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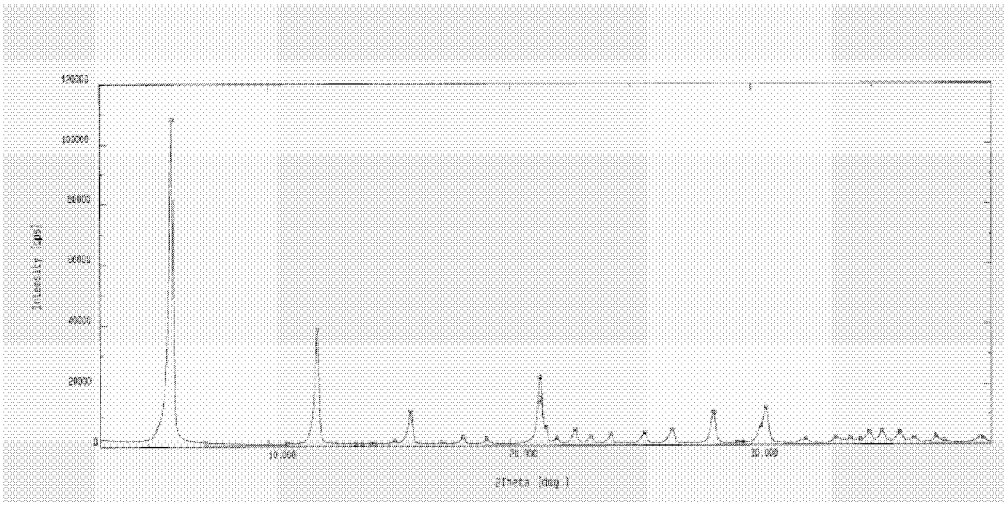
(54) **Title:** PROCESSES FOR THE PREPARATION OF 7-AMINO-3-VINYL CEPHALOSPORANIC ACID

X-ray Diffraction Pattern of Crystalline 7-AVCA



(57) **Abstract:** The invention relates to processes for the preparation of 7-amino-3-vinyl cephalosporanic acid. The invention also relates to a crystalline form of 7-amino-3-vinyl cephalosporanic acid and process for its preparation.

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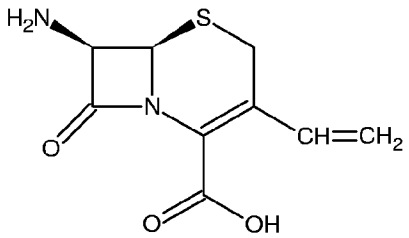
PROCESSES FOR THE PREPARATION OF 7-AMINO-3-VINYL CEPHALOSPORANIC ACID

Field of the Invention

The field of the invention relates to processes for the preparation of pure 7-amino-3-vinyl cephalosporanic acid. The invention also relates to a crystalline form of 7-amino-3-vinyl cephalosporanic acid and process for its preparation.

Background of the Invention

7-amino-3-vinyl cephalosporanic acid of Formula I (herein after 7-AVCA) is an important synthetic intermediate in the preparation of cephalosporin antiobiotics for example, cefdinir.



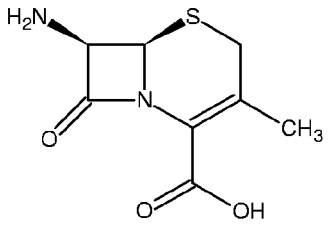
FORMULA I

Several processes have been reported for the preparation of 7-AVCA for example, in *Tetrahedron Letters*, 1982, 23 (21), 2187-2188; U.S. Patent No 4,705,851; and European Patent No 122,002.

European Patent No. 503,453 ("the '453 patent") discloses a process for the preparation of 7-AVCA and its derivatives wherein silyl protected 7-amino-3-haloalkyl cephalosporanic acid is used as the starting material in a Witting type reaction in the presence of a strong base. It is mentioned that in order to maintain a degree of silylation the base used must be free of moisture and should itself not contain any moiety that could be silylated.

U.S. Patent No 6,401,841 discloses a process for the preparation of 7-AVCA and its derivatives which is a modification of the process of the '453 patent, wherein the Wittig reaction using silyl protected 7-aminocephalosporanic acid is carried out in the presence of a weak base.

U.S. Patent No 6,835,829 ("the '829 patent") discloses a process for the purification of 7-AVCA. As per the disclosure of the patent, 7-AVCA obtained by following the process of the '453 patent is contaminated with 7-amino-3-methylcephalosporanic acid of Formula A (7-ADCA).



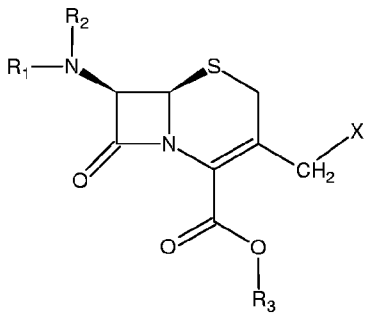
FORMULA A

The process reported in the '829 patent involves further purification of 7-AVCA prepared by methods known in the art, by chromatographic purification or by forming quaternary ammonium salts of the 4-carboxyl group followed by basification to get 7-AVCA or its derivative. 7-AVCA thus purified has 7-ADCA content ranging from 0.1-0.8%.

In general, these processes involve the use of the silyl protected 7-aminocephalosporanic acid and are not favorable commercially because the silylating agents are costly and silyl protecting groups are prone to hydrolysis and require careful control of the reaction conditions so as to ensure moisture free environment. The product obtained by the reported processes is contaminated with undesired compounds thus requiring purification using chromatographic techniques or by quaternary salt formation.

The presence of 7-ADCA impurity in 7-AVCA, leads to the formation of by-products when 7-AVCA is used in the preparation of cephalosporin antibiotics.

The source of 7-ADCA could be the 7-protected amino-3-haloalkylcephalosporanic carboxylate of Formula II,

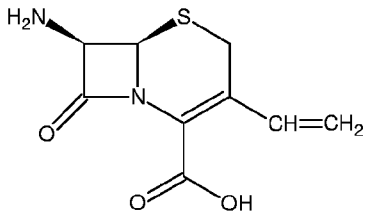


FORMULA II

wherein R_1 and R_2 independently represent hydrogen or a suitable amino protecting group, R_3 represents a suitable carboxyl protecting group, and X represents a halogen, which is the starting material in the preparation of 7-AVCA via Wittig reaction.

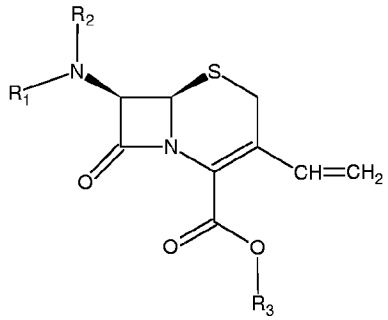
Summary of the Invention

In one general aspect there is provided a process for the preparation of pure 7-amino-3-vinyl cephalosporanic acid (7-AVCA) of Formula I. The process includes:



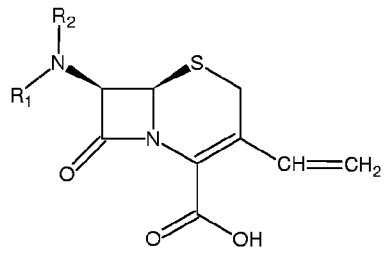
FORMULA I

a) crystallizing diprotected 7-amino-3-vinyl cephalosporanic acid (DPVC) of Formula III, wherein R_1 and R_2 independently represent hydrogen or a suitable amino protecting group and R_3 represents a suitable carboxyl protecting group;



FORMULA III

b) removing the carboxyl protecting group from the DPVC of Formula III obtained in step a) to get monoprotected 7-amino-3-vinyl cephalosporanic acid (MPVC) of Formula IV,



FORMULA IV

wherein R_1, and R_2 are as described above;

c) removing the amino protecting group from the MPVC of Formula IV obtained in step b) to get 7-AVCA of Formula I; and

d) isolating the 7-AVCA of Formula I.

The process may include further drying of the product obtained.

In another general aspect there is provided a crystalline 7-amino-3-vinyl cephalosporanic acid (7-AVCA).

The crystalline 7-AVCA may have the X-ray diffraction pattern of Figure 1 and infrared spectrum of Figure 2. The crystalline 7-AVCA may have a moisture content of about 0.5 to 0.6% w/w as measured by Karl Fischer analysis.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Drawings

Figure 1 is an X-ray powder diffraction pattern of crystalline 7-AVCA.

Figure 2 is an infrared spectrum of crystalline 7-AVCA.

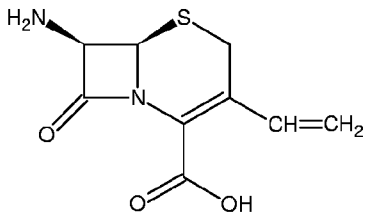
Detailed Description of the Invention

The present inventors have developed a process for the preparation of pure 7-AVCA of Formula I. The inventors have found that the 7-AVCA of Formula I can be prepared without the use of silylating agents or purification by chromatography or quaternary salt formation. The present process enables significant depletion of 7-ADCA during the course of the synthesis. By following the present process, the 7-AVCA is found to have 0.2% or less of

7-amino-3-methylcephalosporanic acid (7-ADCA). The present process does not require any additional purification steps like salt formation or chromatography, thereby reducing the work-up time as well as the cost of production.

The term "pure 7-AVCA" as used herein refers to 7-AVCA having a purity of 99% or more and having 7-ADCA content of 0.2% or less.

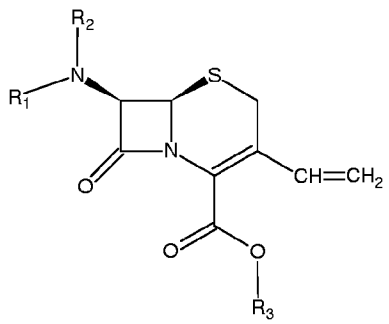
A first aspect of the present invention provides a process for the preparation of pure 7-AVCA of Formula I,



FORMULA I

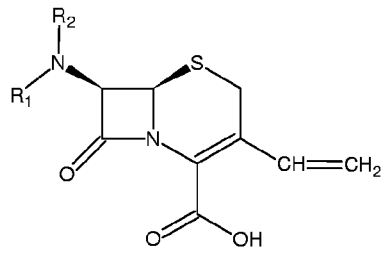
which comprises:

a) crystallizing diprotected 7-amino-3-vinyl cephalosporanic acid (DPVC) of Formula III, wherein R_1 and R_2 independently represent hydrogen or a suitable amino protecting group and R_3 represents a suitable carboxyl protecting group, from a reaction mass with an organic solvent;



FORMULA III

b) removing the carboxyl protecting group from the DPVC of Formula III obtained in step a) to get monoprotected 7-amino-3-vinyl cephalosporanic acid (MPVC) of Formula IV,



FORMULA IV

wherein R_1, and R_2 are as described above;

c) removing the amino protecting group from the MPVC of Formula IV obtained in step b) to get 7-AVCA of Formula I; and

d) isolating the 7-AVCA of Formula I.

The diprotected 7-amino-3-vinyl cephalosporanic acid (DPVC) of Formula III which is used as the starting material can be prepared by methods disclosed in any of the known processes, for example, processes as disclosed in U.S. Patent Nos. 5,401,841; 5,043,439 and WO 98/55485. The DPVC of Formula III may be crystallized from a reaction mixture using an organic solvent. Suitable organic solvents for crystallization of DPVC include C_{1-4} alkanols; C_{3-8} ketones; polar aprotic solvents, and mixtures thereof. Examples of organic solvents include one or more of methanol, ethanol, isopropanol, acetone, dimethyl sulphoxide, and tetrahydrofuran.

The carboxyl protecting group from DPVC of Formula III may be removed in the presence of phenol or phenol ethers for example, anisole, phenetol, and the like to get the monoprotected 7-amino-3-vinyl cephalosporanic acid (MPVC) of Formula IV. The deprotection of DPVC of Formula III can be effected at a temperature of from about 20°C to about 80°C and optionally in the presence of an acid. The amino protecting group from may be removed from the MPVC of Formula IV to get 7-AVCA of Formula I. The acid used for removal of the carboxyl protecting group in DPVC of Formula III can be selected from organic or inorganic acids known to a person having ordinary skills in the art and include hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, p-toluenesulphonic acid, and the like or mixtures thereof.

Removal of the amino protecting group from the MPVC of Formula IV can be carried out using chemical reagents or by enzymatic hydrolysis using Penicillin-G amidase or other

amidases for example, Penicillin-V amidase, capable of hydrolyzing MPVC of Formula IV without affecting the cephem ring. The 7-AVCA of Formula I thus obtained has 0.2% or less of the undesired 7-ADCA. The 7-AVCA of Formula I prepared by the present process does not require any further purification by chromatography or quaternary salt formation.

The amino and carboxyl protecting groups are known to a person skill in the art. Examples of amino protecting groups include, but not limited to, acyl groups such as benzoyl, benzyl carbonyl, and the like. Examples of carboxyl protecting groups include, but not limited to, aralkyl groups such as 4-methoxybenzyl or 2,4-dimethoxybenzyl, benzhydryl, and the like.

A second aspect of the present invention provides a crystalline 7-AVCA having characteristic X-ray diffraction (XRD) pattern of Figure 1 and infrared spectrum of Figure 2.

In general, the crystalline 7-AVCA may be characterized by X-ray diffraction peaks at about 6.00, 7.36, 10.76, 12.02, 13.62, 13.88, 14.26, 14.42, 15.24, 15.88, 17.18, 18.04, 19.02, 21.24, 21.48, 21.94, 22.70, 23.36, 24.18, 25.58, 26.72, 28.44, 29.44, 29.66, 30.40, 30.62, 32.28, 33.52, 34.12, 34.54, 34.90, 35.42, 36.18, 36.78, 37.70, 38.02, 39.52 and 39.64 degrees two-theta values.

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.

Example 1: Preparation of p-methoxybenzyl 7-phenylacetamido-3-vinyl-3-cephem –4-carboxylate (DPVC)

4-methoxybenzyl (6*R*,7*R*)-3-(chloromethyl)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (200 g), sodium iodide (62 g) and triphenyl phosphine (118 g) were added to pre-cooled acetone (1000 ml) at 10–15°C. The reaction mixture was stirred maintaining the temperature at 20–25°C for 90 minutes and monitored by HPLC. The reaction mixture was subsequently cooled to 10–15°C and dichloromethane (2000 ml) was added followed by the addition of formaldehyde (360.8 g) at 10 – 15°C. Sodium hydroxide solution (16.4 g in 400 ml deionized water) was slowly added to the resultant mixture at 10 – 15°C in 5–10 minutes and the temperature was maintained at 10–15°C for 60–70 minutes. The reaction was monitored by HPLC. Deionized water (3600 ml)

was added to this mixture at 10–20°C and the pH was adjusted to 5.5–6.0 by adding 5% aqueous hydrochloric acid. The layers were separated and the dichloromethane was evaporated from the organic layer at 35–40°C under vacuum. Methanol was added to the organic layer after removal of the dichloromethane. The crystals so obtained were filtered under suction and dried in air to get the title compound.

Yield = 141 g (74%)

Example 2: Preparation of 7-amino-3-vinyl-3-cephem – 4 - carboxylic Acid (7-AVCA)

p-methoxybenzyl (6*R*,7*R*)-8-oxo-7-[(phenylacetyl)amino]-3-vinyl-5-thia-1 azabicyclo[4.2.0]oct-2-ene-2-carboxylate (100 g) was added to molten phenol (500 ml) at 45 – 50°C. The mixture was stirred and maintained at 45–50°C for 7 hours (monitored by HPLC) followed by cooling to 35 – 40°C. n-butyl acetate (1000 ml) was added to the mixture at 30–40°C followed by cooling to 10–15°C. Sodium bicarbonate solution (1500 ml, 1.5%) was added to the resultant mixture at 10–20°C and stirred for 10–15 minutes. The layers were separated and the organic layer was re-extracted with sodium bicarbonate solution (1000 ml, 1.5%) at 10–20°C. The layers were again separated. The aqueous layers were combined and washed twice with n-butyl acetate to remove phenol. The washed aqueous layer was subjected to enzymatic hydrolysis using wet Penicillin-G amidase (50 g) at 20–25°C. The reaction mixture was stirred and maintained at a pH of 7.5–7.9 by addition of sodium carbonate solution (5%) at 20– 30°C (monitored by HPLC). The enzyme was filtered and the filtrate was washed with deionized water (200 ml) followed by cooling to 8–10°C. The pH of the cooled solution was adjusted to 2.4–2.5 by addition of hydrochloric acid (10%). The solid so obtained was filtered, washed with deionized water and acetone and dried under vacuum at 40–45°C till moisture content was not more than 1.0%.

Yield = 41.5 g (85%)

HPLC Purity: 99.42%

7-ADCA content: 0.17% (by HPLC)

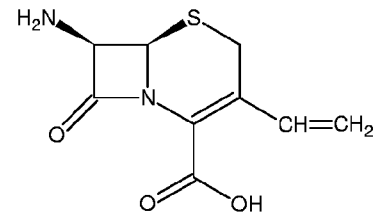
XRD as per Figure 1

IR as per Figure 2.

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.

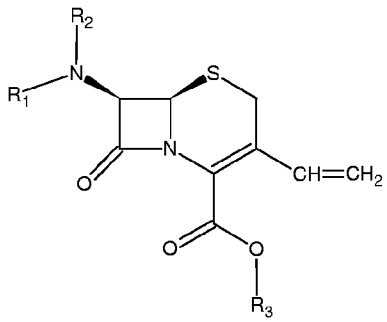
WE CLAIM:

1. A process for the preparation of pure 7-amino-3-vinyl cephalosporanic acid (7-AVCA) of Formula I, the process comprising:



FORMULA I

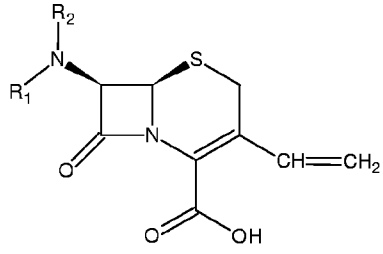
a) crystallizing diprotected 7-amino-3-vinyl cephalosporanic acid (DPVC) of Formula III,



FORMULA III

wherein R_1 and R_2 represent hydrogen or a suitable amino protecting group and R_3 represents a suitable carboxyl protecting group, from a reaction mass with an organic solvent;

b) removing the carboxyl protecting group from the DPVC of Formula III obtained in step a) to get monoprotected 7-amino-3-vinyl cephalosporanic acid (MPVC) of Formula IV,



FORMULA IV

wherein R_1, and R_2 are as described above;

c) removing the amino protecting group from the MPVC of Formula IV obtained in step b) to get the 7-AVCA of Formula I; and

d) isolating the 7-AVCA of Formula I from the reaction mass thereof.

2. The process according to claim 1, wherein the organic solvent comprises one or more of C_{1-4} alkanols; C_{3-8} ketones; polar aprotic solvents, or mixtures thereof.

3. The process according to claim 2, wherein the organic solvent comprises one or more of methanol, ethanol, isopropanol, acetone, dimethyl sulphoxide, and tetrahydrofuran.

4. The process according to claim 3, wherein the organic solvent is methanol.

5. The process according to claim 1, wherein the 7-AVCA has 0.2% or less of 7-amino-3-methylcephalosporanic acid (7-ADCA).

6. The process according to claim 1, wherein R_1 represents benzyl carbonyl, R_2 represents hydrogen and R_3 represents p-methoxybenzyl.

7. The process according to claim 1, wherein the process does not employ purification by chromatography or quaternary salt formation.

8. Crystalline 7-amino-3-vinyl cephalosporanic acid (7-AVCA).

9. The crystalline 7-AVCA of claim 8, wherein the 7-AVCA has the X-ray diffraction pattern of Figure 1.

10. The crystalline 7-AVCA of claim 8, wherein the 7-AVCA has the infrared spectrum of Figure 2.

11. A crystalline 7-amino-3-vinyl cephalosporanic acid (7-AVCA) characterized by X-ray diffraction pattern having peaks at about 6.00, 7.36, 10.76, 12.02, 13.62, 13.88, 14.26, 14.42, 15.24, 15.88, 17.18, 18.04, 19.02, 21.24, 21.48, 21.94, 22.70, 23.36, 24.18, 25.58, 26.72, 28.44, 29.44, 29.66, 30.40, 30.62, 32.28, 33.52, 34.12, 34.54, 34.90, 35.42, 36.18, 36.78, 37.70, 38.02, 39.52 and 39.64 degrees two-theta

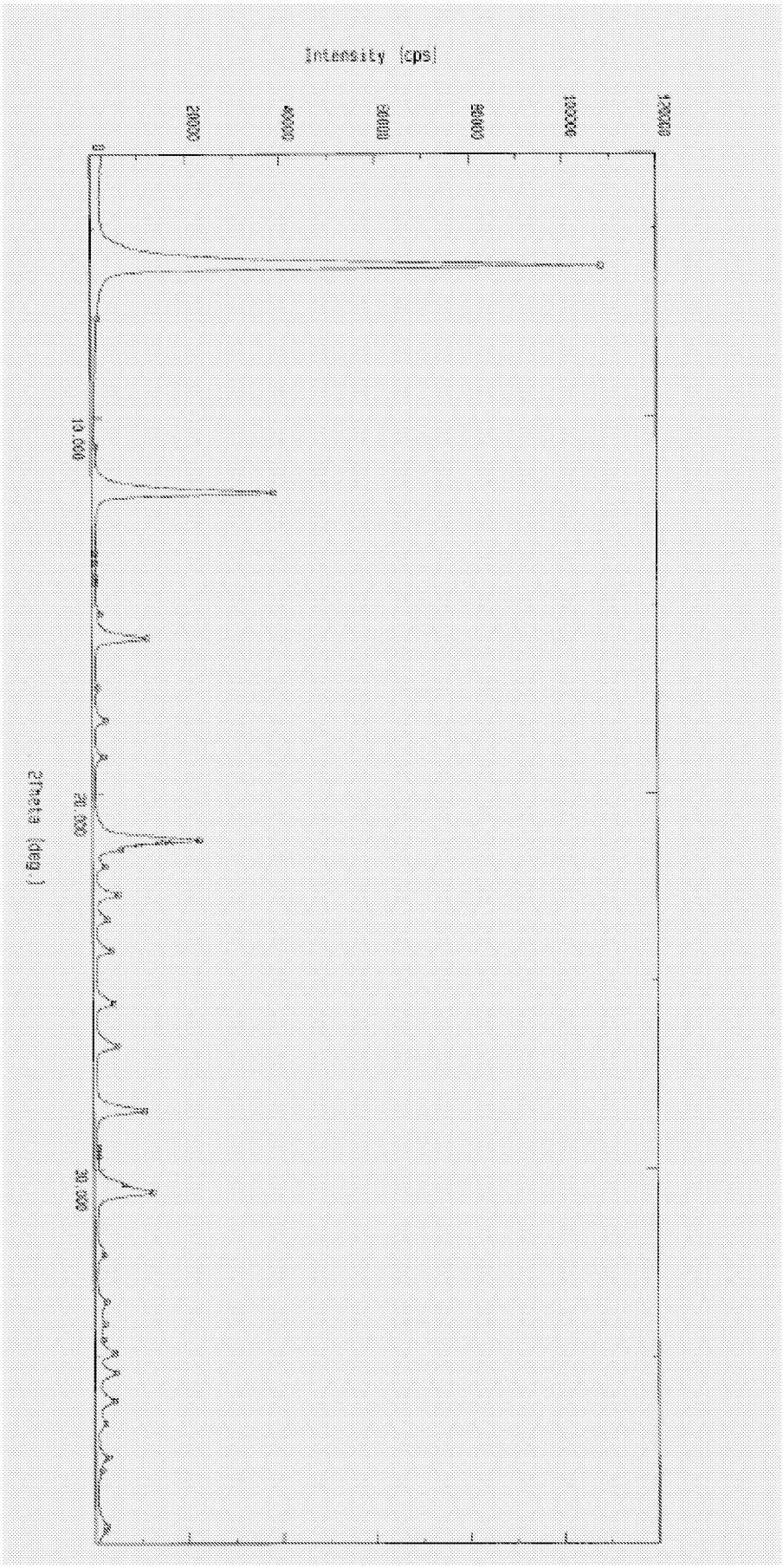


FIGURE 1: X-ray Diffraction Pattern of Crystalline 7-AVCA

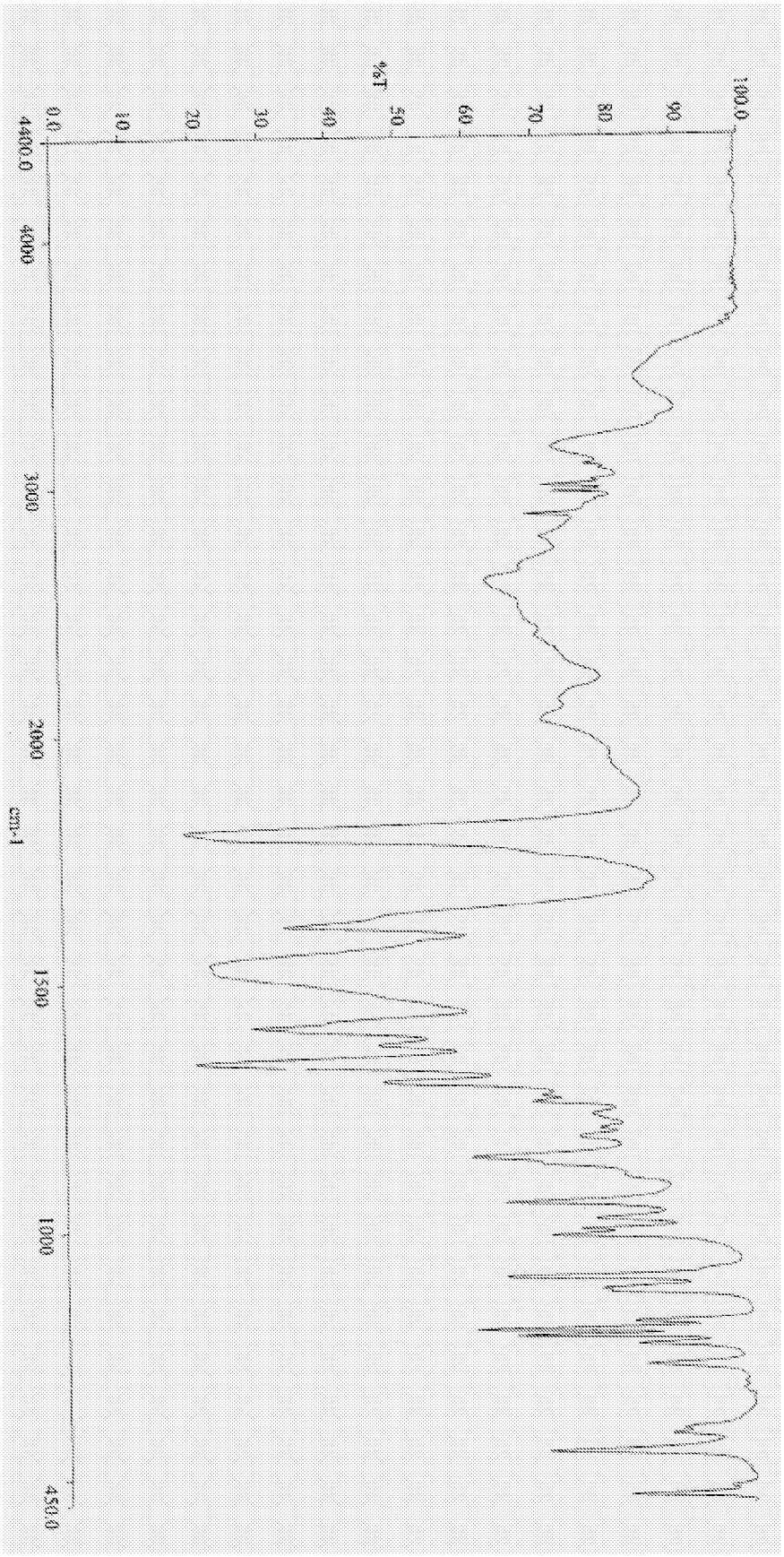


FIGURE 2: Infrared Spectrum of Crystalline 7-AVCA