(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 03/002517 A1

(51) International Patent Classification[7]: C07C 231/02, 233/08

(21) International Application Number: PCT/IL02/00473

(22) International Filing Date: 17 June 2002 (17.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
144066 28 June 2001 (28.06.2001) IL

(71) Applicant *(for all designated States except US)*: **BROMINE COMPOUNDS LTD.** [IL/IL]; Makleff House, P.O. Box 180, 84101 Beer-Sheva (IL).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **OREN, Jacob** [IL/IL]; 9/10 HaShezif Street, Ramot Itzhak, 36847 Nesher (IL).

(74) Agents: **LUZZATTO, Kfir** et al.; Luzzatto & Luzzatto, P.O. Box 5352, 84152 Beersheva (IL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/002517 A1

(54) Title: PROCESS FOR THE PREPARATION OF 1.1-CYCLOHEXANE DIACETIC ACID MONOAMIDE

(57) Abstract: Process for the preparation of 1,1-cyclohexane-diacetic acid monoamide (CHDAAM), by amination of 1,1-Cyclohexane-diacetic anhydride (CDAAn) with aqueous ammonia, neutralization of the reaction mixture, such that crude CHDAAM is precipitated and filtered and by purification of the crude CHDAAM by crystallization from a solvent. The amination is carried out at a temperature kept below 20oC and with aqueous ammonia having a concentration from 25 to 35 wt%, in a molar ratio relative to the CHDAAn from 5 to 10. The neutralization is carried out with an aqueous solution of H2SO4 having a concentration from 30 to 70 wt% and is continued until a slightly acid solution is obtained.

PROCESS FOR THE PREPARATION OF 1,1-CYCLOHEXANE DIACETIC ACID MONOAMIDE

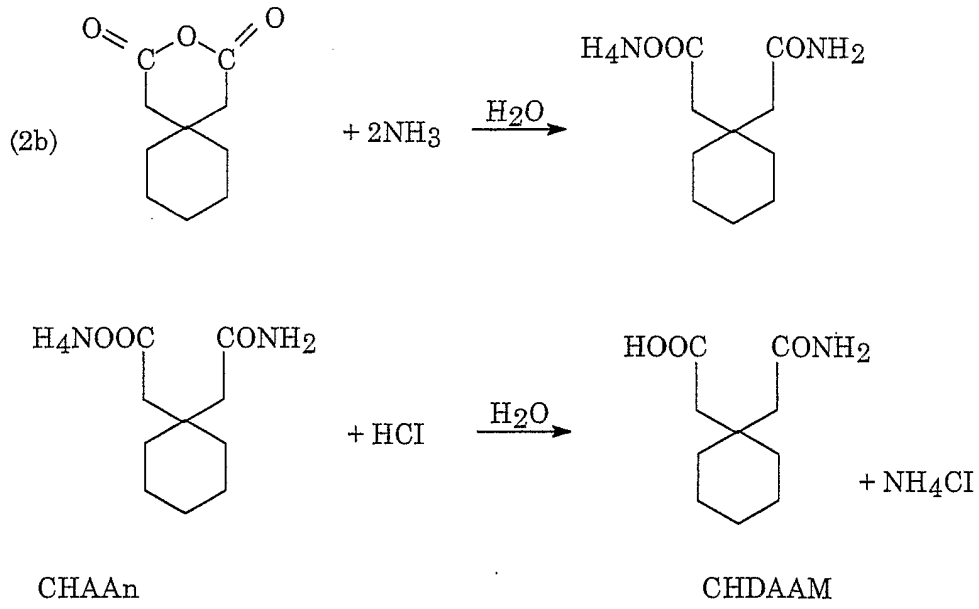
Field of the Invention

This invention relates to an improved process for the preparation of 1,1-cyclohexane-diacetic acid monoamide (CHDAAM) which is a starting material for the production of 1-(aminomethyl)cyclohexaneacetic acid, which is a pharmaceutical compound known as Gabapentin.

Background of the Invention

Skilled persons know how to prepare CHDAAM by the amination of cyclohexanediacetic anhydride (hereinafter CHDAAn), which in turn can be prepared from cyclohexanediacetic acid (hereinafter CHDAA). USP 4,024,175 describes the preparation of 1,1-cyclopentanediacetic acid monoamide from 1,1-cyclopentenediacetic anhydride. The amination is carried out by reacting the anhydride with a 20% aqueous solution of ammonia and, after the reaction has taken place, removing the excess ammonia in a vacuum, acidifying the solution with hydrochloric acid, and then extracting with methylene chloride. Subsequently, the methylene chloride is stripped off to provide 1,1-cyclopentanediacetic acid monoamide.

A similar reaction would produce CHDAAM if the starting material were 1,1-cyclohexanediacetic anhydride. The reaction, for the preparation of CHDAAM, is illustrated by the following scheme:



CHAAn CHDAAM

β-Substituted glutaramic acid can be prepared by:

a) Partial hydrolysis of the corresponding diethyl glutarate, followed by reaction with ammonia and subsequent acidification - see G. H. Jeffery et al., Chem. Soc., p. 1101 (1934).

b) Hydrolysis of the corresponding glutarimide with one equivalent of NaOH, followed by acidification - see G. J. Handley et al, "Compounds derived from β–substituted glutaric acids". Aust. J. Chem., pp. 135, 140, 143, (1960)

It is known in the literature to prepare glutaric anhydrides by refluxing glutaric acids with excess acetic anhydride for several hours, concentrating and finally distilling under reduced pressure (see G.J. Handley et al., "Compounds derived from β-substituted glutaric acids", Aust. J. Chem., 129-144 (1960)).

While USP 4,024,175 merely states that the crude 1,1-cyclopentenediacetic acid monoamide, obtained and described therein, can be further worked up directly, it does not describe such work-up and does not specify the yield and the degree of purity of the final product. The art does not teach an efficient way of carrying out the work-up, and as a result does not provide an efficient complete process for the production of CHDAAM.

It is therefore a purpose of this invention to provide such a complete process, which produces pure CHDAAM in satisfactory yields and with very high purity.

It is another purpose of this invention to provide such a process which is simple, efficient, and reduces the number of operations required.

Summary of the Invention

The process of the invention comprises the steps of:

a) amination of CHDAAn with aqueous ammonia;

b) neutralization of the reaction mixture, whereby crude CHDAAM is precipitated and filtered; and

c) purification of the crude CHDAAM by crystallization from a solvent.

Preferably:

a) the amination is carried out at a temperature kept below 20°C and with aqueous ammonia having a concentration from 25 to 35 wt%, in a molar ratio relative to the CHDAAn from 5 to 10;

b) the neutralization is carried out with an aqueous solution of H_2SO_4 having a concentration from 30 to 60 wt% and is continued until a slightly acid solution is obtained;

c) the solvent of the crystallization is aq. acetonitrile and the crystallized product is washed with the same solvent and dried.

The pure CHDAAM is obtained in a yield of at least 75 mole% over the starting CHDAAn, and with a purity typically above 99%, e.g. 99.5 or more percent. CHDAAM having such a high purity is a new product, since the art does not teach how to achieve it, and as such constitutes an aspect of this invention.

Alternatively, in less preferred embodiments of the invention, the neutralization of the reaction mixture can be carried out with aqueous hydrochloric acid, with or without a previous evaporation of the excess ammonia. In any case, the CHDAAM precipitates when the solution is slightly acid.

Brief Description of the Drawings

In the drawings:

- Fig. 1 is a flow sheet illustrating the steps of the preparation of crude CHDAAM from CHDAAn; and
- Fig. 2 is a flow sheet illustrating the purification of the crude CHDAAM thus obtained.

Detailed Description of Preferred Embodiments

A preferred embodiment of the process of the invention will be described with reference to the flow sheets of the drawings.

Melted crude CHDAAn at 50-70°C, or a solution of CHDAAn in a minimal amount of methylisobutylketone (MIBK), is added to a cold, 28 wt% aqueous solution of NH_3. The molar ratio NH_3:CHDAAn is about 7. The addition of the CHDAAn is carried out at such a rate that it is completed in 2 to 5 hours. In the specific example herein described, 0.8 moles of CHDAAn are added to 5.85 moles of NH_3 in a period of time of 2 hours.

The reaction is exothermic and therefore the reactor must be cooled to keep the temperature of the reaction mass below 20°C. The progress of the reaction is monitored by HPLC. The reaction is very fast and is practically complete immediately after the completion of the addition of the CHDAAn. The reaction mixture is obtained in the form of a clear solution. The final concentration of NH_3 is checked in order to calculate the amount of acid required in the neutralization stage.

The neutralization is then carried out: in the preferred example herein described, it is carried out with aqueous 50wt% H_2SO_4 without prior evaporation of the excess ammonia. In the specific example herein described, 337 ml of the said aqueous, 50% w/w H_2SO_4 are used for the neutralization. During the neutralization, the temperature is maintained below 30°C. The precipitation of crude CAM starts at pH 7-8 and is complete at pH about 5.

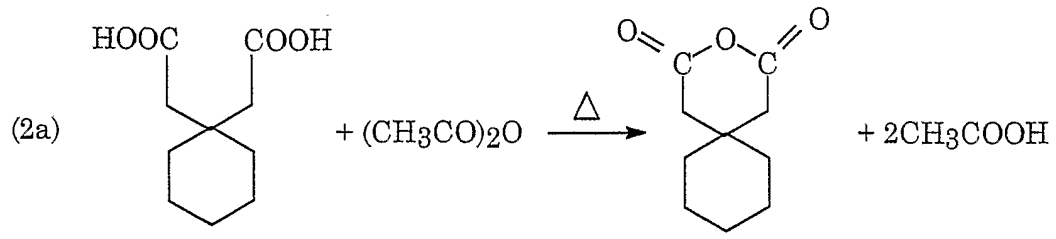
The crude CAM is separated by filtration from the slurry generated in the neutralization stage. It is washed with water and the crude material thus obtained is analyzed by HPLC.

Various solvents can be used for crystallization of the crude CHDAAM but aq. acetonitrile is preferred because it dissolves the organic impurities and because the crystallization yields and throughput are higher than with other solvents. The aq. acetonitrile contains 2 to 25 wt% of water, preferably 1 wt%. Other organic solvents such as, e.g., methanol or methylisobutylketone, could however be used. When aq. acetonitrile is used, its weight ratio thereof to the wet, crude CHDAAM, in the example herein described, is preferably about 1 to 4, more preferably 2.

After crystallization and filtration, the wet cake of CHDAAM is washed with the crystallization solvent, preferably acetonitrile, and dried.

The pure CHDAAM thus obtained has a purity higher than 99.5% and is obtained in a yield of about 75%, based on CHDAAn.

The CHDAAn used as a starting material in the above process can be obtained in ways known in the art. For instance, it can be obtained by reacting CHDAA with excess acetic anhydride under reflux, followed by distillation of the excess acetic anhydride and acetic acid formed from the reaction mixture and final distillation, according to the following reaction scheme:



CHDAAn

Although the preparation of CHDAAn from CHDAA is not a part of the invention, the following references are given for illustrative purposes:

1. French Patent 1,248,764, Spiro(cyclohexane-1,4'-glutarimides), Centre de Lyophilisation Pharmaceutique (1961), CA 57:3320.

2. J. F. Callahan et al., Synthesis of 6,6-pentamethylene-2-aminosuberic acid, a key intermediate in the synthesis of dicarba analogues of Vasopressin antagonists, J. Org. Chem., 53, 1527-1530 (1988), CA 108: 150949.

While embodiments of the invention have been described for purposes of illustration, it will be understood that they are not limitative and that the invention may be carried out with a number of modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

CLAIMS

1. Process for the preparation of 1,1-cyclohexane-diacetic acid monoamide (CHDAAM), which comprises the steps of:

a) amination of 1,1-Cyclohexane-diacetic anhydride (CDAAn) with aqueous ammonia;

b) neutralization of the reaction mixture, whereby crude CHDAAM is precipitated and filtered; and

c) purification of the crude CHDAAM by crystallization from a solvent.

2. Process according to claim 1, wherein the amination is carried out at a temperature kept below 20°C and with aqueous ammonia having a concentration from 25 to 35 wt%, in a molar ratio relative to the CHDAAn from 5 to 10.

3. Process according to claim 1, wherein the neutralization is carried out with an aqueous solution of H_2SO_4 having a concentration from 30 to 70 wt% and is continued until a slightly acid solution is obtained.

4. Process according to claim 1, wherein the solvent of the crystallization is aq. acetonitrile containing 5-25 wt% water.

5. Process according to claim 4, wherein the aq. acetonitrile contains 17 wt% water.

6. Process according to claim 1, further comprising washing the crystallized CAM with the crystallization solvent.

7. Process according to claim 1, wherein the neutralization is carried out with aqueous hydrochloric acid, with or without a previous evaporation of the excess ammonia.

8. Process according to claim 2, wherein the amination is carried out with a molar ratio NH_3:CHDAAn of about 7.

9. Process according to claim 2, wherein the amination is carried out with cooling.

10. Process according to claim 3, wherein the neutralization is carried out without prior evaporation of the excess ammonia and at a temperature below 30°C, until a pH of about 5 has been reached.

11. Process according to claim 4, wherein the weight ratio of acetonitrile to the wet, crude CHDAAM is about 1 to 4.

12. Process according to claim 11, wherein the weight ratio of acetonitrile to the wet, crude CHDAAM is about 2.

13. Process according to claim 1, further comprising preparing the CHDAAn by reacting 1,1-Cyclohexanediacetic acid (CHDAA) with an equimolar amount of acetic anhydride.

14. Process for the preparation of 1,1-Cyclohexanediacetic acid monoamide (CHDAAM), substantially as described and illustrated.

15. 1,1-Cyclohexane-diacetic acid monoamide (CHDAAM), having a purity higher than 99.5%.

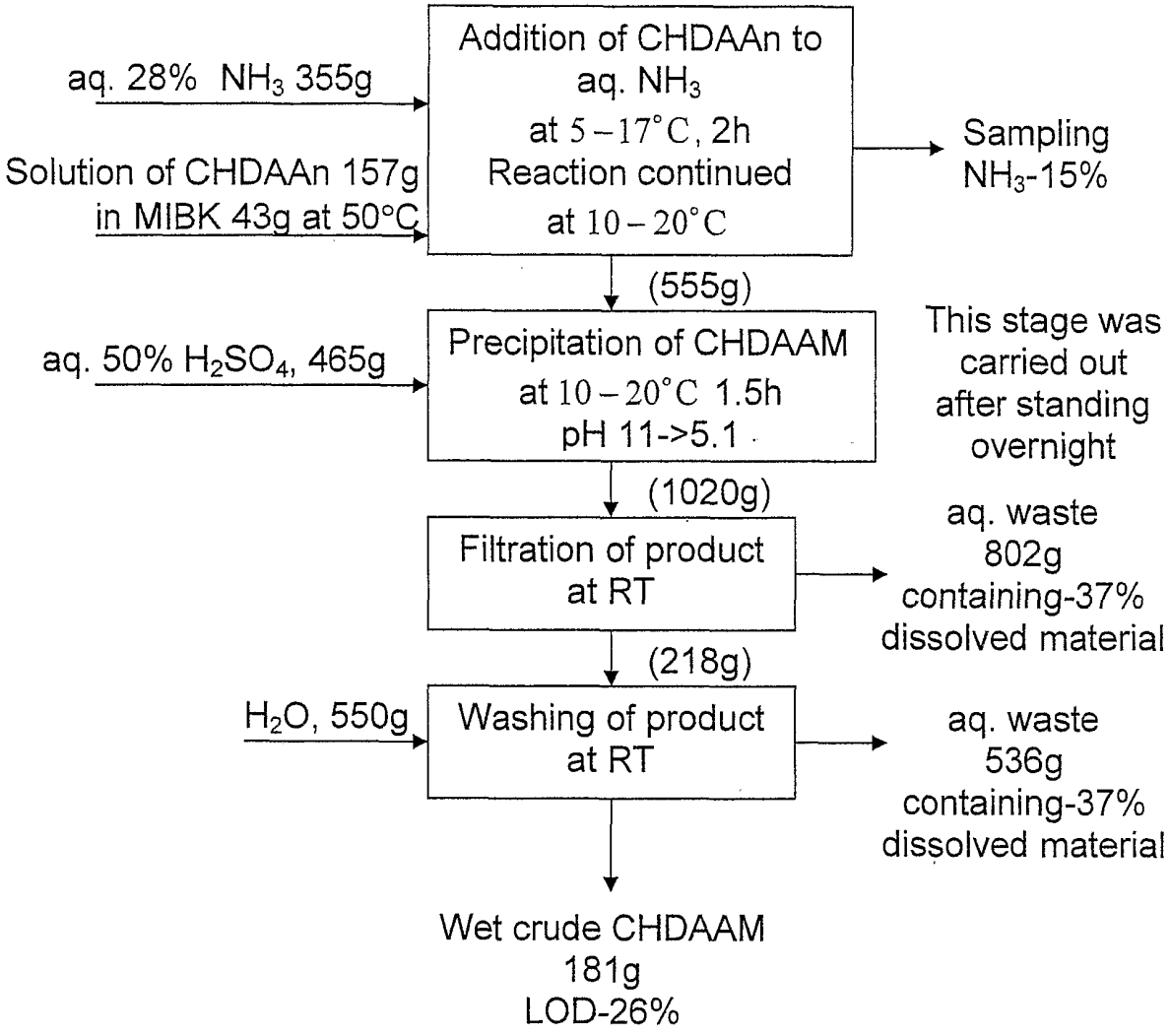

aq. 28% NH3 355g
Solution of CHDAAn 157g in MIBK 43g at 50°C
Addition of CHDAAn to aq. NH3 at 5 – 17°C, 2h Reaction continued at 10 – 20°C
Sampling NH3-15%
(555g)
aq. 50% H2SO4, 465g
Precipitation of CHDAAM at 10 – 20°C 1.5h pH 11->5.1
This stage was carried out after standing overnight
(1020g)
Filtration of product at RT
aq. waste 802g containing-37% dissolved material
(218g)
H2O, 550g
Washing of product at RT
aq. waste 536g containing-37% dissolved material
Wet crude CHDAAM 181g LOD-26%

Fig. 1

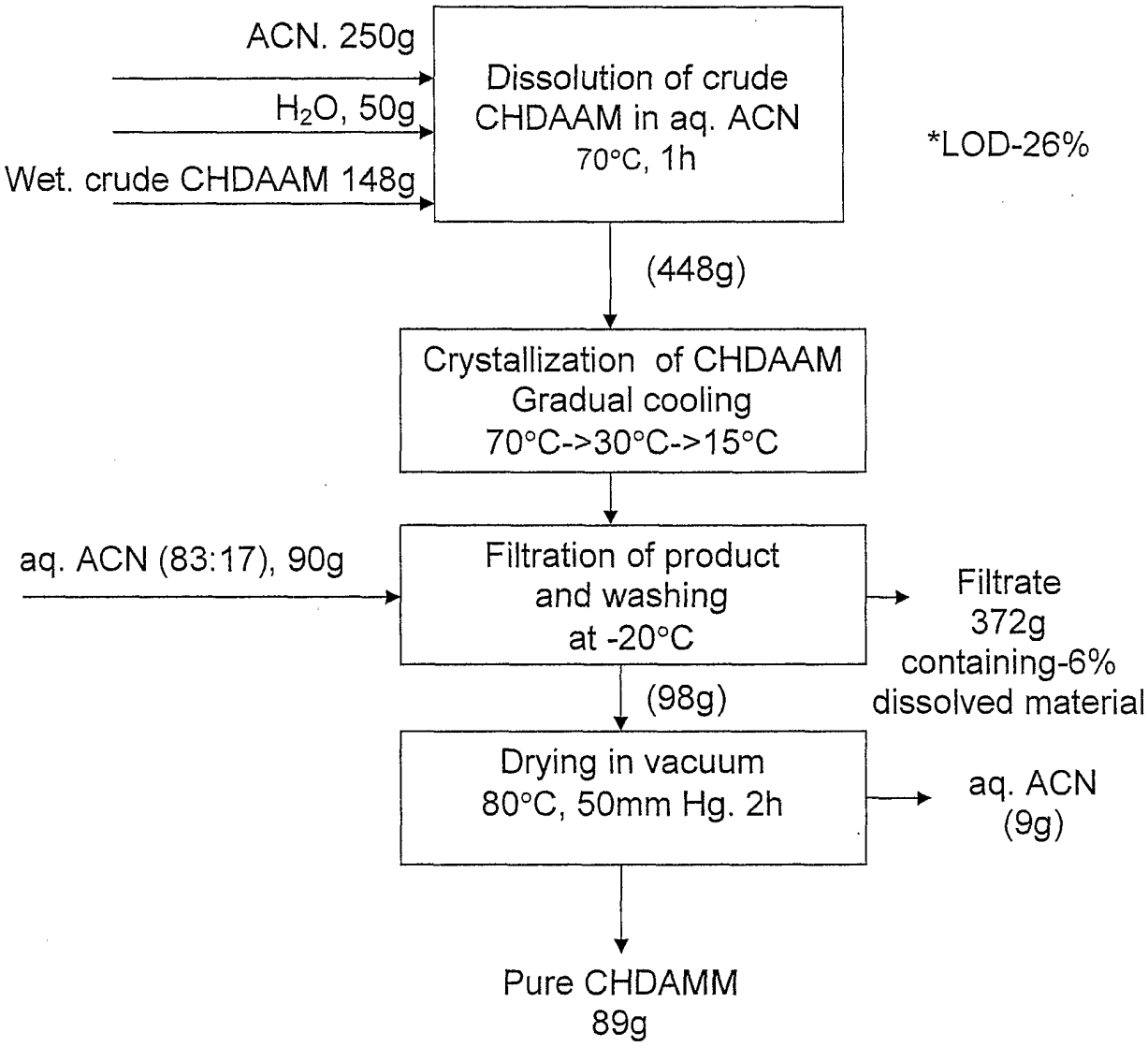

ACN. 250g
H_2O, 50g
Wet. crude CHDAAM 148g
Dissolution of crude CHDAAM in aq. ACN 70°C, 1h
*LOD-26%
(448g)
Crystallization of CHDAAM Gradual cooling 70°C->30°C->15°C
aq. ACN (83:17), 90g
Filtration of product and washing at -20°C
Filtrate 372g containing-6% dissolved material
(98g)
Drying in vacuum 80°C, 50mm Hg. 2h
aq. ACN (9g)
Pure CHDAMM 89g

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 02/00473

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C231/02 C07C233/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 024 175 A (SATZINGER GERHARD ET AL) 17 May 1977 (1977-05-17) cited in the application column 3, line 7 - line 19 column 5, line 46 - line 57; example 4	1-14
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 2001-497525 XP002217483 "Preparation of Cyclohexyl Oxalic Amide" & CN 1 297 885 A (HANGZHOU SHOUXIN FINE CHEM)	15
Y	abstract	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2002	04/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bedel, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 02/00473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4024175 A	17-05-1977	DE 2460891 A1	01-07-1976
		AT 340892 B	10-01-1978
		AT 975075 A	15-05-1977
		AU 8774175 A	23-06-1977
		BE 836835 A1	18-06-1976
		CA 1052811 A1	17-04-1979
		CH 612665 A5	15-08-1979
		CH 612666 A5	15-08-1979
		CH 612664 A5	15-08-1979
		DE 2543821 A1	14-04-1977
		DK 581475 A ,B,	22-01-1976
		ES 443723 A1	16-04-1977
		FI 753613 A ,B,	22-06-1976
		FR 2294697 A1	16-07-1976
		GB 1465229 A	23-02-1977
		IE 42382 B1	30-07-1980
		JP 941538 C	20-02-1979
		JP 51088940 A	04-08-1976
		JP 53024064 B	18-07-1978
		LU 74058 A1	20-07-1976
		MX 4721 E	13-08-1982
		MX 4691 E	02-08-1982
		NL 7514900 A ,B,	23-06-1976
		SE 423385 B	03-05-1982
		SE 7514442 A	22-06-1976
		US 4087544 A	02-05-1978
CN 1297885 A	06-06-2001	NONE	