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(54) Title: PROCESS FOR THE PREPARATION OF PURE 3-ALKOXYMETHYL CEPHALOSPORINS

(57) Abstract: The present invention relates to an improved and industrially advantageous process for the preparation of pure 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids, and salts thereof. In particular, the present invention relates to a process for the preparation of pure 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid (7-AMCA) and salts thereof.

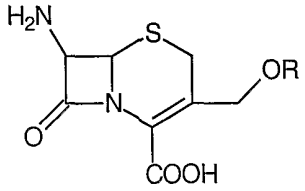
# PROCESS FOR THE PREPARATION OF PURE 3-ALKOXYMETHYL CEPHALOSPORINS

## FIELD OF THE INVENTION

The present invention relates to an improved and industrially advantageous process for the preparation of pure 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids, and salts thereof. In particular, the present invention relates to a process for the preparation of pure 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid (7-AMCA) and salts thereof.

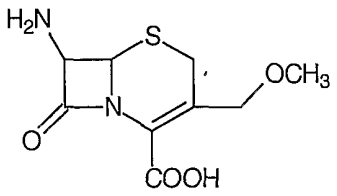
## BACKGROUND OF THE INVENTION

7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids, i.e. compounds of Formula I




**FORMULA I**

wherein R is an alkyl group, and salts thereof, are known in the prior art and are important intermediates in the preparation of various cephalosporin derivatives having a very high and broad spectrum of antimicrobial activity. In particular, 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid (7-AMCA) of Formula II




**FORMULA II**

is a key intermediate in the preparation of cefpodoxime proxetil, an orally active third generation cephalosporin antibiotic.

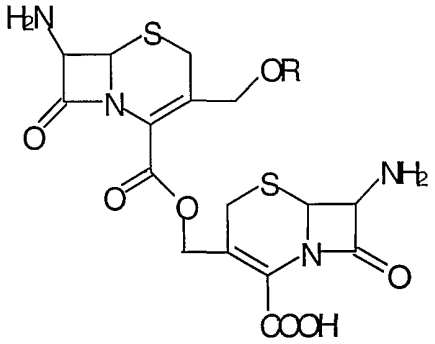
Pharmaceutical compounds are required in highly pure form because of the fear of unknown and potentially harmful effects of impurities. For purposes of patient safety, it is highly desirable to limit the amount of impurities present in any medicament administered to a patient. This is achieved by either devising a process for their preparation in pure form or by additional purification steps like chromatography or recrystallization etc. The former is obviously preferred, as it saves costs as well as time. The purity of intermediates and raw materials is essential for obtaining the target pharmaceutical compounds in high yield and purity.

Several processes are known for the preparation of 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acid, starting from 7-aminocephalosporanic acid (7-ACA).

Japanese patent application 57/192392 describes the reaction of 7-ACA with lower alcohols in the presence of an iodine compound to obtain the 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids. Japanese patent application

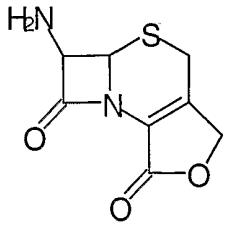
59/163387 proposes the use of a lower alcohol in the presence of a sulfonic acid. European patent, EP 204657 describes the conversion of 7-ACA to 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids using lower alkyl alcohols in the presence of boron trifluoride or a complex thereof, in 60% yield. Japanese patent application 63/115887 describes a variant which involves the additional use of halogenosulfonic acids or alkylsulfonic acids. Japanese patent application 61/45175 achieves the reaction with lower alcohol, an organic sulfonic acid and an alkoxysilane. EP 262744 reports the same conversion using lower alcohols in the presence of a halide of antimony, tin, iron, zinc, bismuth or a complex thereof and optionally boron trifluoride or a complex thereof. The yields are in the range of 40-65% only.

EP 343926 describes the reaction of 7-ACA with a protonic acid or a lewis acid, or a borate complex thereof, and an ortho-organic acid ester or acetal to obtain the 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids. U.S. Patent No. 5,451,675 also provides a process for the production of the 7-amino-3-alkoxymethyl-3-cephem-4-carboxylic acids, comprising reacting 7-ACA with a solution of alkoxysulfonic acid in a lower alcohol in the presence of a trialkyl borate and/or formaldehyde dialkylacetal. However, the products obtained by these methods were found to have an appreciable amount of an impurity, which was hitherto assumed to be a lactone or the β-lactam degradation compounds. A detailed analysis of the undesirable by-products by Liquid Chromatography-Mass Spectrometry has revealed that the major impurity formed using the above procedures is the inter-molecular esterification product of Formula A,



FORMULA A

where R is an alkyl group having from 1-6 carbon atoms along with lactones of Formula B.



FORMULA B

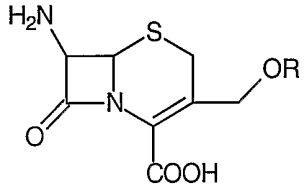
However, all the above mentioned processes suffer from certain limitations and for various reasons are not suitable for commercial production - for example, low yields, use of hazardous or costly reagents or excessive side product formation. A major reason for the low yields and purity is reported to be the formation of undesirable by-products of Formulae A and B due to intramolecular lactonization or decomposition of the β-lactam ring.

## SUMMARY OF THE INVENTION

It is an objective of the present invention to provide a clean reaction resulting in pure products which are obtained by simple isolation procedures involving a single precipitation step, as against the use of column chromatography or successive precipitation steps required in the prior art processes.

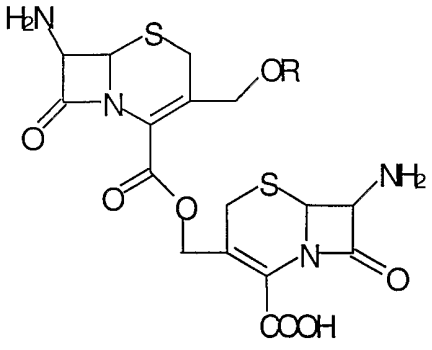
Another object of the present invention is to provide a process which makes use of commercially available non-hazardous alkylsulphonic acids and avoids the use of alkoxysulfonic acids which are in turn prepared from chlorosulfonic acids, which are difficult to handle at large scale because of environmental hazards involved.

The present invention solves the problems associated with the prior art and provides a process for the preparation of compounds of Formula I




**FORMULA I**

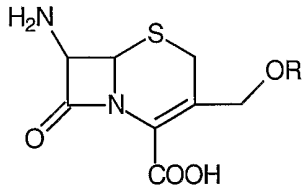
which minimizes the formation of the by product of Formula A,




**FORMULA A**

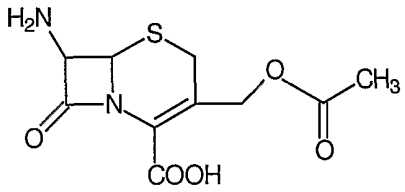
thus yielding pure product, using conditions which are convenient to operate on a commercial scale and operationally safe.

Accordingly, the present invention provides an improved process for the preparation of 3-alkoxymethy-3-cephem-4-carboxylic acid of Formula I,




**FORMULA I**

or a salt thereof in pure form, which process comprises reacting 7-aminocephalosporanic acid (7-ACA) of Formula III,




**FORMULA III**

or a salt thereof, with an alkylsulfonic acid of formula $RSO_3H$ and a trialkylborate of formula $B(OR)_3$ or a formaldehyde dialkyl acetal of formula $CH_2(OR)_2$ in the presence of a lower alcohol of formula ROH; wherein, in each of said compounds of Formulae I, $RSO_3H$, $B(OR)_3$, $CH_2(OR)_2$ and ROH, R is an alkyl group having from 1 to 6 carbon atoms.

## DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formulae I and III may be in the salt form and include salts at the carboxyl group or the amino group. Representative example of salts at the carboxyl group include salts with an alkali metal, such as sodium and potassium; an alkaline earth metal, such as calcium and magnesium; ammonium salts and salts with nitrogen containing organic bases, such as triethylamine, pyridine and dicyclohexylamine. Examples of salts at the amino group include salts with inorganic acids, such as hydrochloric acid and sulfuric acids; carboxylic acids, such as formic acid, oxalic acid and trifluoroacetic acid; and sulfonic acids, such as methanesulfonic acid or p-toluenesulfonic acid.

The compound of formula $RSO_3H$ is an alkylsulfonic acid wherein R is an alkyl group having from I to 6 carbon atoms. Preferably, R represents an alkyl group having from 1 to 4 carbon atoms. Examples of such alkylsulfonic acids include methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, isopropanesulfonic acid, butanesulfonic acid, isobutanesulfonic acid, sec-butanesulfonic acid, t-butanesulfonic acid and hexylsulfonic acid. Preferred alkylsulfonic acids are methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid and butanesulfonic acid, the most preferred being methanesulfonic acid.

The process of the present invention is characterized by using at least one compound selected from the compounds of formula $B(OR)_3$ and the compounds of formula $CH_2(OR)_2$. The compound of formula $B(OR)_3$ is a

trialkyl borate wherein R represents an alkyl group having from 1 to 6 carbon atoms. Preferably, R represent an alkyl group having from 1 to 4 carbon atoms. Examples of such borates include trimethyl borate, triethyl borate, tripropyl borate, triisopropyl borate, tributyl borate, triisobutyl borate, tri-sec-butylborate, tri-t-butylborate and trihexyl borate. Preferred trialkyl borates are trimethyl borate, triethyl borate, tripropyl borate and tributyl borate. Most preferred is trimethyl borate.

The compound of formula $CH_2(OR)_2$ is a formaldehyde dialkyl acetal wherein R represents an alkyl group having from 1 to 6 carbon atom. Preferably, R represent an alkyl group having from 1 to 4 carbon atoms. Examples of formaldehyde dialkyl acetal include methylal, ethylal, formaldehyde dipropyl acetal, formaldehyde diisopropyl acetal, formaldehyde dibutyl acetal, formaldehyde di-sec-butyl acetal, formaldehyde di-t-butyl acetal and formaldehyde dihexyl acetal. Preferred are methylal, ethylal, formaldehyde dipropyl acetal and formaldehyde dibutyl acetal. Most preferred is methylal.

The compound of formula ROH is a lower alcohol, wherein R is an alkyl group having from 1 to 6 carbon atoms. Preferably, R represents an alkyl group having from 1 to 4 carbon atoms. Examples of such alcohols include methanol, ethanol, propanol, isopropanol, butanol, isobutanol, sec-butanol, t-butanol and hexanol. More preferably, methanol, ethanol, propanol and butanol are used. Most preferred being methanol.

It was found that the lower alcohols ROH had a crucial role to play in the selective formation of desired compounds of Formula I and the exclusion of the intermolecular esterification product of Formula A. The molar ratio of lower alcohol ROH used with respect to the starting material 7-ACA of Formula III may be at least 0.1 : 1 so as to minimize the formation of impurities of Formula A. On the other hand, the molar ratio should not exceed 30:1 to obtain best results. The molar ratio of alkyl alcohol to 7-ACA is thus suitably 0.1:1 to 30:1 and preferably 1:1 to 10:1.

The molar ratio of trialkyl borate of formula $B(OR)_3$ to the starting material 7-ACA is generally in the range 0.3:1 to 30:1 and preferably from 1:1 to 10:1.

The molar ratio of formaldehyde dialkylacetal of formula $CH_2(OR)_2$ to 7-ACA is 0.5 : 1 to 30:1 and preferably 1:1 to 10:1.

The alkylsulfonic acid $RSO_3H$ required for the reaction to proceed at a reasonable rate is at least an amount equimolar to the amount of the 7-ACA. Increasing the molar ratio of alkylsulfonic acid to 7-ACA increases the rate of the reaction. However, excess of alkylsulfonic acid leads to increased by-product formation and the molar ratio generally used is 1:1 to 30:1 and preferably 10:1 to 20:1.

The process of the present invention is optionally carried out in the presence of an organic solvent which may include sulfolane, dimethyl sulfoxide, carbonic acid esters, organic acid esters, ethers, nitriles, alkanes,

nitroalkanes, halogenated alkanes, cycloalkanes, carboxylic acids, ketones, or mixtures thereof. The solvent is preferably sulfolane, dimethyl carbonate, dichloromethane, dimethyl sulfoxide or a mixture thereof.

The reaction is best performed in substantially anhydrous conditions. The moisture content of solvents and reagents is therefore kept at a minimum.

The reaction temperature is critical. Very low temperatures such as below -20ºC lead to a very sluggish reaction whereas, temperature above 20ºC leads to increased formation of impurities of Formula A, as well as formation of β-lactam degradation products. Thus, the reaction is generally performed at about -20 to 20ºC, and preferably at about -10 to 5ºC.

The desired product of Formula I or a pharmaceutically acceptable salt thereof, is obtained from the reaction mixture by simple conventional method. Water is added to the reaction mixture and the resultant boric acid is filtered. A water miscible solvent like acetone, methanol or ethanol is added to the filtrate and the pH adjusted to the isoelectric point of the desired product, using aqueous ammonia solution. The resultant precipitate is filtered and washed suitably. The compound of Formula I thus obtained can, if desired, be converted to its salt form by conventional procedures known in the art.

The invention is further illustrated by the following examples and comparative examples, which should not be construed to be limiting the scope of the present invention. The content of the lactone (Formula B) and the

intermolecular esterification impurity (Formula A, when R=$CH_3$) in the desired product are shown as an index for the evaluation of the purity of the desired product.

**Preparation of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid**

**EXAMPLE 1**

A mixture of methanesulfonic acid (26.5g), sulfolane (15ml) and trimethylborate (13.4g) was cooled to -5ºC. 7-ACA (5g) was added to the mixture followed by addition of methanol (2.5ml). Reaction mixture was stirred at 0ºC for about 12 hours. Progress of the reaction was monitored by high performance liquid chromatography (HPLC). Reaction was quenched by addition of water (35ml) at 0-5ºC. The resultant boric acid precipitate was filtered and washed successively with water and acetone. The filtrate was washed with dichloromethane. The acetone washing was then combined with the aqueous portion. The pH of the aqueous portion was adjusted to 3.4 - 3.5 with an aqueous ammonia solution. The precipitate, so obtained was filtered and washed with water followed by methanol. The product was dried under vacuum at ambient temperature till constant weight to get 3.7g of the desired product 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid (Yield 83%, HPLC purity 95%). The content of the lactone (Formula B), and the ester impurity (Formula A, when R=$CH_3$) in the desired product was 0.27% and 0.70%, respectively (by HPLC).

**EXAMPLE 2**

A mixture of methanesulfonic acid(27.5g), sulfolane (6ml) and trimethylborate (6g) was cooled to -5ºC. To this mixture, was added 7-ACA (5g) followed by methanol (2ml). The reaction and its work up were carried out as in Example 1 to obtain 7-AMCA (3.9g, Yield 87%, HPLC purity 95.4%). The content of the lactone and the ester impurity in the product was 0.1% and 1.7%, respectively (by HPLC).

**EXAMPLE 3**

A mixture of methansulfonic acid (27g) and dichloromethane (30ml) was cooled to -5ºC and trimethylborate (6g), 7-ACA (5g) were added to it followed by additional of methanol (2.5ml). The reaction mixture was stirred at 0ºC and monitored by HPLC. Reaction was quenched after 10 hours by addition of water (50ml) at 0-5ºC. Adjusted pH to 0.5 with ammonia solution. The resultant layers were separated. The pH of the aqueous layer was adjusted to 3.5 using aqueous ammonia solution to get a precipitate which was filtered and washed with water followed by methanol. The product was dried under vacuum to obtain 7-AMCA (3.1g, Yield 70%, HPLC purity 95.3%). The content of the lactone and the ester impurity in the product was 0.17% and 1.7%, respectively (by HPLC).

**EXAMPLE 4**

Methanesulfonic acid (22g) and sulfolane (10ml) were cooled to -5ºC. To this mixture was added methylal (5g) followed by 7-ACA (5g) and methanol (1.25ml). The reaction was carried out at 0ºC, monitored by HPLC and

quenched after 10 hours by addition of water (80ml) at 0-5ºC. The product 7-AMCA (2.75g) was obtained by adjusting pH to 3.5, filtering the resultant precipitate which was washed and dried as in Example 1 (Yield 62%, HPLC purity 94.5%). 0.18% of lactone and 1.9% of ester impurity were present in the isolated product (by HPLC).

**COMPARATIVE EXAMPLE 1**

A methanolic solution of methoxysulfonic acid (31g), sulfolane (15ml) and trimethylborate (13.34g) were cooled to -5ºC. 7-ACA (5g) was added and the reaction mixture stirred at 10-12ºC. Progress of reaction was monitored by HPLC and reaction quenched after 1½ h by cooling to -10ºC, followed by addition of water (40ml). 10% ammonia solution (20ml) was then added. The resulting solution was subjected to activated carbon treatment and then washed with dichloromethane. To the aqueous portion was added methanol and pH was adjusted to 3.4-3.5 with ammonia solution at 15-20ºC. The obtained precipitate was filtered and washed with water followed by methanol. The product 7-AMCA was dried at room temperature till constant weight (2.8g, yield 62%, HPLC purity 80.1%). The content of the lactone and the ester impurity in the isolated product was 0.2% and 6.22%, respectively (by HPLC).

**COMPARATIVE EXAMPLE 2**

To dichloromethane (40ml) were added methanesulfonic acid (20g) and trimethylborate (12.5g). The mixture was cooled to -5ºC and 7-ACA (5g) was added. Reaction was carried out and worked up as in Example 3 to obtain 7-AMCA (2.25g, Yield 50%, HPLC purity 82%). 0.28% of lactone and 5.7% of the ester impurity were detected in the isolated product (by HPLC)

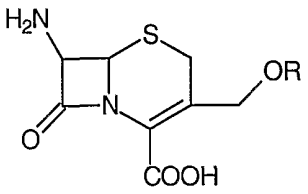
**COMPARATIVE EXAMPLE 3**

Methanesulfonic acid (20g) and sulfolane (10ml) were cooled to -10 to -12ºC and 7-ACA(5g) was added to it followed by trimethylborate (11.25g) maintaining temperature at -5 to -2ºC. Reaction was stirred at 0ºC and monitored by HPLC. Reaction was worked up as in Example 1 to obtain 7-AMCA (3.2g, Yield 72% HPLC purity : 85.5%). 0.17% of lactone and 6% of ester impurity were found in the isolated product. (by HPLC).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

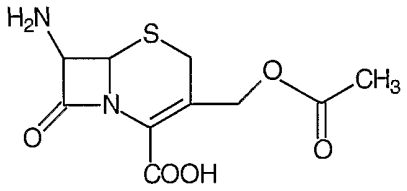
**WE CLAIM :**

1. A process for the preparation of 3-alkoxymethyl-3-cephem-4-carboxylic acid of Formula I




**FORMULA I**

or a salt thereof, which process comprises reacting 7-aminocephalosporanic (7-ACA) of Formula III,




**FORMULA III**

or a salt thereof, with an alkylsulfonic acid of formula $RSO_3H$ and a trialkylborate of formula $B(OR)_3$ or a formaldehyde dialkyl acetal of formula $CH_2(OR)_2$ in the presence of a lower alcohol of formula ROH; wherein, in each of said compounds of Formulae I, $RSO_3H$ and $B(OR)_3$, ($CH_2(OR)_2$,and ROH, R represents an alkyl group having from 1 to 6 carbon atoms.

2. The process of claim 1 wherein R represents an alkyl group having from 1 to 4 carbon atoms.

3. The process of claim 2 wherein R represents a methyl, ethyl, propyl or butyl group.

4. The process of claim 3 wherein R represents a methyl group.

5. The process of claim 1 wherein R represents the same group in said compounds of Formulae I, $RSO_3H$, ROH, $CH_2(OR)_2$ and $B(OR)_3$.

6. The process of claim 1 wherein the molar ratio of alkylsulfonic acid of Formula $RSO_3H$ to 7-ACA is from 1:1 to 30:1.

7. The process of claim 6 wherein the molar ratio of alkylsulfonic acid of Formula $RSO_3H$ to 7-ACA is from 10:1 to 20:1.

8. The process of claim 1 wherein the molar ratio of borate compound of formula $B(OR)_3$ to 7-ACA is from 0.3:1 to 30:1.

9. The process of claim 8 wherein the molar ratio of borate compound of formula $B(OR)_3$ to 7-ACA is from 1:1 to 10:1.

10. The process of claim 1 wherein the molar ratio of formaldehyde dialkyl acetal of Formula $CH_2(OR)_2$ to 7-ACA is from 0.5:1 to 30:1.

11. The process of claim 10 wherein the molar ratio of formaldehyde dialkyl acetal of Formula $CH_2(OR)_2$ to 7-ACA is from 1:1 to 10:1.

12. The process of claim 1 wherein the molar ratio of lower alcohol of Formula ROH to 7-ACA is from 0.1:1 to 30:1.

13. The process of claim 12 wherein the molar ratio of lower alcohol of Formula ROH to 7-ACA is from 1:1 to 10:1.

14. The process of claim 1 wherein the reaction is carried out in an anhydrous or substantially anhydrous system.

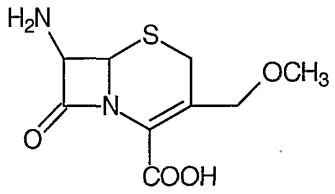
15. The process of claim 1 wherein the reaction is carried out at a temperature of from about -20ºC to 20ºC.

16. The process of claim 15 wherein the reaction is carried out at a temperature of from about -10 to 5ºC.

17. The process of claim 1 wherein the reaction is carried out in the presence of an organic solvent.

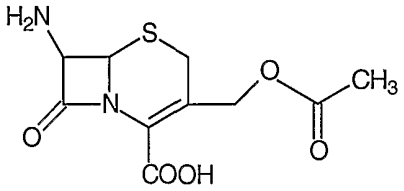
18. The process of claim 17 wherein the reaction is carried out in the presence of an organic solvent selected from a group consisting of sulfolane, dimethyl sulfoxide, carbonic acid esters, organic acid esters, ethers, nitriles, alkanes, nitroalkanes, halogenated alkanes, cycloalkanes, carboxylic acids, ketones, and mixtures thereof.

19. A process for the preparation of 3-methoxymethyl-3-cephem-4-carboxylic acid (7-AMCA) of Formula II,




**FORMULA II**

or a salt thereof, which process comprises reacting 7-aminocephalosporanic acid (7-ACA) of Formula III




**FORMULA III**

with methanesulfonic acid and trimethylborate or methylal in the presence of methanol.