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(21) International Application Number: PCT/SE90/00792 (22) International Filing Date: 29 November 1990 (29.11.90) (30) Priority data: 8904064-6 1 December 1989 (01.12.89) SE (71) Applicant (for all designated States except US): AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only) : JAKSCH, Peter [SE/SE]; Grönkullastigen 22, S-153 00 Järna (SE). (74) Agents: MIKSCH, Gerhard et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE).		(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i>
(54) Title: IMPROVED METHOD OF PREPARING AN INTERMEDIATE FOR THE MANUFACTURE OF BAMBUTEROL		
(57) Abstract The present invention relates to an improved method for the preparation of an intermediate for bambuterol, i.e. for the preparation of 2'-bromo-3,5-di[N,N-dimethylcarbamoyloxy]acetophenone (1), by reacting 3,5-dihydroxyacetophenone with N,N-dimethylcarbamoylchloride in ethyl acetate, isopropylacetate, butylacetate, ethylmethylketone or isobutylmethylketone as a solvent with small amount of pyridine as a catalyst and using crystallized potassium carbonate as a base, quenching with water, removing the solvent and dissolving of the resulting 3,5-di[N,N-dimethylcarbamoyloxy]acetophenone in ethyl acetate, to which dissolved hydrogen bromide is added and then bromine, whereupon the resulting intermediate (1) is collected in the form of crystals.		

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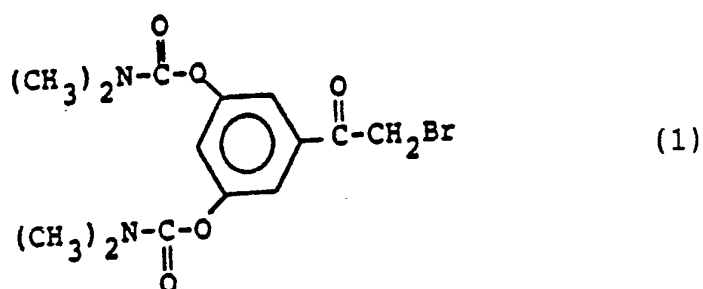
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Improved method of preparing an intermediate for the
manufacture of bambuterol

5 The present invention relates to an improved method for
the preparation of an intermediate for bambuterol, i.e.
for the preparation of 2'-bromo-3,5-di[N,N-dimethyl-
carbamoyloxy]acetophenone, having the formula

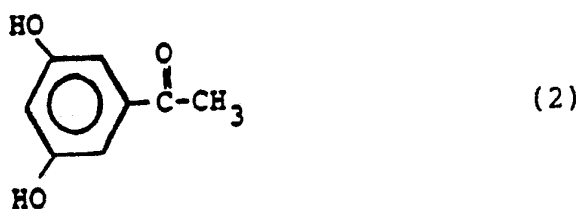
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In US-A-4 451 663 a method of manufacturing the inter-
20 mediate 2'-bromo-3,5-di[N,N-dimethylcarbamoyloxy]-
acetophenone of the formula (1) is disclosed, called route
A2 therein, according to which 3,5-dihydroxyacetophenone,
having the formula

25



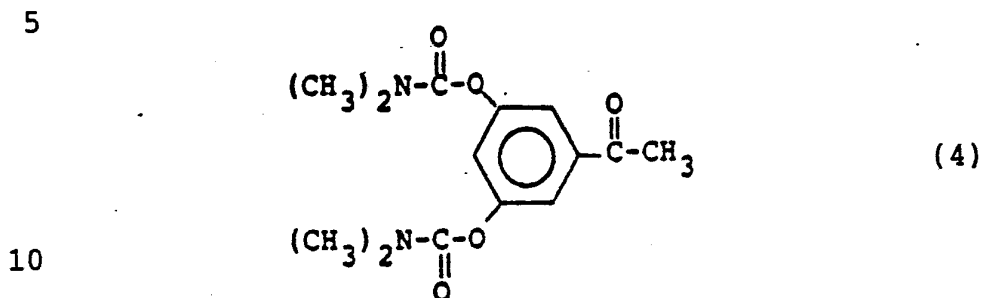
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is reacted with N,N-dimethylcarbamoylchloride (DMCC)
having the formula

35



using pyridine as solvent and base for the uptake of hydrochloric acid formed during the reaction. The resulting compound, 3,5-di-[N,N-dimethylcarbamoyloxy]-acetophenone having the formula

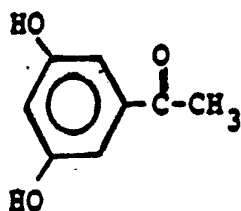


is not isolated but further reacted with bromine in dioxan solvent resulting in the formation of 2'-bromo-3,5-di[N,N-dimethylcarbamoyloxy]acetophenone (1).

There is a great desire to avoid working with pyridine as a solvent. One method was tested in order to avoid using pyridine as a solvent, according to which the reaction was performed in methylene chloride with potassium carbonate as a base with a catalytical amount of pyridine present. The drawbacks with this process was a long reaction time for N,N-dimethylcarbamoylchloride (DMCC), > 24 hours, and a long quenching time for DMCC, > 24 hours, and separation problems in the work-up step (emulsion and small density difference). Methylene chloride is not a preferred solvent either, because of its toxicity.

The object of the invention is to provide an improved method for the preparation of the intermediate 2'-bromo-3,5-di-[N,N-dimethylcarbamoyloxy]acetophenone (1) for the production of bambuterol avoiding the use of pyridine and methylene chloride as solvents and eliminating the separation problems in the work-up step.

This is attained according to the present invention by reacting 3,5-dihydroxyacetophenone

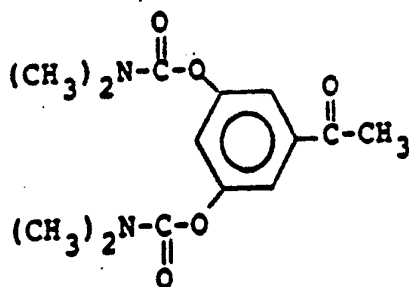


(2)

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with N,N-dimethylcarbamoylchloride, $(\text{CH}_3)_2\text{NCOCl}$, in a solvent, quenching with water, removing the solvent and dissolving of the resulting 3,5-di-[N,N-dimethyl-

10 carbamoyloxy]acetophenone



(4)

15

in ethyl acetate, to which is added dissolved hydrogen

20 bromide and then bromine, whereupon the resulting intermediate (1) is collected in the form of crystals, wherein the reaction between said 3,5-dihydroxyacetophenone (2) and N,N-dimethylcarbamoylchloride (3) is carried out in ethylacetate, isopropylacetate, butyl-

25 acetate, ethylmethylketone or isobutylmethylketone as the solvent with a small amount of pyridine as a catalyst using a base comprising crystallized potassium carbonate.

According to a preferred embodiment of the invention

30 potassium carbonate having a crystal water content of 11 - 13 % is used. This might be achieved by using a mixture of crystallized and calcinated potassium carbonate, resulting in a easily stirred two-phase system.

35

Calcinated potassium carbonate (completely dry) gives a slow and non-complete reaction, and the addition of water to the calcinated potassium carbonate results in a sticky mass which is difficult to stir. Further, free water
5 should not be present in the reaction mixture because of the risk of hydrolysis of the reactants.

The bromination step which according to the invention first involves the addition of HBr, preferably dissolved
10 in ethanol, and a second step charging with bromine, Br₂, has the advantage that the bromination will proceed calmly. When bromination is performed directly with bromine, the reaction will start very slowly and at a certain point it will proceed vigorously and will be hard
15 to control.

The invention will now be described more in detail.

In the first step of the process the base, potassium
20 carbonate, will take care of hydrochloric acid formed. According to the prior art process pyridine will act both as base and solvent. In the process according to the invention however, pyridine will only be present in catalytic amounts. Here the pyridine will initially take
25 up the hydrochloric acid formed, which then will be transferred to the potassium carbonate, which is consumed.

Dry, that is calcinated, potassium carbonate, does not work very well as a base, and the reason is believed to be
30 that it forms a separate phase which is non-miscible with the other phases. If calcinated potassium carbonate and water is used, the water will hydrolyze the N,N-dimethyl-carbamoylchloride (DMCC).

35 According to the invention crystallized potassium carbonate is used as the base. The water will be released slowly and the base will be slowly consumed by the

hydrochloric acid, which is first taken up and then transferred from the catalytic amount of pyridine present in the reaction mixture.

- 5 The crystallized potassium carbonate contains about 1.5 moles of H_2O which corresponds to about 16 %. The optimum water content is 11 - 13 %, and this content is obtained using a mixture of calcinated potassium carbonate and crystallized potassium carbonate.

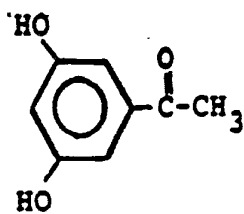
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The synthetic route is described more in detail below.

Flowsheet diagram of synthetic route

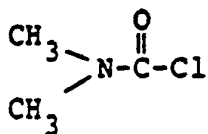
Step 1

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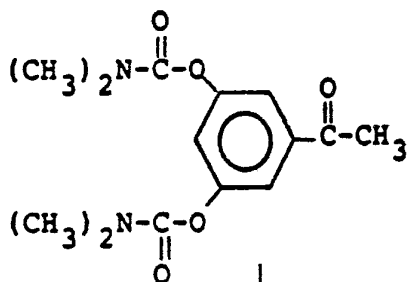


3,5-dihydroxyacetophenone

10

N,N-dimethylcarbamoyl-
chloride

15

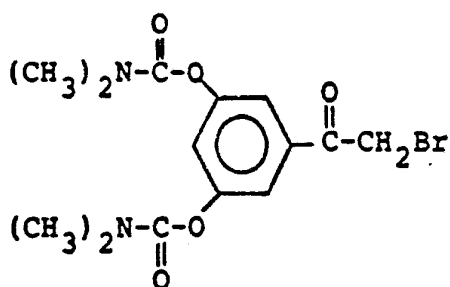
3,5-di-[N,N-dimethylcarba-
moyloxy]acetophenone
(not isolated)

20

25 Step 2

HBr Hydrogene bromide
Br₂ Bromine

30

2'-bromo-3,5-di[N,N-di-
methylcarbamoyloxy]-
acetophenone

35

Step 1

Synthesis of 3,5-di-[N,N-dimethylcarbamoyloxy]acetophenone
500 litre scale

5

Chemicals

	<u>In</u>	kg	molar weight	moles
10	3,5-dihydroxyacetophenone	24.0	152.2	157.7
	Potassium carbonate x 1,5 H ₂ O*	41.0	165.5	247.7
	Potassium carbonate calc.	9.4	138.2	68.0
	Pyridine	1.0	79.1	12.6
	Ethyl acetate	136.0		
15	Dimethylcarbamoylchloride	50.0	107.5	465.1
	Water	180.0		
	Sulphuric acid	≈ 1.0		
20	<u>Out</u>			
	3,5-di-[N,N-dimethylcarbamoyloxy]acetophenone			
	Yield calc. 95 %	44.1	294.3	149.8

- 25 *) The use of the hydrate form of potassium carbonate is essential for a successful reaction.

Procedure

- 30 Into a 500 litre enamelled reactor, connected to a scrubber containing ammonia/ethanol, is charged:

24 kg	3,5-dihydroxyacetophenone
41 kg	potassium carbonate x 1,5 H ₂ O
35 9.4 kg	potassium carbonate calcinated
96 kg (150 l)	ethyl acetate
1.0 kg	pyridine
50 kg	dimethylcarbamoylchloride

This mixture is stirred and heated to $70 \pm 2^\circ\text{C}$, and after stirring for 2 hours at this temperature 120 kg water is charged at 70°C and the mixture is stirred for 1,5 hours at $70 \pm 2^\circ\text{C}$. After cooling to $20-30^\circ\text{C}$ the reaction mixture is separated and the lower water phase is discarded.

To the organic phase is charged 60 kg water and pH is adjusted to 2 - 3 with about 1 kg sulphuric acid.

The phases are separated and the lower water phase is discarded. Ethyl acetate and water are removed by evaporation in the reactor at a jacket temperature of 60°C and vacuum (< 100 mbar). The evaporation residue is dissolved in 40 kg (50 l) ethyl acetate and is used directly in the bromination step.

Step 2

Synthesis of 2'-bromo-3,5-di[N,N-dimethylcarbamoyloxy]acetophenone in laboratory scale

Chemicals

	<u>In</u>	ml	g	molar weight	moles
25	3,5-di-[N,N-dimethylcarbamoyloxy]acetophenone		21.8	294.3	0.074
	dissolved in ethyl acetate	25	20.0		
	Ethanol	16	12.8		
30	Bromine		12.6	159.8	0.079
	Water	36	36.0		
	Ethanol	15	12.0		
	Hydrogen bromide compr.		3.2	80.9	0.040
35	<u>Out</u>				
	2'-bromo-3,5-di[N,N-dimethylcarbamoyloxy]acetophenone				
	Yield calc. 75 %		20.7	373.2	0.055

Procedure

Into a 100 ml three necked flask is charged 21.8 g 3,5-di[N,N-dimethylcarbamoyloxy]acetophenone dissolved in
5 ethylacetate and 3.2 g hydrogen bromide dissolved in 12.8 g (16 ml) ethanol.

At $12 \pm 2^\circ\text{C}$ is charged 12.6 g bromine in 30-60 minutes.

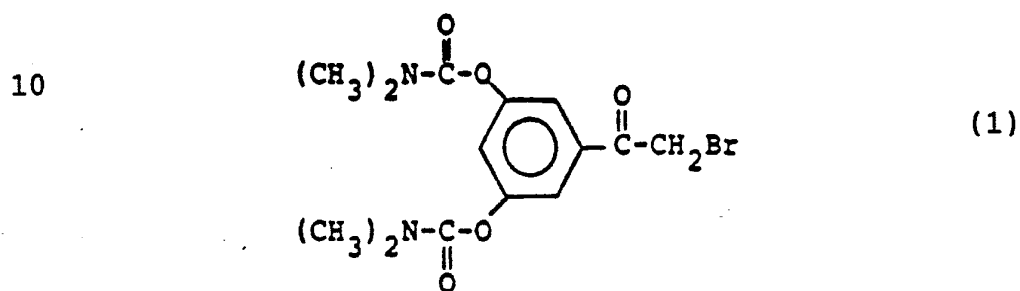
10 After stirring for further 10 minutes at $12 \pm 2^\circ\text{C}$ 36 ml (36 g) water is charged in about 15 minutes.

Thereafter the crystal slurry is cooled to $-14 \pm 2^\circ\text{C}$ and the crystals are collected on a filter and washed with
15 12 g (15 ml) cold (-14°C) ethanol. The crystals are dried at 40°C in vacuum.

The yield is about 20.7 g (75 %).

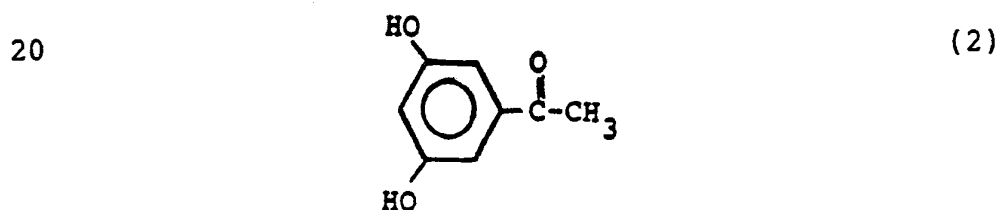
C l a i m s

1. Improved method for the preparation of an intermediate for bamuterol, i.e. for the preparation of
 5 2'-bromo-3,5-di-[N,N-dimethylcarbamoyloxy]-acetophenone, having the formula



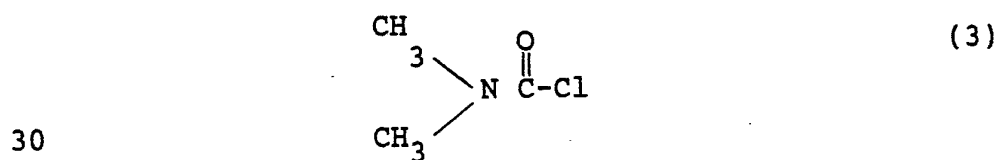
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by reacting 3,5-dihydroxyacetophenone



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with N,N-dimethylcarbamoylchloride,

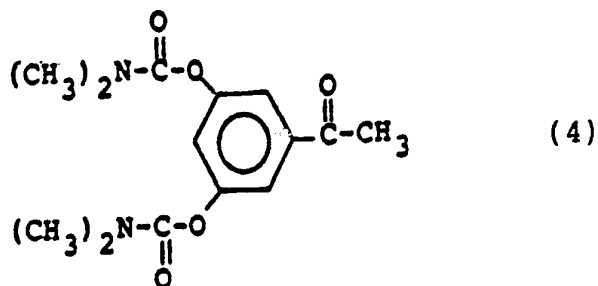


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in a solvent, quenching with water, removing the solvent and dissolving of the resulting 3,5-di-[N,N-dimethylcarbamoyloxy]acetophenone

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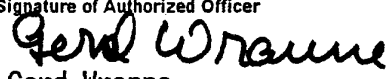
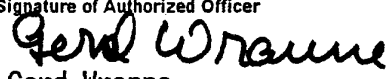
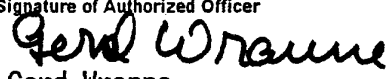


10 in ethyl acetate, to which dissolved hydrogen bromide
is added and then bromine, whereupon the resulting
intermediate (1) is collected in the form of
crystals, characterized in that the
reaction between said 3,5-dihydroxyacetophenone (2)
15 and N,N-dimethylcarbamoylchloride (3) is carried out
in ethylacetate, isopropylacetate, butylacetate,
ethylmethylketone or isobutylmethylketone as the
solvent with a small amount of pyridine as a catalyst
using a base comprising crystallized potassium
20 carbonate.

2. Improved method according to claim 1, characterized in that the base is in the form of a
mixture of crystallized and calcinated potassium
25 carbonate having a total crystal water content of 11-
13 %.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00792

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 C 271/44											
II. FIELDS SEARCHED Minimum Documentation Searched⁷ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black;">Classification System</th> <th style="border: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: 1px solid black; vertical-align: bottom;">C 07 C</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸ SE,DK,FI,NO classes as above			Classification System	Classification Symbols	IPC5	C 07 C					
Classification System	Classification Symbols										
IPC5	C 07 C										
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border: 1px solid black;">Category *</th> <th style="border: 1px solid black;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 15%; border: 1px solid black;">Relevant to Claim No.¹³</th> </tr> <tr> <td style="border: 1px solid black; vertical-align: top;">Y</td> <td style="border: 1px solid black; vertical-align: top;"> US, A, 4451663 (O.A. OLSSON ET AL.) 29 May 1984, see column 22, line 26 - line 55 -- </td> <td style="border: 1px solid black; vertical-align: top;">1-2</td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top;">Y</td> <td style="border: 1px solid black; vertical-align: top;"> GB, A, 1173753 (SCHERING AG) 10 December 1969, see page 15, claim 30; page 2, line 41, the reactionschedule, the examples -- ----- </td> <td style="border: 1px solid black; vertical-align: top;">1-2</td> </tr> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	Y	US, A, 4451663 (O.A. OLSSON ET AL.) 29 May 1984, see column 22, line 26 - line 55 --	1-2	Y	GB, A, 1173753 (SCHERING AG) 10 December 1969, see page 15, claim 30; page 2, line 41, the reactionschedule, the examples -- -----	1-2
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Y	GB, A, 1173753 (SCHERING AG) 10 December 1969, see page 15, claim 30; page 2, line 41, the reactionschedule, the examples -- -----	1-2									
* Special categories of cited documents:¹⁰ "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 "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											
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; vertical-align: top;"> Date of the Actual Completion of the International Search 13th February 1991 </td> <td style="width: 50%; border: 1px solid black; vertical-align: top;"> Date of Mailing of this International Search Report 1991 -02- 20 </td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top;"> International Searching Authority SWEDISH PATENT OFFICE </td> <td style="border: 1px solid black; vertical-align: top;"> Signature of Authorized Officer  Gerd Wranne </td> </tr> </table>			Date of the Actual Completion of the International Search 13th February 1991	Date of Mailing of this International Search Report 1991 -02- 20	International Searching Authority SWEDISH PATENT OFFICE	Signature of Authorized Officer  Gerd Wranne					
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 90/00792**

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4451663	84-05-29	AT-E- 7689	84-06-15
		AU-B- 539976	84-10-25
		AU-D- 7261881	82-01-14
		CA-A- 1180021	84-12-25
		EP-A-B- 0043807	82-01-13
		JP-B- 2026628	90-06-12
		JP-A- 57040453	82-03-06
		JP-A- 63002966	88-01-07
		US-A- 4419364	83-12-06

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		DE-A-B-C 1568621	70-03-19
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		NL-A- 6615986	67-05-16
		US-A- 3404975	00-00-00
		OA-A- 2277	70-05-05