

PATENT SPECIFICATION

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(54) IMPROVED PROCESS FOR 11a-CHLORINATION OF 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:—

This invention relates to an improved process for the preparation of 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal by the chlorination of 5 - oxytetracycline, and the recovery of 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal as an acid addition salt at a pH <1.0.

11a - Chloro - 5 - oxytetracycline - 6,12 - hemiketal is a valuable intermediate for production of the commercially important antibiotics 6 - demethyl - 5 - oxytetracycline and 6 α - deoxy - 5 - oxytetracycline (U.S. Patent Specification Nos. 2,984,686 and 3,200,149). U.S. Patent Specification Nos. 2,984,686 and 3,109,007, issued May 16, 1961 and October 29, 1963, respectively, describe its preparation by the reaction of 5 - oxytetracycline with a chlorinating agent in a reaction-inert solvent at a temperature of from about -25°C. to +50°C., and a pH value near the isoelectric point of the 5 - oxytetracycline. The reaction inert solvent is a water-miscible solvent. The product is precipitated by dilution of the reaction mixture with water and filtration.

Belgian patent specification No. 777,356, granted April 17, 1972, describes the chlorination of 5 - oxytetracycline or its acid addition salts in a suitable solvent at a temperature below 0°C., while maintaining the pH between about 3.5 and 5, to spontaneously precipitate 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal base in the enolic form. The hemiketal base is isolated and subsequently converted to the hydrochloride, sulfosalicylate or p - toluenesulfonate salt by treatment with the appropriate acid at -10°C. to +20°C.

The prior art processes afford inconsistent

and/or relatively poor yields of 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal hydrochloride or other acid addition salt, the quality of which is not always consistent, thus giving rise to difficulties in subsequent process steps for which the hemiketal product serves as intermediate. Additionally, they require isolation of the hemiketal base prior to preparation of an acid addition salt thereof.

It has now been found that 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal hydrochloride and other acid addition salts of consistent and excellent quality can be prepared in high yield by a process which comprises chlorinating 5 - oxytetracycline or an acid addition salt thereof at a temperature of from -10°C. to -40°C. and pH from 6.5 to 7.7 in a water-miscible reaction-inert solvent or mixture thereof with water, followed by immediate lowering of the pH of the reaction mixture to <1.0 by addition of a strong mineral acid. The 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal is recovered as an acid addition salt, formed with the strong mineral acid used.

The process permits easy recovery of 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal as a stable, crystalline acid addition salt by filtration or centrifugation. The product thus obtained, when dehydrated with hydrogen fluoride, affords essentially quantitative yields of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - oxytetracycline. This latter compound is an important intermediate in the synthesis of 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - oxytetracycline and of 6 α - deoxy - 5 - oxytetracycline.

The process of this invention comprises reacting 5 - oxytetracycline with a chlorinating agent in a reaction-inert solvent. Suitable chlorinating agents are chlorine, N - chloro-lower alkanolic acid amides, e.g. N - chloroacetamide, N - chloro - hydrocarbon dicarboxylic acid imides, e.g. N - chlorosuccinimide, or N - chlorophthalimide, and N - chloro - lower alkanoylanilides, e.g. N - chloroacetanilide, or propionanilide; 3 - chloro- and 3,5 - dichloro- 5,5 - dimethyl-

hydantoin, pyridinium perchloride hydrohalides, e.g. pyridinium perchloride hydrochloride, and lower alkyl hypochlorites, e.g. tertiary butyl hypochlorite. It is obvious that, in general, any chlorinating agent commonly employed in the art is operable, but the above are favored. The preferred chlorinating agent is N - chlorosuccinimide because of its ease of handling and use, its rapid reaction with 5 - oxytetracycline, and the high yields of chlorinated product it affords.

By "reaction-inert solvent" is meant a solvent which, under the conditions of the reaction, does not react in an undesired manner with either starting compounds or final products. A minimum of laboratory experimentation will permit the selection of suitable solvents for the present process. The solvents are water-miscible solvents and mixtures thereof with water. Exemplary of such solvents are dioxane, tetrahydrofuran, acetone dimethyl ether of diethylene glycol (diglyme), dimethyl ether of ethylene glycol (monoglyme), acetonitrile, methyl ethyl ketone, monoethyl ether of ethylene glycol, N,N - dimethylformamide, N,N - dimethylacetamide, and mixtures of such solvents with water. Such solvents provide a single phase reaction mixture for the chlorination reaction and permit easy and complete recovery of the desired hemiketal acid addition salt. An especially useful solvent is a mixture of acetone and water.

The chlorination is conducted at a temperature of from $-10^{\circ}\text{C}.$ to $-40^{\circ}\text{C}.$ and desirably at a temperature of from $-30^{\circ}\text{C}.$ to $-40^{\circ}\text{C}.$ Higher temperatures, that is, temperatures up to $+10^{\circ}\text{C}.$ are generally avoided in order to minimize side-reactions which tend to reduce the yield of the 11a - chloro - 6,12 - hemiketal product. Lower temperatures are avoided in order to eliminate the need for special cooling means.

The 5 - oxytetracycline can be used in the base form or as an acid addition salt. The hydrochloride salt is the favored salt since it is a stable, readily available form of the antibiotic.

A slight excess of chlorinating agent, desirably from 1.1 to 1.4 moles per mole of 5 - oxytetracycline base or acid addition salt thereof, is generally used. The rate of reaction does, of course, depend upon the chlorinating agent selected but the reaction is generally completed in a matter of minutes.

The pH, or more appropriately when operating in an anhydrous solvent, the apparent pH, of the chlorination reaction mixture can range from 6.5 to 7.7 and advantageously should be in the range of 7.3 to 7.5 for optimum yield. In view of the difficulty in measuring apparent pH it is more convenient, at least from a practical standpoint when using 5 - oxytetracycline

hydrochloride as reactant, to define this parameter in terms of the amount of base used to neutralize the hydrochloride salt. On this basis, from 0.20 to 0.40 gram of triethylamine per gram of 5 - oxytetracycline hydrochloride (equivalent to from one to two moles of triethylamine per mole of oxytetracycline hydrochloride, or other monobasic acid addition salt) is used to achieve the appropriate pH range.

Immediately following the chlorination reaction, which occurs at a rapid rate, the reaction mixture is treated with a strong mineral acid to drop the pH to <1.0 . Mineral acids such as hydrochloric, sulfuric, hydrofluoric, hydrobromic and perchloric acid can be used. The preferred mineral acid is hydrogen chloride, either in gaseous or solution form, since it forms the stable, easily recoverable hydrochloride salt, the salt of 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal generally used in the industrial production of 6 α - deoxy - 5 - oxytetracycline.

The 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal salt is recovered from the acid mixture by addition of a non-solvent for the salt. The insolubility of the hydrochloride salt in acetone is the main reason why acetone-water is the favored solvent for this process and the reason for hydrogen chloride being the preferred acidifying agent for the final step of this process.

The selection of the best reaction conditions, e.g. temperature, solvent, chlorinating agent, acidifying agent and recovery method, is a matter of routine experimentation.

EXAMPLE I

11a - Chloro - 5 - Oxytetracycline - 6,12 - Hemiketal Hydrochloride

A jacketed, glass-lined reactor charged with acetone (24 liters), deionized water (4.5 liters) and 5 - oxytetracycline hydrochloride (5 kg., 10.06 moles) is stirred and cooled to $-40^{\circ}\text{C}.$ by means of liquid nitrogen. Triethylamine (1.6 liters, 11.5 moles), pre-cooled to $-40^{\circ}\text{C}.$ is added to the mixture over a 30-second period with simultaneous addition of liquid nitrogen to maintain the temperature at $-40^{\circ}\text{C}.$ A slurry of N - chlorosuccinimide (1.695 kg., 11.5 moles) in acetone (3.8 liters), pre-cooled to $-40^{\circ}\text{C}.$, is then added over a two-minute period with simultaneous and continuous addition of liquid nitrogen to hold the temperature at $-40^{\circ}\text{C}.$ When the addition is complete, the introduction of liquid nitrogen is stopped and the reaction mixture stirred for three minutes. A solution of acetone (54 liters), pre-cooled to $8^{\circ}\text{C}.$, to which hydrogen chloride gas (1.2 kg., 33 moles) has been added is then introduced into the reaction mixture over a two-minute period. To expedite precipitation of the hydrochloride salt

125 g. of crystalline 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal hydrochloride are added to the reaction mixture when approximately half of the acetone-HCl solution is added. Crystallization begins immediately. The reaction mixture is warmed to 15°-18°C using 60°C. water in the jacket. The product is granulated for one hour at 15°-20°C. and then for 1.5 hours at -5° to -10°C. The product is recovered by filtration, washed with acetone (3×3 liters) and dried at 30°-35°C. in a vacuum dryer (yield=78.4%).

Similar results are obtained when the chlorination is conducted at temperatures of -30°, -20° and -10°C.

EXAMPLE II

The procedure of Example I is repeated but using, in place of hydrogen chloride gas, equivalent amounts of the following acids in acetone solution:

hydrogen bromide
hydrogen fluoride
sulfuric acid
perchloric acid
concentrated hydrochloric acid

In each instance, precipitation of the acid addition salts is expedited by addition of seed crystals of the corresponding acid addition salt.

EXAMPLE III

The procedure of Example I is repeated, but using as starting material, an equivalent amount of the following forms of 5 - oxytetracycline:

- (a) free base,
- (b) hydrofluoride salt,
- (c) hydroiodide salt,
- (d) perchlorate salt,
- (e) 2 - naphthalenesulfonate salt,
- (f) 2 - hydroxy - 5 - sulfo - benzoate (sulfosalicylate) salt,
- (g) p - toluenesulfonate salt,
- (h) citrate salt,
- (i) tartrate salt,
- (j) benzoate salt,

In each instance yields of 11a - chloro -

5 - oxytetracycline - 6,12 - hemiketal hydrochloride comparable to those of Example I are obtained.

WHAT WE CLAIM IS:—

1. In the process for the 11a - chlorination of 5 - oxytetracycline or an acid addition salt thereof by means of a chlorinating agent in a reaction-inert solvent to provide 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal, the improvement which comprises conducting the chlorination at a temperature of from -10°C to -40°C. and a pH of from 6.5 to 7.7 in a water-miscible reaction-inert solvent, or mixture thereof with water, followed by addition of a strong mineral acid to lower the pH of the reaction mixture thus obtained to <1.0; the 11a - chloro - 5 - oxytetracycline - 6,12 - hemiketal being recovered as an addition salt with the strong mineral acid used.

2. The process of claim 1, wherein the chlorinating agent is N - chlorosuccinimide.

3. The process of claim 1 or 2, wherein the strong mineral acid is hydrogen chloride.

4. The process of any of the preceding claims, wherein the reaction-inert solvent is acetone in admixture with water.

5. The process of any of the preceding claims, wherein the chlorination is conducted at a temperature of from -30°C to -40°C.

6. The process of any of the preceding claims, wherein 5 - oxytetracycline is used as the hydrochloride salt.

7. A process for the 11a - chlorination of 5 - oxytetracycline or an acid addition salt thereof as claimed in claim 1, substantially as described herein.

8. An 11a - Chlorinated 5 - oxytetracycline - 6,12 - hemiketal mineral acid addition salt whenever prepared by the process according to claim 1 substantially as described herein.

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Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 998294.



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