

PATENT SPECIFICATION

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(54) RHODIUM-CONTAINING CATALYST AND USE THEREOF IN PREPARATION OF 6-DEOXY-5-OXYTETRACYCLINE

(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 invention relates to a rhodium-containing hydrogenation catalyst and to a process for the preparation thereof. The invention is also concerned with a process for hydrogenating 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline to obtain α - 6 - deoxy - 5 - oxytetracycline in the presence of the said catalyst.

United Kingdom Patent Specification No. 995032 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 said process results in the production of β - 6 - deoxytetracyclines as well as α - 6 - deoxytetracyclines. The present invention provides a substitute catalyst which produces a higher ratio of α - isomer to β - isomer.

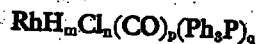
It is known that a diaceto (triphenyl phosphine) rhodium (II) complex of the formula:—



as described by Stephenson et al, J. Chem. Soc. 3632—40 (1965) is stereospecific in the hydrogenation of 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline to the extent that the ratio of α - to β - isomers of 6 - deoxy - 5 - oxytetracycline is greater than 9:1. The catalyst of the present invention which is of unknown structure is stereospecific to about the same extent but is not

of the same structure as the aforesaid Stephenson et al catalyst. This may be demonstrated by observing, for example, that whereas the carbon content of the catalyst of the present invention is 67.77%, the carbon content of Stephenson et al is only 54.6%, and that the OCOCH_3 absorption is absent in the NMR and IR spectra.

There are a number of other hydrogenation catalysts known in the prior art which are of the general formula



wherein m, n, p and q range from 0 to 3. A variety of such catalysts have been prepared and either on the basis of colour, melting point, IR spectrum or carbon and hydrogen and chlorine percentages, it has been found that these are not the same as the catalysts prepared by the process of the present invention.

The present invention is based upon the discovery that 6 - deoxy - 6 - demethyl - 6 - methylenetetracycline may be catalytically hydrogenated, in the presence of a specific catalyst, to obtain a stereoselectivity which favours production of the α - isomer over the β - isomer by a ratio of at least 9:1.

In accordance with the present invention there is provided a process for preparing a rhodium-containing hydrogenation catalyst which comprises reacting 1 mol of rhodium trichloride with 2 mols of sodium acetate in methanol at a temperature from 50°C. to the reflux temperature of the reaction mixture, then reacting the resulting reaction mixture with 2 mols of triphenylphosphine at a temperature of from 50°C. to the reflux temperature of the reaction mixture and recovering the resulting insoluble material comprising the catalyst. The presence of methanol in the preparation of the aforesaid catalyst is essential. For example, replacement of methanol by ethanol in the aforesaid process fails to produce the desired catalyst.

Preferably, the rhodium chloride is in the form of the trihydrate of rhodium trichloride. Moreover, the reaction mixture preferably contains from 1 to 5% of water based on the weight of methanol.

The invention also provides a hydrogenation catalyst which comprises the insoluble material produced by the above described process.

The catalyst of the present invention may be readily recovered by a variety of means since it precipitates from the reaction mixture. Filtration is as convenient a means as any and may be followed by washing the recovered material with methanol.

Although the structural identity of the catalyst of the present invention has not been determined because crystals of suitable size could not be obtained for structural determination by X-ray analysis, there is a wealth of available property information. The catalyst has a carbon atom content of 67.77% by weight, a hydrogen content of 4.89% by weight and a chlorine content of about 4.02% by weight. Additionally, it melts with decomposition at 135° to 140°C. It is brownish red in colour and soluble in benzene, tetrahydrofuran and chloroform. The infrared spectrum thereof run in KBr disc at a concentration of 1% by weight exhibits characteristic sharp bands at 2.90, 3.25, 5.05, 6.25, 6.72, 6.94, 7.61, 7.80, 8.45, 8.62, 8.90, 9.15, 9.73, 10.00, 10.85, 11.75, 13.49, 13.85 and 14.80 μ . Moreover, it demonstrates no evidence of hydrogen bonded to an sp^3 hybridized carbon in an NMR study. It has an envelope of aromatic protons from 6.6 to 8.0 ppm with prominences at 7.0 and 7.4 ppm being observed in the NMR spectrum when run at 60 mc. in deuteriochloroform as solvent against tetramethylsilane as reference standard. It exhibits a shoulder at 350 to 375 $m\mu$ in its UV curve run in methanol as solvent using a 2 cm. cell with absorption maxima occurring at 258, 265, 272, and 360 $m\mu$. The $E_{1\%}^{1\text{cm}}$ values are 10,354, 1,082.8, 1,040.4 and 20.46, respectively, at a concentration of 0.001%. With thin layer chromatography, it (a) demonstrates a pink spot with R_f 0.4 and a yellow spot with R_f 0.8 when a chloroform solution thereof is subjected to ascending chromatography on a silica gel plate which is developed with ethyl acetate - chloroform in a volume ratio of 1:2 and sprayed with iodoplatinic acid; (b) demonstrates with the system of (a), except for the use of a spray of phenylcarbazine, a trace of a purple spot with R_f 0.2, a white spot with R_f 0.4 and a purple spot with R_f 0.8 and (c) demonstrates with the system of (a), except for the use of benzene as the developing solvent, a brown spot with R_f 0.6.

The present invention further provides a process for preparing α - 6 - deoxy - 5 - oxytetracycline, which comprises hydrogenating 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline, an acid addition salt

thereof or a polyvalent metal salt complex thereof in the presence of a catalytic amount of a hydrogenation catalyst as described above.

Suitable starting materials for the hydrogenation process of the present invention are 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline, the acid addition salts thereof and polyvalent metal salt complexes thereof and the preparation of these starting materials is disclosed in United Kingdom Patent Specification No. 995032. In general, the method of preparation involves treatment of an 11a - halo - 6, 12 - hemiketal of oxytetracycline with a strong acid of the dehydrating type such as sulphuric, trifluoroacetic, polyphosphoric or perchloric acid, or hydrogen fluoride. Optimum conditions are readily determined by routine experimentation. Generally, the selected 11a - haloketal 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., diethylether, to precipitate an 11a - chloro - 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline product. Obtaining the corresponding desired 11a - deshalo compound may be accomplished by either chemical or catalytic reduction using procedures well known to those skilled in the art and exemplified in Example IV of United Kingdom Patent Specification No. 995032. It will be noted in that example that 11a - fluorine atoms are removed by chemical reduction employing zinc dust and dilute hydrochloric acid; whereas 11a, chlorine atoms may be removed by either chemical or catalytic reduction. The 6 - methylene starting compounds used in the hydrogenation process of the present invention may be converted to acid addition salts or polyvalent metal salt complexes by standard procedures prior to hydrogenation as disclosed in United Kingdom Patent Specification No. 995032.

The aforesaid 11a - halo - 5 - oxytetracycline - 6,12 - hemiketal precursors of the starting compounds for the hydrogenation process of the present invention may be prepared in accordance with Examples I and II of United Kingdom Patent Specification No. 995032.

Appropriate reaction-inert solvents for the hydrogenation process of the present invention include those which serve substantially to dissolve the starting compounds but which do not adversely react with either the starting compounds or the product. Examples of such solvents include ethers such as diethyl ether, tetrahydrofuran, dioxan, 1,2 - dimethoxyethane, aliphatic ketones such as acetone and

methyl ethyl ketone; low molecular weight esters such as ethyl acetate and butyl acetate; mono- and polyhydric alcohols such as methanol, ethanol, isopropanol, ethylene glycol, propylene glycol and diethylene glycol; alkoxy substituted alkanols such as 2 - methoxyethanol and 2 - (2 - ethoxyethoxy)ethanol; alkanolic acids such as acetic acid and propionic acid; tertiary amides such as N,N - dimethylformamide, N,N - dimethylacetamide and N - methylpyrrolidone and mixtures thereof.

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

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

The expression "catalytic amount" as used 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 substrate. The preferred amount is from 1 to 10 mol %.

The reaction product may be isolated from the reaction medium by standard methods. For example, the product often may be precipitated by the addition 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 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 may be performed.

EXAMPLE 1

To a flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet were sequentially added 1 litre of methanol, 2.75 g (10.4 mmol) rhodium trichloride trihydrate, 30 ml of water and 1.715 g (20.8 mmol) sodium acetate. The mixture was then refluxed for 1 hour. Based on separate thin layer chromatography and IR studies, it was determined that at best only traces of rhodium acetate were present. Following the aforesaid

refluxing for 1 hour, 5.474 g (20.8 mmols) of triphenyl phosphine were added to the reaction mixture. Immediate precipitation was observed but reflux was continued for 3 hours more. Following reflux, the reaction mixture was cooled and the methanol-insoluble material was filtered off, washed with methanol and dried to afford 4.43 g of brownish-red coloured crystals having a melting point of 183°C. with decomposition starting at approximately 148°C. One gram of the aforesaid was repulped for 5 minutes in refluxing methanol and 910 mg were recovered by filtration. Thin layer chromatography and IR were the same as those for the originally recovered materials. The melting point of the prepulped material was 135° to 140°C. with decomposition. The infrared spectrum of this product has no absorption corresponding to OCOCH_3 . It is unaffected by exposure to air but chloroform solutions thereof are not stable. It may be stored under nitrogen.

EXAMPLE 2

A Parr bottle was charged with 25 mg of catalyst prepared in accordance with Example 1, 2 g of 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - oxytetracycline hydrochloride and 30 ml of deaerated methanol. The bottle was flushed with nitrogen and then with hydrogen. It was then charged with hydrogen to a pressure of 45 psig and the reaction mixture was heated to 70°C. for approximately 3.5 hours. The reaction mixture was cooled, removed from the bottle and diluted with 100 ml of methanol. Thirty ml of a 10% aqueous solution of sulfosalicylic acid and 20 ml of water were added to the diluted reaction mixture with stirring. A precipitate formed immediately and stirring was continued for one hour. The mixture was refrigerated and then filtered. The filter cake was washed with warm methanol and then dried to obtain 2.73 g, yield of 98.8%. Ultraviolet assay showed that the product was 99.7% pure α - 6 - deoxy - 5 - oxytetracycline.

When using the intermediate reaction product of Example 1 above (obtained by reacting rhodium trichloride trihydrate and sodium acetate) in the hydrogenation procedure of this Example, the product obtained contains about equal amounts of α - and β - 6 - deoxy - 5 - oxytetracycline.

On substituting rhodium acetate,



in the above-described hydrogenation procedure while using 46 mg thereof (0.2089 mmols), assay of the reaction mixture shows a yield of the β - epimer which is greater than that of the α - epimer which, in turn, was greater than the amount of unreacted 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline hydrochloride starting material.



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WHAT WE CLAIM IS:—

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1. A process for preparing a rhodium-containing hydrogenation catalyst which comprises reacting 1 mol of rhodium trichloride with 2 mols of sodium acetate in methanol at a temperature from 50°C. to the reflux temperature of the reaction mixture, then reacting the resulting reaction mixture with 2 mols of triphenylphosphine at a temperature of from 50°C. to the reflux temperature of the reaction mixture and recovering the resulting insoluble material comprising the catalyst.
 2. A process according to claim 1, wherein the reaction mixture contains from 1 to 5% of water based on the weight of methanol.
 3. A process according to either one of claims 1 or 2, wherein the rhodium trichloride is the trihydrate of rhodium trichloride.
 4. A hydrogenation catalyst which comprises the insoluble material produced by a process according to any one of the preceding claims.
 5. A process for preparing α - 6 - deoxy - 5 - oxytetracycline, which comprises hydro-

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generating 6 - deoxy - 6 - demethyl - 6 - methylene - 5 - oxytetracycline, an acid addition salt thereof, or a polyvalent metal salt complex thereof, in the presence of a catalytic amount of a catalyst according to Claim 4.

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6. A process for preparing a hydrogenation catalyst according to claim 1 substantially as hereinbefore described with reference to Example 1.

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7. A rhodium-containing hydrogenation catalyst according to claim 4 substantially as hereinbefore described with reference to Example 1.

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8. A process for preparing α - 6 - deoxy - 5 - oxytetracycline according to claim 5 substantially as hereinbefore described with reference to Example 2.

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