea; and particularly preferred are methanol and N-methyl-2-pyrrolidone. Such solvents often give best results when they contain from 5 to 80 volume per cent water.

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35 Particular virtues of the foregoing solvents include the following:

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45 (1) Rhodium metal, even prior to addition of the phosphine, remains relatively stable in these media. However, it is advisable to introduce the phosphine promptly when a solvent such as methanol is employed to avoid the possibility of catalyst degradation.

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55 (2) It is well known in the catalyst art that different lots of the same catalyst exhibit variable performance in their intended function. The enumerated media, however, have been found to give consistently high product yields even with so-called inferior catalyst batches.

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65 (3) Enhanced solubility provided by many of these media often permit the use of particularly high substrate concentrations, up to 30% by weight and more.

(4) These media provide optimum results at relatively low weight ratios of catalyst to substrate, often at ratios of 1:2 and lower.

(5) Particularly high conversion of substrate, high yields of α -isomer and predom-

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ant formation of α -isomer are afforded with these media.

(6) Ease of recovery of high quality α -isomer.

As in other hydrogenations of tetracycline-type antibiotics, temperature is not a particularly critical condition so long as it is high enough to promote adequate reaction rates and does not become so high as to promote undesired by-product formation. In general, temperatures of from 0° C. to 100° C. are operable. At the lower end of this range, e.g. below 10° C. the reaction is too slow to be of practical value. At the upper end of this range, e.g. at 95° C. or higher, decomposition of reactant and products occurs. Temperatures of from 25° C. to 90° C. are favored. Within this range, a temperature of from 70° C. to 90° C. is particularly preferred.

The rhodium metal employed as catalyst in the present invention can be of the supported or non-supported type. Examples of suitable catalyst supports include carbon, silica, alumina and barium sulfate. The rhodium is preferably used in supported form, e.g., rhodium-on-carbon, rhodium-on-barium sulfate, rhodium-on-barium carbonate and rhodium-on-alumina. The particularly preferred form is 5% rhodium-on-carbon. The expression "Catalytic amount" as used herein is well understood by those skilled in the art of hydrogenations on tetracycline-type compounds and typical amounts are illustrated by the examples appearing hereinafter. Best results are usually achieved with from 0.0001 to 2 parts by weight of catalyst (metal), dry basis, per part of substrate, although higher or lower ratios are also employed successfully. Typically, a 1:3 molar ratio of catalyst to 6-methylenetetracycline compound may be used. Rhodium-on-carbon, the preferred catalyst, is commercially available as a 50% wet (with water) mixture containing 5% rhodium-on-carbon (dry basis) and is conveniently used in this form.

The pressure employed during hydrogenation may range from sub-atmospheric to 2,000 p.s.i. or even higher if suitable equipment is available. Sub-atmospheric pressures down to 100 mm. Hg or even lower can be employed successfully, but for speed and convenience hydrogen pressures of one atmosphere or higher are usually preferred. In general, pressures ranging up to 1000 p.s.i. are quite adequate since they promote hydrogenation within a reasonable time.

The 6-methylenetetracycline compounds to be reduced may be in amphoteric form, in the form of polyvalent metal salt complexes (e.g. calcium, barium, zinc, magnesium), or pharmaceutically-acceptable or pharmaceutically-unacceptable acid addition salts of the compounds. Among the pharmaceutically-acceptable salts are those of mineral acids, including hydrochloric, hydriodic, hydro-

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bromic, phosphoric, metaphosphoric, nitric and sulfuric acids. Also included are salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, succinic, arylsulfonic, e.g., p-toluenesulfonic and sulfosalicylic acids. The pharmaceutically-unacceptable acid addition salts include those of hydrofluoric acid and perchloric acid.

10 The 6-methylenetetraacycline compounds (formula I) are preferably used as acid addition salts. The favored salts are the hydrochlorides, sulfosalicylates, p-toluene-sulfonates, perchlorates and perborates.

15 The salts can be preformed or can be formed *in situ* by addition of an equimolar amount of the appropriate acid to the reaction mixture containing the 6-methylenetetraacycline base to form an acid addition salt. It has been observed that the rate of the hydrogenation reaction and the yield of the desired α -epimer are unexpectedly improved by the presence of an excess of acid over and above that required to form an acid-addition salt with the 6-methylenetetraacycline reactant. In other words, a molar ratio of acid to 6-methylenetetraacycline base greater than 1:1 appears to exert a promoting effect upon reaction rate and yields. The excess acid; i.e., the amount of acid present beyond that required to form the acid addition salt of the 6-methylenetetraacycline base, can be the same or different from that used to form the acid addition salt of the 6-methylenetetraacycline. The important feature is that the total acid present be such as to provide a total molar ratio of acid to 6-methylenetetraacycline base of from 1.1 to 2.0. Alternatively, an excess of from 0.1 to 1.0 mole of acid per mole of 6-methylenetetraacycline acid addition salt is favored. Total molar ratios of acid to 6-methylenetetraacycline base of from 1.5 to 2.0 are preferred. The presence of a greater molar ratio, for example, even up to five moles of acid per mole of 6-methylenetetraacycline base does not appear detrimental to the process. Para-toluene sulfonic acid and hydrochloric acid are especially useful as promoters.

50 Other substances also have a promoter effect on the reaction. In addition to the above-mentioned acids, it has been observed that stannous chloride exerts a pronounced promoter effect, even beyond that observed with the above-mentioned excesses of acids. Under a given set of conditions, the use of stannous chloride appears to be more effective than does p-toluenesulfonic acid in promoting the reaction. The use of other metal chlorides, such as those of platinum, cadmium, silver, lead, copper, sodium and mercury, are useful promoters for reactions wherein chloride is present. Lewis acids appear to function as promoters of the reaction.

65 Such promoters are generally used at levels of from 0.1 mole to 5 moles, per mole of 6-methylenetetraacycline acid addition salt used.

Higher levels appear to be of no value. The preferred range is from 0.1 to 1.0 moles per mole of 6-methylenetetraacycline acid addition salt. The phosphines of value in this improved process are those of the formula:



wherein each of R_1 and R_2 is phenyl or substituted phenyl wherein the substituent is selected from halo, lower alkoxy, dimethylamino and lower alkoxy, dimethylamino and lower alkyl; and R_3 is R_1 , hydrogen or lower alkyl. The preferred phosphine is triphenylphosphine primarily because of its availability and, hence, economy relative to that of other phosphines defined herein.

The terms "lower alkoxy" and "lower alkyl" as used herein are intended to embrace alkoxy and alkyl groups of from 1 to 4 carbon atoms, inclusive.

The 6-demethyl-6-deoxy-6-methylenetetraacycline reactants of formula I above are known compounds. Their preparation by 11a-dehalogenation of the corresponding 11a-halo-6-demethyl-6-deoxy-6-methylenetetraacyclines by chemical or catalytic reduction is described in detail in J. Am. Chem. Soc. 85, 3943-53 (1963), and United States Patents 2,984,646 and 3,183,267. The favored procedure comprises catalytic reduction of the 11a-chloro derivatives in a reaction-inert solvent in the presence of a noble metal catalyst, e.g., palladium, and preferably rhodium, at a temperature of from 0° C. to 60° C. and a hydrogen pressure of from atmospheric to superatmospheric pressures. Rhodium is especially preferred for this step since it serves as catalyst for hydrogenation of the 6-methylene group. Palladium or platinum afford, at best, very poor hydrogenation of the 6-methylene group under the conditions of this process and are not favored for the dehalogenation step since no advantage is realized by the use of different catalysts when the process is run as a two step, "one-pot" process.

The dehalogenation step, especially when conducted by catalytic reduction over a noble metal catalyst, and particularly over rhodium (supported or unsupported), permits a convenient tie-in with the process of catalytic hydrogenation of the 6-methylene group. As will be indicated later the total dehalogenation and hydrogenation of an 11a-halo compound can be carried out as a unitary process, but preferably dehalogenation is effected with rhodium alone and the phosphorus compound added for hydrogenation. The overall process, beginning with an 11a-halo, especially an 11a-chloro-6-demethyl-6-deoxy-6-methylenetetraacycline, becomes in fact a "one-pot" process. To the reaction mixture containing the 11a-dehalo compound, produced under the conditions described above, tri-

value. The moles per acid addition in this formula: 70

aryl or substituent is dimethylamino and in or lower triphenyl-availability at of other 75

and "lower to embrace to 4 carbon 80

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cially when ver a noble er rhodium nits a con- of catalytic group. As dehalogena- -halo com- ary process, ffectd with 120

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ion mixture d; produced above, tri-

phenylphosphine (or other appropriate phosphine as defined herein) and usually additional catalyst, preferably rhodium-on-carbon, are added and the resulting mixture contacted with hydrogen under conditions described herein. If palladium is used in the dehalogenation step, the addition of rhodium is necessary to achieve satisfactory hydrogenation of the 6-methylene group. If rhodium is used for dehalogenation, it can be added all at once or stepwise as is discussed below:

A preferred embodiment of this invention comprises hydrogenation of an acid addition salt of the 11a-chloro derivative over 5% rhodium-on-carbon in a reaction-inert medium, e.g., methanol, at pressures of from sub-atmospheric to superatmospheric and at temperatures of from 0° C. to 60° C. Sufficient hydrogen is introduced to achieve only 11a-dechlorination. The preferred salts of the 11a-chloro derivatives are the p-toluenesulfonate, perchlorate and perborate salts. These salts are preferred since, as noted above, such salts of the 11a-deschloro compounds appear to be of especial value in the subsequent hydrogenation of the 6-methylene group. Other salts of value for the 11a-dechlorination are the hydrochlorides and sulfosalicylates.

This method is especially preferred for large scale reactions since the reaction mixture of the 11a-dechlorinated compound then contains a portion of the preferred catalyst for the final hydrogenation step. Additionally, an amount of acid equivalent on a molar basis to the 11a-chloro compound converted to 11a-deshalo compound is produced thus obviating the need to add more acid. It is then only necessary to add the remaining portion of the rhodium catalyst (rhodium-on-carbon is preferred) and a suitable phosphine, preferably triphenylphosphine, to continue the process.

A further advantage of beginning with the appropriate 11a-chloro derivative is the fact that any of the 11a-chloro reactant which is not dehalogenated is carried over to the next step of the process thus affording further opportunity for additional dehalogenation to occur.

When the herein described process is run as a "one-pot" process beginning with an 11a-chloro derivative of a compound of Formula I, dehalogenation is accomplished by catalytic reduction. The amount of catalyst, preferably 5% rhodium-on-carbon, used is a catalytic amount, said expression having the previously given definition. Suitable solvents are lower alkanols, e.g. methanol, ethanol as well as a variety of other solvents such as those enumerated above in connection with the hydrogenation of the 6-methylene group.

The dehalogenation reaction mixture is then charged with additional catalyst, e.g. 5% rhodium-on-carbon. The amount of catalyst added at this point can vary widely, e.g., from one to fifty times the amount used in

the dehalogenation step. For reasons of economy from 2 to 25 times the amount of catalyst used in the dehalogenation step is a practical charge of additional catalyst. Alternatively, all the rhodium to be used in the overall reaction can be added in the dehalogenation step, thus necessitating the addition of only an appropriate phosphine in the hydrogenation step. It is, however, preferred to add rhodium to each of the steps of the overall process; 25% to 50% of the total amount being added to the 11a-dehalogenation step and the remaining portion to the hydrogenation step.

The phosphine can also be added to the reaction mixture prior to the dehalogenation. However, the yields of 6-deoxytetracyclines generally obtained in this manner are less than that obtained when the phosphine is added after the dehalogenation step, that is, after the reaction of about one mole of hydrogen per mole of 11a-halotetracycline compound present.

The amount of phosphine added, preferably triphenylphosphine, can also vary widely. Molar ratios of phosphine to noble metal catalyst of from 2 to 10 are satisfactory in the process of this invention. The favored molar ratio is from 3—9; and the preferred ratio is from 3 to 6 moles of phosphine per mole of total noble metal used.

A further preferred embodiment of this invention comprises 11a-dechlorination of an appropriate 11a - chloro - 6 - demethyl- 6 - deoxy - 6 - methylenetetracycline by treatment thereof with a tertiary phosphine. Secondary phosphines or tertiary phosphites can also be used. Tertiary phosphines, especially tertiary aryl phosphines wherein the aryl group is phenyl or substituted phenyl as defined herein, are preferred because of the favorable yield afforded by such agents.

The process comprises treating the 11a-chloro - 6 - demethyl - 6 - deoxy - 6-methylenetetracycline, usually as the hydrochloride or p-toluenesulfonate salt since these are the forms in which the 11a-chloro compounds are generally isolated, in a molar proportion of from one to three moles of phosphine per mole of 11a-chloro compound. The reaction is conducted in a hydroxylic containing solvent such as water and lower alkanols (preferably methanol or ethanol) at a temperature of from 20° to the boiling point of the solvent system for periods of up to three hours. To the reaction mixture containing the deshalo compound, a catalytic amount of a noble metal catalyst and an appropriate phosphine as defined herein are added. Hydrogen is then introduced into the system and the hydrogenation of the 11a-deshalo compound carried out in the manner described above.

The reaction mixtures are conveniently monitored and assayed to determine the approximate extent of the reaction and

approximate yields of α - to β -isomers by thin layer chromatography on silica gel plates, buffered at pH 6, using the solvent system tetrahydrofuran-water (95—5 by volume).
 5 The plates are developed with ammonia and visualized under ultra-violet light (366 m μ). More precise determination of the extent and yields of the reactions are achieved by high pressure liquid chromatography. This is
 10 accomplished using the Chromatronix 3100 chromatograph (Chromatronix Inc., Berkely, Calif.). The column used is a 2m. $\times$ 2.1 mm. column filled with Dupon SAX, a quaternary ammonium substituted methacrylate polymer coated 1% by weight on "Zipax" (registered
 15 trademark of E.I. Dupont De Nemours & Co. Inc., Wilmington, Delaware).

The solvent system is 0.001M ethylenediaminetetracetic acid, plus 0.005 M sodium acetate adjusted to 6.0 with acetic acid. A
 20 pressure of 1250 lbs. (equal to 0.5 ml. per minute) is used. The instrument has a 12 m μ injection valve.

Example I.

25 A Parr bottle is charged with 5% rhodium-on-carbon (2.88 g. of 50% wet material; 0.70 mH of rhodium), triphenylphosphine (0.55 g., 2.1 mM) and N-methyl-2-pyrrolidone (10 ml.). The mixture is shaken for 0.5 hour
 30 at 70° C. under 10 p.s.i. of nitrogen at the end of which time a slurry of 6 - demethyl - 6 - deoxy - 6-methylene - 5-hydroxytetracycline hydrochloride (3.70 g., 7.7 mM) and stannous chloride (0.329 g., 1.5 mM) in N - methyl - 2 - pyrrolidone
 35 (40 ml.) is added into the bottle via a syringe. The bottle is then filled with hydrogen at 50 p.s.i. and shaken overnight at 70° C. for 18 hours. Thin layer chromatography of the
 40 reaction mixture showed the reaction went to completion to give 96% α - and 4% β -6-deoxy-5-hydroxytetracycline.

The thin layer chromatography is conducted on silica gel plates. The plates are
 45 prepared by spraying them to saturation with a pH 6.0 phosphate-citric acid buffer and then drying. The system 95% tetrahydrofuran-5% water is added and the plates developed in ammonia and visualized under 366 m μ
 50 ultraviolet light. In this system 6 - demethyl - 6 - deoxy - 6 - methylene - 5-hydroxytetracycline has an R_f = 0.31; 6 α - 5 - hydroxytetracycline an R_f = 0.50; and 6 β - 5 - hydroxytetracycline an
 55 R_f = 0.25.

A known mixture of the above compounds is run for comparison.

Example II.

60 A Parr bottle is charged with 5% rhodium-on-carbon (0.572 gms., 50% wet material; 0.14 mM of rhodium), triphenylphosphine (0.113 gms., 0.43 mM) and 1.26 ml. con-

centrated hydrochloric acid followed by a solution of 6 - demethyl - 6 - deoxy - 6-methylene - 6 - hydroxytetracycline hydrochloride (3.39 gms., 7.0 mM) in methanol
 65 (35 ml.) containing 7.0 mM of p-toluenesulfonic acid. The bottle is then filled with hydrogen at 50 p.s.i. and shaken overnight at 75° C. for 20 hours. Thin layer chromatography of the reaction mixture showed pre-
 70 dominantly α - 6 - deoxy - 5 - hydroxytetracycline and trace levels of starting materials and 6 β -epimer.

Example III.

A stainless steel autoclave is charged with 2.88 gms of 5% rhodium-on-carbon (50% wet, 0.70 mM of rhodium) tri-(4-chlorophenyl)phosphine (0.76 gms., 2.1 mM) and a
 80 solution of 6 - demethyl - 6 - deoxy - 6-methylene - 5 - hydroxytetracycline (33.9 gms., 8.0 mM) in 360 cc. methanol containing 70.0 mM of p-toluenesulfonic acid. The reaction mixture is pressurized with hydrogen
 85 gas to 200 p.s.i., temperature adjusted to 75° C. and the reaction mixture stirred for 17 hours. High pressure chromatography of the reaction mixture indicates the presence of 81% α - 6 - deoxy - 5 - hydroxytetracycline and 1.6% β -epimer. Addition of 340 cc.
 90 10% aqueous solution of 5-sulfosalicylic acid permits isolation of α - 6 - deoxy - 5-hydroxytetracycline as the 5-sulfosalicylic acid salt in 80% yield.

Example IV.

A Parr bottle is charged with 5% rhodium-on-carbon (2.88 gms., 50% wet material; 0.70 mM of rhodium), tri-(4-chlorophenyl)phosphine (0.76 gms., 2.1 mM) in 13 cc.
 100 methanol. The mixture is shaken for a half-hour at 62° C., under nitrogen atmosphere, at the end of which time a solution of 3.39 gms., 7.0 mM, of 6 - deoxy - 6 - demethyl-6 - methylene - 5 - hydroxytetracycline hydrochloride in 37 cc. of methanol, containing
 105 7.0 mM of p-toluenesulfonic acid, is added. The bottle is then filled with hydrogen at 50 p.s.i. and shaken overnight at 75° C. for 18 hours. High pressure liquid chromatography of the reaction mixture indicates the presence of 80% α - 6 - deoxy - 5 - hydroxytetra-
 110 cycline and 1.5% 6 β - epimer. α - 6-Deoxy - 5 - hydroxytetracycline may be isolated in 78% yield as the 5-sulfosalicylic acid salt.

Example V.

The procedure of Example I is repeated but using the following acid addition salts of 6-demethyl - 6 - deoxy - 6 - methylene - 5-hydroxytetracycline and the conditions of
 120 temperature, pressure, solvent and phosphine listed below:

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of 3.39
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is added.
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α - 6-
may be
salicylic 115

reated but
alts of 6-
lene - 5-
tions of 120
phosphine

Example V

Acid Salt*	Solvent**	T °C.	Time (Hrs.)	P (p.s.i.)	R ₁	R ₂	R ₃
HCl	NMP	70	28	14	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
HCl	NMP	70	18	50	4-ClC ₆ H ₄	4-ClC ₆ H ₄	4-ClC ₆ H ₄
HCl	NMP	70	18	200	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅
HCl	NMP	80	20	200	C ₆ H ₅	C ₆ H ₅	H
HCl	NMP	75	18	50	2-ClC ₆ H ₄	2-ClC ₆ H ₄	2-ClC ₆ H ₄
HCl	NMP	70	18	50	3-ClC ₆ H ₄	3-ClC ₆ H ₄	3-ClC ₆ H ₄
HCl	NMP	70	18	50	4-Me ₂ NC ₆ H ₄	4-Me ₂ NC ₆ H ₄	4-Me ₂ NC ₆ H ₄
HCl	NMP	70	18	100	4-Et ₂ NC ₆ H ₄	4-Et ₂ NC ₆ H ₄	4-Et ₂ NC ₆ H ₄
HCl	NMP	70	18	75	C ₆ H ₅	C ₆ H ₅	4-ClC ₆ H ₄
HCl	CH ₃ OH	70	18	75	C ₆ H ₅	C ₆ H ₅	4-BrC ₆ H ₄
HCl	NMP	75	20	65	C ₆ H ₅	C ₆ H ₅	4-Me ₂ NC ₆ H ₄
HCl	NMP	70	18	1000	4-tolyl	4-tolyl	4-tolyl
PTS	NMP	70	20	200	4-tolyl	4-tolyl	CH ₃
PTS	NMP	80	18	100	C ₆ H ₅	4-tolyl	CH ₃
PTS	NMP	80	18	100	C ₆ H ₅	4-BrC ₆ H ₄	4-Me ₂ NC ₆ H ₄
PTS	NMP	80	18	100	4-tolyl	4-tolyl	4-MeOC ₆ H ₄
HCl	CH ₃ OH	80	18	100	4-ClC ₆ H ₄	4-ClC ₆ H ₄	4-ClC ₆ H ₄
citrate	CH ₃ OH	75	24	50	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
tartrate	NMP	75	24	50	2-tolyl	2-tolyl	2-tolyl
PTS	THF	70	24	50	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
PTS	THF	60	36	100	C ₆ H ₅	4-tolyl	C ₂ H ₅
PTS	C ₂ H ₅ OH	50	18	200	C ₆ H ₅	4-MeOC ₆ H ₄	n-C ₄ H ₉
HBr	NMP	80	16	100	4-ClC ₆ H ₄	4-ClC ₆ H ₄	4-ClC ₆ H ₄
HCl	dioxane	80	15	500	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
PTS	NMP	50	20	2000	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
PTS	Acetone	80	18	1000	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅
PTS	Glyme	75	24	1000	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅

* PTS = P-toluenesulfonate; THF = tetrahydrofuran; NMP = N-methyl-2-pyrrolidone;

** Glyme = 2-Methoxyethanol

Example VI.

To a 500 ml. Parr bottle is added 11a-chloro - 6 - demethyl - 6 - deoxy - 6-methylene - 5 - hydroxytetracycline p-toluenesulfonate (5.0 g., 7.1 mM), 5% rhodium-on-carbon (100 mg. of 50% wet material; 0.49 mM of rhodium) and methanol (30 ml.). The flask and contents are purged with nitrogen and then hydrogen at 50 p.s.i. introduced into the flask. The bottle is shaken at room temperature overnight. Assay of the reaction mixture by thin layer chromatography according to the procedure given in Example I showed the 11a-deschloro compound to be the predominant product.

The Parr bottle containing the 11a-deschloro compound is purged with nitrogen and charged with 5% rhodium-on-carbon (2.88 g. of 50% wet material; 0.70 mM of rhodium) and triphenylphosphine (0.55 g., 2.1 mM). The bottle is pressurized to 50 p.s.i. with hydrogen (after appropriate purging) and shaken at 75° C. overnight. The reaction mixture is cooled, methanol (30 ml.) and gaseous hydrogen chloride (2 molar equivalents) added. The slurry is filtered and the filtrate diluted to twice its volume with water. Sulfosalicylic acid (33 ml. of a 10% aqueous solution) is added to the diluted filtrate and the resulting slurry stirred overnight. The sulfosalicylate salt is filtered off and the filter cake dried (3.65 g.). High pressure liquid chromatography (HPLC) according to the above-mentioned procedure showed 55.5% of 6 α - and 1.8% of 6 β -deoxy - 5 - hydroxytetracycline and about 2% of 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline present. This yield of 6 α -isomer corresponds to 65% based upon the starting 11a-chloro derivative.

Example VII.

A. In an atmosphere of nitrogen, 5% rhodium-on-carbon (2.88 g. of 50% wet material; 0.70 mM rhodium), triphenylphosphine (0.55 g. 2.1 mM) and N - methyl - 2 - pyrrolidone (13 ml.) are placed in a Parr bottle, heated and shaken at 70° C. for half-hour. A slurry of 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline hydrochloride 3.7 g., 7.72 mM) in N-methyl-2-pyrrolidone (37 ml.) is then added while maintain a nitrogen atmosphere. The nitrogen is purged, hydrogen (50 p.s.i) introduced, and the mixture heated to 70° C. and shaken for 16 hours.

Assay of the reaction mixture as in Example I showed 55% of α - and 5% β -6-deoxy-5-hydroxytetracycline, and 45% of starting material to be present.

B. The reaction mixture is filtered and recharged with 5% rhodium-on-carbon (2.88 g. of 50% wet material) and triphenylphosphine (0.55 g.). Hydrogenation as above for an

additional 16 hours showed, upon assay, 82% yield of α - and 3% yield of β -isomer. 15% of starting material still remained.

Example VIII.

The procedure of Example VIII-A is repeated but with the addition of p-toluenesulfonic acid (1.465 g., 7.72 mM) to the initial charge of catalyst and triphenylphosphine.

After 16 hours reaction time, assay showed 82% α - and 2% β -6 - deoxy - 5 - hydroxytetracycline and 16% starting material.

Further hydrogenation according to Example VII-B showed, upon assay, complete conversion of starting material and a 95% yield of α - and 2% yield of β -6 - deoxy - 5 - hydroxytetracycline. Unknown products accounted for the remaining 3% of material.

Example IX.

Repetition of the procedure of Example VIII-A but using N - methyl - 2 - pyrrolidone-water (1—1 by volume) in place of N-methyl - 2 - pyrrolidone as solvent afforded 55% α -6 - deoxy - 5 - hydroxytetracycline and 45% unreacted material when assayed by the procedure of Example I.

Example X.

Repetition of Example VII-A using N - methyl - 2 - pyrrolidone - methanol (1—1 by volume) as solvent in place of N-methyl - 2 - pyrrolidone showed 80% α -6 - deoxy - 5 - hydroxytetracycline and 20% unreacted material in the reaction mixture.

Example XI.

The procedure of Example VII-A is repeated but adding $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$ (0.68 mM) to the original charge of catalyst and triphenylphosphine. Assay of the reaction mixture shows 85% α -6 - deoxy - 5 - hydroxytetracycline, 10% starting material and 5% decomposition products to be present.

Example XII.

Repetition of the procedure of Example VIII but using tetrahydrofuran as solvent in place of N-methyl-2-pyrrolidone showed, after 16 hours reaction time, 76% α - and 1% β -6 - deoxy - 5 - hydroxytetracycline; and 23% unreacted starting material.

Example XIII.

Following the procedure of Example I, 6 - demethyl - 6 - deoxy - 6 - methylenetetracycline is hydrogenated to predominantly the α - isomer of 6 - demethyl - 6 - deoxytetracycline.

Example XIV.

The procedure of Example III is repeated using 6 - demethyl - 6 - deoxy - 6-methylenetetracycline as substrate to produce a product consisting primarily of 6 α -deoxytetracycline.

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mer. 15% 65

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Example
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Example I,
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6- α -deoxy-

Example XV.

11a - chloro - 6 - demethyl - 6 - deoxy-
6 - methylenetetracycline is hydrogenated
according to the procedure of Example VI to
5 give primarily 6 - α - deoxytetracycline.

Example XVI.

The procedure of Example VI is repeated
but without the addition of triphenylphosphine
to the reaction mixture of the 11a-deschloro
10 compound.

Assay of the reaction mixture according to
the procedure set forth in Example I showed
the ratio of β - to α -isomer to be greater than
5 to 1.

Example XVII.

15 A solution of 11a - chloro - 6 - deoxy-
6 - demethyl - 6 - methylene - 5 - hydroxy-
tetracycline p-toluenesulfonate (10.0 g., 0.154
mM) in methanol (52 ml.) is added under
a nitrogen atmosphere to a Parr bottle, previ-
ously flushed with nitrogen, and containing
20 5% rhodium-on-carbon (0.20 g. of 50% wet
material, 0.05 mM). The bottle and con-
tents are purged with nitrogen and then hydro-
gen at 55 p.s.i. introduced into the Parr
bottle. The reaction mixture is shaken at 26° C.
for approximately 14 hours. Thin layer
chromatography of the reaction mixture
showed the 11a-deschloro compound and a
30 trace of α - 6 - deoxy - 5 - hydroxytetra-
cycline to be present. The bottle is depressur-
ized and then purged with nitrogen.

To the Parr bottle containing the 11a-des-
chloro compound is added a mixture of 5%
35 rhodium-on-carbon (0.429 g. of 50% wet
material, 0.105 mM) triphenylphosphine
(0.226 g., 0.86 mM) and methanol (12 ml.).
The bottle is purged with nitrogen and then
hydrogen and then pressurized to 50 p.s.i. with
40 hydrogen. It is shaken at 68°—72° C. for
about 8 hours. The reaction mixture is cooled,
removed from the bottle and acidified with
concentrated hydrochloric acid (11.0 ml.).
The acidified mixture is then filtered, and
45 the solid washed with methanol to give a
total filtrate volume of 100 ml. The addition
of sulfosalicylic acid to the filtrate accord-
ing to the procedure of Example VI precipi-
tates 8.85 g. of sulfosalicylate salt. HPLC
50 showed 59.9% of α - and 1.33% of β -6-
deoxy-5-hydroxytetracycline and about 0.8%
of 6 - deoxy - 6 - demethyl - 6 - methylene-
5 - hydroxytetracycline present.

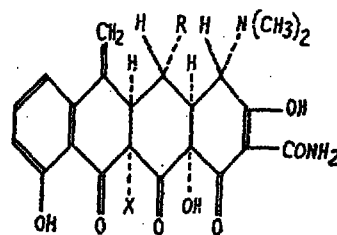
Example XVIII.

55 A mixture of 11a - chloro - 6 - demethyl-
6 - deoxy - 6 - methylene - 5 - hydroxytetra-
cycline p-toluenesulfonate (2.97 g., 4.51 mM),
methanol (30 ml.), water (4 ml.) and tri-
phenylphosphine (1.205 g. 4.60 mM) is
60 shaken in a Parr bottle under an atmosphere
of nitrogen at room temperature for three
hours.

The Parr bottle containing the 11a-des-
chloro compound is purged with nitrogen and
charged 5% rhodium-on-carbon (1.69 g. of
65 50% wet material; 0.41 mM of rhodium)
and triphenylphosphine (0.32 g., 1.23 mM).
The bottle is pressurized to 50 p.s.i. with
hydrogen (after appropriate purging) and
shaken at 75° C. overnight. The reaction
70 mixture is cooled, methanol (30 ml.) and
gaseous hydrogen chloride (2 molar equiva-
lents) added. The slurry is filtered and the
filtrate diluted to twice its volume with water.
Sulfosalicylic acid (33 ml. of a 10% aqueous
75 solution) is added to the diluted filtrate and
the resulting slurry stirred overnight. The
sulfosalicylate salt is filtered off and the filter
cake dried. The principal product is α -6-
80 deoxy-5-hydroxytetracycline.

WHAT WE CLAIM IS:—

1. A process for the production of 6-methyl-
6-deoxytetracyclines wherein hydrogen is
introduced into a reaction-inert solvent medium
containing a catalytic amount of rhodium
85 metal and a tetracycline compound which is a
tetracycline base of the Formula:



or an acid addition salt thereof wherein:

R is hydrogen or hydroxyl; and X is hydro-
90 gen, chloro, or fluoro and the hydrogen is
maintained in contact with the said reaction
mixture at a temperature of from 0° to
100° C. and at a pressure of from atmospheric
95 to 2000 p.s.i., to hydrogenate the 6-methylene
group and dehalogenate the 11a-halo group if
present the reaction being conducted in the
presence of (a) from 2 to 10 moles, per mole
of rhodium metal, of a compound of the
Formula: $R_1R_2R_3P$ wherein each of R_1 and
100 R_2 is the same or different and is phenyl or
substituted phenyl wherein the substituent is
halo, lower alkoxy, dimethylamino or lower
alkyl; and

R_3 is R_1 , is hydrogen or lower alkyl; and
105 (b) at least 1 mole of acid per mole of tetra-
cycline base, or from 0.1 to 1.0 mole of
stannous chloride per mole of tetracycline acid
addition salt.

2. A process according to claim 1, wherein
110 X is fluoro or chloro and the reaction is
carried out until reaction of two moles of
hydrogen per mole of said tetracycline com-
pound occurs.

3. A process according to claim 2, wherein
115 hydrogen is introduced into said reaction-inert



Example XV.

11a - chloro - 6 - demethyl - 6 - deoxy-6 - methylenetetracycline is hydrogenated according to the procedure of Example VI to give primarily 6 - α - deoxytetracycline.

Example XVI.

The procedure of Example VI is repeated but without the addition of triphenylphosphine to the reaction mixture of the 11a-deschloro compound.

Assay of the reaction mixture according to the procedure set forth in Example I showed the ratio of β - to α -isomer to be greater than 5 to 1.

Example XVII.

A solution of 11a - chloro - 6 - deoxy-6 - demethyl - 6 - methylene - 5 - hydroxy-tetracycline p-toluenesulfonate (10.0 g., 0.154 mM) in methanol (52 ml.) is added under a nitrogen atmosphere to a Parr bottle, previously flushed with nitrogen, and containing 5% rhodium-on-carbon (0.20 g. of 50% wet material, 0.05 mM). The bottle and contents are purged with nitrogen and then hydrogen at 55 p.s.i. introduced into the Parr bottle. The reaction mixture is shaken at 26° C. for approximately 14 hours. Thin layer chromatography of the reaction mixture showed the 11a-deschloro compound and a trace of α - 6 - deoxy - 5 - hydroxytetracycline to be present. The bottle is depressurized and then purged with nitrogen.

To the Parr bottle containing the 11a-deschloro compound is added a mixture of 5% rhodium-on-carbon (0.429 g. of 50% wet material, 0.105 mM) triphenylphosphine (0.226 g., 0.86 mM) and methanol (12 ml.). The bottle is purged with nitrogen and then hydrogen and then pressurized to 50 p.s.i. with hydrogen. It is shaken at 68°—72° C. for about 8 hours. The reaction mixture is cooled, removed from the bottle and acidified with concentrated hydrochloric acid (11.0 ml.). The acidified mixture is then filtered, and the solid washed with methanol to give a total filtrate volume of 100 ml. The addition of sulfosalicylic acid to the filtrate according to the procedure of Example VI precipitates 8.85 g. of sulfosalicylate salt. HPLC showed 59.9% of α - and 1.33% of β -6-deoxy-5-hydroxytetracycline and about 0.8% of 6 - deoxy - 6 - demethyl - 6 - methylene-5 - hydroxytetracycline present.

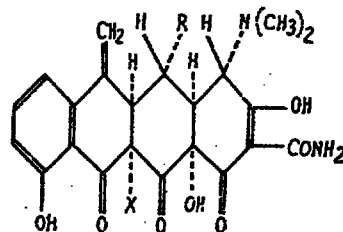
Example XVIII.

A mixture of 11a - chloro - 6 - demethyl-6 - deoxy - 6 - methylene - 5 - hydroxytetracycline p-toluenesulfonate (2.97 g., 4.51 mM), methanol (30 ml.), water (4 ml.) and triphenylphosphine (1.205 g. 4.60 mM) is shaken in a Parr bottle under an atmosphere of nitrogen at room temperature for three hours.

The Parr bottle containing the 11a-deschloro compound is purged with nitrogen and charged 5% rhodium-on-carbon (1.69 g. of 50% wet material; 0.41 mM of rhodium) and triphenylphosphine (0.32 g., 1.23 mM). The bottle is pressurized to 50 p.s.i. with hydrogen (after appropriate purging) and shaken at 75° C. overnight. The reaction mixture is cooled, methanol (30 ml.) and gaseous hydrogen chloride (2 molar equivalents) added. The slurry is filtered and the filtrate diluted to twice its volume with water. Sulfosalicylic acid (33 ml. of a 10% aqueous solution) is added to the diluted filtrate and the resulting slurry stirred overnight. The sulfosalicylate salt is filtered off and the filter cake dried. The principal product is α -6-deoxy-5-hydroxytetracycline.

WHAT WE CLAIM IS:—

1. A process for the production of 6-methyl-6-deoxytetracyclines wherein hydrogen is introduced into a reaction-inert solvent medium containing a catalytic amount of rhodium metal and a tetracycline compound which is a tetracycline base of the Formula:



...I.

or an acid addition salt thereof wherein:

R is hydrogen or hydroxyl; and X is hydrogen, chloro, or fluoro and the hydrogen is maintained in contact with the said reaction mixture at a temperature of from 0° to 100° C. and at a pressure of from atmospheric to 2000 p.s.i., to hydrogenate the 6-methylene group and dehalogenate the 11a-halo group if present the reaction being conducted in the presence of (a) from 2 to 10 moles, per mole of rhodium metal, of a compound of the Formula: $R_1R_2R_3P$ wherein each of R_1 and R_2 is the same or different and is phenyl or substituted phenyl wherein the substituent is halo, lower alkoxy, dimethylamino or lower alkyl; and

R_3 is R_1 , is hydrogen or lower alkyl; and (b) at least 1 mole of acid per mole of tetracycline base, or from 0.1 to 1.0 mole of stannous chloride per mole of tetracycline acid addition salt.

2. A process according to claim 1, wherein X is fluoro or chloro and the reaction is carried out until reaction of two moles of hydrogen per mole of said tetracycline compound occurs.

3. A process according to claim 2, wherein hydrogen is introduced into said reaction-inert



- solvent medium containing a catalytic amount of rhodium metal and at tetracycline compound of Formula I, wherein X is fluoro or chloro and hydrogen is maintained in contact with the reaction mixture at a temperature of from 0° C. to 60° C. until replacement of X group is substantially complete;
- 5 A further catalytic amount of a rhodium metal is added to the reaction mixture and from 2 to 10 moles per mole of total rhodium metal present of the compound of the Formula $R_1R_2R_3P$ hydrogen is contacted with the reaction mixture at a temperature of from 70° C. to 95° C., until reduction of the 6-methylene group is substantially complete.
- 10 4. A process according to claim 3, wherein R is hydroxy and X is chloro.
- 15 5. A process according to any one of claims 1 to 4, wherein the tetracycline compound is present as an acid addition salt.
- 20 6. A process according to claim 1, wherein R is hydroxyl.
- 25 7. A process according to any one of claims 1 to 6, wherein R_3 is R_1 .
- 30 8. A process according to any one of claims 1 to 7, wherein the rhodium used is rhodium-on-charcoal, the temperature is from 70° C. to 95° C., and the pressure is from one atmosphere to 1000 p.s.i.
9. A process according to any one of claims 1 to 8, wherein the molar ratio of acid to tetracycline compound is from 1.5 to 1 to 2 to 1.
10. A process according to any one of claims

1 to 9, wherein the acid is p-toluenesulfonic acid or hydrochloric acid. 35

11. A process according to any one of claims 1 to 10, wherein each of R_1 , R_2 and R_3 is phenyl or 4-chlorophenyl. 40

12. A process according to any one of the preceding claims, wherein the reaction-inert solvent medium is methanol, ethanol, acetone, 2-methoxy-ethanol, N-methyl-2-pyrrolidone, tetrahydrofuran or dioxane. 45

13. A process according to claim 12, wherein from 5 to 80 volume per cent water is present in the reaction mixture. 50

14. A process according to any one of claims 1 to 9 or 11 to 13, wherein the reaction is conducted in the presence of stannous chloride. 55

15. A process according to any one of claims 1 or 5 to 14, wherein the tetracycline compound is 6 - demethyl - 6 - deoxy - 6-methylene - 5 - hydroxytetracycline hydrochloride. 60

16. A process for the production of 6-methyl - 6 - deoxytetracyclines, substantially as described in the Examples.

17. A 6 - methyl - 6 - deoxytetracycline whenever prepared by a process as claimed in any one of the preceding claims. 65

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court,
Chancery Lane,
London, W.C.2.