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PATENT SPECIFICATION

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(54) PREPARATION OF α -6-DEOXY-5-HYDROXYTETRACYCLINE

(71) We, PFIZER INC., a corporation organised 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 a process for the preparation of the antibiotic α -6-deoxy-5-hydroxytetracycline and acid addition salts thereof by reduction of 6-deoxy-6-demethyl-6-methylene-5-hydroxy-tetracycline with dicobalt octacarbonyl, triphenyl phosphine and a mineral acid, e.g. hydrochloric acid, in a reaction solvent medium in which the reagents are soluble.

The reaction of 6-methylene tetracyclines, 11a-halo-6-methylenetetracyclines, acid addition salts thereof and polyvalent metal salt complexes thereof with hydrogen in the presence of a heterogeneous noble metal catalyst to produce the corresponding epimeric α - and β -6-deoxytetracyclines is disclosed in United Kingdom Patent Specification No. 995,032. The use of a poisoned noble metal catalyst to achieve the same conversion but with an increase in the ratio of α - to β -6-deoxytetracycline is disclosed in United Kingdom Patent Specification No. 1,195,456. United Kingdom Patent Specification No. 995,031 discloses the use of catalytic reduction using hydrogen and a noble metal catalyst to achieve only 11a-dehalogenation of 11a-halo-6-methylenetetracyclines. Additionally, reduction of 11a-halo-6-methylenetetracyclines, salts and complexes thereof in the presence of a noble metal catalyst using a hydrazine as the hydrogen source is also known. United Kingdom Patent Specification No. 1,296,340 discloses the use of Raney nickel and Raney cobalt as catalysts for such reductions.

Rhodium halide complexes containing tertiary phosphine or arsine ligands, their preparation and use as homogeneous hydrogenation catalysts are disclosed in United States Patent Specification No. 3,639,439. Soluble

complexes of the platinum group of metals, particularly of rhodium, which contain a halide and a tertiary phosphine, arsine, stibine or amine, their preparation and use as hydrogenation catalysts are also disclosed in United Kingdom Patent Specifications Nos. 1,138,601, 1,219,763; 1,121,642 and 1,121,643. Such catalysts are reported to provide an improved process for hydrogenation of unsaturated organic compounds, particularly of olefins, compared to the use of heterogeneous catalysts.

Another known process involves the preparation of α -6-deoxytetracyclines by homogeneous catalytic hydrogenation using tris(triphenylphosphine)chlororhodium as catalyst. The catalyst reportedly may be preformed or may be prepared directly in the reaction medium by dissolving rhodium trichloride in the medium in the presence of between one and three molar equivalents of triphenylphosphine.

United States Patent Specification No. 3,692,864 discloses the hydrogenation of unsaturated organic molecules using homogeneous metal complexes of the iron triad type (nickel, cobalt, iron) with tertiary phosphines. Typical of the complexes described is chlorotris(triphenylphosphine)cobalt.

Numerous publications disclose homogeneous catalysis as a promising approach to hydrogenation reactions, including regioselective, selective and asymmetric reductions. Knowles *et al.*, *Chem. Commun.*, p. 1445 (1968), and Horner *et al.*, *Angew. Chem.*, Int. Ed., 7, 942 (1968) disclose the use of complexes of univalent rhodium with optically active tertiary phosphine ligands as homogeneous catalysts to achieve asymmetric catalytic hydrogenation. Recent publications presenting rather a comprehensive review of the art: Harmon *et al.*, *Chem. Rev.*, 73, 21—52 (1973); Knowles *et al.*, *Chem. Commun.*, p. 10 (1972); Grubbs *et al.*, *J. Am. Chem. Soc.*, 93, 3062 (1971); Kagan *et al.*, *J. Am. Chem. Soc.*, 94, 6429 (1972); and "Homogeneous Catalysis, Industrial Applications and Implications," Vol. 70, Advances in Chemistry Series, published by the American Chemical Society,

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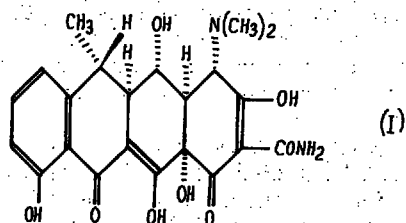
Washington, D.C. (1968); "Aspects of Homogeneous Catalysis" Vol. 1, pp. 5-75 (1970), edited by R. Ugo and published by Carlo Manfredi, Milan, Italy; and Vol'Pin *et al.*, *Russian Chemical Reviews* 38, 273-289 (1969).

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

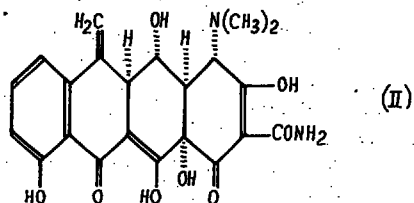
All the preceding prior art references disclose the reduction of a substrate by employing hydrogen gas in the presence of a reduction catalyst.

Fichteman, *et al.*, *J. Org. Chem.*, 33, 1281, (1968) and Taylor, *et al.*, *J. Org. Chem.*, 37, 3913 (1972) report the use of cobalt hydrocarbonyl, $\text{HCo}(\text{CO})_3$ or $\text{HCo}(\text{CO})_4$, as a compound capable of reducing olefins or aromatic substrates, the said cobalt hydrocarbonyl being formed by the reduction of dicobalt octacarbonyl using hydrogen gas at an elevated temperature.

In accordance with the present invention there is provided a process for the preparation of a tetracycline of the formula:—



or an acid addition salt thereof, preferably the hydrochloride, which comprises contacting a 6-deoxy-6-demethyl-6-methylene-5-hydroxytetracycline of the formula:—



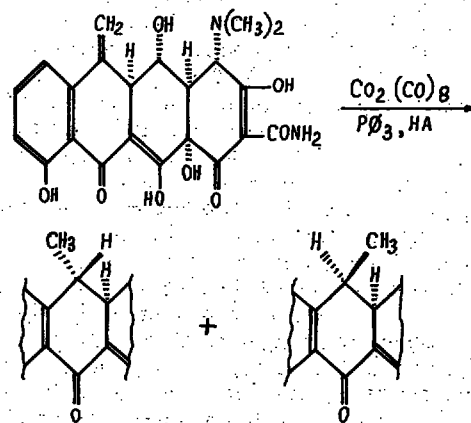
with dicobalt octacarbonyl, triphenyl phosphine and a mineral acid, preferably hydrochloric acid, in a molar ratio of 6-deoxy-6-demethyl-6-methylene-5-hydroxytetracycline/dicobalt octacarbonyl/triphenyl phosphine acid of 1.0/1.0 to 5.0/0.1 to 0.25/1.0 to 7.5, preferably 1.0/1.0/0.1/1.5, in a solvent for the reactants and under an inert atmosphere at a reaction temperature of 80° to 115°C.

Completely unexpected in the process of

the present invention is the facile reduction of the exocyclic double bond of the 6-methylenetetracycline without the need for hydrogen gas either in the reaction itself or in the formation of the reaction reagents, as well as the finding that the tetracycline molecule is not destroyed or irreversibly complexed by the reagents $\text{Co}_2(\text{CO})_8$, hydrochloric acid and/or triphenyl phosphine.

An equally unexpected finding which renders the present process of commercial interest is the highly specific nature of the reduction, resulting in almost exclusive formation of the antibiotic α -6-deoxy-5-hydroxytetracycline as opposed to the corresponding β -epimer.

The aforementioned reduction reaction may be depicted by the following reaction scheme:



α -6-deoxy-5-hydroxytetracycline + β -6-deoxy-5-hydroxytetracycline

wherein HA represents a mineral acid, preferably hydrochloric acid.

The said reaction is carried out in a solvent for the reactants. It is preferred that said solvent be of such a nature that all the reactants are maintained in solution under the reaction conditions of the process. Accordingly, it is preferred to employ a solvent for dissolving the dicobalt octacarbonyl and the mineral acid addition salt of the 6-methylenetetracycline. The most practical solvent for this purpose is a mixture of a liquid aromatic solvent, such as benzene, toluene or xylene, and an aprotic, highly polar solvent such as dimethylformamide, dimethylacetamide or hexamethylphosphoramide. The aromatic solvents serve as excellent solvents for maintaining the cobalt carbonyl in solution, and polar, aprotic solvents serve a similar role for the 6-methylenetetracycline, the triphenyl phosphine and mineral acid. In employing these solvents for the present process it is preferred that only a minimal amount of the said solvents be employed to just solubilize the reactants used. Use of proportionately larger amounts of solvents will lead to longer reac-

tion times and allow for decomposition of either the reactants or products formed.

The preferred solvents for the process of the present invention are benzene-dimethylformamide and benzene-dimethylacetamide.

As previously mentioned, the atmosphere above the reaction surface is of an inert nature, not reacting to any appreciable extent with either the starting reagents or products. Gases such as oxygen, air or carbon dioxide have a noticeable deleterious effect on the successful formation of the desired products. Accordingly, such gases as nitrogen, argon or helium make suitable atmospheres, those preferred being nitrogen and argon.

Although the reaction temperature range over which the reduction process may be conducted is relatively broad, being from 80° to 115°C., exceeding these limitations has an adverse effect on the outcome of said reaction. A reaction temperature below 70°C. leads to very slow reduction and often to an incomplete reaction, even after prolonged reaction times, while reaction temperatures in excess of 115°C. cause extensive decomposition of the desired α - 6 - deoxy - 5 - hydroxytetracycline product. The preferred reaction temperature, allowing adequate formation of the desired product without extensive decomposition of said product, is from 90° to 95°C.

Reaction times are dependent on a number of reaction variables, including reaction temperature, inherent reactivity of the starting reagents and concentration of the reactants in the solvent medium. By judiciously employing only sufficient solvent to dissolve all the starting reagents, as has been previously discussed, and utilizing a temperature range of 90° to 95°C., the reaction process of the present invention may be completed in 4 hrs.

A necessary feature of the process of the present invention is the use of a mineral acid. For this purpose hydrochloric acid appears to produce optimum results, although other mineral acids such as hydrofluoric, hydrobromic, hydroiodic, sulphuric, sulphurous, phosphoric or nitric acid can be employed. The 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline starting material may be added as the free base and the mineral acid, e.g. hydrochloric acid, added separately to the reaction mixture, or alternatively, the starting tetracycline may be added as the hydrochloric acid addition salt and additional hydrochloric acid added, if necessary. Due to the poor storability of the starting tetracycline as the free base and the stability and accessibility of the hydrochloride salt, the latter is preferred as the starting material.

Under reaction conditions wherein only one mole or equivalent of hydrochloric acid is employed, the desired α - 6 - deoxy - 5 - hydroxytetracycline as the hydrochloride salt is formed, but not in optimum yield or purity. It is preferred, therefore, to employ more than

one mole or equivalent of acid per mole of 6 - methylenetetracycline, and accordingly, to achieve this, additional acid may be added to the reaction mixture. Since the α - 6 - deoxy - 5 - hydroxytetracycline product is not stable under the reaction conditions of the present process in the presence of too high an acid concentration, it is desirable that no more than 7.5, more preferably no more than 3.5, equivalents of acid per mole of tetracycline be employed, and is further preferred that the amount of acid, e.g. hydrochloric acid, employed be 1.5 to 2.0 equivalents per mole of tetracycline starting material.

Of those aforementioned mineral acids employed in the present process, the preferred mineral acid is hydrochloric acid. When hydrochloric acid is employed, it is often convenient to add the hydrochloric acid or some other mineral acid to a solution of the commercially available 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline hydrochloride in a polar, aprotic solvent until the desired proportions of acid are reached.

Another of the starting reagents which profoundly influences the product formation of the present process is triphenyl phosphine. Other phosphines, including trialkyl, tricycloalkyl and substituted triphenyl phosphines, have been employed but without the success associated with triphenyl phosphine. Furthermore, the amount of this reagent employed has a marked influence on the molar ratio between α - 6 - deoxy - 5 - hydroxytetracycline, the desired product of the present process, and β - 6 - deoxy - 5 - hydroxytetracycline. A ratio of 0.1 to 0.25 equivalents of triphenyl phosphine per mole of 6 - methylenetetracycline is operable in providing a favourable ratio between the α - and β - 6 - deoxy - 5 - hydroxytetracycline products, with a preferred ratio of 0.1 equivalent of triphenyl phosphine per mole of tetracycline starting material.

Regarding the amount of dicobalt octacarbonyl used in the present process, it has been found that the use of as much as 2 to 5 equivalents per mole of 6 - methylenetetracycline offers no advantage over one equivalent in terms of the total reduction as well as the α - and β - 6 - deoxy 5 - hydroxytetracycline distribution in the product. Use of from less than one equivalent to as small as 0.1 equivalent causes a continuous marked reduction in the total amount of products formed. For economic reasons, one equivalent of dicobalt octacarbonyl is employed per mole of starting tetracycline.

The order of adding the reactants for the present process is not critical, although slightly higher reduction yields are obtained employing a procedure wherein the reactants dicobalt octacarbonyl, triphenyl phosphine, the mineral acid and the aprotic, polar solvent are stirred at 85°C. for approximately 10 min. prior to

the addition of the 6 - methylenetetraacycline or acid addition salt.

In exploring the scope of the reaction variables of the present process, it is extremely time-consuming to assay the reaction mixture by isolation and identification of the reduction products, and, consequently, time-saving assays such as thin-layer-chromatography and high-pressure-liquid-chromatography are frequently employed.

At the completion of the reaction, the α - 6 - deoxy - 5 - hydroxytetraacycline product exists in the reaction mixture as the acid addition salt, preferably the hydrochloride. Regarding isolation of the α - 6 - deoxy - 5 - hydroxytetraacycline from the reaction mixture, it is preferred that the mixture be filtered and the aromatic solvent removed under reduced pressure. The residual polar solvent is then filtered and treated with a saturated aqueous solution of sulphosalicylic acid. The subsequent addition of water precipitates the sulphosalicylic acid salts of the reduction products as well as any unreacted 6 - methylenetetraacycline. Further purification is carried out by recrystallization from methanol-water.

The preferred reaction conditions for the reduction of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetraacycline to α - 6 - deoxy - 5 - hydroxytetraacycline employs contacting the above-mentioned tetraacycline, dicobalt octacarbonyl and triphenyl phosphine in the molar ratio of 1.0/1.0/0.1 with hydrochloric acid in a solvent of benzene-dimethylacetamide or benzene-dimethylformamide in an inert atmosphere of nitrogen or argon at a reaction temperature of 90°C to 95°C.

The chemistry of tetracyclines and their use as antibiotics in the treatment of various microbial infections is well known and documented extensively in the medical literature. Much of the background on these agents, including α - 6 - deoxy - 5 - hydroxytetraacycline, and how it is used as a therapeutic agent, is reviewed by R. K. Blackwood, *Encyclopedia of Chemical Technology*, 20, 1-33 (1969).

The Examples which follow illustrate the invention and the manner in which it may be performed.

EXAMPLE 1

To 5.5 mg. (0.021 m mole) of triphenyl phosphine in 5 ml. of dry benzene contained in a sealed three-necked flask under a nitrogen atmosphere is added *via* a syringe through a rubber diaphragm covering a neck opening 360 mg. (1.05 m moles) of dicobalt octacarbonyl in 10 ml. of the same solvent. After stirring for 30 min. at room temperature, 100 mg. (0.21 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetraacycline hydrochloride in 10 ml. of dimethylformamide was syringed into the reaction flask, and the re-

sulting solution heated to 70°C. for 18 hrs. The required mineral acid is provided by 0.21 m mole of hydrochloric acid introduced in the form of the acid addition salt of the said tetraacycline.

A sample of the reaction mixture is removed and chromatographed on a silica gel plate which has been previously treated with a spray of 0.005 N sodium acetate solution, 0.002 N ethylenediamine tetraacetic acid adjusted to pH 6 with acetic acid and subsequently dried at 110°C. overnight. The chromatography, which is conducted in an ascending system of 95% tetrahydrofuran and 5% water, is developed in ammonia, α - 6 - deoxy - 5 - hydroxytetraacycline appearing as a yellow spot under a 366 m μ ultraviolet lamp. The results indicate a molar ratio of α - 6 - deoxy - to β - 6 - deoxy - 5 - hydroxytetraacycline of 5 to 1.

The remainder of the reaction mixture is filtered, and the benzene removed under reduced pressure. The residual green solution is filtered, and the filtrate treated first with 2 ml. of a 10% aqueous solution of sulphosalicylic acid, followed by 6 ml. of water. The resulting slurry, after stirring for 10 min., is filtered and the solids washed with water and dried.

The solids are dissolved in a minimum amount of water and placed on a high pressure liquid chromatography column packed with a quaternary ammonium-substituted methacrylate polymer coated at a rate of 1% on a controlled-surface-porosity support (United States Patent Nos. 3,485,658 and 3,505,785). The product is eluted with a buffer of 0.005 N sodium acetate solution, 0.02N ethylenediamine tetraacetic acid adjusted to pH 5.8 with acetic acid, under a pressure of 1700 lbs/sq. in. An ultraviolet monitor (254 m μ) at the column exit measures the tetracycline in the eluate. Ultraviolet measurement is, in turn, recorded with an ultraviolet pen-recorder. Measurements indicate that the yield of α - 6 - deoxy - and β - 6 - deoxy - 5 - hydroxytetraacycline is 35 to 40% of which 83% is the desired α - epimer and 17% the β - epimer.

EXAMPLE 2

By a procedure similar to that in Example 1, 72 mg. (0.21 m mole) of dicobalt octacarbonyl in 5 ml. of benzene is added to 5.5 mg. (0.021 m mole) of triphenyl phosphine in 5 ml. of benzene under a nitrogen atmosphere, followed by 100 mg. (0.21 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetraacycline hydrochloride in 10 ml. of dimethylformamide, the mixture being maintained under a nitrogen atmosphere. To the resulting reaction mixture is added 1 ml. of benzene containing 19.6 mg. (0.21 m mole) of sulphuric acid and the mixture heated to

70°C. for 16 hrs. High-pressure-liquid-chromatography assay of the reaction mixture, carried out as in Example 1, indicates that the reduction provides predominantly the α - 6 - deoxy - 5 - hydroxytetracycline.

EXAMPLE 3

Substantially similar results are obtained when phosphoric acid, hydrobromic acid, hydroiodic acid and nitric acid are used in place of sulphuric acid in the procedure of Example 2.

EXAMPLE 4

Into a three-necked flask filled with an argon atmosphere is charged 35 mg. (0.13 m mole) of triphenyl phosphine in 0.5 ml. of benzene and 180 mg. (0.52 m mole) of dicobalt octacarbonyl in 4.5 ml. of benzene, and the resulting solution is stirred at room temperature for 15 min. A solution of 250 mg. (0.52 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline hydrochloride in 2.5 ml. of dimethylacetamide is added, followed by 0.6 ml. of a 1:1 (vol./vol.) solution of dimethylacetamide - 12N - hydrochloric acid (3.4 m moles), and the reaction mixture heated to 115°C. for 4 hrs.

Following the heating period, the mixture is allowed to cool, and is filtered. The filtrate is evaporated under reduced pressure to remove the benzene and again filtered. A solution of 5.0 ml. of a 10% aqueous sulphosalicylic acid is added to the filtrate, followed by 15 ml. of water. The precipitated sulphosalicylic acid salt is filtered and dried, 445 mg. (72% yield). High-pressure-liquid-chromatography assay of a sample of the salts according to the procedure described in Example 1 indicates the product to be 75 to 80% α - 6 - deoxy - 5 - hydroxytetracycline, 1 to 2% β - 6 - deoxy - 5 - hydroxytetracycline and 15 to 20% unreduced 6 - methylene - 5 - hydroxytetracycline.

The crude product is recrystallized from methanol-water and converted to the hydrochloride salt by addition to an ethanol-water solution containing hydrochloric acid. The precipitated hydrochloride salt is further purified by recrystallization from ethanol containing a minimum amount of water.

EXAMPLE 5

To 27.5 mg. (0.104 m mole) of triphenyl phosphine in 5 ml. of benzene under a nitrogen atmosphere is added 180 mg. (0.52 m mole) of dicobalt octacarbonyl in 5 ml. of the same solvent, 250 mg. of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxy - tetracycline hydrochloride in 5 ml. of dimethylformamide and 18 mg. (0.52 m mole) of hydrogen chloride in 1 ml. of dimethylformamide, and the resulting reaction mixture heated at 85°C. for 3.0 hrs. High-pressure-liquid-chromatography indicates that there is no remaining tetracycline starting material and the reduction is complete.

The reaction mixture is cooled to room temperature and worked-up as described in Example 1. The sulphosalicylic acid salts, 260 mg., consist of 98% α - 6 - deoxy - 5 - hydroxytetracycline and 2% β - 6 - deoxy - 5 - hydroxytetracycline. The crude sulphosalicylic acid salts are converted to the hydrochloride salts by addition of said salts to ethanol-water containing hydrochloric acid. Further recrystallization from methanol-water provides pure α - 6 - deoxy - 5 - hydroxytetracycline hydrochloride.

EXAMPLE 6

Starting with 27.5 mg. (0.1 m mole) of triphenyl phosphine in 25 ml. of benzene, 342 mg. (1 m mole) of dicobalt octacarbonyl in 10 ml. of benzene, and 399 mg. (1 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline in 40 ml. of dimethylformamide containing 54 mg. (1.5 m moles) of hydrogen chloride, the procedure of Example 1 is repeated to give α - 6 - deoxy - 5 - hydroxytetracycline in comparable yields.

COMPARATIVE EXAMPLE

The procedure of Example 5 is repeated with the exception that the indicated phosphine is used in place of triphenyl phosphine. The yields represent those of α - 6 - deoxy - 5 - hydroxytetracycline (α - doxy), β - 6 - deoxy - 5 - hydroxytetracycline (β - doxy) and starting material 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline (methacycline).

	Phosphine	% α - doxy	% β - doxy	% Methacycline
	(C ₆ H ₅) ₃ P	19	~0.3	80
	(cycloC ₆ H ₁₁) ₃ P	23	<1	77
100	(p - CH ₃ OC ₆ H ₄) ₃ P	26—55	0.5—3	42—74
	(p - FC ₆ H ₄) ₃ P	38	~0.6	61

WHAT WE CLAIM IS:—

1. A process for the preparation of α - 6 - deoxy - 5 - hydroxytetracycline of the formula (I) herein or an acid addition salt thereof, which comprises contacting 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetra-

cycline or an acid addition salt thereof with dicobalt octacarbonyl, triphenyl phosphine and a mineral acid in a molar ratio of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline/dicobalt octacarbonyl/triphenyl phosphine/acid of 1.0/1.0 to 5.0/0.1 to 0.25/



70°C. for 16 hrs. High-pressure-liquid-chromatography assay of the reaction mixture, carried out as in Example 1, indicates that the reduction provides predominantly the α - 6 - deoxy - 5 - hydroxytetracycline.

EXAMPLE 3

Substantially similar results are obtained when phosphoric acid, hydrobromic acid, hydroiodic acid and nitric acid are used in place of sulphuric acid in the procedure of Example 2.

EXAMPLE 4

Into a three-necked flask filled with an argon atmosphere is charged 35 mg. (0.13 m mole) of triphenyl phosphine in 0.5 ml. of benzene and 180 mg. (0.52 m mole) of dicobalt octacarbonyl in 4.5 ml. of benzene, and the resulting solution is stirred at room temperature for 15 min. A solution of 250 mg. (0.52 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline hydrochloride in 2.5 ml. of dimethylacetamide is added, followed by 0.6 ml. of a 1:1 (vol./vol.) solution of dimethylacetamide - 12N - hydrochloric acid (3.4 m moles), and the reaction mixture heated to 115°C. for 4 hrs.

Following the heating period, the mixture is allowed to cool, and is filtered. The filtrate is evaporated under reduced pressure to remove the benzene and again filtered. A solution of 5.0 ml. of a 10% aqueous sulphosalicylic acid is added to the filtrate, followed by 15 ml. of water. The precipitated sulphosalicylic acid salt is filtered and dried, 445 mg. (72% yield). High-pressure-liquid-chromatography assay of a sample of the salts according to the procedure described in Example 1 indicates the product to be 75 to 80% α - 6 - deoxy - 5 - hydroxytetracycline, 1 to 2% β - 6 - deoxy - 5 - hydroxytetracycline and 15 to 20% unreduced 6 - methylene - 5 - hydroxytetracycline.

The crude product is recrystallized from methanol-water and converted to the hydrochloride salt by addition to an ethanol-water solution containing hydrochloric acid. The precipitated hydrochloride salt is further purified by recrystallization from ethanol containing a minimum amount of water.

EXAMPLE 5

To 27.5 mg. (0.104 m mole) of triphenyl phosphine in 5 ml. of benzene under a nitrogen atmosphere is added 180 mg. (0.52 m mole) of dicobalt octacarbonyl in 5 ml. of the same solvent, 250 mg. of 6 - deoxy - 6 - demethyl - 6 - methylene 5 - hydroxy - tetracycline hydrochloride in 5 ml. of dimethylformamide and 18 mg. (0.52 m mole) of hydrogen chloride in 1 ml. of dimethylformamide, and the resulting reaction mixture heated at 85°C. for 3.0 hrs. High-pressure-liquid-chromatography indicates that there is no remaining tetracycline starting material and the reduction is complete.

The reaction mixture is cooled to room temperature and worked-up as described in Example 1. The sulphosalicylic acid salts, 260 mg., consist of 98% α - 6 - deoxy - 5 - hydroxytetracycline and 2% β - 6 - deoxy - 5 - hydroxytetracycline. The crude sulphosalicylic acid salts are converted to the hydrochloride salts by addition of said salts to ethanol-water containing hydrochloric acid. Further recrystallization from methanol-water provides pure α - 6 - deoxy - 5 - hydroxytetracycline hydrochloride.

EXAMPLE 6

Starting with 27.5 mg. (0.1 m mole) of triphenyl phosphine in 25 ml. of benzene, 342 mg. (1 m mole) of dicobalt octacarbonyl in 10 ml. of benzene, and 399 mg. (1 m mole) of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline in 40 ml. of dimethylformamide containing 54 mg. (1.5 m moles) of hydrogen chloride, the procedure of Example 1 is repeated to give α - 6 - deoxy - 5 - hydroxytetracycline in comparable yields.

COMPARATIVE EXAMPLE

The procedure of Example 5 is repeated with the exception that the indicated phosphine is used in place of triphenyl phosphine. The yields represent those of α - 6 - deoxy - 5 - hydroxytetracycline (α - doxy), β - 6 - deoxy - 5 - hydroxytetracycline (β - doxy) and starting material 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline (methacycline).

	Phosphine	% α - doxy	% β - doxy	% Methacycline
	(C ₆ H ₅) ₃ P	19	~0.3	80
	(cycloC ₆ H ₁₁) ₃ P	23	<1	77
100	(p - CH ₃ OC ₆ H ₄) ₃ P	26-55	0.5-3	42-74
	(p - FC ₆ H ₄) ₃ P	38	~0.6	61

WHAT WE CLAIM IS:—

1. A process for the preparation of α - 6 - deoxy - 5 - hydroxytetracycline of the formula (I) herein or an acid addition salt thereof, which comprises contacting 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetra-

cycline or an acid addition salt thereof with dicobalt octacarbonyl, triphenyl phosphine and a mineral acid in a molar ratio of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline/dicobalt octacarbonyl/triphenyl phosphine/acid of 1.0/1.0 to 5.0/0.1 to 0.25/



1.0 to 7.5 in a solvent for the reactants and under an inert atmosphere at a reaction temperature of 80° to 115°C.

5 2. A process according to claim 1, wherein the reaction temperature is 90° to 95°C.

3. A process according to either one of claims 1 or 2, wherein the acid addition salt is the hydrochloride.

10 4. A process according to any one of the preceding claims wherein the mineral acid is hydrochloric acid.

15 5. A process according to any one of claims 1 to 3 wherein the mineral acid is sulphuric acid, phosphoric acid, hydrobromic acid, hydroiodic acid or nitric acid.

20 6. A process according to any one of the preceding claims, wherein the molar ratio of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - hydroxytetracycline/dicobalt octacarbonyl/triphenyl phosphine/mineral acid is 1.0/1.0/0.1/1.5.

7. A process according to any one of the preceding claims, wherein the solvent is a mixture of benzene and dimethylformamide or benzene and dimethylacetamide.

8. A process according to any one of the preceding claims, wherein the inert atmosphere is nitrogen or argon.

9. A process for the preparation of α - 6 - deoxy - 5 - hydroxytetracycline or an acid addition salt thereof according to claim 1 and substantially as hereinbefore described with reference to Examples 1 to 6.

10. α - 6 - deoxy - 5 - hydroxytetracycline hydrochloride whenever prepared by a process according to any one of the preceding claims.

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