(CONVENTION. By one or more persons and/or a Comp

621040

COMMONWEALTH OF A

Patents Act 1952-1969

PATENT OFFICE LODGED AT SUB-OFFICE 24 FEB Melbourne ONE HUNDRED DOLLARS

PATENT OFFICE SUB-OFFICE AUSTRALIA FIFTY DOLLARS

CONVENTION APPLICATION FOR A PATENT

FEE STAMP TO VALUE OF $150 ATTACHED MAIL OFFICER

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

We (1) HOECHST AKTIENGESELLSCHAFT

of 45 Bruningstrasse, D-6230 Frankfurt/Main 80,

Federal Republic of Germany

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

CRYSTALLIZED CEPHEM-ACID ADDITION SALTS, AND A PROCESS FOR THE PREPARATION THEREOF

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

P37 06 020.1

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) Federal Republic of Germany on 25th February 1987

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 23rd day of February 1988

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

LODGED AT SUB-OFFICE 24 FEB 1988 Melbourne

HOECHST AKTIENGESELLSCHAFT

by D. B. Mischlewski

Registered patent Attorney

Form 7

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI. FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST AKTIENGESELLSCHAFT of 45, Brüningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany for a patent for an invention entitled:
CRYSTALLIZED CEPHEM-ACID ADDITION SALTS, AND A PROCESS FOR THE THE PREPARATION THEREOF

We Johann-Heinrich Reuter, 4 Bodenheimer Straße, D-6500 Mainz,
Franz Lapice, 2 Sandweg, D-6233 Kelkheim (Taunus),
Federal Republic of Germany
do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in the Federal Republic of Germany
under No. P 37 06 020.1 on February 25, 1987
by HOECHST AKTIENGESELLSCHAFT

3. a) Rudolf Lattrell, 6h Heuhohlweg, D-6240 Königstein/Taunus
b) Walter Dürckheimer, 45 Im Lerchenfeld, D-6234 Hattersheim am Main
c) Reiner Kirrstetter, 8a Altenhainer Straße, D-6233 Kelkheim (Taunus)
a) - c) Federal Republic of Germany

~~is~~/are the actual inventor(s) of the invention and the facts upon which HOECHST AKTIENGESELLSCHAFT

is entitled to make the application are as follows:

The said HOECHST AKTIENGESELLSCHAFT

is the assignee of the said
Rudolf Lattrell, Walter Dürckheimer, Reiner Kirrstetter

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt/Main, Federal Republic of Germany
this 18th day of December 1987.

To the Commissioner of Patents

HOECHST AKTIENGESELLSCHAFT

Prokurist
ppa. Reuter

Authorized signatory
i.V. Lapice

PAT 510

(12) PATENT ABRIDGMENT (11) Document No. AU-B-12106/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 621040

(54) Title
CRYSTALLIZED CEPHEM-ACID ADDITION SALTS, AND A PROCESS FOR THE PREPARATION THEREOF

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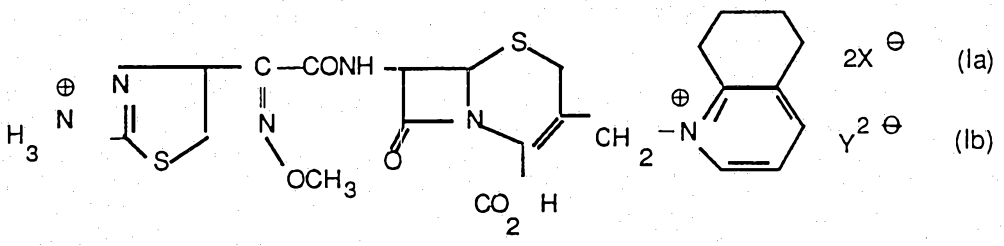
(56) Prior Art Documents
AU 22893/83 C07D 501/46

(57) Claim

1. A crystallized cephem-acid addition salt of the formula I



I

in which X^- represents an anion of a monobasic inorganic or organic acid (formula Ia) and

$Y2^-$ represents an anion of a diabasic inorganic or organic acid (formula Ib),

and its hydrate.

5. A method of combatting bacterial infections in mammals comprising administering thereto in pharmaceutically effective quantities a cephem derivative of the formula I as claimed in Claim 1.

COMMONWEALTH OF AUSTRALIA 621040 Form 10

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany

Actual Inventor: RUDOLF LATTRELL, WALTER DURCKHEIMER, REINER KIRRSTETTER

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

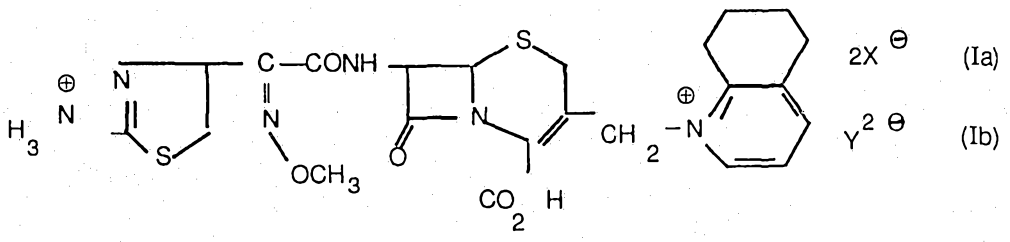
CRYSTALLIZED CEPHEM-ACID ADDITION SALTS, AND A PROCESS FOR THE PREPARTION THEREOF

The following statement is a full description of this invention, including the best method of performing it known to :- us

Description

Crystallized cephem-acid addition salts, and a process for the preparation thereof.

The invention relates to crystallized acid-addition salts of an antibiotic of the formula Ia or Ib and the hydrates thereof, and a process for the preparation of these compounds.



I

In the general formula I, X^- denotes the anion of a monobasic acid, and Y^{2-} denotes the anion of a dibasic acid, where X and Y may be an inorganic or organic anion.

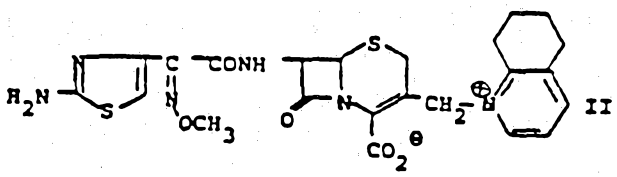
As an inorganic anion, X^- or Y^{2-} denotes, for example, Cl^-, Br^-, I^-, F^-, NO_3^-, CLO_4^-, $-SCN^-$ or HSO^{4-}, in particular physiologically acceptable anions such as, for example, Cl^-, Br^-, HSO^{4-} and SO_4^-. As an organic anion, X^- is the anion of an aliphatic mono-, di- or tricarboxylic acid, for example $CH_3CO_2^-$, $CF_3CO_2^-$ or $CCl_3CO_2^-$, in particular the anion of a physiologically acceptable acid, such as, for example, the monomaleate anion $HOOCCH{=}CHCO_2^-$.

The sulfate, which is distinguished by a very low tendency towards incorporation of organic solvents into the crystal lattice, is very particularly suitable for parenteral administration. The dihydroiodide is particularly suitable for isolation of the betaine of the formula II from the

reaction batches.

The process for the preparation of the acid-addition salts of the formulae Ia and Ib comprise

1) reacting a cephem-betaine of the formula II



II

with monobasic acids of the formula IIIa or dibasic acids of the formula IIIb

$$H^+X^-$$ IIIa

$$2H^+Y^{2-}$$ IIIb

in which X and Y have the abovementioned meaning, or

2) reacting a cephem-betaine of the formula II with acids of the formula IIIa or IIIb which have been produced in situ, these acids being produced from the corresponding salts of the formula IVa or IVb respectively

$$ZX \text{ or } ZX_2$$ IVa

$$Z_2Y \text{ or } ZY$$ IVb

in which Z denotes a monovalent or divalent metal cation, for example Na^+, K^+, Ag^+ or Mg^{2+}, or an ammonium ion, through addition of a strong acid, such as, for example, the mineral acids HCl and H_2SO_4, or

3) preparing a water-soluble salt of the formula I, for example a dihydrochloride or sulfate, in accordance with process 1 and reacting this salt with salts of the formula IVa or IVb in which X^- and Y^{2-} denote the anion

of a sparingly water-soluble salt, for example I^-.

The preparation of the betaine of the formula II on which the salts of the general formula I according to the invention are based is described in European Patent No. 0,064,740 (Example 51).

In accordance with process 1, a monobasic or dibasic acid of the formula IIIa or IIIb is added to a solution of the compound II in water or in a mixture of water and a water-miscible organic solvent, such as, for example, methanol, ethanol, isopropanol, acetone, tetrahydrofuran or acetonitrile. The acids H^+X^- and $2H^+Y^{2-}$ can be added as solids or in solution, for example in water or in water-miscible, abovementioned organic solvents, or in mixtures of water and these solvents.

The formation of the salts of the formulae Ia and Ib is carried out at temperatures between -20 and +80°C, preferably between -5 and +30°C. The salts crystallize spontaneously on standing, while stirring or after seeding, or by precipitation by means of a solvent such as acetone or ethanol.

The acid of the formula III must be added in at least twice the equimolar amount, but it is also possible to employ an excess.

After addition of the acid III, a solution forms initially which can be filtered, it possibly being advantageous in some cases to clarify the solution using activated charcoal before filtration.

The process can also be carried out by adding the cephem base II, directly or dissolved in water, to a solution of the acid III.

The starting compound of the formula II can also be liberated from its salts by treatment with a basic ion exchanger,

for example the solid exchanger Amberlite IRA 93 or the liquid exchanger Amberlite LA-2, in aqueous solution, and then converted into an acid-addition salt as described above.

In accordance with process 2, the salt of the formula IVa or IVb is added in at least twice the equimolar amount up to a ten-fold excess to the solution of the compound II, and the fundamental acid H^+X^- or $2H^+Y^{2-}$ is liberated by adding a strong mineral acid, such as, for example, HCl or H_2SO_4.

In this way, the corresponding sparingly soluble salts can be prepared using acids, for example from HI or HSCN produced in situ.

In accordance with process 3, a salt of the formula IVa or IVb whose fundamental anion forms a sparingly soluble acid-addition salt with the compound II, for example the dihydroiodide or dihydroperchlorate of the compound II, is added to the solution of a salt Ia or Ib in water. The reaction and crystallization are carried out as described for process 1.

The compounds of the formulae Ia and Ib obtained in accordance with the process described above are isolated, for example, by filtration or centrifugation and are dried at atmospheric pressure or in vacuo, expediently with the aid of a dehydrating agent, such as, for example, concentrated sulfuric acid or phosphorus pentoxide. Depending on the drying conditions, the compound of the formula I is produced here as the hydrate or in anhydrous form.

The compounds of the general formula I obtained according to the invention exhibit remarkably good antibacterial activities, both against Gram-positive and Gram-negative bacterial germs.

The compounds of the formula I are also unexpectedly highly

active against penicillinase- and cephalosporinase-forming bacteria. Since, in addition, they exhibit favorable toxicological and pharmacological properties, they represent valuable chemotherapeutic agents.

The invention thus also relates to medicament preparations for treatment of microbial infections in mammals (both in humans and in animals), which preparations are characterized in that they contain one or more compounds according to the invention, in particular the physiologically acceptable acid-addition salts.

The products according to the invention can also be used in combination with other active compounds, for example from the series comprising the penicillins, cephalosporins or aminoglycosides.

The compounds of the general formula I can be administered subcutaneously, intramuscularly, interarterially or intravenously, and also intratracheally or locally in animals, such as, for example, into the udder of milk-giving animals.

Medicament preparations which contain one or more compounds of the general formula I as active compound can be produced by mixing the compounds of the formula I with one or more pharmacologically acceptable excipients or diluents, such as, for example, buffer substances, and converted into a formulation which is suitable for parenteral administration.

Diluents which may be mentioned are, for example, polyglycols, ethanol and water. Buffer substances are, for example, organic compounds, such as, for example, N',N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, N-methylglucymine (sic), N-benzylphenethylamine, diethylamine or tris(hydroxymethyl)aminomethane, or inorganic compounds, such as, for example, phosphate buffer, sodium bicarbonate or sodium carbonate. Suspensions or solutions in water, with or without buffer substances, are preferably possible

for parenteral administration.

Suitable doses of compounds of the general formula I are about 0.4 to 20 g/day in the case of administration to humans, preferably 0.5 to 4 g/day for an adult of approximate body weight 60 kg.

Single or in general multiple doses can be administered, it being possible for the individual dose to contain the active compound in an amount of about 50 to 1000 mg, preferably from about 1200 to 500 mg.

In the case of administration to animals, all mammals are possible in principle, in particular pets and useful animals in view of their importance. The dosage varies in the individual species of animal and can be, for example, between about 2.5 and 150, preferably between 5 and 50, mg/kg of body weight of the animal.

It was expected that, as a consequence of the monobasic function of the starting material, salt formation would take place with one mole of acid. It was therefore surprising that acid-addition salt formation does not take place, according to the invention, until 2 moles of acid have been added and that crystalline salts of increased stability compared to the betaine form and to the corresponding amorphous salts are produced.

The following illustrative embodiments for acid-addition compounds, which can be prepared according to the invention, of the compound II, 1-[[(6R,7R)(Z)-7-[[2-(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-en-3-yl]methyl]-5,6,7,8-tetrahydroquinolinium hydroxide, internal salt, serve to further illustrate the invention, but do not represent a limitation.

Example 1:

Sulfate of the compound II (process 1)

A mixture of 8.2 g (0.01 mol) of the dihydroiodide salt of the compound II (Example 2a), 15 ml of Amberlite LA-2 (Serva 40610), 30 ml of water and 50 ml of EtOAc is stirred at 20°C for 30 minutes. After 15 minutes, the dihydroiodide salt has dissolved. The phases are separated and the aqueous phase is washed with 50 ml of toluene. After addition of 0.6 g of animal charcoal, the aqueous phase, which contains the betaine II, is stirred for 15 minutes, filtered, cooled to 10°C and acidified to pH 1.3 using 6 N sulfuric acid. 60 ml of cold ethanol are then added while stirring. After a short time, crystallization of the sulfate commences. The suspension is stirred at 5°C for 4 hours and filtered, and the precipitate is washed twice with 15 ml of ethanol in each case and dried in vacuo over P_2O_5 to constant weight.

Yield: 5.2 g (80.7 %) of colorless crystals, decomp. 182°C.

$C_{23}H_{24}N_6O_5S_2 \times H_2SO_4 \times H_2O$ (644.7)
calc.: C 42.8 H 4.4 N 13.1 S 14.9 H_2O 2.8 %
found: C 42.6 H 4.2 N 13.0 S 14.7 H_2O 3.1 %

Example 2:

Dihydroiodide of the compound

a) Isolation of II from reaction batches

22.6 g (0.17 mol) of 5,6,7,8-tetrahydroquinoline is (sic) added dropwise while stirring to a solution, cooled to 5°C, of 28 g (0.14 mol) of trimethyliodosilane in 200 ml of dichloromethane. 9.1 g (0.02 mol) of 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]cephalosporanic acid are then introduced into the stirred solution. The mixture is refluxed for 2 hours, then cooled to 5°C and hydrolyzed while adding dropwise 60 ml of a mixture of

57 per cent strength hydroiodic acid:water: ethanol (1:4:8). The dihydroiodide salt precipitates as a pale yellow precipitate. After 4 hours at 0°C, the mixture is filtered, and the precipitate is washed with 100 ml of methylene chloride and 100 ml of acetone and dried in air.

Yield: 13 g (79.2 %) of pale yellow crystals, decomp. > 200°C

$C_{23}H_{24}N_6O_5S_2 \times 2HI \times 2H_2O$ (820.5)

calc.: C 33.7 H 3.7 N 10.2 S 7.8 I 30.9 H_2O 4.3%

found: C 32.5 H 3.6 N 9.8 S 7.3 I 30.5 H_2O 3.8%

b) Dihydroiodide of the compound II (process 1)

25 ml of 1 N aqueous hydroiodic acid are added to a solution of 0.01 mol of II, prepared in accordance with Example 1. A yellow precipitate forms immediately, and is filtered off under suction, washed with water and dried. The compound is identical in all properties to the compound described above.

c) Dihydroiodide of the compound II (process 3)

6.45 g (0.01 mol) of the sulfate (Example 1) are dissolved in 200 ml of water, and a solution of 5.5 g (0.035 mol) of potassium iodide in 5 ml of water is then added. Crystallization of the pale yellow dihydroiodide salt commences after a short time. After 2 hours, the precipitate is filtered off under suction, washed with water and dried. The compound is identical in all properties to the compound described above.

Example 3:

Dihydrothiocyanate of the compound II (process 2)

6 ml of 1 N HCl are added to a solution of 1.06 g (2 mmol) of II and 0.58 g (6 mmol) of potassium rhodanide in 6 ml

of water while shaking. The crystal suspension formed is stirred at 10°C for 2 hours, and the precipitate is filtered off under suction and washed twice with 5 ml of ice water in each case. After drying over P_2O_5 in vacuo, 0.78 g (59 % of theory) of colorless crystals, decomp. 166°C, is obtained.

$C_{23}H_{24}N_6O_3S_2 \times 2HSCN \times H_2O$ (664.8)
calc.: C 45.2 H 4.3 N 16.9 S 19.3 H_2O 2.7 %
found: C 45.0 H 4.4 N 16.5 S 18.3 H_2O 1.5%

Example 4:

Dihydronitrate of the compound II (process 1)

5 ml of 1N nitric acid are added to the solution of 1.06 g (2 mmol) of II in 6 ml of water while shaking. The crystalline precipitate formed is filtered off under suction, washed twice with 3 ml of ice water in each case and dried over P_2O_5.
Yield: 0.92 g (67 % of theory) of colorless crystals, decomp. > 140°C.

$C_{23}H_{24}N_6O_5S_2 \times 2HNO_3 \times H_2O$ (672.7)
calc.: C 41.1 H 4.2 N 16.7 S 9.5 H_2O 2.7 %
found: C 40.9 H 4.1 N 16.6 S 9.3 H_2O 2.7 %

Example 5:

Dihydroperchlorate of the compound II (process 1)

5 ml of 1 N perchloric acid are added to the solution of 1.06 g (2 mmol) of II in 6 ml of water. The precipitate formed is filtered off under suction, washed three times with 3 ml of water in each case and dried over P_2O_5 in vacuo.
Yield: 1.2 g (80 %) of colorless crystals, decomp. > 160°C.
$C_{23}H_{24}N_6O_5S_2 \times 2HClO_4 \times H_2O$ (747.6)
calc.: C 37.0 H 3.8 Cl 9.5 N 11.2 S 8.6 H_2O 2.4 %

found: C 36.8 H 3.8 Cl 10.1 N 11.8 S 8.6 H_2O 2.8 %

Example 6:

Dihydrotetrafluoroborate of the compound II (process 1)

5 ml of 1 N tetrafluoroboric acid are added to the solution of 1.06 g (2 mmol) of II in 6 ml of water. After the mixture has been standing for 1 hour in an ice bath, the precipitate formed is filtered off under suction, washed with 2 ml of ice water and dried over P_2O_5.
Yield: 0.85 g (59 %) of colorless crystals, decomp. 178°C

$C_{23}H_{24}N_6O_5S_2 \times 2HBF_4 \times H_2O$ (722.3)
calc.: C 38.3 H 3.9 F 21.0 N 11.6 S 8.9 H_2O 2.5 %
found: C 38.5 H 4.1 F 20.3 N 11.4 S 8.6 H_2O 2.8 %

Example 7:

Dihydrobromide of the compound II (process 1)

1 ml of 4 N hydrobromic acid are (sic) added to the solution of 1.06 g (2 mmol) of II in 6 ml of water. After the mixture has been standing for 4 hours in an ice bath, the precipitate formed is filtered off under suction, washed with 1 ml of ice water and dried over P_2O_5.
Yield: 0.11 g (75 %) of colorless crystals, decomp. 188°C

$C_{23}H_{24}N_6O_5S_2 \times 2HBr \times H_2O$ (708.5)
calc.: C 39.0 H 4.0 Br 22.6 N 11.9 S 9.1 H_2O 2.6 %
found: C 38.5 H 3.8 Br 21.8 N 11.6 S 8.9 H_2O 2.9 %

Example 8:

Dihydrochloride of the compound II (process 1)

A solution of 1.06 g (2 mmol) of II in 6 ml of water is acidified to pH 1.3 using concentrated hydrochloric acid. After some time, a precipitate deposits out of the solution.

After standing for 24 hours at 0°C, the precipitate is filtered off under suction and dried over P_2O_5.
Yield: 0.2 g (16 %) of colorless crystals, decomp. 190°C.
20 ml of ethanol are added to the mother liquor, the mixture is concentrated in vacuo, and a further 6 ml of ethanol are added to the concentrated solution (3 ml). The solution is decanted from a little resin. After standing for a relatively long period, a second crystal fraction deposits out of the solution, and is filtered off under suction and dried over P_2O_5.
Yield: 0.3 g (24 %) of colorless product, decomp. >180°C

$C_{23}H_{24}N_6O_5S_2 \times 2HCl \times H_2O$ (619.5)
calc.: C 44.6 H 4.6 Cl 11.4 N 13.6 S 10.3 H_2O 2.9 %
found: C 44.1 H 4.7 Cl 11.6 N 13.4 S 10.0 H_2O 3.3 %

Example 9

Dihydromaleate of the compound II (process 1)

18 ml of acetone are added to a solution of 1.06 g (2 mmol) of II and 0.58 g (5 mmol) of maleic acid in 6 ml of water. A slight turbidity is removed by filtration. After standing overnight at 0°C, a colorless product crystallizes from the solution. The product is filtered off under suction, washed three times with 10 ml of acetone in each case and dried over P_2O_5.
Yield: 1.0 g (63 %) of colorless crystals, decomp. 135-140°C

$C_{23}H_{24}N_6O_5S_2 \times C_8H_8O_8 \times H_2O$ (796.8)
calc.: C 46.7 H 4.3 N 10.5 S 8.0 H_2O 2.3 %
found: C 46.9 H 4.5 N 10.8 S 8.2 H_2O 2.2 %

COMPARATIVE EXAMPLE 1

Materials:

a) Crystalline salts

The sulfate has been prepared according to working example 1 and the dihydrobromide according to working example 7 of the instant application.

b) Corresponding amorphous salts (cf. cited US 4,667,028, col. 8, l. 41)

Sulfate: A mixture of 10 mmols of the betaine (Formula II in the instant application) ~~(Application Serial No. 159,395)~~ and 10 mmols of sulfuric acid in 100 ml of water (pH = 2.5) are freeze dried.

The dihydrobromide was prepared in an anlogous manner from the betaine and two equivalents of hydrobromic acid.

c) The betaine was obtained by freeze-drying the aqueous phase of working example 1 of the instant application. ~~US Patent Application Serial No. 159,395 (cf. page 7, line 10 et seq.).~~

Test Method:

25.00 ± 1 mg of the salts have been sealed in vessels and stored at 40°C and 60°C, respectively. For determination of the active compound, the HPLC-method (high pressure liquid chromatography) was applied. The content of the vessel was dissolved in 100 ml of distilled water and 20 µl were analysed on a nucleosid column (10 C 18, 10 µm, 250 x 4,6 mm), phosphate buffer, pH 3,3/CH_3CN; flow rate 2 ml/min; UV-detection at 270 mm.

Discussion:

The preparation of crystalline cephalosporin salts is not a matter of course but affords a high degree of experimental experience and of sophisticated working procedures. A prerequisite for technical scale production and isolation of labile cephalosporins is the formation of crystalline products which allow easy isolation and purification. Furthermore, the preparation of crystalline end products is extremely important for stability reasons. For example, the crystalline sulfate or dihydrobromide are much more stable than the amorphous preparations.

As it is demonstrated by Figures 1 and 2, after storage at 40°C and 60°C the crystalline salts are much more stable than the corresponding amorphous forms, e.g. after 6 weeks at 60°C the crystalline sulfate is still 91% pure, whereas the amorphous sulfate is completely decomposed (Figure 1). The corresponding data for the dihydrobromide are 87 % and 57 % (Figure 2). The betaine shows also a fast decomposition: After 4 weeks at 60°C, only 15 % of the active compound are found (Figure 3).

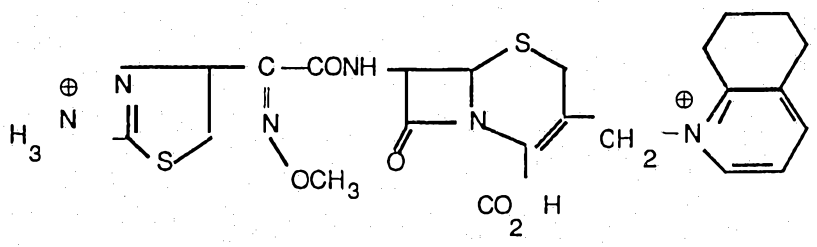
Conclusion:

The data clearly demonstrate that the crystalline salts of the instant application have an unexpected superior high stability compared to the amorphous forms (cf. US

4,667,028) and also the betaine and lead therefore to formulations of much higher purity and safety for human application. It is evident that all the compounds of the instant case, being in a crystalline form have the same degree of superiority over the disclosures of the prior art.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A crystallized cephem-acid addition salt of the formula I



I

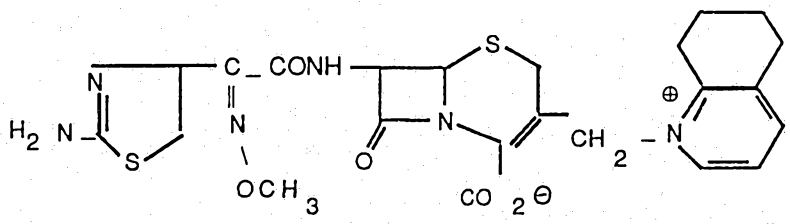
in which X^- represents an anion of a monobasic inorganic or organic acid (formula Ia) and

$Y2^-$ represents an anion of a diabasic inorganic or organic acid (formula Ib),

and its hydrate.

2. A process for the preparation of an acid-addition salt of the formula I, which comprises

a) reacting a cephem-betaine of the formula II



II

with a monobasic inorganic or organic acid of the formula IIIa or a dibasic inorganic or organic acid of the formula IIIb

$H+X^-$ IIIa

$2H+Y^{2-}$ IIIb

in which X and Y represent the anions of these acids,

b) reacting a cephem-betaine of the formula II with an acid of the formula IIIa or IIIb produced in situ, this acid being produced from the corresponding salt of the formula IVa or IVb respectively.

ZX or ZX_2 IVa

Z_2Y or ZY IVb

in which Z denotes a monovalent or divalent metal cation, through addition of a strong acid, or

c) reacting a water-soluble salt of the formula I, obtained in accordance with a), with a salt of the formula IVa or IVb in which X^- and Y^{2-} denote the anion of a sparingly water-soluble salt of a monobasic or dibasic inorganic or organic acid.

3. A pharmaceutical preparation which is active against bacterial infections in mammals, in which the said preparation contains a cephem derivative of the formula I in adjunct with pharmaceutically acceptable carriers or excipients.

4. A process for the production of pharmaceutical preparations which are active against bacterial infections in mammals, wherein a cephem derivative of the formula I as active compound is admixed with one or more pharmaceutically conventional excipients, diluents or buffer substances in a pharmacologically effective ratio, and converted into a formulation suitable for administration to a patient.

5. A method of combatting bacterial infections in mammals comprising administering thereto in pharmaceutically effective quantities a cephem derivative of the formula I as claimed in Claim 1.

DATED this 19th day of November, 1991

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Figure 1 Sulfate

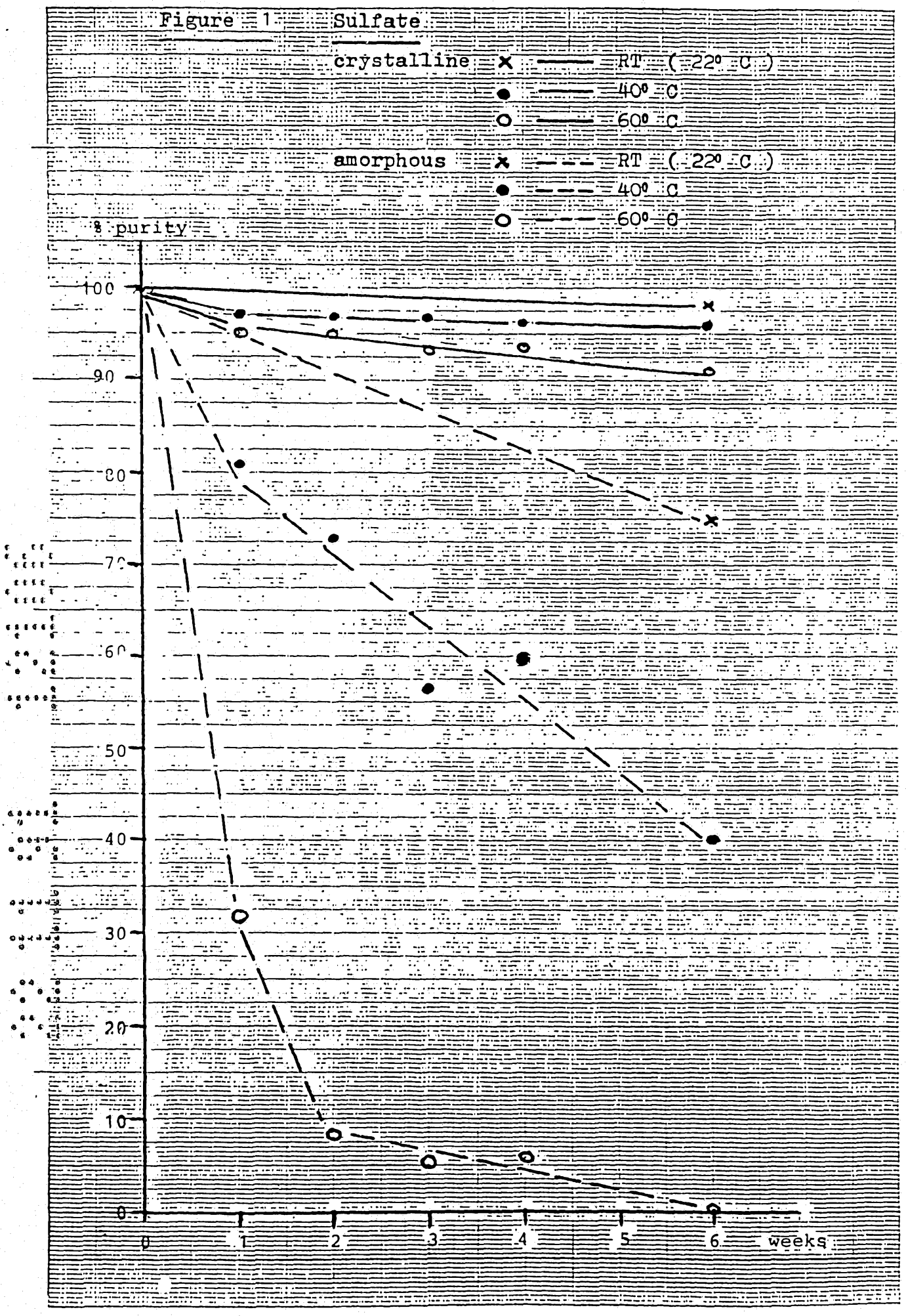

Figure 2 Dihydrobromide

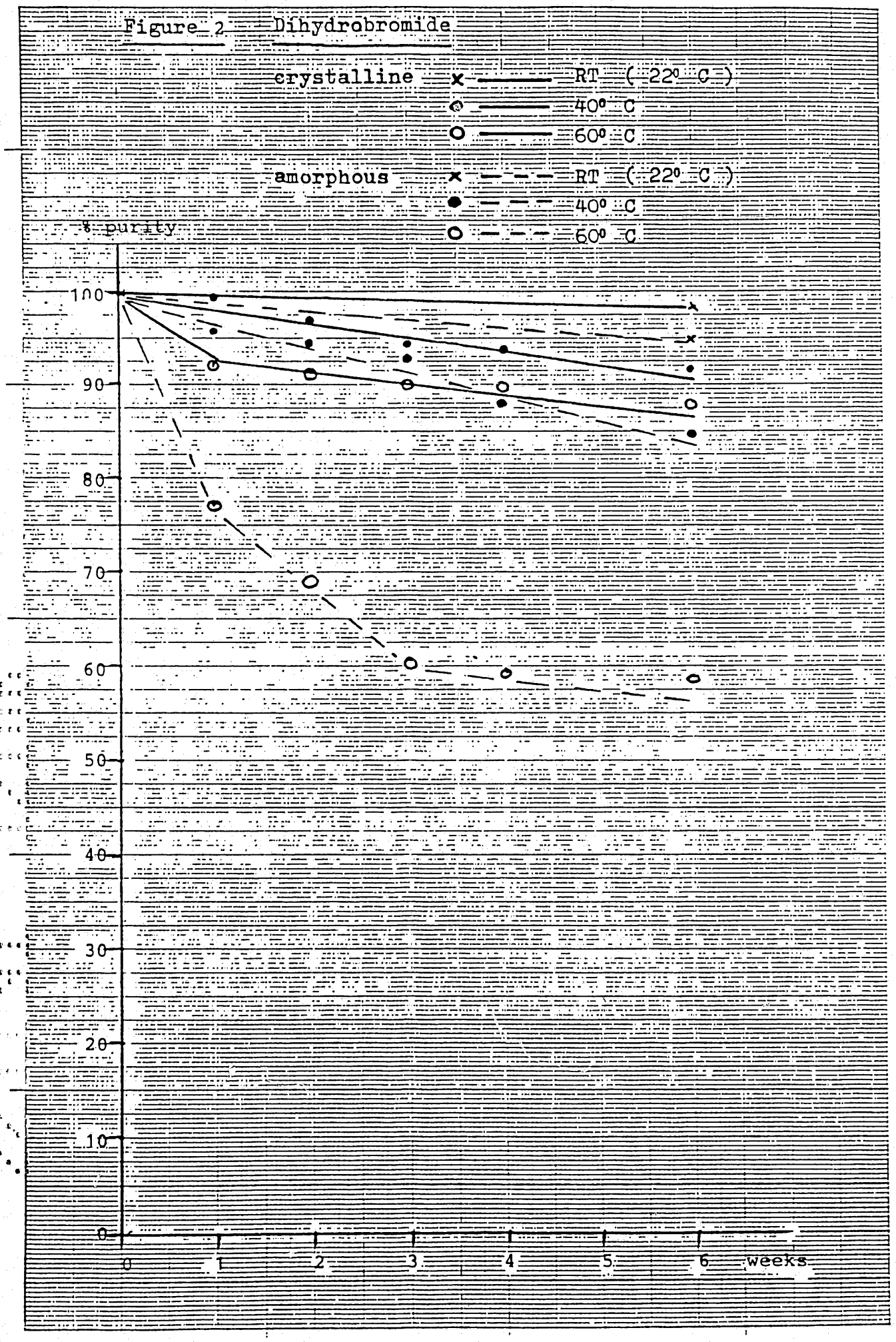

Figure 3 Betaine